Steven M. Donn
Sunil K. Sinha *Editors*

Manual of Neonatal Respiratory Care

Fourth Edition

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Foreword

A successful transition from fetal to neonatal life is dependent upon the profound cardiorespiratory adaptations occurring at this time. Unfortunately, these events frequently require medical intervention, especially in preterm infants. The consequences of the resultant pathophysiologic changes and therapeutic interventions in such neonates may have long-lasting effects on the developing respiratory system and even the neurodevelopmental outcome of this high-risk population.

Recognition of the importance of neonatal respiratory management was an early milestone in the history of neonatology. The role of surfactant deficiency in the etiology of neonatal respiratory distress syndrome was sealed over 50 years ago, and this paved the way for the introduction of assisted ventilation for this population in the 1960s. I was privileged to be introduced to neonatal pediatrics in the early 1970s at a time when the advent of continuous positive airway pressure demonstrated how physiologic insight can be translated into effective therapy. The decade of the 1970s offered so many other innovations in neonatal respiratory care. These included noninvasive blood gas monitoring, xanthine therapy for apnea, and our first real understanding of the pathogenesis and management of meconium aspiration syndrome, group B streptococcal pneumonia, and persistent fetal circulation or primary pulmonary hypertension of the newborn, three frequently interrelated conditions. The decade ended in remarkable fashion with the introduction of exogenous surfactant therapy and recognition that the novel new technique of high-frequency ventilation allows effective gas exchange in sick neonates. However, many key questions in neonatal respiratory care still need to be addressed.

For preterm infants the enormous challenge remains to reduce the unacceptably high incidence of bronchopulmonary dysplasia which approaches 50 % in the smallest survivors of neonatal intensive care. The current fourth edition meets this dilemma head on by clearly acknowledging such issues as the increasing role of noninvasive ventilatory techniques and the challenge of optimizing oxygenation, both in the delivery room and beyond. It remains to be seen, however, whether the latest supportive ventilatory measures, together with safe pharmacotherapy, can diminish morbidity in NICU graduates. New sections on data collection and quality improvement demonstrate their key roles in addressing these challenges.

For preterm or term infants with malformations of the respiratory system, advances in pre- and postnatal imaging and surgical techniques hold promise for improved outcome. Great strides are being made simultaneously in our understanding of the molecular basis for normal and abnormal lung development. Furthermore, it is being increasingly recognized that genotypic characteristics may greatly influence the consequences of subsequent environmental exposures on lung development. These scientific advances need to be translated into improving adverse neonatal outcomes, such as the unacceptably high rate of wheezing disorders and asthma in the survivors of neonatal intensive care. As care providers to neonates, it is our responsibility to encourage clinical trials and other patient-based investigation that will allow us to optimize the outcome of neonatal respiratory care.

The fourth edition of the *Manual of Neonatal Respiratory Care* is comprehensive and provides an important educational tool to address many of these challenges. It is, again, thoroughly edited by the accomplished trans-Atlantic team of Steven Donn and Sunil Sinha. Once again, they have assembled physician/scientist leaders in the field of Developmental Pulmonology, who provide a true international perspective to neonatal respiratory care. Both prior and new contributors provide a concise overview that spans neonatal physiology, pathogenesis of disease, and unique approaches to management of both simple and complex neonatal respiratory disorders. The result is a comprehensive text that provides a strongly international insight into neonatal respiratory care in a user-friendly, practical format.

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Preface

Since the publication of the third edition of this Manual in 2012, much has happened in the field of neonatal respiratory care. We are experiencing somewhat of a divergence—equipment continues to become more technologically advanced, but management philosophy is moving towards a more simplistic approach, characterized by an increasing popularity of noninvasive support. This edition of the *Manual of Neonatal Respiratory Care* encompasses both aspects of the change in neonatal practice.

Standard chapters have been updated to reflect advances in both equipment and practice. We have eliminated chapters dealing with equipment which is no longer in use and replaced them with newer chapters that reflect the worldwide approaches to neonatal respiratory failure, such as sustained inflation, optimization of lung volume, and the use of volumetric capnography, aerosol therapy, and management of chylothorax. A major addition is an expansive chapter on disorders of the neonatal airway. We have expanded our contributors to include experts from all over the world. A special emphasis has been placed on noninvasive ventilation, including CPAP, nasal cannula therapy, nasal intermittent positive pressure ventilation, and associated devices.

New additions to the book also include chapters on assessment of large databases and implementation of quality improvement programs in neonatal respiratory care. Chronic ventilation of the baby with nonrespiratory ventilator dependency is now also addressed.

A major feature that we have added to this edition is the adoption of a standard taxonomy to classify mechanical ventilators. We have long felt that this has been a shortcoming within the industry, and that manufacturers often refer to the same thing by different and confusing terminology, frequently resulting in jeopardy to patient safety. We were very fortunate to enlist the services of Rob Chatburn in this regard. He has been a champion of a singular classification system. Not only did he author a chapter on this (chapter 44), he graciously and painstakingly co-edited the chapters on mechanical ventilation and inserted a "Mode Map" for each of the devices included in this edition. We are most grateful to him for taking the time and effort to do so.

Others participating in the preparation of this edition are also due a debt of gratitude, including Susan Peterson, who standardized the format and appearances of 100 chapters from more than 100 contributors; Brian Halm, our development editor at Springer; Andy Kwan, our publishing editor at

Springer; and Shelley Reinhardt, a former acquisitions editor at Springer, who was instrumental in continued support of the Manual at the inception of the fourth edition. Most of all, we thank our esteemed group of contributors for continuing to share their time and expertise in the hope of improving the care of newborns in respiratory distress.

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Section VIII Commonly Used Neonatal Ventilators

Section IX Adjunctive Therapies

Abbreviations

$\dot{V}$	Flow
$\ddot{V}$	Rate of change of flow
°C	Degrees Celsius (Centigrade)
°K	Degrees, Kelvin
a	Arterial
A	Alveolar
a/A	Arterial/alveolar ratio
A/C	Assist/control
AAC	Automatic airway compensation
A-aDO_2	Alveolar-arterial oxygen gradient
ABG	Arterial blood gas
ACT	Activated clotting time
ADP	Adenosine diphosphate
AH	Absolute humidity
ALTE	Apparent life-threatening event
AM	Morning
AMP	Adenosine monophosphate
Ao	Aortic
AOI	Apnea of infancy
AOP	Apnea of prematurity
AP	Antero-posterior
ARDS	Adult (or acute) respiratory distress syndrome
ASD	Atrial septal defect
ATP	Adenosine triphosphate
ATPS	Ambient temperature and pressure, saturated with water vapor
BAER	Brainstem audiometric evoked responses
BP	Blood pressure
BPD	Bronchopulmonary dysplasia
BPM (bpm)	Beats or breaths per minute
BR	Breath rate
BTPS	Body temperature and pressure, saturated with water vapor
C	Compliance
C20	Compliance over last 20 % of inflation
CCAM	Congenital cystic adenomatoid malformation
cAMP	Cyclic adenosine monophosphate

CBF	Cerebral blood flow
CBG	Capillary blood gas
cc	Cubic centimeter
C_D or C_{DYN}	Dynamic compliance
CDH	Congenital diaphragmatic hernia
CDP	Constant distending pressure
CF	Cystic fibrosis
cGMP	Cyclic guanosine monophosphate
CHAOS	Congenital high airway obstruction syndrome
CHD	Congenital heart disease
C_L	Compliance
CLD	Chronic lung disease
CLE	Congenital lobar emphysema
cm	Centimeter
CMV	Cytomegalovirus
CMV	Conventional mechanical ventilation
CNS	Central nervous system
CO	Cardiac output
CO_2	Carbon dioxide
CO-Hb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPL	Congenital pulmonary lymphangiectasis
CPR	Cardiopulmonary resuscitation
CPT	Chest physiotherapy
CRP	C-reactive protein
CSF	Cerebrospinal fluid
C_{ST}	Static compliance
CT	Computed tomography
CVP	Central venous pressure
CXR	Chest x-ray (radiograph)
D	End-diastole
D5W	Dextrose 5 % in water
DCO_2	Gas transport coefficient for carbon dioxide
DIC	Disseminated intravascular coagulation
dL	Deciliter
DNA	Deoxyribonucleic acid
DPG	Diphosphoglycerate
DPPC	Dipalmitoyl phosphatidyl choline
DR	Delivery room
E	Elastance
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDRF	Endothelial-derived relaxing factor
EEG	Electroencephalogram
EF	Ejection fraction
ELBW	Extremely low birth weight
EMG	Electromyogram

EMLA	Eutectic mixture of Lidocaine and Prilocaine
ERV	Expiratory reserve volume
ET	Endotracheal
$ETCO_2$	End-tidal carbon dioxide
ETCPAP	Endotracheal continuous positive airway pressure
ETT	Endotracheal tube
F or f	Frequency
F or Fr	French
FCV	Flow control valve, flow-cycled ventilation
FDA	Food and Drug Administration (US)
FDP	Fibrin degradation products
FGF	Fibroblast growth factor
FiO_2	Fraction of inspired oxygen
FIO_2	Fraction of inspired oxygen
FOE	Fractional oxygen extraction
FRC	Functional residual capacity
FSP	Fibrin split products
FTA	Fluorescent treponemal antibody
g	Gram
G	Gravida
g	Gauge
GA	Gestational age
GBS	Group B streptococcus
GER	Gastro-esophageal reflux
GERD	Gastro-esophageal reflux disease
GIR	Glucose infusion rate
gm	Gram
GNP	Gross national product
GTP	Guanosine triphosphate
GUI	Graphics user interface
h or hr	Hour
H_2O	Water
Hb	Hemoglobin
HCH	Hygroscopic condenser humidifiers
HCO_3^-	Bicarbonate
HFNC	High flow nasal cannula
HFO	High-frequency oscillation
HFOV	High-frequency oscillatory ventilation
HFV	High-frequency ventilation
Hg	Mercury
Hgb	Hemoglobin
HME	Heat and moisture exchanger
HR	Heart rate
HSV	Herpes simplex virus
Hz	Hertz
I	Inertance
I:E	Inspiratory:expiratory ratio
IC	Inspiratory capacity

Ig	Immunoglobulin
IL	Interleukin
IMV	Intermittent mandatory ventilation
INO	Inhaled Nitric Oxide
IO	Intraosseous
IP	Inspiratory pressure
IPPV	Intermittent positive pressure ventilation
IRV	Inspiratory reserve volume
IUGR	Intrauterine growth restriction
IV	Intravenous
IVC	Inferior vena cava (l)
IVH	Intraventricular hemorrhage
IVS	Interventricular septum
K	Constant
kDa	Kilodalton
kg	Kilogram
kPa	Kilopascal
L	Liter
LA	Left atrium
LBW	Low birth weight
LCD	Liquid crystalline display
LED	Light emitting diode
LHR	Ratio of lung diameter to head circumference
LOS	Length of stay
LPM (lpm)	Liters per minute
LVEDD	Left ventricular end-diastolic dimension
LVID	Left ventricular internal diameter
LVIDD	Left ventricular internal diameter at diastole
LVIDS	Left ventricular internal diameter at systole
LVO	Left ventricular output
m	Meter
MAP	Mean airway pressure
MAP	Mean arterial pressure
MAS	Meconium aspiration syndrome
mcg	Microgram
MD	Minute distance
mEq	Milliequivalent
MetHb	Methemoglobin
mg	Milligram
MIC	Mean inhibitory concentration
min	Minute
mL (ml)	Milliliter
mm	Millimeter
MMV	Mandatory minute ventilation
mo	Month
mOsm	Milliosmoles
MRI	Magnetic resonance imaging
MSAF	Meconium-stained amniotic fluid

msec	Millisecond
MV	Minute ventilation
NAVA	Neurally adjusted ventilatory assist
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NIPPV	Noninvasive positive pressure ventilation
NIRS	Near-infrared spectroscopy
NO	Nitric Oxide
NO_2	Nitrogen Dioxide
NOS	Nitric oxide synthase
O_2	Oxygen
OI	Oxygenation index
OSI	Oxygen saturation index (100 xPaw x FiO_2/SpO_2)
P	Pressure
P50	Point of 50 % saturation of hemoglobin with oxygen
Pa-ACO_2	Arterial to alveolar CO_2 gradient
$PACO_2$	Partial pressure of carbon dioxide, alveolar
$PaCO_2$	Partial pressure of carbon dioxide, arterial
Pa-etCO_2	Arterial to end-tidal CO_2 gradient
PAO2	Partial pressure of oxygen, alveolar
PaO_2	Partial pressure of oxygen, arterial
PAV	Proportional assist ventilation
Paw	Airway pressure
Pāw	Mean airway pressure
PB	Periodic breathing
PC	Pressure control
PCA	Post-conceptional age
PCR	Polymerase chain reaction
PDA	Patent ductus arteriosus
PE	Elastic pressure
$PECO_2$	Partial pressure of mean expiratory CO_2
PEEP	Positive end-expiratory pressure
$PetCO_2$	Partial pressure of end-tidal CO_2
PFC	Persistent fetal circulation, perfluorocarbon
PG	Prostaglandin
PH_2O	Partial pressure of water vapor
PI	Inspiratory pressure
P_I	Pressure, inertital
PICC	Percutaneous intravenous central catheter
PIE	Pulmonary interstitial emphysema
PIP	Intrapleural pressure
PIP	Peak inspiratory pressure
PL	Pressure limit
PLV	Partial liquid ventilation
PMA	Post-menstrual age
PMA	Pre-market approval (US)
PN_2	Partial pressure of nitrogen
PPHN	Persistent pulmonary hypertension of the newborn

ppm	Parts per million
PR	Resistive pressure
prbc	Packed red blood cells
PRVC	Pressure-regulated volume control
PSI	Pounds per square inch
PSIG	Pounds force per square inch gauge
PST	Static pressure
PSV	Pressure support ventilation
PT	Prothrombin time
PTP	Transpulmonary pressure
PTT	Partial thromboplastin time
PTV	Patient-triggered ventilation
PUFA	Polyunsaturated fatty acids
PV-IVH	Periventricular-intraventricular hemorrhage
PVL	Periventricular leukomalacia
PvO_2	Mixed central venous oxygen tension
PvO_2	Partial pressure of oxygen, venous
PVR	Pulmonary vascular resistance
q	Every
Q	Perfusion
r	Radius
R	Resistance
R_{AW}	Airway resistance
RBC	Red blood cell
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
RE	Expiratory resistance
REM	Rapid eye movement
RH	Relative humidity
RI	Inspiratory resistance
ROP	Retinopathy of prematurity
ROS	Reactive oxygen species
RR	Respiratory rate, relative risk
RSV	Respiratory syncytial virus
RV	Reserve volume
RVO	Right ventricular output
S	End-systole
S1 (2,3,4)	First (second, third, fourth) heart sound
SaO_2	Arterial oxygen saturation
sec	Second
sGC	Soluble guanylate cyclase
SIDS	Sudden infant death syndrome
SIMV	Synchronized intermittent mandatory ventilation
SNAP	Score for neonatal acute physiology
SOD	Superoxide dismutase
SP	Surfactant protein
SpO_2	Pulse oximetry saturation

SpO_2/FiO_2	Ratio of pulse oximetry oxygen saturation to fraction of inspired oxygen
sq	Square
STPD	Standard temperature and pressure, dry
SV	Stroke volume
SVC	Superior vena cava (l)
SvO_2	Venous oxygen saturation
SVR	Systemic vascular resistance
T	Temperature
TBW	Total body water
$TcPCO_2$	Transcutaneous carbon dioxide level
TCPL (V)	Time-cycled, pressure-limited (ventilation)
$TcPO_2$	Transcutaneous oxygen level
TCT	Total cycle time
T_E or T_e	Expiratory time
TEF	Tracheo-esophageal fistula
TGF	Transforming growth factor
TGV	Total or thoracic gas volume
THAM	Tris–hydroxyaminomethane
T_I or T_i	Inspiratory time
TLC	Total lung capacity
TLV	Total liquid ventilation
TPN	Total parenteral nutrition
TPV	Time to peak velocity
TRH	Thyroid releasing hormone
TTN, TTNB	Transient tachypnea of the newborn
TTV	Targeted tidal volume
U	Units
UAC	Umbilical artery catheter
V	Volume, velocity
µm	Micrometer
HFJV	High-frequency jet ventilation
V/Q	Ventilation/perfusion
V_A	Alveolar ventilation
VA	Anatomic volume
V-A	Veno-arterial
VAP	Ventilator-associated pneumonia
VAPS	Volume assured pressure support
VC	Vital capacity
VCF	Velocity of circumferential fiber shortening
VCO_2	Carbon dioxide elimination
VCV	Volume controlled ventilation
VD	Dead space volume
VD_{alv}	Alveolar dead space
VD_{aw}	Airway dead space
VD_{phys}	Physiologic dead space
VDRL	Venereal disease research laboratory
$VECO_2$	Expiratory CO_2 volume per breath

VEGF	Vascular endothelial growth factor
VILI	Ventilator-induced lung injury
VLBW	Very low birthweight
VS	Volume support
VSD	Ventricular septal defect
V_T	Tidal volume
V_{TE}	Expired tidal volume
V_{TI}	Inspired tidal volume
VTI	Velocity time interval
V-V	Venovenous
WBC	White blood cell
wks	Weeks
yrs	Years

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Section I

Lung Development and Maldevelopment

Development of the Respiratory System

1

Vinod K. Bhutani

I. Introduction
   A. The neonatal respiratory system is a complex organ with a life-sustaining function on the initiation and maintenance of ongoing dynamic interactions among multiple tissue types of diverse embryonic origins.
   B. It has two functional areas: the conducting system and the gas exchange system.
      1. Nasal passages, pharynx, larynx, trachea, bronchi, and bronchioles are generally supported by cartilage until the terminal bronchioles and prevent airway collapse during expiration.
      2. The surrounding tissues include airway smooth muscle that regulate airway resistance, whereas the fibroelastic supportive tissue offers elasticity during both respiratory cycles.
      3. The structural mucosal layers are lined by motile ciliary cells, mucus-producing goblet cells, and basal cells that provide for regeneration and healing.
      4. The submucosal layers contain seromucous glands and Clara cells.
      5. The gas exchange system comprises respiratory non-cartilaginous bronchioles that lead to alveolar ducts, sacs and alveoli. These areas are lined by squamous Type I pneumocytes (that produce prenatal lung fluid in utero) and the cuboidal Type II pneumocytes that manufacture and secrete surfactant. The gas exchange areas interface through the blood–air barrier with pulmonary vasculature.
      6. Our understanding of the genetic, molecular, and cellular developmental processes that continue during lifetime are perturbed by maturation, disease, environmental factors, and recovery.
   C. The complex process of mammalian lung development includes lung airway branching morphogenesis and alveolarization, together with angiogenesis and vasculogenesis.
      1. Severe defects of any of these developmental events will lead to neonatal respiratory failure and death in infants. However, the impact of milder structural or functional defects, occurring as a result of aberrant lung development, has been neglected in the past because of a

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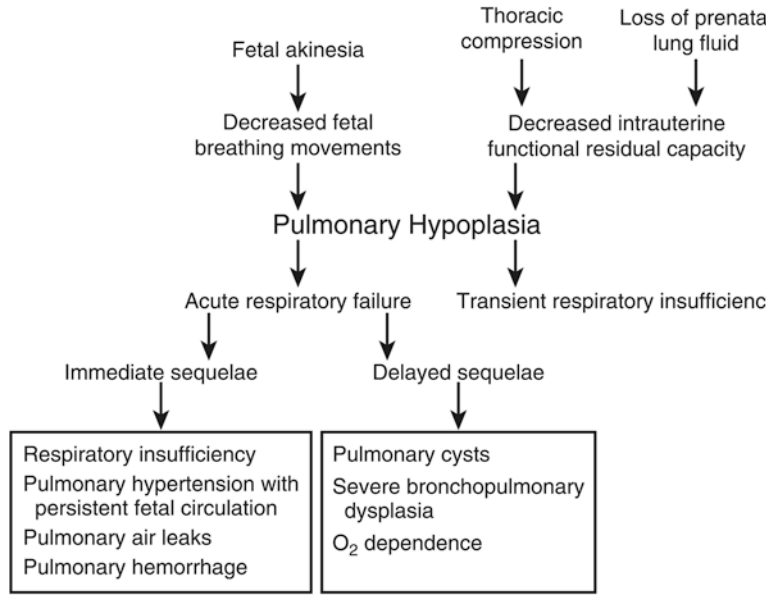

Fig. 1.1 Probable mechanisms and sequelae of pulmonary development during prolonged amniotic leak (Modified from Bhutani VK, Abbasi S, Weiner S: Neonatal pulmonary manifestations due to prolonged amniotic leak. Am J Perinatol 1986; 3:225, © Thieme Medical Publishers, with permission)

relative lack of early respiratory signs, plus the technical difficulties of making an anatomic or physiologic diagnosis in vivo.

2. Accumulated data obtained as a result of significant advancements in human genomic studies and rodent genetic manipulation indicate that early abnormal lung development may indeed be a significant susceptibility factor in certain respiratory diseases that become clinically detectable during childhood or even during later life, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and asthma.

D. The lung arises from the floor of the primitive foregut as the laryngotracheal groove at about the 26th day of fetal life (approximately 4–6 weeks' gestation in humans) (Fig. 1.1).

1. The proximal portion of this primitive structure gives rise to the larynx and trachea, which becomes separated from the esophagus, while progenitor cells located at the distal part of the primitive trachea give rise to the left and right main stem bronchi.
2. Branching morphogenesis of the left and right bronchi forms specific lobar, segmental, and lobular branches. This process extends through the canalicular stage of lung development up to approximately 20 weeks' gestation in humans.
3. The first 16 of these 23 airway generations are stereo-specific in humans, the remainder being fractal in geometry, but with a distinct proximal–distal pattern of diameter and epithelial differentiation that are genetically "hard wired."
4. Alveolarization begins at approximately 20 weeks in humans and continues at least up to 7 years of age, giving rise to an eventual alveolar gas diffusion surface 70 m^2 in area by 1 μm in thickness.
5. This enormous surface is closely apposed to an alveolar capillary network capable of accommodating a blood flow between 5 L/min at rest and 25 L/min at maximal oxygen consumption in the young and fit adult.
6. The entire developmental process of the lung is orchestrated by finely integrated and mutually regulated networks of transcriptional factors, growth factors, matrix components, and physical forces.

7. Factors that adversely impact the developing lung include human prematurity, oxygen exposure, early corticosteroid exposure, incorrect amounts of growth factor (platelet-derived growth factor, fibroblast growth factor [FGF], vascular endothelial growth factor, transforming growth factor [TGF]-β family, and Wnt) signaling, abnormal regulation, or injury of the pulmonary capillary vasculature. Individually and cumulatively, these all result in hypoplasia of the alveolar epithelial surface, with a resulting deficiency in gas transport, particularly during exercise. For example, survivors of human prematurity with bronchopulmonary dysplasia will desaturate on maximal exercise during childhood, and some are now entering young adulthood with increasingly severe gas diffusion problems.
8. In addition, physical forces play an important role in regulating lung formation.
    a. In utero, the lung is a hydraulic, fluid-filled system.
    b. Secretion of fluid into the airway lumen is osmotically driven by active chloride secretion through chloride channels. This gives rise to a continuous forward flow of lung liquid that drains into the amniotic fluid.
    c. The larynx acts as a hydraulic pinchcock valve and maintains and intraluminal hydraulic pressure of approximately 1.5 cm H_2O in the airways.
    d. Excess fluid drainage during fetal life results in hypoplasia of the lung.
    e. Conversely, obstruction of the trachea in embryonic lung in culture can result in a doubling of the rate of airway branching.
    f. Moreover, physiologic fluctuations in intraluminal pressure caused by coordinated peristaltic contractions of airway smooth muscle have been shown to play an important role in embryonic lung branching morphogenesis.
    g. Fetal breathing movements cause cyclic fluctuation of intratracheal pressure during fetal life.
    h. Following cord clamping and the resulting rush of catecholamines at birth, the lung lumen dries out and rapidly switches to air breathing.
    i. Clearance of lung intraluminal liquid is mediated by cessation of chloride secretion into the lumen and activation of active sodium transport out of the lumen. Null mutation of sodium transporter channel genes (α-epithelial sodium channel, α-EnaC) is lethal neonatally because it abrogates this net osmotically driven fluid uptake.
    j. "Erection" of alveolar septa is relatively poorly understood. Nevertheless, correct organization of the elastin matrix niche is important, as is remodeling of the alveolar capillary network. This suggests that vascular hydraulic perfusion pressure may play a key role in the emergence of septal structures into the alveolar space.
    k. This concept is further supported by a requirement for vascular endothelial growth factor secretion by the alveolar epithelium to maintain vascular integrity and remodeling, and hence correct epithelial branching as well as alveolar morphogenesis.

E. Prenatal development of the respiratory system is not complete until sufficient gas exchange surface has formed to support the newborn at birth.
F. Pulmonary vasculature must also achieve sufficient capacity to transport carbon dioxide and oxygen through the lungs.
G. Gas exchange surface must be structurally stable, functional, and elastic to require minimal effort for ventilation and to be responsive to the metabolic needs of the infant.
H. Structural maturation of the airways, chest wall, and respiratory muscles and neural maturation of respiratory control are integral to the optimal function of the gas exchange "unit."
I. Respiratory system development continues after birth and well into childhood (Table 1.1).
J. Fundamental processes that impact on respiratory function
    1. Ventilation and distribution of gas volumes
    2. Gas exchange and transport

Table 1.1 Magnitude of lung development: from fetal age to adulthood

	30 weeks	Term	Adult	Fold increase after term PCA
Surface area (sq. m)	0.3	4.0	100	23
Lung volume (mL)	25	200	5000	23
Lung weight (g)	25	50	800	16
Alveoli (number)	Few	50m	300m	6
Alveolar diameter (μm)	32	150	300	10
Airway branching (number)	24	24	24	0

Table 1.2 Stages of prenatal and postnatal structural lung development

Phase	Post conceptional age	Length: terminal bronchiole to pleura	Lung development
Embryonic	0–7 weeks	<0.1 mm	Budding from the foregut
Pseudoglandular	8–16 weeks	0.1 mm	Airway division commences and terminal bronchioles formed
Canalicular	17–27 weeks	0.2 mm	• 3 generations of respiratory bronchioles • Primitive saccules formation with Type I and II epithelial cells, • Capillarization
Saccular	28–35 weeks	0.6 mm	Transitional saccules formed • True alveoli appear
Alveolar	>36 weeks	11 mm	Terminal saccules formed • True alveoli appear
Postnatal	2 months	175 mm	5 generations of alveolar ducts • Alveoli form with septation
Early childhood	6–7 years	400 mm	Airways remodeled • Alveolar sac budding occurs

3. Pulmonary circulation
4. Mechanical forces that initiate breathing and those that impede airflow
5. Organization and control of breathing

II. Lung Development

A. Background. The lung's developmental design is based upon the functional goal of allowing air and blood to interface over a vast surface area and an extremely thin yet intricately organized tissue barrier. The developmental maturation is such that growth (a quantitative phenomenon) progresses separately from maturation (a qualitative phenomenon). A tension skeleton comprised of connective tissue fibers determines the mechanical properties of the lungs: axial, peripheral, and alveolar septal.

1. Axial connective tissue fibers have a centrifugal distribution from the hilum to the branching airways.
2. Peripheral fibers have a centripetal distribution from the pleura to within the lungs.
3. Alveolar septal fibers connect the axial and peripheral fibers.

B. Functional anatomy (Table 1.2)

1. Fetal lung development takes place in seven phases.
2. Demarcations are not exact but arbitrary with transition and progression occurring between each.
3. Little is known about the effects of antenatal steroids on the transition and maturation of fetal lung development.

Table 1.3 Factors that influence fetal lung maturation

Physical	Hormonal	Local
Fetal respiration	Glucocorticoids	cAMP
Fetal lung fluid	Prolactin	Methylxanthines
Thoracic volume (FRC)	Insulin	
	Sex hormones	

Table 1.4 Chemical features of fetal fluids

	Osmolality (mOsm/L)	Protein (g/dL)	pH	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)
Fetal lung fluid	300	0.03	6.27	140	6.3	144	2.8
Fetal plasma	290	4.1	7.34	140	4.8	107	24
Amniotic fluid	270	0.1–0.7	7.07	110	7.1	94	18

C. Factors that impact fetal lung growth
   1. Physical, hormonal, and local factors play a significant role (Table 1.3).
   2. The physical factors play a crucial role in the structural development and influence size and capacity of the lungs.
   3. Hormonal influences may be either stimulatory or inhibitory.

D. Fetal lung fluid and variations in lung development. Production, effluence, and physiology are dependent on physiologic control of fetal lung fluid.
   1. Production. Secretion commences in mid-gestation, during the canalicular phase, and composition distinctly differs from fetal plasma and amniotic fluid (Table 1.4).
   2. Distending pressure—daily production rates of 250–300 mL/24 h result in distending pressure of 3–5 cm H_2O within the respiratory system. This hydrostatic pressure seems to be crucial for fetal lung development and the progressive bifurcations of the airways and development of terminal saccules.
   3. Fetal breathing—during fetal breathing movements, tracheal egress of lung fluid (up to 15 mL/h) during expiration (compared to minimal loss during fetal apnea) ensures that lung volume remains at about 30 mL/kg (equivalent to the functional residual capacity, FRC). Excessive egress has been associated with pulmonary hypoplasia (Fig. 1.1), whereas tracheal ligation has been associated with pulmonary hyperplasia.

III. Upper Airway Development

A. Airways are heterogeneous, conduct airflow, and do not participate in gas exchange.
   1. Starting as the upper airways (nose, mouth, pharynx, and larynx), they lead to the trachea. From here, the cartilaginous airways taper to the small bronchi and then to the membranous airways and the last branching, the terminal bronchioles (Table 1.5).
   2. The lower airways and the gas exchange area commence with the respiratory bronchioles.
   3. The upper airways are not rigid, but are distensible, extensible, and compressible. The branching is not symmetrical and dichotomous but irregular. The lumen is not circular and subject to rapid changes in cross-sectional area and diameter because of a variety of extra-mural, mural, and intra-mural factors.

B. Anatomy includes the nose, oral cavity, palate, pharynx, larynx, hyoid bone, and extrathoracic trachea

C. Function is to conduct, humidify, warm (or cool) to body temperature, filter air into the lungs. Also help to separate functions of respiration and feeding as well as share in the process of vocalization.

Table 1.5 Classification, branching, and lumen size of adult human airways

Branch order	Name	Number	Diameter (mm)	Cross-sectional area (cm^2)
0	Trachea	1	18	2.54
1	Main bronchi	2	12.2	2.33
2	Lobar bronchi	4	8.3	2.13
3	Segmental bronchi	8	5.6	2.00
4	Subsegmental bronchi	16	4.5	2.48
5–10	Small bronchi	32–1025	3.5–1.3	3.11–13.4
11–14	Bronchioles	2048–8192	1.99–0.74	19.6–69.4
15	Terminal bronchiole	32,768	0.66	113
16–18	Respiratory bronchioles	65,536–262,144	0.54–0.47	180–534
19–23	Alveolar ducts	524,288–8,388,608	0.43	944–11,800
24	Alveoli	300,000,000	0.2	

D. Patency control—stable pressure balance between collapsing forces (inherent viscoelastic properties of the structures and that of the constricting tone) and the dilator forces of supporting musculature help to maintain upper airway patency. Negative pressure in the airways, neck flexion, and changes in the head and neck posture narrow the airways. Both intrinsic and extrinsic muscles of the upper airway can generate dilator forces, such as flaring of the ala nasi.

IV. Lower Airway Development
   A. Anatomy
      1. Conducting airways of the intrathoracic trachea
      2. Respiratory gas exchange portions of terminal and respiratory bronchioles and alveolar ducts
   B. Function of airway smooth muscle
      1. Tone is evident early in fetal life and plays significant role in controlling airway lumen.
      2. In presence of respiratory barotrauma, there appears to be a propensity for airway reactivity, perhaps a component of the smooth muscle hyperplasia seen in bronchopulmonary dysplasia (BPD).
      3. Patency control. Excitatory and inhibitory innervations lead to bronchoconstriction or dilatation, respectively.
      4. Narrow airways. Narrowing of the airways leads to increased resistance to airflow, an increased resistive load during breathing, and thereby an increased work of breathing and wasted caloric expenditure. Clinical factors associated with airway narrowing are listed in Table 1.6.

V. Thoracic and Respiratory Muscle Development
   A. Anatomy
      1. Three groups of skeletal muscles are involved in respiratory function.
         a. Diaphragm
         b. Intercostal and accessory muscles
         c. Abdominal muscles
      2. These comprise the respiratory pump that helps conduct the air in and out of the lungs.
      3. During quiet breathing, the primary muscle for ventilation is the diaphragm.
      4. The diaphragm is defined by its attachments to the skeleton.
         a. That part attached to the lumbar vertebral regions is the crural diaphragm.
         b. That part attached to the lower six ribs is the costal diaphragm.
         c. Both converge and form a single tendon of insertion.

Table 1.6 Clinical conditions associated with narrowing of the airways

Airway inflammation	• Mucosal edema • Excessive secretions • Inspissation of secretions • Tracheitis
Bronchoconstriction	• Reactive airways • Exposure to cold, dry air • Exposure to bronchoconstricting drugs
Bronchomalacia	• Prolonged mechanical ventilation • Congenital • Secondary to vascular abnormality
Trauma	• Foreign body • Mucosal damage from ventilation, suction catheters • Subglottic stenosis
Congenital	• Choanal stenosis • High arched palate
Chemical	• Aspiration of gastric contents • Hyper-/hypo-osmolar fluid in the airways

5. Innervation of the diaphragm is by alpha motor neurons of the third through fifth cervical segments, the phrenic nerve.
6. Attached to the circumference of the lower thoracic cage, its contraction pulls the muscle downward, displaces the abdomen outwards, and lifts up the thoracic cage.
7. In the presence of a compliant thoracic cage, relative to the lungs, the thoracic cage is pulled inward (sternal retraction).
8. The concomitant pressure changes during inspiration are reduction of intrapleural pressure and an increase in the intra-abdominal pressure.

B. Respiratory contractile function
1. Strength, endurance, and the inherent ability to resist fatigue may assess the performance of the respiratory muscles.
2. Strength is determined by the intrinsic properties of the muscle (such as its morphologic characteristics and types of fibers).
3. Clinically, strength may be measured by the pressures generated at the mouth or across the diaphragm at specific lung volumes during a static inspiratory or expiratory maneuver.
4. Endurance capacity of a respiratory muscle depends upon the properties of the system as well as the energy availability of the muscles.
5. Clinically, endurance is defined as the capacity to maintain either maximal or sub-maximal levels of ventilation under isocapneic conditions. It may be standardized either as maximal ventilation for duration of time, or ventilation maintained against a known resistive load, or sustained ventilation at a specific lung volume (elastic load). It is also determined with respect to a specific ventilatory target and the time to exhaustion (fatigue).
6. Respiratory muscles fatigue when energy consumption exceeds energy supply.
7. Fatigue is likely to occur when work of breathing is increased, strength reduced, or inefficiency results so that energy consumption is affected.
8. Hypoxemia, anemia, decreased blood flow to muscles, and depletion of energy reserves alter energy availability.
9. Clinical manifestations of respiratory muscle fatigue are progressive hypercapnia or apnea.

Table 1.7 Postnatal maturation of the lung

	Number of alveoli	Surface area (m^2)	Respiratory rate (per minute)
Birth	24,000,000	2.8	45 (35–55)
5–6 months	112,000,000	8.4	27 (22–31)
~1 year	129,000,000	12.2	19 (17–23)
~3 year	257,000,000	22.2	19 (16–25)
~5 year	280,000,000	32.0	18 (14–23)
Adult	300,000,000	75	15 (12–18)

C. Postnatal maturation
   1. Lung size, surface area, and volume grow in an exponential manner for about 2 months after term gestation.
   2. Control of breathing (feedback control through chemoreceptors and stretch receptors), and the neural maturation of the respiratory centers also appear to coincide with maturation at about 2 months postnatal age.
   3. Beyond this age, lung volumes continue to increase during infancy, slowing during childhood but still continuing to grow structurally into early adolescence (Table 1.7).
   4. It is this biologic phenomenon that provides a scope of recovery for infants with BPD.
   5. In health, the increasing lung volume and cross-sectional area of the airways is associated with a reduction in the normal respiratory rate.

VI. Descriptive Embryology of the Lung. The following paragraphs briefly describe the anatomical changes which occur during lung development. Changes in gene expression can be found at: www.ana.ed.ac.uk/database/lungbase/lunghome.html.
   A. The anatomical development of the lung can be regarded as a continuous process from the advent of the laryngotracheal groove until adulthood, although obvious radical physiologic changes occur at birth. The description below is based on human respiratory development, though other mammals follow a very similar developmental program, especially during the early phases.
   B. The respiratory system begins as a ventral outgrowth (laryngotracheal groove) from the wall of the foregut, close to the fourth and sixth pharyngeal pouches. The groove deepens and grows downwards to form a pouch-like evagination, fully open to the foregut. Two longitudinal folds of tissue (tracheo-esophageal folds) on either side of the groove grow together and fuse, forming a new tube (laryngotracheal tube) distinct from the foregut.
   C. Communication with the foregut is maintained via a longitudinally oriented slit-like opening (laryngeal orifice).
   D. Proliferation of the underlying mesenchyme forms swellings around the laryngeal orifice (epiglottal swelling and arytenoid swellings) from which the epiglottis, glottis, laryngeal cartilages and musculature will develop.
   E. At the same time, the laryngotracheal tube elongates downwards and penetrates the underlying splanchnopleuric mesoderm. A distinct swelling develops at the distal end and is termed the *lung bud* (respiratory diverticulum).
   F. Approximately 28 days after fertilization, the lung bud branches to form the left and right primary bronchial buds, which will ultimately develop into the left and right lungs. Branching is in part directed by the interaction of the epithelium with the underlying splanchnic mesoderm.
   G. By the fifth week, elongation, branching, and budding of the two bronchial buds gives rise to three bronchial stems on the right and two on the left—these are the foundation for the lobular organization of the mature lung.

H. Dichotomous branching continues for approximately 10 weeks, establishing the conducting portion of the airways. Up to 24 orders of branches are generated, the final level being the prospective terminal bronchioles. New branches are being formed within a rapidly proliferating, homogeneous mesenchyme.

I. Differentiation of the mesenchyme and epithelia begins in the more proximal regions of the airways and progresses distally, beginning during week 10 when mesenchymal cells condense around the larynx and trachea. These will form smooth muscle and supporting cartilages. The pulmonary arteries and veins develop in parallel with the conducting portion of the lungs and follow the same branching pattern.

J. Initially the airway lumina are very narrow, with a thick pseudostratified epithelial lining. From week 13 onward, the lumina enlarge and the epithelium thins to a more columnar structure. The pluripotent epithelial cells differentiate to ciliated cells and goblet cells, initially in the proximal regions of the developing lung and progressing distally.

K. From weeks 16 to 24, the primordia of the respiratory portions of the lungs are formed. The terminal bronchioles divide to form two respiratory bronchioles, which in turn branch to form 3–6 primitive alveolar ducts, ending in terminal sacs.

L. At the same time, extensive angiogenesis within the peripheral mesenchyme leads to vascularization of the developing respiratory structures. The cuboidal intermediate cells of the lower airways differentiate to form ciliated cells and Clara cells. Peripheral mesenchymal cells differentiate to form the visceral pleura, the remaining mesenchymal cells gain the characteristics of stromal fibroblasts.

M. By week 26, the terminal sacs have started to dilate, and will eventually differentiate into alveolar complexes. The stroma thins, bringing the growing capillary network into close association with the immature alveoli. The cuboidal cells of the terminal sac epithelium differentiate into alveolar type II cells, which secrete low levels of surfactant. Where cells with type II phenotype juxtapose a capillary, they differentiate into type I cells, which flatten and can provide a functional though inefficient blood–air barrier if the infant is born prematurely.

N. During subsequent weeks there is a rapid expansion of the respiratory portion of the lung. Terminal saccules dilate and branch to form further generations of terminal saccules, vascularized septa form within growing terminal sacs, and Type I cells continue to flatten and spread, increasing the surface area available for gas exchange. The parenchyma of the lung continues to thin, and fibroblasts lay down the collagen and elastin fiber components of the stroma.

O. The composition of pulmonary surfactant is developmentally regulated. By week 30, there is a significant rise in the amount of surfactant secreted from the type II cells.

P. By week 36, the stroma of the lung has thinned to the extent that capillaries may protrude into the prospective alveolar airspaces.

Q. The final stages of maturation of the respiratory system occur after 36 weeks' gestation and continue into adulthood. At around 36 weeks, the first mature alveoli appear, characterized by thin walled interalveolar septa with a single layered capillary network. The diameter of the capillaries is sufficiently large that they may span the alveolar walls and interact with the airspaces on both sides.

R. New alveoli are generated by a process of septal subdivision of existing immature alveoli. There is a growth spurt soon after birth, though new alveoli continue to form at a high rate for up to 3 years.

S. As the alveoli mature and the walls thin, there is a decrease in the relative proportion of stroma to total lung volume, which contributes significantly to growth for 1–2 years after birth. By 3

years, the overall morphology of the lung has been established and subsequent expansion occurs through a proportional growth of all lung components until adulthood.

VII. Developmental Stages (*Human*)

A. Embryonic phase (3–7 weeks) Initial budding and branching of the lung buds from the primitive foregut. Ends with the development of the presumptive broncho-pulmonary segments.

B. Pseudoglandular phase (7–16 weeks). Further branching of the duct system (up to 21 further orders) generates the presumptive conducting portion of the respiratory system up to the level of the terminal bronchioles. At this time the future airways are narrow with few lumina and a pseudostratified squamous epithelium. They are embedded within a rapidly proliferating mesenchyme. The structure has a glandular appearance.

C. Canalicular phase (16–24 weeks). The onset of this phase is marked by extensive angiogenesis within the mesenchyme that surrounds the more distal reaches of the embryonic respiratory system to form a dense capillary network. The diameter of the airways increases with a consequent decrease in epithelial thickness to a more cuboidal structure. The terminal bronchioles branch to form several orders of respiratory bronchioles. Differentiation of the mesenchyme progresses down the developing respiratory tree, giving rise to chondrocytes, fibroblasts and myoblasts.

D. Terminal sac phase (24–36 weeks). Branching and growth of the terminal sacs or primitive alveolar ducts. Continued thinning of the stroma brings the capillaries into apposition with the prospective alveoli. Functional type II pneumocytes differentiate via several intermediate stages from pluripotent epithelial cells in the prospective alveoli. Type I pneumocytes differentiate from cells with a type II-like phenotype. These cells then flatten, increasing the epithelial surface area by dilation of the saccules, giving rise to immature alveoli. By 26 weeks, a rudimentary though functional blood/gas barrier has formed. Maturation of the alveoli continues by further enlargement of the terminal sacs, deposition of elastin foci and development of vascularized septae around these foci. The stroma continues to thin until the capillaries protrude into the alveolar spaces.

E. Alveolar phase (36 weeks—term/adult). Maturation of the lung indicated by the appearance of fully mature alveoli begins at 36 weeks, though new alveoli will continue to form for approximately 3 years. A decrease in the relative proportion of parenchyma to total lung volume still contributes significantly to growth for 1–2 years after birth; thereafter, all components grow proportionately until adulthood.

2 Malformations, Deformations, and Disorders of the Neonatal Airway

Janet Lioy, Elizabeth Greubel, and Steven Sobol

I. Nose

Nasal obstruction in the neonate is often overlooked but becomes symptomatic almost immediately as infants are preferential nasal breathers. Septal deviation from positional deformation during delivery can account for nasal distress in the immediate neonatal period. Presentation may be cyclical with cyanosis relieved by crying, but airway distress and feeding difficulties often persist, suggesting the diagnosis of nasal obstruction. The differential diagnosis for nasal obstruction includes: choanal stenosis/atresia, piriform aperture stenosis, nasal septal deviation/inflammation, nasolacrimal duct cyst (bilateral or unilateral), nasal hemangioma and other rare tumors, and encephalocele/glioma.

A. Choanal atresia and stenosis (bilateral and unilateral) (Fig. 2.1)

1. Etiology and Epidemiology
   a. Failure of recanalization of the buccal pharyngeal membrane during 4th–12th week of gestation leads to atresia (complete obstruction) or stenosis (narrowing) of the posterior choanae.
   b. May be unilateral or bilateral
   c. Most common abnormality is bony/membranous obstruction.
   d. May be associated with skull base or midline defect, especially when presenting as part of a syndrome
   e. May be an isolated defect or part of a complex well-defined genetic syndrome
   f. 1:7000 live births, female-to-males equal
   g. Fifty percent associated with syndrome or additional anomalies
2. Pathogenesis
   a. Atresia occludes passage of air or drainage of nasal secretions.
   b. Stenosis increases airway resistance.

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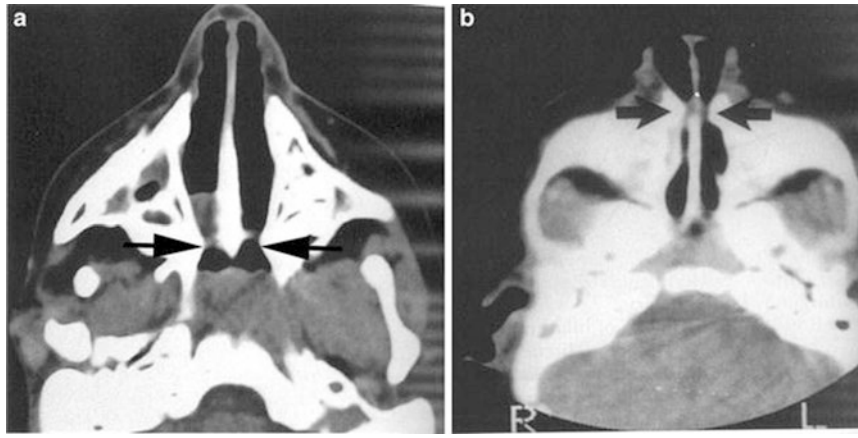

Fig. 2.1 CT scan of head showing: (**a**) Choanal atresia and (**b**) piriform aperture stenosis. Note the differences in location of these embryologically different but similar clinical nasal obstructions

3. Clinical Presentation
   a. Neonate with bilateral atresia/stenosis will present with labored breathing, desaturation, cyclical cyanosis, and feeding difficulties and bradycardia if severe.
   b. Relieved by crying or cut hole nipple with sucking
   c. Unilateral stenosis often presents with unilateral rhinorrhea/sinusitis, rarely with respiratory distress.
4. Diagnostic Evaluation
   a. Failure to pass a 5/6 French catheter
   b. Nasal endoscopy revealing the atretic plate
   c. Non-contrast fine cut CT scan of the skull base/sinuses. Expert consultation with pediatric ENT, genetics
   d. Recently, fetal MRI can point toward a craniofacial malformation, which may reveal abnormalities of the midface.
5. Medical Management
   a. Conservative management—oral airway or "cut hole" nipple, and side or prone positioning may help initially.
   b. Intubation often necessary with bilateral atresia
6. Surgical Management
   a. Endoscopic approach most common. Serves to dilate and or repair the membranous and bony narrowing often with a posterior septectomy.
   b. Bilateral atresia should be repaired once workup is complete.
   c. Unilateral atresia/stenosis repair can be delayed until childhood to allow for skull and patient growth.
7. Multidisciplinary Collaboration:
   Genetics: (associated syndromes: CHARGE, other craniofacial genetic malformations now diagnosable by mutation analysis)

B. Piriform aperture and nasal stenosis
   1. Etiology and Epidemiology
      a. Overgrowth of the nasal inlet or medial position of the nasal process of the maxilla at the level of the piriform aperture bilaterally
      b. Craniofacial or skull base anomalies are associated with partial obstruction of the nasal inlet.

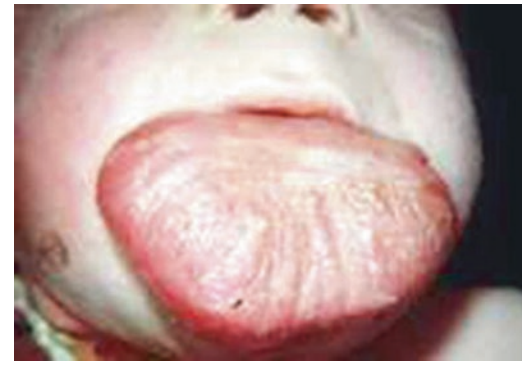

Fig. 2.2 Photograph of infant with Beckwith–Wiedemann syndrome showing extreme macroglossia

   c. Often seen with a single central incisor or anterior pituitary abnormalities related to holoprosencephaly spectrum of genetic disorders with specific genetic mutation
   d. Overall rarely in isolation
2. Clinical Presentation
   a. The narrowed aperture or nasal cavity leads to increased nasal resistance. Difficulty breathing and/or feeding.
   b. Anterior rhinoscopy identifies a narrowed nasal inlet; may be unable to pass 6 French catheter or 2.2 mm scope into the nasal aperture.
3. Diagnostic Evaluation
   a. Clinical evaluation is complemented by non-contrast CT scan of the skull and sinuses inclusive of the pituitary and maxillary dentition.
   b. Diagnosis is made when the nasal aperture is less than 11 mm on axial CT scan.
   c. Genetic consultation for every piriform aperture stenosis
4. Medical Management
   a. Observation if minimally symptomatic
   b. Conservative management with nasal saline or steroids if moderate symptomatology
   c. Oral breathing appliance such as cut hole nipple or intubation for acute respiratory distress
5. Surgical Management
   a. Most often required when piriform aperture width is <5 mm.
   b. Most common approach is sublabial with drill out of the piriform aperture, nasal dilation, with or without stent placement.
6. Multidisciplinary Collaboration
   a. Endocrinology/Neurology: association with anterior pituitary abnormalities, holoprosencephaly spectrum
   b. Dentistry/Oral Maxillary Facial Surgery later in life, since median central incisor is often seen
   c. Genetics: Always indicated

II. Oropharynx/Tongue

In neonates and infants, the oropharyngeal airway is a very complex structure. Sucking, swallowing, and breathing can become quickly compromised and may be obstructed by a prolapsing tongue base or a space occupying mass. When the oropharynx is obstructed, airflow ceases from the nasal cavity or mouth into the larynx. The differential diagnosis for oropharyngeal obstruction includes: macroglossia (Fig. 2.2); tongue base obstruction, (TBO), from severe retro/micrognathia (Fig. 2.3) with glossoptosis (Fig. 2.4); nasopharyngeal mass extension; oropharyngeal mass; vallecular cyst; an undescended thyroid; or a thyroglossal duct cyst.

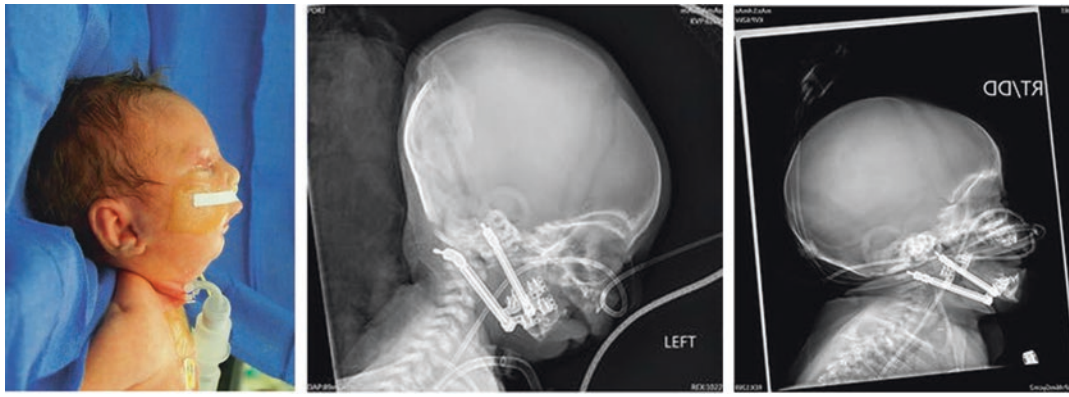

Fig. 2.3 (**a**–**c**) Preoperative and postoperative photographs and radiographs of patient undergoing mandibular distraction osteogenesis through a submandibular approach

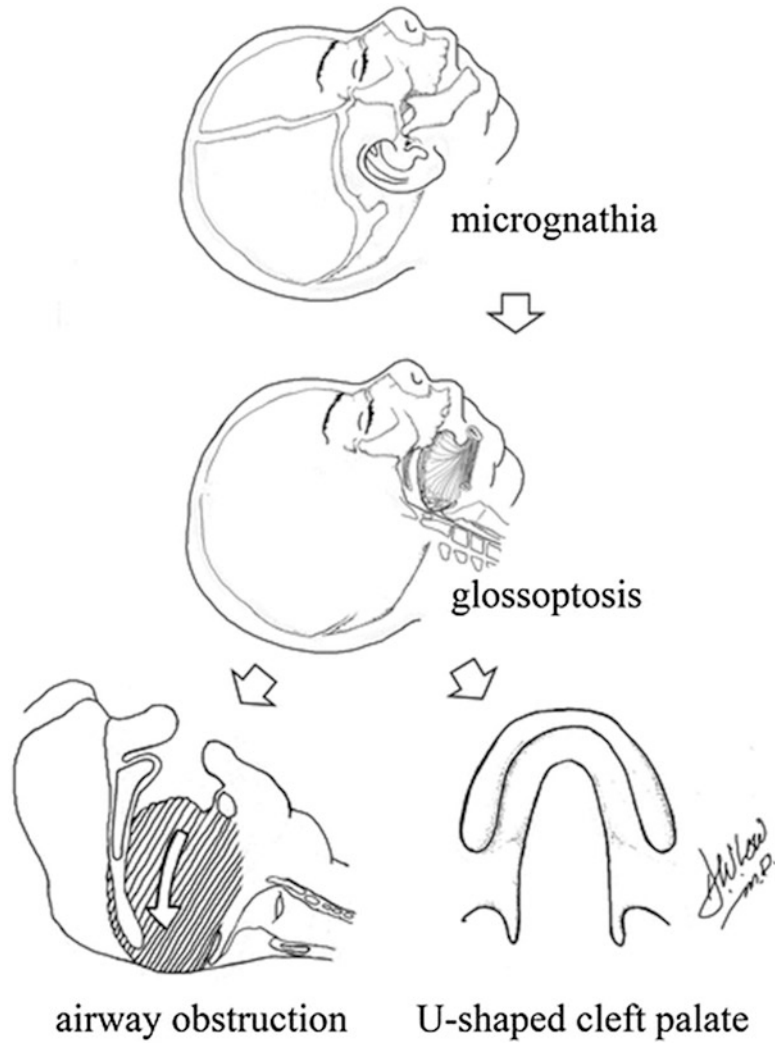

Fig. 2.4 The "domino effect" of Pierre Robin sequence

A. Glossoptosis or Macroglossia
   1. Etiology and Epidemiology
      a. Most commonly associated with Pierre Robin Sequence or Stickler's Syndrome, where congenital micrognathia leads to glossoptosis (tongue base obstruction of the posterior pharynx) and airway distress. Macroglossia causing obstruction also seen in Beckwith–Wiedemann syndrome.
      b. Many cases associated with a secondary cleft palate—U shaped—involving the soft palate
      c. 1 in 8500–14,000 births
   2. Pathogenesis
      Airway obstruction is secondary to displacement of the tongue into the hypopharynx occluding the airway at the level of the epiglottis.
   3. Clinical Presentation
      a. Obvious retro/micrognathia and airway distress in the neonate with apparent obstruction, which may be positional (worse on back), feeding difficulties, including airway distress or desaturation during feeding
      b. Macroglossia obstructing oral cavity
   4. Diagnostic Evaluation
      a. Clinical diagnosis is complemented by a modified polysomnogram configured for neonates to quantify the severity of obstruction.
      b. Awake flexible nasopharyngolaryngoscopy can aid in assessment of the tongue base position relative to the posterior pharyngeal wall.
      c. Imaging with plain film or more commonly CT scan with 3D reconstructions of the face is obtained if considering surgical management.
      d. Often, fetal ultrafast MRI can elucidate findings prior to birth and allow for appropriate airway expertise at delivery.
   5. Medical Management
      a. Prone or side lying positioning
      b. Nasal trumpet/nasopharyngeal airway
      c. LMA with mask ventilation if unable to mask ventilate during acute respiratory distress
      d. Airway support with high flow nasal catheter or positive pressure ventilation
   6. Surgical Management
      a. Previously, tongue–lip adhesion, (TLA), the tongue musculature is sutured to that lower lip musculature to prevent ptosis of tongue base; the adhesion is later released.
      b. Recently, mandibular distraction osteogenesis, (MDO), has replaced TLA as primary management of many of these neonates. The mandible is advanced forward using a distraction osteogenesis technique with internal and external devices. Under the guidance of experienced surgeons, MDO has become a popular choice.
      c. Tracheostomy—definitive management in refractory or complicated cases
   7. Collaboration
      a. Plastic or otorhinolaryngologic surgery: May consider mandibular distraction osteogenesis (MDO) for non-complex cases associated with micrognathia.
      b. Genetics: More than 40 associated syndromes. Most common: Goldenhar's syndrome, CHARGE syndrome, Stickler and 22q11.2 deletion syndrome

B. Vallecular cyst
   1. Etiology and Epidemiology

   a. Related to either a trapped minor salivary gland or a variant of a thyroglossal duct cyst present solely in the tongue base
   b. Congenital airway cysts occur in 1.87–3.49 cases per 100,000 live births. Vallecular cysts account for ~10.5 %.
2. Pathogenesis
   a. Cyst may grow slowly or rapidly, leading to a spectrum of airway signs. Most commonly presents within the first 2 weeks of life.
   b. Secondary laryngomalacia may occur from the Bernoulli effect.
3. Clinical Presentation
   a. Most commonly presents with inspiratory stridor similar to laryngomalacia
   b. If large, may lead to complete airway obstruction with distress
   c. Can be associated with feeding difficulties
4. Evaluation
   a. Bedside awake flexible fiber-optic nasopharyngeal laryngoscopy
   b. Formal microlaryngoscopy demonstrates a mucus filled cyst in the vallecula between the tongue base and laryngeal surface of the epiglottis
5. Management
   a. Surgical management is the mainstay of treatment.
   b. Microlaryngoscopy and bronchoscopy with endoscopic marsupialization or excision with microlaryngeal instruments, microdebrider, or laser
   c. Preservation of lingual surface of the epiglottis is important to prevent vallecular scarring.
   d. Cyst recurrence is rare.
6. Multidisciplinary Collaboration:
   Speech therapy: for evaluation and management of aspiration, if indicated

III. Larynx

Disorders of the larynx are some of the most common disorders causing a myriad of signs in neonates. The larynx consists of the supraglottic, glottic, and subglottic structures and signs are commonly associated with stridor or noisy breathing. Some congenital anomalies present immediately with airway distress, while others are asymptomatic or discovered later in infancy or childhood as feeding and growing difficulties arise. Supraglottic anomalies affect the airway at the level of the epiglottis which sits immediately superior to the vocal cords. The most common disorders include laryngomalacia (Fig. 2.5), bifid epiglottis (Fig. 2.6), saccular cyst, and laryngeal cleft.

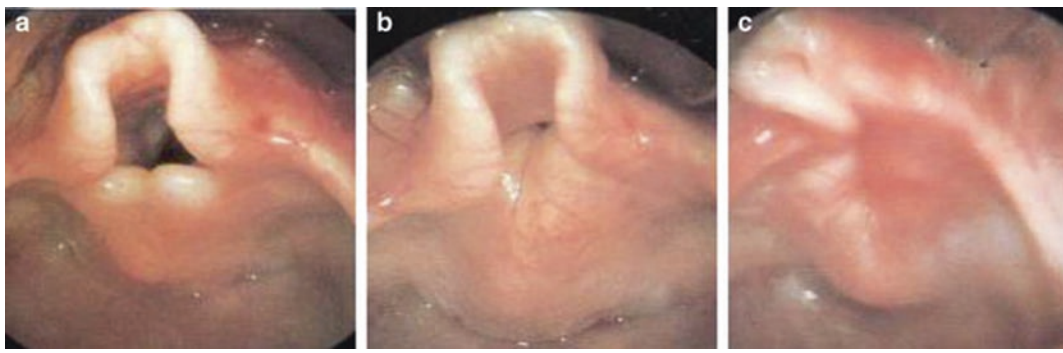

Fig. 2.5 (**a**–**c**) Photographs showing severe laryngomalacia

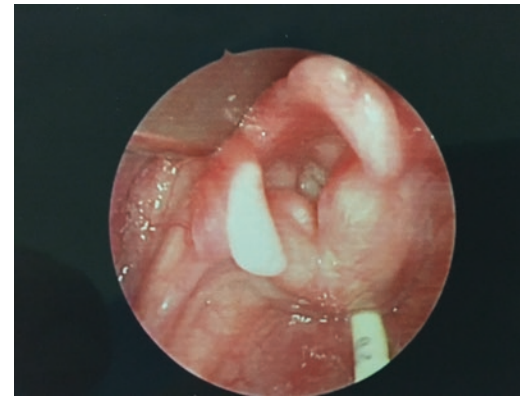

Fig. 2.6 Bifid epiglottis. A rare congenital airway anomaly potentially causing airway obstruction and early clinical signs

A. Laryngomalacia
   1. Etiology and Epidemiology
      Most common cause of stridor in infants, resulting from dynamic collapse of the supraglottic structures into the laryngeal inlet during inspiration
   2. Incidence is unknown but accounts for 70–95 % of all neonatal stridor.
      Incidence of synchronous airway lesions is ~15 % (more frequent in severe cases).
   3. Pathogenesis:
      Collapse related to omega-shaped epiglottis, short aryepiglottic folds, and/or redundant supraarytenoid tissue and cuneiform cartilages
   4. Clinical Presentation
      a. Fluttering inspiratory stridor most pronounced while supine, crying, sleeping, or with feeding
      b. Obstructive sleep apnea may be present.
      c. Severe cases may present with failure to thrive or respiratory distress.
      d. High concomitant incidence of gastroesophageal reflux
   5. Diagnostic Evaluation
      a. Awake fiber-optic laryngoscopy demonstrates an omega-shaped epiglottis, short aryepiglottic folds, and/or redundant and prolapsing soft tissue over the arytenoid cartilages.
      b. Microlaryngoscopy and bronchoscopy may be necessary to rule out significant synchronous airway lesions.
      c. Reflux evaluation may be indicated when feeding or swallowing signs are present.
   6. Medical Management
      a. Most cases self-resolve over 12–18 months and require no medical treatment.
      b. Reflux management should be considered in patients with feeding or respiratory concerns.
   7. Surgical Management
      a. Consider microlaryngoscopy and bronchoscopy in recalcitrant cases to identify secondary airway lesions.
      b. Supraglottoplasty is performed with microlaryngeal instruments or laser for children with failure to thrive, cyanotic spells, severe OSA, or recurrent respiratory admissions.
   8. Multidisciplinary Collaboration
      a. Pulmonary: may consider PSG to evaluate for central and obstructive sleep apnea.

   b. Speech therapy: preoperative and postoperative aspiration risk
   c. Surgical fundoplication if significant reflux is present and recalcitrant to medical therapy.

B. Bifid Epiglottis
   1. Etiology and Epidemiology
      a. Clefted epiglottis involving at least 2/3 of the height of the epiglottis. The embryology is not clear though the epiglottis is derived from the hypobranchial eminence with likely involvement of the fourth branchial pouch.
      b. May have associated anomalies of the hypothalamus and oral cavity
      c. Usually does not present as an isolated anomaly; incidence not well reported
      d. Associated with Pallister–Hall syndrome
      e. Midline cleft within the epiglottis rendering it incompetent
   2. Clinical Presentation
      a. Inspiratory stridor, worse with feeding
      b. Choking or gagging with feeds, if aspirating
   3. Diagnostic Evaluation
      a. Awake flexible laryngoscopy.
      b. Consider rigid laryngoscopy and bronchoscopy to assess for additional anomalies.
      c. Modified barium swallow to assess epiglottic competency and aspiration risk
   4. Management
      a. Medical and genetic workup for associated conditions including: Pallister–Hall, polydactyly, congenital hypothyroidism, and hypothalamic dysfunction
      b. Surgical management is not well described.
   5. Multidisciplinary Collaboration
      a. Genetics: commonly associated with anomalies of the hands/feet (most commonly syndactyly), oral cavity, and hypothalamic–pituitary axis
      b. Endocrine: Hypothalamus and pituitary axis abnormalities
      c. Speech therapy if aspiration or feeding issues

C. Saccular cyst (Fig. 2.7)
   1. Etiology and Epidemiology
      a. Cystic blockage at the glottic opening, which extends between the false and true vocal folds
      b. Originates from an obstruction of the excretory duct of laryngeal epithelial mucus glands

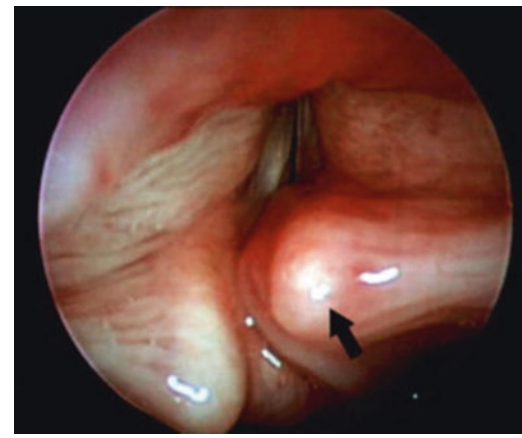

Fig. 2.7 Saccular cyst with prolapsed arytenoid causing airway obstruction with stridor

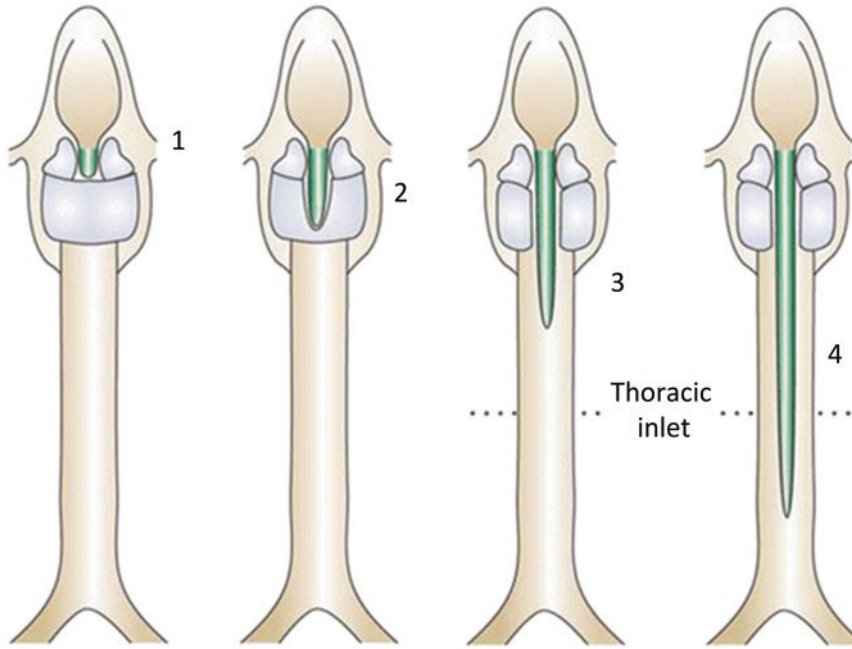

Fig. 2.8 The Benjamin and Inglis cleft classification

c. Congenital airway cysts occur in 1.87–3.49 cases per 100,000 live births.
d. Saccular cysts account for ~25 %.

2. Pathogenesis
   a. Cystic accumulation of fluid within the laryngeal saccule
   b. May partially or completely block the laryngeal inlet
3. Clinical Presentation
   a. May present with the spectrum of airway obstruction depending on the size and location.
   b. Most commonly presents with stridor similar to laryngomalacia but may also be associated with hoarse cry or cyanotic spells and may progress to complete airway obstruction as the cyst enlarges.
4. Diagnostic Evaluation
   a. Fiber-optic laryngoscopy.
   b. Anterior cysts project medially into the laryngeal ventricle.
   c. MRI or CT complementary to determine origin and extent of cyst once identified.
5. Management
   a. Surgical management is the mainstay of treatment.
   b. Microlaryngoscopy and bronchoscopy with endoscopic excision may be used for medially projecting lesions using cold instrumentation or laser excision/marsupialization.
6. Multidisciplinary Collaboration
   Speech therapy for evaluation and management of aspiration, if indicated

D. Laryngeal/interarytenoid cleft (Fig. 2.8)
1. Etiology and Epidemiology
   a. Type I cleft defined as supraglottic cleft—depth of the interarytenoid notch extends to the level of the vocal cords—diastasis of the interarytenoid musculature

b. Type II cleft involves the superior posterior cricoid cartilage—incomplete fusion of the posterior cricoid ring.
c. Historical incidence is 0.1–0.47 % with type 1 clefts being most common.

2. Pathogenesis
   Branchial anomaly—failure of the cricoid (sixth arch) to fuse posteriorly
3. Clinical Presentation
   a. Aspiration and/or chronic cough
   b. Recurrent pneumonia
4. Diagnostic Evaluation
   a. Videofluoroscopic swallow study
   b. Microlaryngoscopy with suspension laryngoscopy and palpation of the interarytenoid space
5. Medical Management
   Trial of conservative management involves anti-reflux therapy, a thickened liquid feeding regimen, and maneuvers during feeding to prevent aspiration.
6. Surgical Management
   Surgery is recommended if persistent signs despite medical management or if severity warrants immediate treatment. Surgical intervention includes interarytenoid bulking procedure with injection, endoscopic laryngeal cleft repair, and open laryngeal cleft repair through a laryngofissure.
7. Multidisciplinary Collaboration
   Speech therapy for evaluation and management of aspiration risk once cleft identified

IV. Glottic Airway
Glottic anomalies affect the airway involving the vocal cords. Glottic anomalies lead to a dysphonic or aphonic cry and may also present with stridor. In the most extreme case of laryngeal agenesis the laryngeal structures fail to form and present prenatally requiring an EXIT procedure (Chap. 17) in order to secure the airway. Other anomalies discussed below include vocal cord paralysis and laryngeal/glottic web.

A. Bilateral Vocal Cord Paralysis (Fig. 2.9)
   1. Etiology and Epidemiology
      a. Most common etiology is idiopathic. Other causes secondary to medical conditions include: Arnold–Chiari malformation, intracranial hemorrhage, hydrocephalus, meningocele, and myasthenia gravis.

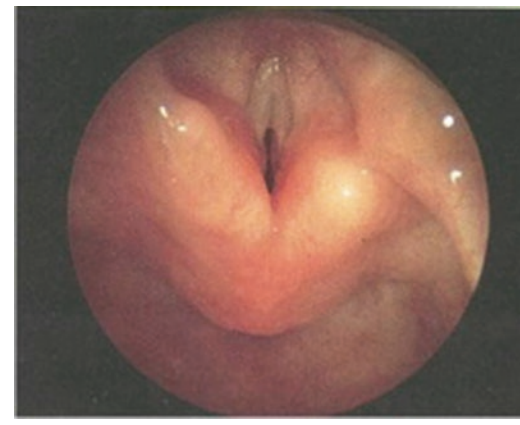

Fig. 2.9 Vocal cord paralysis causing airway obstruction at delivery

   b. Second most common cause of neonatal stridor
   c. Incidence of 0.75 cases per million births per year
2. Pathogenesis
   Bilateral abductor paralysis leads to medial position of the vocal cords which limits glottic opening, leading to stridor and increased airway resistance.
3. Clinical Presentation
   a. High-pitched inspiratory or biphasic stridor is the most common manifestation, but may also include dyspnea, chronic aspiration, and cyanosis.
   b. Voice may range from weak to normal depending on the site of the lesion.
4. Diagnostic Evaluation
   a. Fiber-optic laryngoscopy with patient awake
   b. Microlaryngoscopy and bronchoscopy with palpation of the arytenoid to rule out cricoarytenoid joint fixation and posterior glottis stenosis
   c. MRI (including imaging of the posterior fossa and course of recurrent laryngeal nerves) to investigate intracranial and compressive causes is paralysis
   d. Laryngeal EMG may be used to monitor motor function and recovery.
   e. Videofluoroscopic swallow study (VFSS) or fiber-optic endoscopic evaluation of swallow (FEES) may be used to detect aspiration.
5. Medical Management
   a. Spontaneous resolution of idiopathic paralysis occurs in up to 70 % of patients up to 11 years later.
   b. Treatment for underlying condition with VP shunt or posterior fossa decompression may result in recovery of function in secondary cases.
6. Surgical Management
   a. Tracheotomy is traditionally recommended for persistent paralysis with respiratory distress or failure to thrive (up to 50 % of patients).
   b. Endoscopic transverse cordotomy, arytenoidectomy, arytenoid lateralization, open or endoscopic laryngotracheoplasty with posterior costochondral grafting, and laryngeal reinnervation procedures are options for treatment.
   c. Reinnervation uses superior branch of phrenic nerve anastomosed to the posterior cricoarytenoid muscle and ansa-hypoglossal to laryngeal adductors.
7. Multidisciplinary Considerations
   a. Neurology and/or neurosurgery: evaluate central causes of paralysis.
   b. Speech therapy: evaluation and management for aspiration risk

B. Laryngeal/glottic web (Fig. 2.10)
1. Etiology and Epidemiology
   a. Partial failure of laryngeal recanalization during gestation
   b. Rare, but can be fatal at birth if unrecognized
2. Pathogenesis
   a. Anterior glottic involvement is most common leading to impaired vocalization.
   b. Respiratory distress can occur if there is posterior or inferior extension leading to increased airway resistance.
3. Clinical Presentation
   a. Severe stridor
   b. Depending on length of involvement and subglottic extent, may result in significant respiratory distress
   c. Rare interarytenoid webs present with stridor secondary to inability to abduct the vocal cords

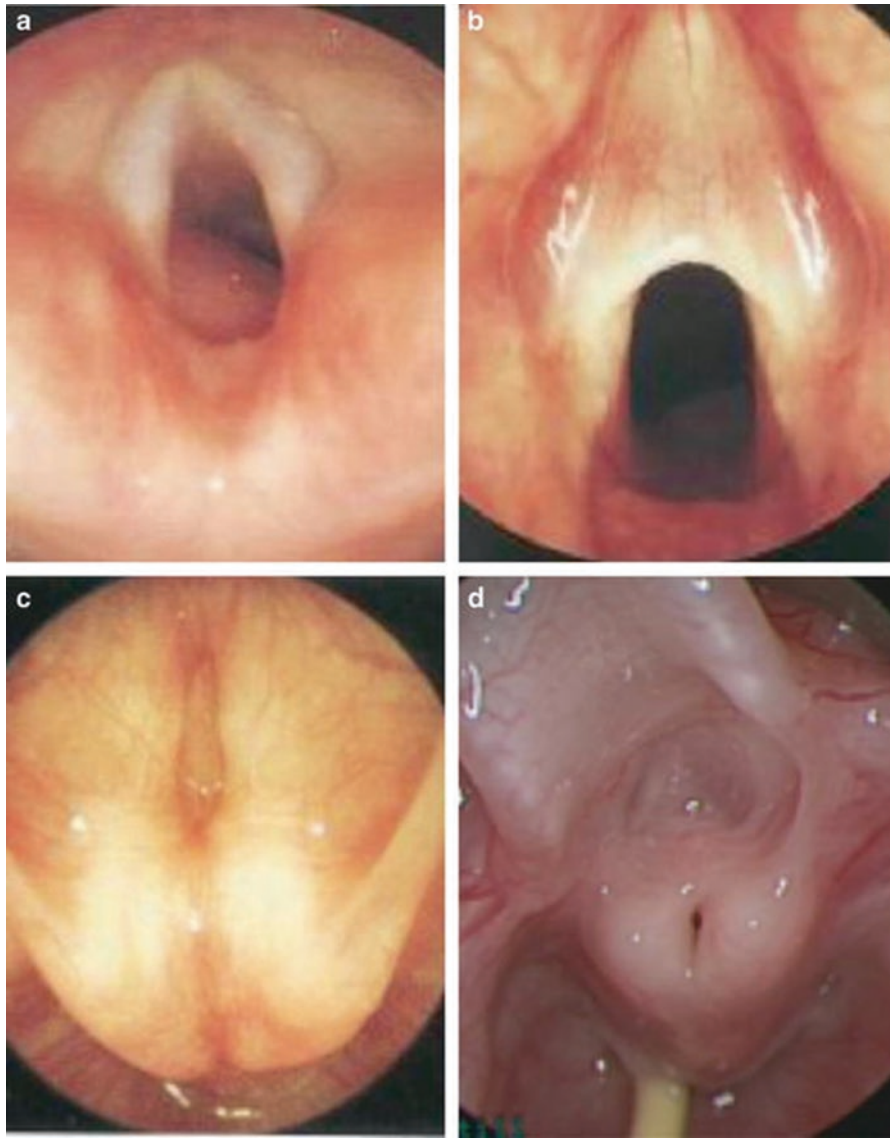

Fig. 2.10 MLB pictures of congenital laryngeal anomalies causing airway obstruction. (**a**) Glottic lymphangioma; (**b**) laryngeal web; (**c**) tracheal atresia; (**d**) vocal cord atresia

4. Diagnosis
   a. Fiber-optic laryngoscopy for identification, microlaryngoscopy and bronchoscopy to assess character and inferior extent of web
   b. Described according to the Cohen classification:
      (1) Type I: Thin glottic web without subglottic extension, <35 % airway obstruction
      (2) Type II: Thicker web with minimal subglottic extension, 35–50 % airway obstruction
      (3) Type III: Solid web with subglottic involvement, 50–75 % airway obstruction
      (4) Type IV: Solid web with subglottic involvement and stenosis, 75–90 % airway obstruction

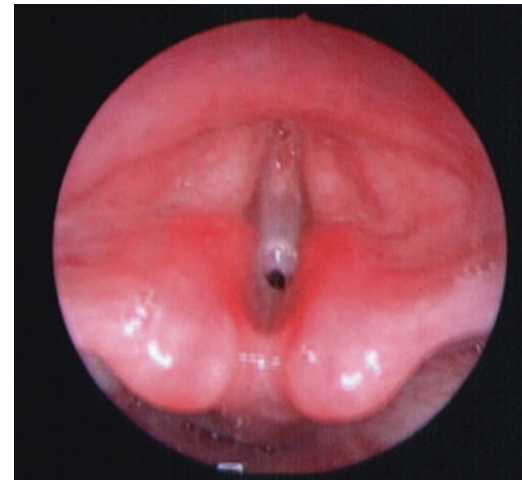

Fig. 2.11 Congenital laryngeal atresia with near-total fusion of the true vocal folds. Note the small glottis airway posteriorly

5. Management
   a. Surgical management is the mainstay of treatment.
   b. Thin webs may be managed endoscopically with lysis and dilation.
   c. More complex webs may be treated with endoscopic unilateral local flap reconstruction.
   d. Large webs with cartilaginous subglottic involvement most commonly require laryngotracheoplasty with anterior grafting. Persistent webs can be managed with endoscopic or open keel insertion and tracheostomy.
6. Multidisciplinary Collaboration
   Genetics: evaluation for 22q11.2 deletion and other associated disorders

C. Laryngeal agenesis/CHAOS (Complete High Airway Obstruction Syndrome)
1. Etiology and Epidemiology
   a. Complete failure of laryngeal recanalization at approximately 10 weeks' gestation
   b. Rare
2. Pathogenesis
   Congenital laryngeal atresia (Fig. 2.11) results in a lack of connection between the upper and lower airway. The defect may be isolated or occur in association with other congenital abnormalities, notably the presence of a tracheoesophageal fistula, esophageal atresia, and encephalocele.
3. Clinical Presentation
   a. Acute respiratory distress at birth
   b. Presence of polyhydramnios during gestation may lead to fetal diagnosis.
4. Diagnosis
   a. Fetal diagnosis made using ultrasound and complemented with fetal MRI. In addition to polyhydraminos, fetal findings include: flat diaphragms, distal airway dilation, and echogenic lungs. Synchronous tracheoesophageal fistula allows egress of fetal lung fluid and may prevent prenatal diagnosis.
   b. Postnatal diagnosis results in acute respiratory failure with inability to ventilate.
5. Management
   a. Primary management is surgical with tracheostomy.
   b. Prenatal diagnosis warrants delivery by EXIT (Chap. 17) procedure. Uterotomy is performed with preservation of placental blood flow and recirculation of amniotic fluid.

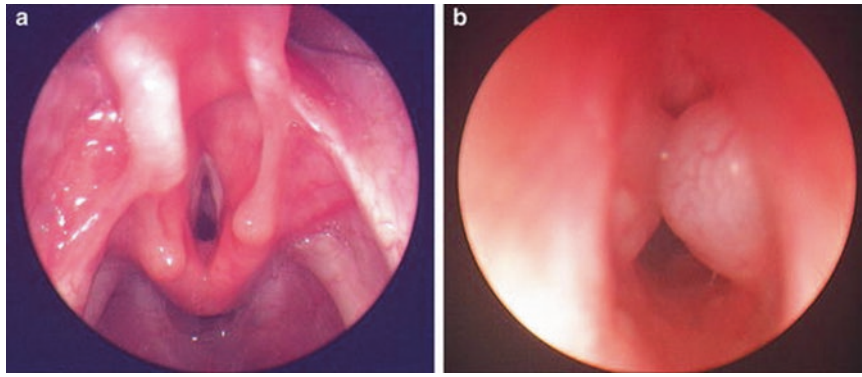

Fig. 2.12 Subglottic cysts viewed from (**a**) above the vocal cords and (**b**) below the vocal cords

c. Postnatally diagnosed cases are managed by emergent tracheostomy.
d. May consider laryngotracheoplasty in select cases for definitive management

6. Multidisciplinary Collaboration
Special delivery unit for planned EXIT procedure.

V. Subglottic Airway

The subglottic airway is the area immediately below the vocal cords, extending to the level of the inferior edge of the cricoid cartilage. Narrowing of the subglottis is typically from a fixed lesion and typically presents with biphasic stridor. Anomalies discussed below include subglottic cysts, subglottic stenosis, and hemangioma.

A. Subglottic cyst (Fig. 2.12)

1. Etiology and Epidemiology
a. Most commonly associated with prematurity and a history of intubation
b. Results from obstruction of subglottic mucus glands secondary to subepithelial fibrosis
c. Unknown etiology
2. Pathogenesis
Single or multiple cysts may occur as fixed lesions in the immediate subglottis, increasing airway resistance.
3. Clinical Presentation
a. Infant with a history of prematurity and prior intubation who presents with biphasic stridor should raise clinical suspicion.
b. May also be associated with apnea, recurrent croup, or feeding problems
4. Diagnosis
Microlaryngoscopy and bronchoscopy demonstrate obvious cysts or asymmetric subgottic narrowing.
5. Medical Management
Asymptomatic cysts may be managed with observation with consideration of medical management of acid reflux.
6. Surgical Management
a. Endoscopic marsupialization: technique is surgeon-dependent, most commonly performed using microlaryngeal instrumentation or the CO_2 laser.
b. High recurrence rates range from 12 to 70 %.
7. Multidisciplinary Collaboration
a. Pulmonary: often associated with lower airway pathology
b. Gastroenterology: acid reflux may potentiate or worsen subglottic inflammation.

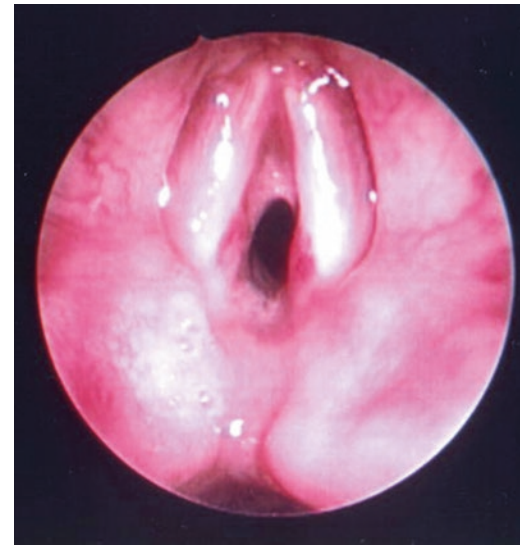

Fig. 2.13 Acquired subglottic stenosis in an infant with a history of prolonged intubation

B. Subglottic stenosis (Fig. 2.13)
   1. Etiology and Epidemiology
      a. Membranous subglottic stenosis from embryologic failure of laryngeal recanalization
      b. Cartilaginous subglottic stenosis secondary to either cricoid cartilage deformity or entrapment of the first tracheal ring within the cricoid cartilage
      c. Acquired in 95 % of cases, most commonly secondary to intubation trauma
      d. Congenital in 5 % of cases
   2. Pathogenesis
      Subglottic narrowing leading to increased airway resistance
   3. Clinical Presentation
      a. Biphasic stridor is most common.
      b. Depending on severity, children may be asymptomatic, have episodes of recurrent croup in mild cases, or respiratory distress in severe cases.
   4. Diagnosis
      a. Fiber-optic laryngoscopy may reveal evidence of subglottic narrowing, but gold standard diagnosis and classification via microlaryngoscopy and bronchoscopy
      b. Airway films may demonstrate subglottic narrowing.
      c. Degree of stenosis identified using Cotton-Myer classification
   5. Management
      a. Grade I stenosis most commonly managed conservatively and often outgrown with time
      b. Endoscopic procedures including lysis and dilation for symptomatic grade I and II membranous stenosis
      c. Grade III membranous stenosis may be treated with endoscopic techniques, but often requires open laryngotracheal reconstruction.
      d. Symptomatic cartilaginous stenoses require airway expansion via laryngotracheoplasty with or without tracheostomy depending on degree of stenosis and health of the patient.
      e. Grade IV stenoses require tracheostomy and laryngotracheoplasty or cricotracheal resection.

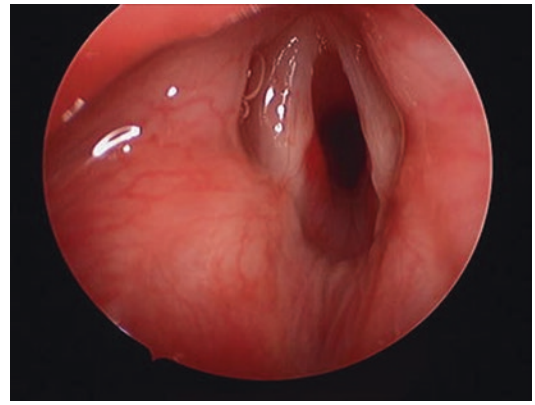

Fig. 2.14 Airway hemangioma

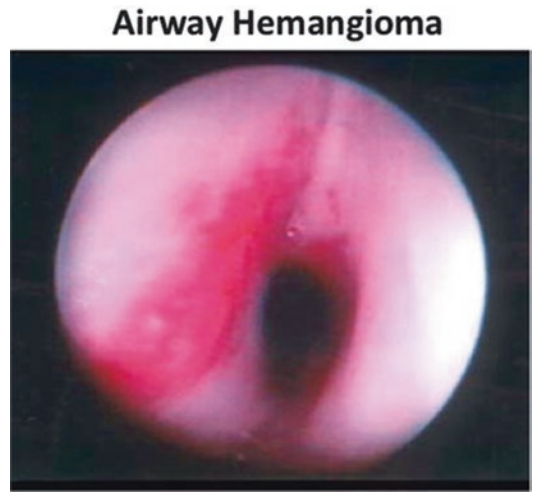

Fig. 2.15 Hemangioma on posterior wall of glottic and subglottis

6. Multidisciplinary Collaboration
   a. Pulmonary: often associated with lower airway pathology
   b. Gastroenterology: acid reflux may potentiate or worsen stenoses.

C. Hemangioma (Figs. 2.14 and 2.15)
1. Etiology and Epidemiology
   a. Hemangiomas occur secondary to an abnormal proliferation of small blood vessels.
   b. Hemangioma is the most common tumor of infancy.
   c. Incidence of 1–2.6 % at birth and ~10 % by 1 year of age.
   d. Female-to-male ratio 3:1; 60 % occur in the head and neck.
2. Pathogenesis
   Benign vascular tumor involving the subglottis, glottis, and/or supraglottis with a natural history similar to cutaneous hemangiomas, including proliferation and involution phases
3. Clinical Presentation
   a. Inspiratory or biphasic stridor. Approximately 30 % of cases present at birth, with nearly all cases symptomatic by 6 months. Signs worsen during the proliferative phase.

b. Natural history: Proliferative phase (first 8–12 months of life), quiescence, slow involution (begins at about 12 months of age and involute at variable rates typically over 5–8 years)

4. Diagnosis
   a. Eighty percent are noted within the first month of life, typically presenting at 2–4 weeks of age.
   b. Cutaneous hemangiomas are present in 50 % of children with subglottic hemangiomas.
   c. "Beard distribution" facial hemangioma is more likely to have a synchronous airway hemangioma.
   d. Airway X-ray shows asymmetric subglottic narrowing.
   e. Microlaryngoscopy and bronchoscopy reveal a compressible soft tissue mass with vascular congestion.
5. Medical Management
   a. Small subglottic hemangiomas with resulting low-grade obstruction are managed with propranolol. Dosing escalates to a maximum of 3 mg/kg. Propranolol carries a risk of hypoglycemia and is contraindicated in children with severe asthma.
   b. Moderate to large hemangiomas with respiratory distress can be acutely managed with intralesional or systemic steroids.
6. Surgical Management
   a. Mass is routinely soft and compressible allowing for intubation even in severe stenoses.
   b. Hemangiomas refractory to propranolol are managed with laryngotracheoplasty with open submucosal resection of the lesion.
7. Multidisciplinary Collaboration
   Dermatology: Evaluate patient for systemic medical therapy.

VI. Trachea

The trachea begins immediately below the cricoid and extends distally to the carina where the mainstem bronchi diverge. Tracheal anomalies often require multidisciplinary intervention with pediatric surgery and/or cardiothoracic surgery. The timing and clinical presentation of tracheal anomalies are more variable, as the pathology is more heterogeneous. Anomalies discussed below include complete tracheal rings, vascular extrinsic rings, tracheal cleft, tracheoesophageal fistula, and tracheomalacia.

A. Complete tracheal rings (Fig. 2.16)
   1. Etiology and Epidemiology
      a. Abnormal development of the tracheal rings, likely after the 8th week of gestation
      b. The typical C shaped cartilage is fused posteriorly and there is a lack of the posterior membranous trachea.

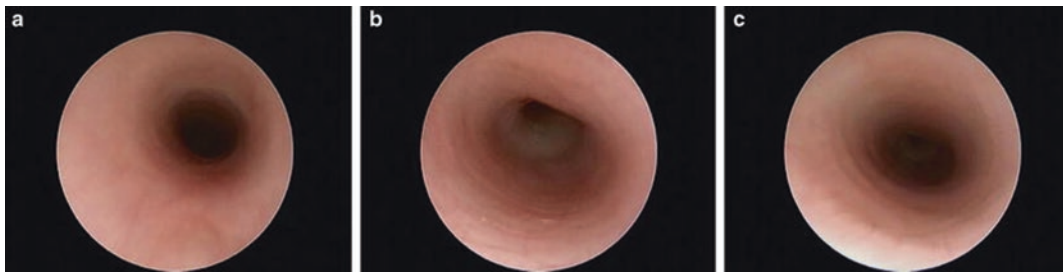

Fig. 2.16 Endoscopic views of a child with long-segment complete tracheal rings. (**a**) View showing beginning of rings; (**b**) view showing midsection of rings; (**c**) view showing distal segment of rings

c. Associated with other malformations of trachea
d. Incidence estimated to be 1 in 64,500

2. Pathogenesis
   a. The posterior membranous portion of the trachea is absent leading to fixed, narrowed dimension of the trachea.
   b. May involve a few tracheal rings or the entire length of the trachea (sleeve trachea)
3. Clinical Presentation
   a. Loud noisy stridor may be inspiratory (cervical trachea), expiratory (thoracic trachea), or biphasic.
   b. Signs may not be apparent until >50 % stenosis and may be uncovered in a setting of respiratory illness which exacerbates the narrowing.
4. Diagnosis
   a. Plain chest films may provide indication of stenosis by demonstrating a narrowed air column.
   b. Airway fluoroscopy can be utilized to assess narrowing and associated pulmonary tree anomalies, which are present in up to 20 % of cases.
   c. CT or MRI along with vascular studies may be used to further evaluate the stenosis as well as evaluate for vascular malformations/anomalies and extrinsic compression.
   d. Rigid bronchoscopy remains the gold standard for diagnosis to assess the length of involvement.
5. Medical Management
   In select cases patients with mild signs may be monitored and respiratory illness may require steroids and close monitoring.
6. Surgical Management
   a. Slide tracheoplasty performed through a sternal or cervical approach is the current surgical modality of choice.
   b. Augmentation using cartilage or perichondrium has been used for repair (variable results).
7. Multidisciplinary Collaboration
   a. Cardiothoracic surgery: For thoracic tracheal involvement, may require ECMO or temporary cardiac bypass for surgical management
   b. Vascular malformations present in up to 50 % of cases

B. Vascular extrinsic rings (Fig. 2.17)

1. Etiology and Epidemiology
   a. Abnormal development of branchial arch system
   b. Rare; frequently associated with other cardiac abnormalities
2. Pathogenesis
   Anomalous branching pattern of the vessels originating from the aortic arch or pulmonary trunk
3. Clinical Presentation
   a. Degree of respiratory problems and/or feeding difficulties varies depending on degree and site of compression at the trachea, the bronchi, and/or the esophagus.
   b. Range from asymptomatic to severe respiratory distress
   c. May present as recurrent pulmonary infection, cough, stridor, and/or dysphagia
4. Diagnosis
   a. Barium esophagogram, echocardiography, computed tomography (CT), magnetic resonance imaging (MRI), and angiography aid in diagnosis.

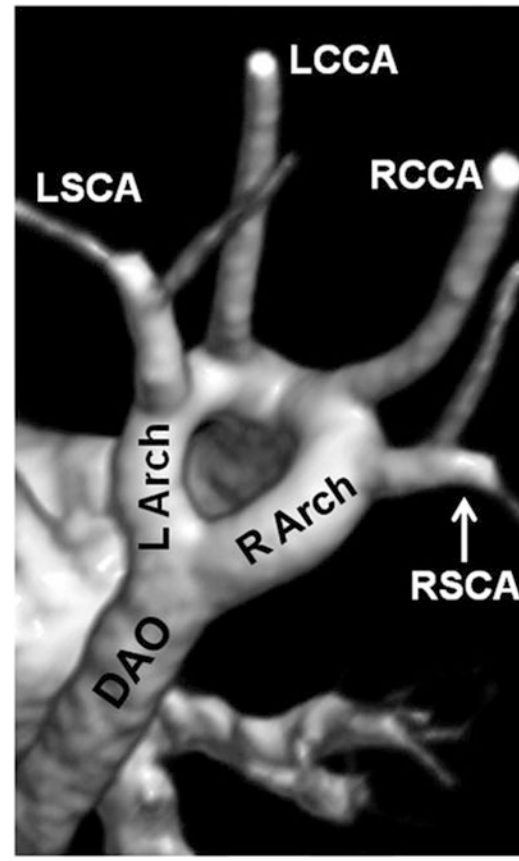

Fig. 2.17 Magnetic resonance angiogram of an unobstructed double aortic arch viewed from right posterior oblique with cranial angulation. Note that the right aortic arch is slightly larger. *DAO* descending aorta, *L Arch* left-sided arch, *LCCA* left common carotid artery, *LSCA* left subclavian artery, *R Arch* right-sided arch, *RCCA* right common carotid artery, *RSCA* right subclavian artery

   b. Rigid bronchoscopy and esophagoscopy for definitive evaluation and to identify synchronous tracheobronchial anomalies including complete rings and abnormal bronchial take off
5. Medical Management
   None
6. Surgical Management
   a. Heterogeneous anomalies, therefore no single surgical operation defined
   b. Cardiothoracic surgery most common service to address surgical needs
   c. Most frequently managed with vessel pexy or division with or without re-implantation
7. Multidisciplinary Considerations
   a. Cardiology: Cardiac evaluation and identification of secondary cardiac anomalies
   b. Cardiothoracic surgery: Definitive surgical management
   c. Pediatric surgery: May be involved with esophageal management

C. Tracheal Clefts (Fig. 2.8)
1. Etiology and Epidemiology
   a. Incomplete development of the tracheoesophageal septum
   b. Associated syndromes include: Pallister–Hall, Opitz-Frias, and VACTERL.
   c. Clefts are present in 6 % of patients with tracheoesophageal fistula.

2. Pathogenesis
   a. Most commonly present with aspiration. As a result, may have respiratory distress or cyanosis with feeding. Severe aspiration leads to failure to thrive or recurrent pneumonia.
   b. Excessive redundant mucosa may also cause stridor and airway obstruction.
   c. Type III and IV have high mortality.
3. Clinical Presentation
   a. High index of suspicion for this anomaly in children with aspiration
   b. Additionally, may present with difficult intubation or difficulty ventilating secondary to a large air leak
4. Diagnosis
   a. Modified barium swallow or FEES exam may show a posterior to anterior aspiration pattern.
   b. Fiber-optic laryngoscopy demonstrates the "Ram sign" in large clefts with redundant soft tissue adjacent to the arytenoids, which prolapse into the cleft margin.
   c. Formal diagnosis requires microlaryngoscopy and bronchoscopy with palpation of the posterior commissure.
   d. Suspension with use of vocal cord spreaders may aid in diagnosis.
   e. Clefts are commonly described according to the Benjamin–Inglis classification.
      (1) Type I: Involves the interarytenoid region down to and including the vocal cords
      (2) Type II: Extension into the cricoid cartilage
      (3) Type III: Extension through the cricoid into the cervical trachea
      (4) Type IV: Extension into the intrathoracic trachea
5. Management
   a. Endoscopic management with suture approximation may be feasible with smaller clefts.
   b. Open repair via a transtracheal or lateral pharyngotomy approach is often indicated for deeper clefts.
   c. Often require ECMO or cardiopulmonary bypass (CPB) for repair of type IV cleft
   d. Despite repair, mortality >90 % for patients with a type IV cleft
6. Multidisciplinary Collaboration
   a. General surgery for management of esophagus and often gastric exclusion. Microgastria common associated finding.
   b. Pulmonology: severe often-recalcitrant tracheobronchomalacia may lead to prolonged tracheostomy dependence.

D. Tracheoesophageal fistula and pouches
1. Etiology and Epidemiology
   a. No unifying theory proposed to address this heterogeneous group of anomalies
   b. Likely multifactorial, 50 % associated with other malformations
   c. Incidence of 1 in 2500–4500 live births
   d. Associated with VACTERL, CHARGE, Fanconi anemia, Opitz G, and Goldenhar
2. Pathogenesis
   a. Various degrees of esophageal atresia with or without associated fistula
   b. Connection to the trachea prevents egress of saliva and feeds into stomach and provides direct connection for gastric contents to pass into the tracheobronchial tree.
   c. Respiratory signs are often exacerbated by associated tracheobronchomalacia.
3. Clinical Presentation
   a. Most patients are symptomatic within first few hours of life.
   b. Excessive saliva, pooling of secretions are often the first noted findings.

c. Feeding difficulties with coughing, regurgitation, cyanosis with feeds, and potentially respiratory distress

4. Diagnosis
   a. AP/Lateral X-ray with air or contrast to aid in delineation of the pouch, coiled catheter/feeding tube may be seen.
   b. Fluoroscopy for more detailed evaluation of the anomaly
   c. Microlaryngoscopy and bronchoscopy for evaluation of the tracheal pouch and endoscopic evaluation with rubber catheter pull through
   d. Ladd and Gross classification.
      (1) Type A—Esophageal atresia (EA) without fistula (6%)
      (2) Type B—EA with proximal fistula (5%)
      (3) Type C—EA with distal fistula (84%)
      (4) Type D—EA with double fistula (1%)
      (5) Type E—Tracheo-esophageal fistula without atresia—H-type (4%)
5. Medical Management
   a. Sump catheter for salivary and gastric diversion to prevent pneumonitis prior to surgical management
   b. Positioning to minimize secretion burden on lungs. Elevate head of bed.
   c. Antibiotics may be indicated.
6. Surgical Management
   a. Surgical management for repair once medically able
   b. The operative approach to an infant with EA depends greatly on the specific type of anomaly present and the occurrence of associated anomalies.
7. Multidisciplinary Considerations
   a. Pediatric surgery: Often primary team for management
   b. Genetics: 50% of patients have associated malformations.

E. Tracheomalacia (Fig. 2.18)
1. Etiology and Epidemiology
   a. Primary tracheomalacia is an isolated weakness of the tracheal wall, which leads to airway sign.
   b. Secondary tracheomalacia is weakness of the tracheal wall that occurs as a result of extrinsic compression by a vascular anomaly or in association with a tracheoesophageal fistula or tracheal cleft.

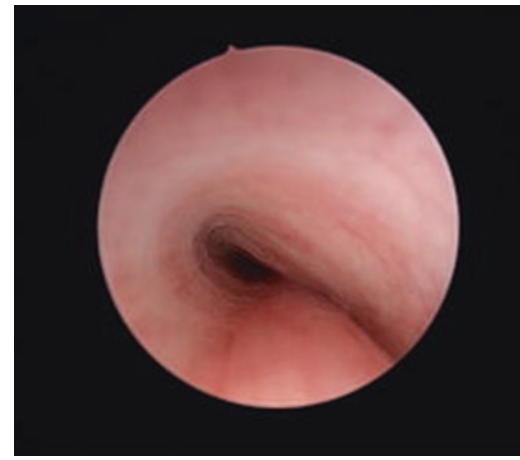

Fig. 2.18 Tracheomalacia in association with innominate artery compression and a large thymus

   c. Secondary tracheomalacia commonly persists after surgical repair of the associated tracheal anomalies.
   d. Seen more often with premature infants on long term ventilation with severe ventilator dependent respiratory failure
   e. Rare
   f. May be associated with syndromic conditions and other anomalies of the tracheobronchial tree
2. Pathogenesis
   Weakness of the cartilaginous trachea leads to varying degrees of dynamic collapse of the tracheal wall during expiration, which increases airway resistance.
3. Clinical Presentation
   a. Most common presentation is expiratory stridor/wheeze.
   b. Wide spectrum of respiratory signs ranging from chronic cough to life-threatening recurrent apnea
4. Diagnosis
   a. Bronchoscopy.is the gold standard for diagnosis.
   b. Radiological airway screening/fluoroscopy, chest CT, MRI, or tracheobronchogram may also be helpful for diagnosis if no bronchoscopy available.
5. Medical Management
   a. Mild cases should be observed.
   b. Supportive management with inhaled agents, chest physiotherapy, positive pressure ventilation with CPAP or BiPAP may be indicated for more severe cases.
6. Surgical Management
   a. May require short or long term tracheostomy for positive pressure.
   b. Internal airway stenting, endoscopic interventions are rarely indicated and controversial.
   c. Management of extrinsic compression with vessel, (aortopexy) or diversion
   d. Management of tracheoesophageal fistula
7. Multidisciplinary Collaboration
   a. Pulmonology: Flexible bronchoscopy, medial management, noninvasive ventilation
   b. Cardiothoracic of pediatric surgery: Surgical management of associated conditions

Suggested Reading

Ayari S, Aubertin G, Girschig H, Van Den Abbeele T, Mondain M. Pathophysiology and diagnostic approach to laryngomalacia in infants. Eur Ann Otorhinolaryngol Head Neck Dis. 2012;129(5):257–63.

Belden CJ, Mancuso AA, Schmalfuss IM. CT features of congenital nasal piriform aperture stenosis: initial experience. Radiology. 1999;213(2):495–501.

Coran AG, Adzick NS, Krummel TM, editors. Pediatric surgery. 7th ed. St. Louis: Elsevier Saunders; 2012. p. 893–918.

Dobbie AM, White DR. Laryngomalacia. Pediatr Clin North Am. 2013;60(4):893–902.

Evans KN, Sie KC, Hopper RA, Glass RP, Hing AV, Cunningham ML. Robin sequence: from diagnosis to development of an effective management plan. Pediatrics. 2011;127(5):936–48.

Ho AS, Koltai PJ. Pediatric tracheal stenosis. Otolaryngol Clin North Am. 2008;41(5):999–1021.

Kir M, Saylam GS, Karadas U, Yilmaz N, Çakmakçi H, Uzuner N, Güzeloğlu M, Ugurlu B, Oto Ö. Vascular rings: presentation, imaging strategies, treatment, and outcome. Pediatr Cardiol. 2012;33(4):607–17.

Lioy J, Sobol S, editors. Disorders of the neonatal airway: fundamentals for practice. Berlin: Springer; 2015.

Sharma N, Srinivas M. Laryngotracheobronchoscopy prior to esophageal atresia and tracheoesophageal fistula repair—its use and importance. J Pediatr Surg. 2014;49(2):367–9.

Tsai YT, Lee LA, Fang TJ, Li HY. Treatment of vallecular cysts in infants with and without coexisting laryngomalacia using endoscopic laser marsupialization: fifteen-year experience at a single-center. Int J Pediatr Otorhinolaryngol. 2013;77(3):424–8.

Tsurumi H, Ito M, Ishikura K, Hataya H, Ikeda M, Honda M, Nishimura G. Bifid epiglottis: syndromic constituent rather than isolated anomaly. Pediatr Int. 2010;52(5):723–8.

Wine TM, Dedhia K, Chi DH. Congenital nasal piriform aperture stenosis: is there a role for nasal dilation? JAMA Otolaryngol Head Neck Surg. 2014;140(4):352–6.

Developmental Lung Anomalies

3

Mohammad A. Attar and Subrata Sarkar

I. Anomalies by Developmental Stage
   A. Most pulmonary malformations arise during the embryonic and the pseudoglandular stages of lung development.
   B. The spectrum of developmental malformations related to lung bud formation, branching morphogenesis, and separation of the trachea from the esophagus includes laryngeal, tracheal, and esophageal atresia; tracheoesophageal fistula; pulmonary aplasia; and bronchogenic cysts.
   C. Development abnormalities related to the pseudoglandular stage of lung development and failure of the pleuroperitoneal cavity to close properly include intralobar pulmonary sequestration, cystic adenomatoid malformation, tracheomalacia and bronchomalacia, and congenital diaphragmatic hernia.
   D. The spectrum of abnormalities arising at the canalicular and the saccular stage of lung development are related to growth and maturation of the respiratory parenchyma and its vasculature and include acinar dysplasia, alveolar capillary dysplasia, and pulmonary hypoplasia.
   E. Acute lung injury in the neonatal period may alter subsequent alveolar and airway growth and development.

II. Congenital Anomalies in the Lung Can Be Categorized as Malformations in:
   A. The tracheobronchial tree (Chap. 2)
   B. Distal lung parenchyma
   C. Abnormalities in the pulmonary arterial and venous trees and the lymphatics

III. Malformations of Lung Parenchyma
   A. Congenital Lobar Emphysema (CLE)
      1. Can be lobar, regional or segmental, or pulmonary overinflation
      2. CLE may result from malformation in the bronchial cartilage with absent or incomplete rings, a cyst in the bronchus, a mucus or meconium plug in the bronchus, or from extrinsic bronchial obstruction caused by dilated vessels, or intrathoracic masses such as bronchogenic cysts, extralobar sequestration, enlarged lymph nodes, and neoplasms. These

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lesions cause air trapping, compression of the remaining ipsilateral lung or lobes, and respiratory distress.
3. CLE usually affects the upper and middle lobes on the right, and the upper lobe on the left.
4. Age at the time of diagnosis is closely related to the severity of the respiratory distress and the amount of functioning lung.
5. Diagnosis is by radiography, which reveals the lobar distribution of the hyperaeration with compression of adjacent pulmonary parenchyma.

B. Pulmonary Agenesis and Aplasia
1. A form of arrested lung development that results in the absence of the distal lung parenchyma
2. Pulmonary agenesis is the complete absence of one or both lungs, including bronchi, bronchioles, vasculature, and respiratory parenchyma.
3. Pulmonary aplasia occurs when only rudimentary bronchi are present; each ends in a blind pouch, with no pulmonary vessels or respiratory parenchyma.
4. This defect arises early in lung development when the respiratory primordium bifurcates into the right and left primitive lung buds.
5. Unilateral pulmonary agenesis is more common than bilateral.
6. Radiography shows homogeneous density in place of the lung, the ribs appear crowded on the involved side, and there is mediastinal shift. A CT scan of the chest confirms the absence of lung tissue.

C. Pulmonary Hypoplasia
1. Develops as a result of other anomalies in the developing fetus. Many of these anomalies physically restrict growth or expansion of the peripheral lung.
2. It occurs in infants with renal agenesis or dysplasia, bladder outlet obstruction, loss or reduction of the amniotic fluid from premature rupture of membranes, diaphragmatic hernia, large pleural effusions, congenital anomalies of the neuromuscular system, and chromosomal anomalies, including trisomy 13, 18, and 21.

D. Congenital Diaphragmatic Hernia (CDH)
1. CDH occurs in 1 per 2000–3000 births.
2. Fifty percent are associated with other malformations, especially neural tube defects, cardiac defects, and malrotation of the gut.
3. In CDH, the pleuroperitoneal canal fails to close. This allows the developing abdominal viscera to bulge into the pleural cavity and stunts the growth of the lung.
4. The most common site is the left hemithorax, with the defect in the diaphragm being posterior (foramen of Bochdalek) in 70 % of infants.
5. The severity of the resulting pulmonary hypoplasia varies, probably depending upon the timing of the onset of compression, with early, severe compression of the lungs associated with more hypoplasia.
6. There is a decrease in the alveolar number and size and a decrease in the pulmonary vasculature.
7. Infants with a large CDH present at birth with cyanosis, respiratory distress, a scaphoid abdomen, decreased breath sounds on the side of hernia, and displacement of heart sounds to the opposite side.
8. The prenatal diagnosis is often made by ultrasonography, which is often precipitated by the occurrence of polyhydramnios.
9. Often there is severe pulmonary hypertension, likely because of the increased proportion of muscular arteries in the periphery of the lung, which results in increased pulmonary vascular resistance.

E. Congenital Pulmonary Airway Malformation (CPAM)
   1. CPAM is a pulmonary maldevelopment of small airways and distal lung parenchyma with bronchiolar overgrowth that has cystic and non-cystic forms.
   2. CPAMs were previously known as congenital cystic adenomatoid malformations (CCAMs) which were divided into three major types based upon the size of the cysts and their cellular characteristics (predominantly bronchial, bronchiolar, or bronchiolar/alveolar duct cells). Under the current classification scheme, two additional types (Type 0 arising from the trachea, and type 4 lesions having alveolar/distal acinar origin) were added.
   3. Simpler classification based on anatomic and ultrasonographic findings includes two major types: macrocystic and microcystic.
      a. In the macrocystic type, the cysts are visible on fetal ultrasonography, and the prognosis is better.
      b. In the microcystic type, the cysts are smaller, and the mass has a solid appearance.
   4. Prognosis is worse if the cystic mass is very large and associated with mediastinal shift, polyhydramnios, pulmonary hypoplasia, or hydrops fetalis.
   5. After birth, because they are connected to the airways, cysts fill with air, produce further compression of the adjacent lung, and result in respiratory distress.
   6. The widespread use of antenatal ultrasonography has resulted in an increase in the prenatal diagnosis of CPAM. Spontaneous regression of CPAM with normal appearing lungs at birth can occur.
   7. CPAMs associated with respiratory distress are surgically resected. Patients without respiratory distress may have CPAMs evaluated by chest CT and have surgical resection at a year of life because of the potential increased risks for bleeding, infection and malignancy.

F. Bronchopulmonary Sequestration
   1. Develops as a mass of non-functioning lung tissue, not connected to the tracheobronchial tree and receives its blood supply from one or more anomalous systemic arteries
   2. There are two forms of bronchopulmonary sequestration depending on whether it is within (intralobar) or outside (extralobar) the visceral pleural lining.
   3. Most infants with bronchopulmonary sequestration are asymptomatic in the neonatal period.
   4. If the sequestration is sufficiently large, there may be persistent cyanosis and respiratory distress.
   5. Some cases may present with large unilateral hydrothorax, possibly secondary to lymphatic obstruction or congestive heart failure secondary to large left-to-right shunting through the sequestration.
   6. The classic appearance on chest radiography consists of a triangular or oval-shaped basal lung mass on one side of the chest, usually the left.
   7. Diagnosis is confirmed with chest CT and magnetic resonance angiography.

G. Alveolar Capillary Dysplasia
   1. There is misalignment of the pulmonary veins.
   2. Characterized by inadequate vascularization of the alveolar parenchyma resulting in reduced number of capillaries in the alveolar wall
   3. This malformation causes persistent pulmonary hypertension in the newborn and is uniformly fatal.

H. Congenital Pulmonary Lymphangiectasis (CPL)
   1. Extremely rare condition consists of markedly distended or dilated pulmonary lymphatics, which are found in the bronchovascular connective tissue, along the interlobular septae, and in the pleura. It may be primary, secondary, or generalized.

2. This condition has been associated with Noonan, Ulrich–Turner, and Down syndromes.
3. Primary lymphangiectasis is a developmental defect in which the pulmonary lymphatics fail to communicate with the systemic lymphatics. Affected infants present with respiratory distress and pleural effusions.
4. Secondary lymphangiectasis is associated with cardiovascular malformations.
5. Generalized lymphangiectasis is characterized by proliferation of the lymphatic spaces and occurs in the lung as part of a systemic abnormality, in which multiple lymphangiomas are also found in the bones, viscera, and soft tissues.
6. Patients with pulmonary lymphangiectasis present with non-immune hydrops fetalis and pleural effusions. Pleural effusions are typically chylous. Pleural effusions in the neonatal period may be serous with minimal triglycerides, particularly before enteral feeding is established.

I. Other congenital anomalies of pulmonary lymphatics that present with chylothorax (Chap. 73). These anomalies can be characterized by dilatation and proliferation of lymphatic capillaries (lymphangiomatosis) that may be limited to the lungs and associated with chylothorax or involve other organs like spleen and bones and usually is progressive. Congenital chylothorax could also be idiopathic (not associated with lymphangectasia or lymphangiomas) as part of congenital lymph dysplasia syndrome (Milroy disease) or as part of a syndrome that includes lymphatic dysplasia (like Turner, Noonan, and Ehlers–Danlos).

J. Other conditions that manifest as interstitial lung disease
1. Disorders of surfactant protein (SP) B and C (deficiencies and dysfunction) that are associated with lamellar body anomalies related to ABCA3 gene deficiency, thyroid transcription factor 1 (TTF1) deficiency, or alveolar epithelia cell granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor deficiency
2. Lung injury related to cystic fibrosis and alpha-1 antitrypsin deficiency may also present as pulmonary dysfunction and emphysema.
3. Diagnostic evaluation for these conditions is usually attempted because of persistent severe respiratory failure in the neonatal period that does not respond to conventional therapy or extracorporeal membrane oxygenation.

Suggested Reading

Abman SH, editor. Fetal and neonatal physiology. 4th ed. Philadelphia: W B Saunders; 2011. p. 864–77.

Bengtsson B-OS. Neonatal lymphatic (chylous) disorders. NeoReviews. 2013;14:e600–12.

Keller RL, Guevara-Gallardo S, Farmer DL. Malformations of the mediastinum and lung parenchyma. In: Gleason CA, Devaskar SU, editors. Avery's diseases of the newborn. 9th ed. Philadelphia: Elsevier/Saunders; 2012. p. 672–97.

Nogee LM. Genetic basis of children's interstitial lung disease. Pediatr Allergy Immunol Pulmonol. 2010; 23:15–24.

Sandu K, Monnier P. Congenital tracheal anomalies. Otolaryngol Clin N Am. 2007;40:193–217.

Wert SE. Normal and abnormal structural development of the lung. In Polin RA, Fox WW, Abman Sit (eds.): Fetal and Neonatal physiology, philadelphia, Elsever Saunders 2011, pp. 864–76.

Section II

Principles of Mechanical Ventilation

Spontaneous Breathing

4

Vinod K. Bhutani

I. Introduction
   A. Air, like liquid, moves from a region of higher pressure to one with lower pressure.
   B. During breathing and just prior to inspiration, no gas flows because the gas pressure within the alveoli is equal to atmospheric pressure.
   C. For inspiration to occur, alveolar pressure must be less than atmospheric pressure.
   D. For expiration to occur, alveolar pressure must be higher than atmospheric pressure.
   E. Thus, for inspiration to occur, the gradient in pressures can be achieved either, by lowering the alveolar pressure ("negative," "natural," spontaneous breathing) or, raising the atmospheric pressure ("positive," "pressure," mechanical breathing).
   F. The clinical and physiologic implications of forces that influence inspiration and expiration are discussed in this section.

II. Signals of Respiration
   A. Each respiratory cycle can be described by the measurement of three signals: driving pressure (P), volume (V), and time (Fig. 4.1).
   B. The rate of change in volume over time defines flow ($\dot{V}$).
   C. The fundamental act of spontaneous breathing results from the generation of P, the inspiratory driving force needed to overcome the elastic, flow-resistive, and inertial properties of the entire respiratory system in order to initiate V.
      1. This relationship has been best described by Röhrer using an equation of motion in which the driving pressure (P) is equal to the sum of elastic (P_E), resistive (P_R) and inertial pressure (P_I) components, thus:

$$P = P_E + P_R + P_I$$

      2. In this relationship, the elastic pressure is assumed to be proportional to volume change by an elastic constant (E) representing the elastance (or elastic resistance) of the system.
      3. The resistive component of pressure is assumed proportional to airflow by a resistive constant (R) representing inelastic airway and tissue resistances.

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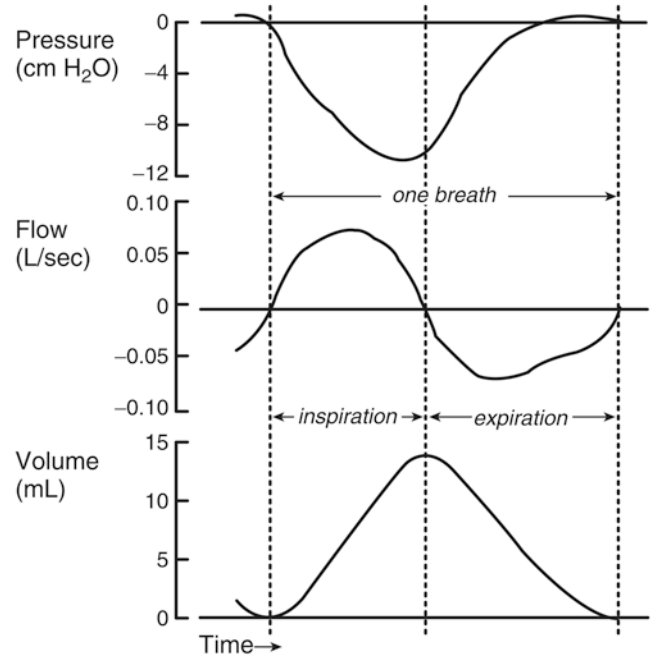

Fig. 4.1 Graphic representation of a respiratory cycle demonstrating pressure, flow, and volume waveforms. Volume is obtained by integration (area under the curve) of the flow signal (Modified from Bhutani VK, Sivieri EM, Abbasi S: Evaluation of pulmonary function in the neonate. In Polin RA, Fox WW [Eds.]: *Fetal and Neonatal Physiology*, second edition, Philadelphia, W.B. Saunders, 1998, p. 1144, with permission.)

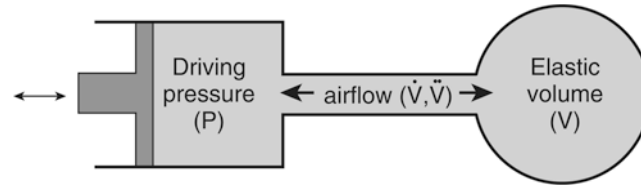

Fig. 4.2 Linear, first order model of the respiratory system, where applied pressure causes gas to flow through a tube

4. In addition, the inertial component of pressure is assumed to be proportional to gas and tissue acceleration ($\ddot{V}$) by an inertial constant (I). Therefore:

$$P = EV + R\dot{V} + I\ddot{V}$$

5. This is a linear, first order model in which the respiratory system is treated as a simple mechanical system (Fig. 4.2), where applied pressure P causes gas to flow through a tube (the respiratory airways) which is connected to a closed elastic chamber (alveoli) of volume V. In this ideal model E, R, and I are assumed to be constants in a linear relationship between driving pressure and volume.
6. Under conditions of normal breathing frequencies (relatively low airflow and tissue acceleration) the inertance term is traditionally considered negligible, therefore:

$$P = EV + R\dot{V}$$

7. In respiratory terminology, elastance is usually replaced by compliance (C), which is a term used to represent the expandability or distensibility of the system. Since compliance is simply the reciprocal of elastance, the equation of motion can be rewritten as:

$$P = V / C + R\dot{V}$$

8. This simplified form of the Röhrer equation is the basis for most evaluations of pulmonary mechanics where measurements of P, V, and $\dot{V}$ are used to compute the various components of respiratory system compliance, resistance, and work of breathing.

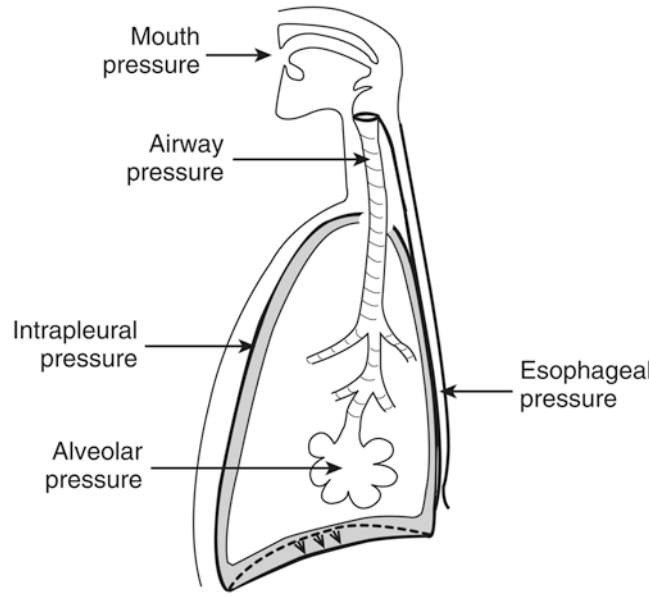

Fig. 4.3 Schematic representation of components of respiratory pressures used in pulmonary function studies. Esophageal pressure approximates intrapleural pressure (Modified from Bhutani VK, Sivieri EM, Abbasi S: Evaluation of pulmonary function in the neonate. In Polin RA, Fox WW [Eds.]: *Fetal and Neonatal Physiology*, second edition, Philadelphia, W.B. Saunders, 1998, p. 1153, with permission.)

D. One can further study the nonlinear nature of the respiratory system using more advanced nonlinear models and by analyzing two-dimensional graphic plots of P–V, V–$\dot{V}$ and P–$\dot{V}$ relationships.

E. Because the inherent nature of the respiratory signals is to be variable (especially in premature infants), it is imperative that the signals are measured in as steady state as feasible and over a protracted period of time (usually 2–3 min).

III. Driving Pressure

A. During spontaneous breathing the driving pressure required to overcome elastic, airflow-resistive, and inertial properties of the respiratory system is the result of intrapleural pressure (P_{IP}) changes generated by the respiratory muscles (Fig. 4.3).

B. During a respiratory cycle both the intrapleural and alveolar pressures change.

1. Just before the commencement of an inspiratory cycle, the intrapleural pressure is subatmospheric (−3 to −6 cm H_2O) because of the elastic recoil effect of the lung.
2. At this time, the alveolar pressure is atmospheric (zero), because there is no airflow and thus no pressure drop along the conducting airways. At this time, the alveolar pressure is atmospheric zero, because there is no airflow and thus no pressure drop along the conducting airways.
3. During a spontaneous inspiration, forces generated by the respiratory muscles cause the intrapleural pressure to further decrease producing a concomitant fall in alveolar pressure so as to initiate a driving pressure gradient which forces airflow into the lung.
4. During a passive expiration, the respiratory muscles are relaxed and the intrapleural pressure becomes less negative.
5. Elastic recoil forces in the now expanded lung and thorax cause alveolar pressure to become positive and thus the net driving pressure forces air to flow out of the lungs.
6. With forced expiration, the intrapleural pressure rises above atmospheric pressure.
7. The magnitude of the change in the alveolar pressure depends on the airflow rate and the airway resistance but usually varies between 1 and 2 cm H_2O below and above atmospheric pressure during inspiration and expiration, respectively.
8. This range of alveolar pressure change can be markedly increased with air trapping or airway obstruction.

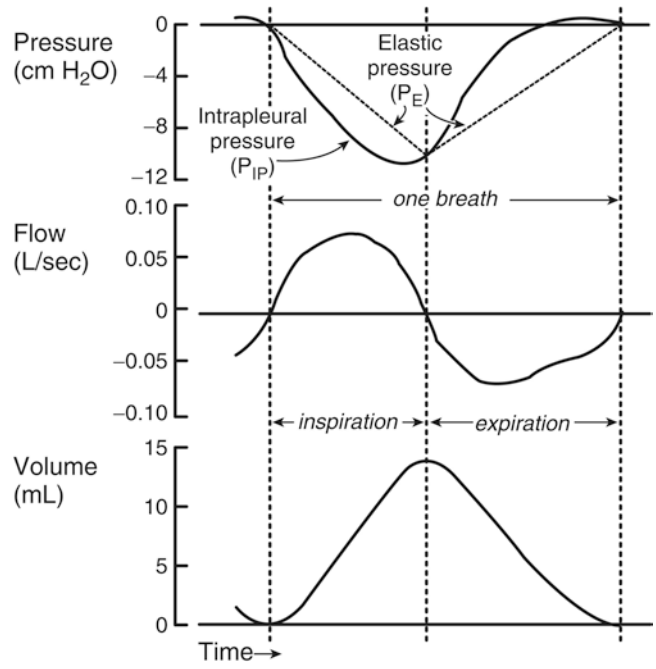

Fig. 4.4 During tidal breathing, airflow is zero at end-inspiration and end-expiration, where it reverses direction. The pressure difference between these two points represents the net elastic pressure at end-inspiration. The elastic component of intrapleural pressure at other points can be approximated by a straight line connecting points of zero flow

C. Following are some physiologic observations of changes in intrapleural pressure during spontaneous breathing
   1. Under some conditions respiratory airflow is zero or very close to zero:
      a. During tidal breathing, airflow is zero at end inspiration and end expiration where it reverses direction (Fig. 4.4).
      b. During slow static inflation, airflow can be approximated as zero.
      c. In both cases the resistive component of driving pressure as described above is zero or $RV=0$ and P_{IP} is equal to elastic pressure only:

$$P_{IP} = P_E = V / C$$

   2. The elastic component of intrapleural pressure can be estimated on the pressure tracing by connecting with straight lines the points of zero flow at end-expiration and end-inspiration. The vertical segment between this estimated elastic pressure line and the measured intrapleural pressure (solid line) represents the resistive pressure component (Fig. 4.5).
   3. Resistive pressure is usually maximum at points of peak airflow, which usually occurs during mid inspiration and mid expiration.
   4. Transpulmonary pressure (P_{TP}) is the differential between intrapleural pressure and alveolar pressure. This is the portion of the total respiratory driving pressure which is attributed to inflation and deflation of the lung specifically.

D. With mechanical ventilation, of course, the driving pressure is provided by the ventilator. In contrast to spontaneous breathing, where a negative change in intrapleural pressure is the driving pressure for inspiration, the mechanical ventilator applies a positive pressure to an endotracheal tube. Nonetheless, in both cases there is a positive pressure gradient from the mouth to the alveoli. In both cases the transpulmonary pressure gradient is in the same direction.

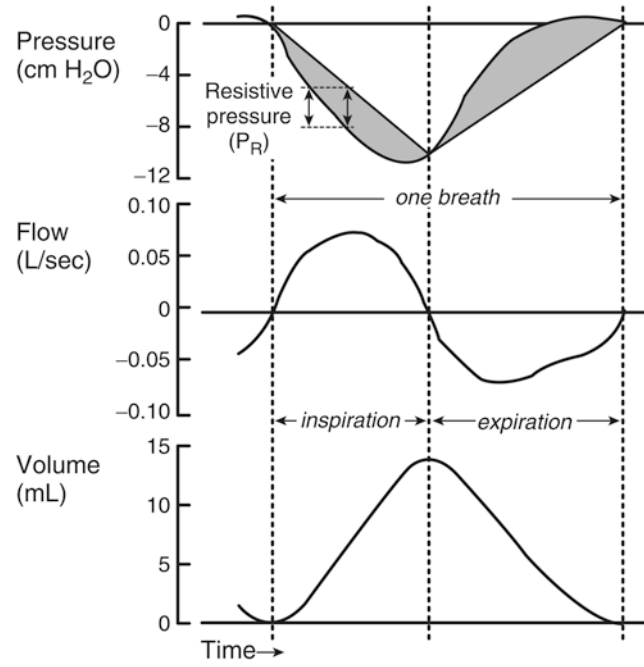

Fig. 4.5 The elastic component of intrapleural pressure can be estimated on the pressure tracing by connecting points of zero flow at end-expiration and end-inspiration with a straight line. The vertical distance between this estimate and the measured intrapleural pressure is the resistive pressure component (*solid line*)

IV. Factors that Impact Mechanics of Airflow

Factors that influence the respiratory muscles and respiratory mechanics have an effect on how air flows in and out of the lungs. These are characterized by physical, physiologic, and pathophysiologic considerations.

A. Physical Factors

1. The pattern of airflow is affected by the physical properties of the gas molecules, the laminar or turbulent nature of airflow, and the dimensions of the airways, as well as the other effects described by the Poiseuille equation (Chap. 8).
2. The elastic properties of the airway, the transmural pressure on the airway wall, and structural features of the airway wall also determine the mechanics of airflow.
3. In preterm newborns, the airways are narrower in diameter and result in a higher resistance to airflow. The increased airway compliance increases the propensity for airway collapse or distension. If a higher transmural pressure is generated during tidal breathing (as in infants with bronchopulmonary dysplasia, or, during positive pressure ventilation), the intrathoracic airways are likely to be compressed during expiration (Fig. 4.6).
4. During forced expiration, the more compliant airways are also likely to be compressed in the presence of a high intrathoracic pressure.
5. Increased distensibility of airways, as when exposed to excessive end-distending pressure, can result in increased and wasted dead space ventilation.
6. Turbulence of gas flow, generally not an issue in a healthy individual, can lead to a need for a higher driving pressure in the sick preterm infant with structural airway deformations as encountered in those with BPD.

B. Physiologic

1. The tone of the tracheobronchial smooth muscle provides a mechanism to stabilize the airways and prevent collapse.
2. An increased tone as a result of smooth muscle hyperplasia or a hyper-responsive smooth muscle should lead to a bronchospastic basis of airflow limitation.

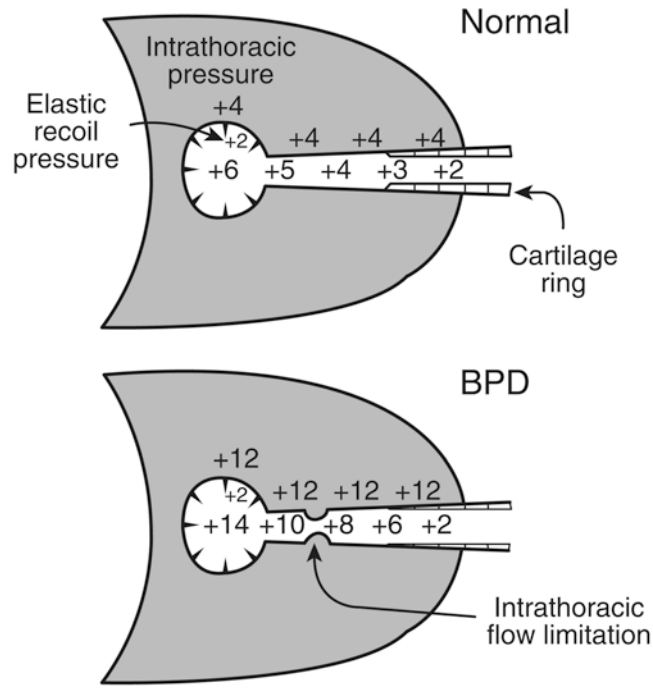

Fig. 4.6 Schematic comparison of normal and abnormal airflow. Infant with bronchopulmonary dysplasia (BPD) has higher transmural pressure generated during tidal breathing and thoracic airways are likely to be compressed during expiration, resulting in a flow limitation (Modified from Bhutani VK, Sivieri EM: Physiological principles for bedside assessment of pulmonary graphics. In Donn SM [Ed.]: *Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications.* Armonk, NY, Futura Publishing Co., 1998, p. 63, with permission.)

3. The bronchomalactic airway may be destabilized in the presence of tracheal smooth muscle relaxants.
4. The effect of some of the other physiologic factors, such as the alveolar duct sphincter tone, is not yet fully understood.

C. Pathophysiologic states
1. Plugging of the airway lumen, mucosal edema, cohesion, and compression of the airway wall lead to alterations in tracheobronchial airflow.
2. Weakening of the airway walls secondary to the structural airway barotrauma and the consequent changes of tracheobronchomalacia also result in abnormal airflow patterns.
3. BPD related airflow effects have also been previously described.

V. Lung Volumes

Ventilation is a cyclic process of inspiration and expiration. Total or minute ventilation (MV) is the volume of air expired each minute. The volume of air moved in or out during each cycle of ventilation is the tidal volume (V_T) and is a sum of the air in the conducting zone (V_D, or dead space) and the respiratory zone (V_A, or alveolar space). Thus,

$$\text{MV} = \left(V_A + V_D\right) \times \text{Frequency}$$

The process of spontaneous breathing generally occurs at about mid total lung capacity such that about two-thirds of the total capacity is available as reserve.

A. Ventilatory Volume:
1. Tidal Volume (V_T): volume of air inspired with each breath.
2. Minute Ventilation: (MV): product of frequency (F, the number of tidal volumes taken per minute) and V_T.
3. Dead Space (V_D): volume in which there is no gas exchange.
   a. Dead space refers to the volume within the respiratory system that does not participate in gas exchange and is often the most frequent and unrecognized cause for hypercapnia.

b. It is composed of several components.
   (1) Anatomic dead space is the volume of gas contained in the conducting airway.
   (2) Alveolar dead space refers to the volume of gas in areas of "wasted ventilation", that is, in alveoli that are ventilated poorly or are under-perfused.
   (3) The total volume of gas that is not involved in gas exchange is called the physiologic dead space. It is the sum of the anatomic and alveolar dead space.
c. In a normal person, the physiologic dead space should be equal to the anatomic dead space. For this reason, some investigators refer to physiologic dead space as pathological dead space.
d. Several factors can modify the dead space volume.
   (1) Anatomic dead space increases as a function of airway size and the airway compliance. Because of the interdependence of the alveoli and airways, anatomic dead space increases as a function of lung volume. Similarly, dead space increases as a function of body height, bronchodilator drugs, and diseases such as BPD, tracheomegaly, and oversized artificial airways.
   (2) Anatomic dead space is decreased by reduction of the size of the airways, as occurs with bronchoconstriction, tracheomalacia, or a tracheostomy.

4. Alveolar Volume (V_A): volume in which gas exchange occurs:

$$V_A = V_T - V_D.$$

5. Alveolar Ventilation (V_A): product of frequency and V_A

B. Lung Reserve Volumes

Reserve volumes represent the maximal volume of gas that can be moved above or below a normal tidal volume (Fig. 4.7). These values reflect the balance between lung and chest wall elasticity, respiratory strength, and thoracic mobility.

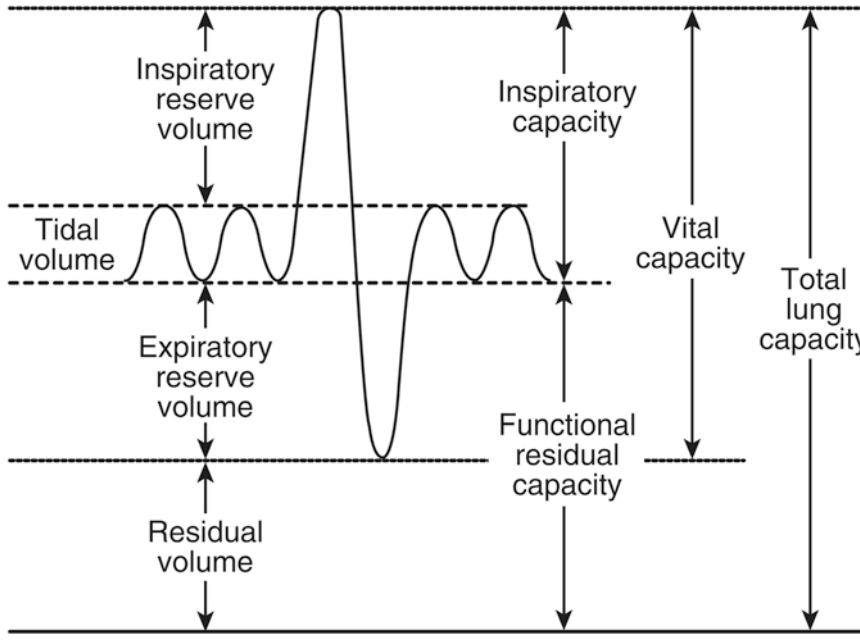

Fig. 4.7 Graphic representation of lung volumes and capacities (Modified from Bhutani VK, Sivieri EM: Physiological principles for bedside assessment of pulmonary graphics. In Donn SM [Ed.]: *Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications.* Armonk, NY, Futura Publishing Co., 1998, p. 67, with permission.)

Table 4.1 Lung volumes in term newborns

Ventilatory volumes	Normal values for term newborns	Static lung volumes	Normal values for term newborns
V_T	5–8 mL/kg	RV	10–15 mL/kg
F	40–60 b/min	FRC	25–30 mL/kg
V_D	2–2.5 mL/kg	TGV	30–40 mL/kg
MV	200–480 mL/min/kg	TLC	50–90 mL/kg
V_A	60–320 mL/min/kg	VC	35–80 mL/kg

1. Inspiratory reserve volume (IRV) is the maximum volume of gas that can be inspired from the peak of tidal volume.
2. Expiratory reserve volume (ERV) is the maximum volume of gas that can be expired after a normal tidal expiration. Therefore, the reserve volumes are associated with the ability to increase or decrease tidal volume. Normal lungs do not collapse at the end of the maximum expiration.
3. The volume of gas that remains is called the residual volume (RV).

C. Lung Capacities

The capacity of the lungs can be represented in four different ways: total lung capacity, vital capacity, inspiratory capacity, and functional residual capacity (Fig. 4.7).

1. Total lung capacity (TLC) is the amount of gas in the respiratory system after a maximal inspiration. It is the sum of all four lung volumes. The normal values as well as the values of static lung volumes for term newborns are shown below in Table 4.1.
2. Vital capacity (VC) is the maximal volume of gas that can be expelled from the lungs after a maximal inspiration. As such, the vital capacity is the sum of IRV + TV + ERV. Inspiratory capacity (IC) is the maximal volume of gas that can be inspired from the resting end-expiration level; therefore it is the sum of TV + IRV.
3. Functional residual capacity (FRC) is the volume of gas in the lung when the respiratory system is at rest; that is, the volume in the lung at the end of a normal expiration that is in continuity with the airways. The size of the FRC is determined by the balance of two opposing forces:
   a. Inward elastic recoil of the lung tending to collapse the lung
   b. Outward elastic recoil of the chest wall tending to expand the lung. Functional residual capacity is the volume of gas above which a normal tidal volume oscillates. A normal FRC avails optimum lung mechanics and alveolar surface area for efficient ventilation and gas exchange.
4. Residual volume (RV): volume of air remaining in the respiratory system at the end of the maximum possible expiration.

$$\text{Expiratory Reserve Volume}\left(\text{ERV}\right) = \text{FRC} - \text{RV}.$$

D. It is important to note that thoracic gas volume (TGV) is the total amount of gas in the lung (or thorax) at end-expiration. This value differs from FRC and the difference would indicate the magnitude of air trapping.

Pulmonary Gas Exchange

5

Vinod K. Bhutani

I. Introduction
   A. Pulmonary circulation plays a critical gas exchange function of the lung.
   B. Processes governing pulmonary vascular development, especially with regard to the origin, differentiation, and maturation of the various cell types within the pulmonary vascular wall, include factors which control development and also provide insight into the genetic diversity of pulmonary vascular wall cells.
   C. These findings begin to provide explanations for the tremendous functional heterogeneity of the pulmonary vascular cells under both normal and pathophysiologic conditions. In the future, we will need to focus more attention on understanding from where and when endothelial and smooth muscle cells arise in the course of pulmonary arterial, bronchial, and pulmonary venous development.
   D. We will need to identify the environmental signals and signaling molecules that contribute to the terminal differentiation of specific vascular cells at the local level, and which confer unique properties to these cells.
   E. We will need to use model systems that allow us to accurately mark and follow cell fates within the complex environment that obviously contributes to the ultimate phenotype of the pulmonary vascular cell of interest, as well as model systems where cell migration, cell–cell interaction, and proper environmental cues remain intact.
   F. We will need to take into account the fact that angioblasts may arise from many distant sites, and at certain stages of lung development could even come from the bone marrow-derived pool of circulating stem cells.
   G. Because it is clear that oxygen tension plays such a critical role in directing development of many organs, we need to take into account the oxygen tension at which experiments are performed.
   H. Further, we need to address the role that the nervous system may play in directing vascular development within the lung.

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I. In doing all of the above, we will come to a better understanding of the unique origins of the macrocirculation and microcirculation of the lung, and may also provide new insight into the unique expansion and function of the selective cell types that play critical roles in many pulmonary diseases

II. Transition at Birth
   A. Independent pulmonary gas exchange to replace the maternal placental gas exchange mechanism needs to be established within the first few minutes after birth.
   B. In order to effect this transition, several physiologic changes occur:
      1. Adjustments in circulation
      2. Pulmonary mechanics
      3. Gas exchange
      4. Acid–base status
      5. Respiratory control
   C. Upon transition, gas exchange takes place through an air-liquid interphase of alveolar epithelium with alveolar gas in one compartment and blood in the other (vascular) compartment. An understanding of gas laws, alveolar ventilation, and pulmonary vasculature are important in facilitating optimal pulmonary gas exchange.

III. Brief Outline of Cardiopulmonary Adaptations
   A. Prior to birth, the fetus is totally dependent on the placenta (Fig. 5.1) and has made cardiopulmonary adjustments for optimal delivery of oxygen, whereas, the maternal physiology has been adapted to maintain fetal normocapnia.
   B. The salient features and sequence of events that occur during fetal to neonatal transition are listed in Table 5.1.

IV. Application of Gas Laws for Pulmonary Gas Exchange
   A. There are fundamental laws of physics that pertain to the behavior of gases and thereby impact gas exchange.
   B. An understanding of these laws is also specifically pertinent to the clinician in his/her ability not only to measure and interpret blood gas values but also to evaluate the impact on gas exchange during clinical conditions of hypothermia, high altitude, and use of gas mixtures of varying viscosities and densities.

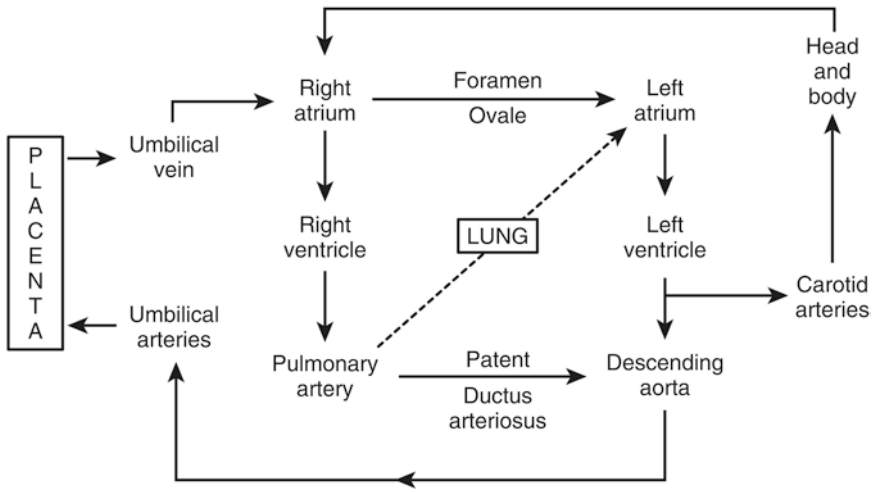

Fig. 5.1 Schematic representation of fetal circulation (From Bhutani VK: Extrauterine adaptations in the newborn. Sem Perinatol 1997; 1:1–12, with permission.)

Table 5.1 Salient features of extrauterine cardiopulmonary adaptations

Parameter	Mother (second trimester)	Fetus (before labor)	Newborn (before first breath)	Newborn (at about 6 h)
PaO_2	80–95 Torr	<25 Torr in pulmonary artery	16–18 Torr	80–95 Torr
$PaCO_2$	~34 Torr	40–42 Torr	45–65 Torr	34 Torr
pH	~7.45	7.35–7.40	7.10–7.30	7.35–7.40
Pulmonary blood flow	Equivalent to cardiac output	13–25 % cardiac output	~25 % cardiac output	90–100 % cardiac output
Shunts	Placental shunts	– Placental shunts – Foramen ovale – Ductus arteriosus	– Foramen ovale – Ductus arteriosus – Intrapulmonary shunts	– Foramen ovale closed – Ductus arteriosus usually closed – Intrapulmonary shunts
Pulmonary mechanics	– Air-filled Lungs – Hyperventilation	– Liquid-filled – FRC at 30 mL/kg	– Air and fluid (16–19 mL/kg) in the lungs	– Air-filled – FRC at 30 mL/kg
Control of respiration	Progesterone-mediated hyperventilation	Fetal breathing dependent more on stretch	First breath initiated by non-specific respiratory	Rhythmic respiratory cycles based on chemoreceptors

Table 5.2 Laws that describe gas behavior

Law	Description
Boyle's law	At constant temperature (T), a given volume (V) of gas varies inversely to the pressure (P) to which it is subjected.
Charles's law	Gas expands as it is warmed and shrinks as it is cooled.
Dalton's law	The total pressure exerted by a mixture of gases is equal to the sum of the partial pressure of each gas.
Amagat's law	The total volume of a mixture of gases is equal to the sum of the partial volume of each gas at the same temperature and pressure.
Henry's law	At constant temperature, any gas physically dissolves in a liquid in proportion to its partial pressure, although the solubility coefficient decreases with increasing temperature and differs from one gas to another.
Graham's law	The rate of diffusion of a gas is inversely proportional to the square root of its density.
Fick's law	The transfer of solute by diffusion is directly proportional to the cross-sectional area available for diffusion and to the difference in concentration per unit distance perpendicular to that cross section.
Ideal gas equation	Summation of above laws: $PV = nRT$, where R is a numerical constant
van der Waals's equation	Refinement of the ideal gas equation based upon the attractive forces between molecules and upon the volume occupied by the molecules.
Barometric pressure and altitude	The decrease in barometric pressure is not linear with increasing altitude; weather, temperature, density of atmosphere, acceleration of gravity, etc. influence it.

C. A brief description of the pertinent and clinically relevant gas laws is listed in Table 5.2.

D. One of the most fundamental and widely used relationships to describe pulmonary gas exchange is summarized as:

$$PaCO_2 = 863(V_{CO2}/V_A)$$

where, in a steady state and with negligible inspired carbon dioxide, the alveolar pressure of carbon dioxide ($PaCO_2$) is proportional to the ratio of the rates of carbon dioxide elimination (V_{CO2}) and alveolar ventilation (V_A). This equation helps to summarize several of the gas laws. The applications of the laws are thus:

1. $PaCO_2$: when measured in dry gas as a percentage, Dalton's law needs to be applied to convert the value to partial pressure. The partial pressure of carbon dioxide, rather than its percentage composition, is the significant variable because Henry's law of solubility states that the gas is physically dissolved in liquid and in equilibrium with the gas phase at the same partial pressure.
2. 863: this peculiar number is derived from the need to standardize measurements from body temperature (310 °K) to standard pressure and temperature (760 mmHg•273 °K). Based on the product 310 × (760/273), we obtain the value 863 (in mmHg) providing the constant for the relationship in the above equation.
3. V_{CO2}/V_A: These values are measured at ambient temperature and pressure, saturated with water vapor (ATPS). Carbon dioxide output needs to be converted to STPD (standard temperature, pressure, dry) using Boyle's and Charles's laws, while alveolar ventilation has to be corrected to BTPS (body temperature, pressure, and saturated with water vapor).

V. Development of Pulmonary Vasculature
   A. The main pulmonary artery develops from the embryonic left sixth arch.
      1. The sixth arches appear at about 32 days after conception (5 mm embryo stage) and give branches to the developing lung bud.
      2. Branches from the aorta that supply the lung bud and the right arch disappear subsequently.
      3. By 50 days (18 mm embryo stage), the adult pattern of vascularization has commenced.
   B. Before the main pulmonary veins are developed, the vessels drain into the systemic circulation of the foregut and trachea.
      1. These connections are lost as the main pulmonary vein develops.
      2. A primitive pulmonary vein appears as a bud from the left side of the atrial chamber at about 35 days.
      3. Starting as a blind capillary, it bifurcates several times to connect with the developing lung bud.
      4. Subsequently, the first two branches are resorbed to form the left atrium at about the 7th week.
   C. The branches of the pulmonary arterial system maintain a position next to the bronchial structures as both develop during the glandular and canalicular stages of lung development.
   D. By 16 weeks there is a complete set of vessels that lead to the respiratory bronchioles, terminal bronchioles, and the terminal sacs.

VI. Onset of Pulmonary Gas Exchange
   A. The physiologic processes that facilitate the onset of postnatal pulmonary gas exchange (described in the series of events depicted in Fig. 5.2)
      1. The effect of ventilation on reducing pulmonary vascular resistance (a)
      2. The effect of acidosis correction to enhance pulmonary blood flow (b)
      3. The effect of driving pressure and successful establishment of respiration during first breaths to achieve an optimal functional residual capacity (c)
      4. The effect of driving pressure to maintain optimal tidal volume and achieve the least work of breathing (d)
   B. These events highlight the other series of biochemical and physiologic events that concurrently occur to successfully establish and maintain the matching of ventilation to perfusion.

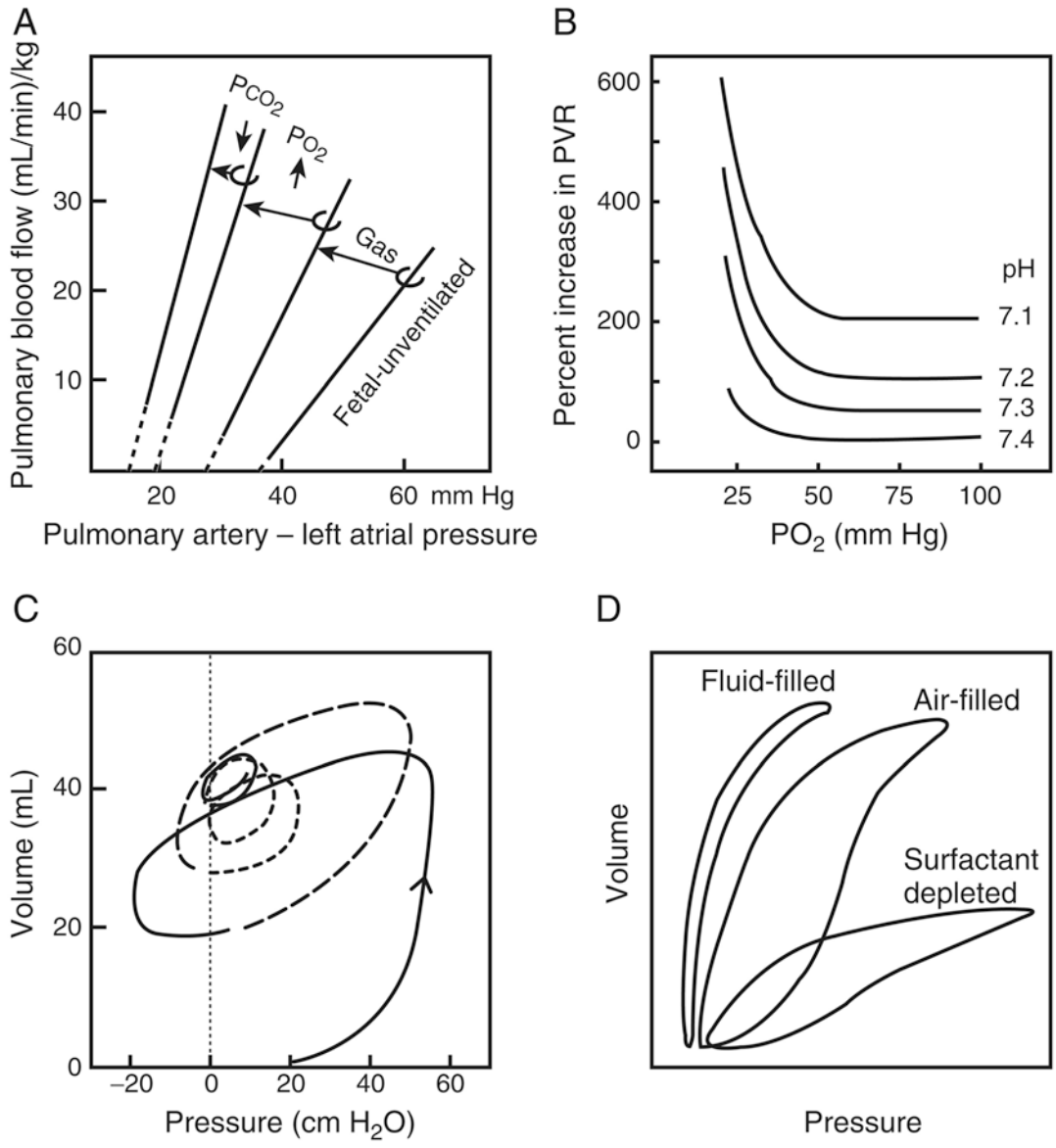

Fig. 5.2 Physiologic processes that facilitate onset of postnatal pulmonary gas exchange. (**a**) Effect of ventilation on reducing pulmonary vascular resistance (PVR). (**b**) Effects of acidosis correction on reducing PVR. (**c**) First breaths and establishment of optimal functional residual capacity. (**d**) Effect of driving pressure to maintain optimal tidal volume and work of breathing (Modified from Bhutani VK: Differential diagnosis of neonatal respiratory disorders. In Spitzer AR [Ed.]: *Intensive Care of the Fetus and Neonate*. St. Louis, Mosby-Year Book, 1996, p. 500, with permission.)

C. Maladaptations delay transition to adequate pulmonary gas exchange (Maladaptation my result from central/peripheral nervous system abnormalities as well as cardiopulmonary problems.).
D. Though it has been well established that a newborn is more likely to have events that lead to hypoxemia or maintain adequate oxygenation with an inability to compensate hemodynamically, it has also been realized that a newborn is more tolerant of hypoxemia than an adult. Reasons for occurrences of hypoxemic events:

1. Reduced FRC relative to the oxygen consumption
2. Presence of intrapulmonary shunts that lead to *V*/*Q* mismatching
3. A high alveolar-arterial oxygen gradient

E. Hypercapnia that results from an inability to maintain adequate alveolar ventilation in the face of mechanical loads also results in lower alveolar oxygen tension.

F. From a hemodynamic perspective, impaired oxygen delivery may occur because:
1. Low P_{50} values because of high oxygen affinity of the fetal hemoglobin
2. Increased blood viscosity
3. Lower myocardial response to a volume or pressure load
4. Inadequate regional redistribution of the cardiac output

G. The relationship between arterial oxygen and carbon dioxide values and how these relate to hypoxemia and respiratory failure are shown in Fig. 5.3.

H. The effect of oxygen inhalation on the composition of alveolar and blood gas tensions is shown in Table 5.3.

VII. Optimal Pulmonary Gas Exchange

A. Failure to establish optimal pulmonary gas exchange leads to either oxygenation or ventilation failure.

B. Factors that impact on adequacy of neonatal gas exchange (especially a preterm newborn) are listed in Table 5.4.

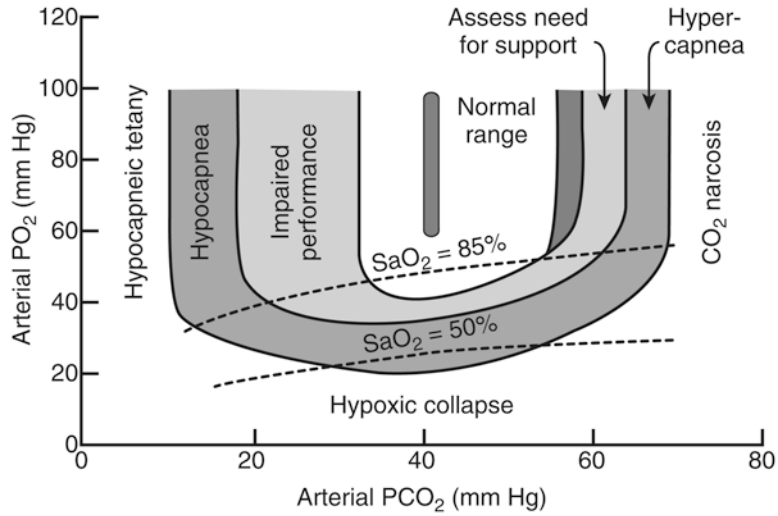

Fig. 5.3 The relationship between alveolar oxygen and carbon dioxide values and how these relate to hypoxemia and respiratory failure (Modified from Bhutani VK: Differential diagnosis of neonatal respiratory disorders. In Spitzer AR [Ed.]: *Intensive Care of the Fetus and Neonate*. St. Louis, Mosby-Year Book, 1996, p. 501, with permission.)

Table 5.3 Effect of oxygen inhalation (100 %) on composition of alveolar and blood gas tensions

	Inspired dry gas		Alveolar gas		End pulmonary capillary blood		Arterial blood		End-systemic capillary blood	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2	Air	O_2
***P*$_{O2}$ (Torr)**	1591	760	104	673	104	673	100	640	40	53.5
P_{CO2} (Torr)	0.3	0	40	40	40	40	40	40	46	46
P_{H2O} (Torr)	0.0	0	47	47	47	47	47	47	47	47
***P*$_{N2}$ (Torr)**	600.6	0	569	0	569	0	573	0	573	0
P_{total} (Torr)	760	760	760	760	760	760	760	727	706	146.5[a]
O_2Sat (%)					98	100	98	100	75	85.5

[a]What happens to the total gas tension when a baby breathes 100 % oxygen: the total venous gas tension is now at 146.5 Torr

Table 5.4 Factors that impact on adequacy of neonatal gas exchange

Factors for gas exchange	Impact of prematurity
Neural control of respiration	Immaturity
Mechanical loads: elastic and resistive	High chest wall to lung compliance ratio
Stability of end-expiratory lung volume	Compliant airways with pre-end expiratory closure of airways
Ventilation–perfusion matching	Reactive pulmonary vasculature
Hemoglobin dissociation curve properties	Fetal hemoglobin characteristics
Match cardiac output to oxygen consumption	High neonatal oxygen consumption
Ability to maintain alveolar ventilation	Propensity for respiratory muscle fatigue

C. Respiratory failure can initially lead to increased respiratory effort in an attempt at compensation, followed by an inability to ventilate, or apnea.
D. The concurrent changes in arterial oxygen and carbon dioxide gas tensions during both health and disease are shown in Fig. 5.3.

VIII. Physiologic Principles to Improve Pulmonary Gas Exchange
A. The physiologic principles that may be utilized to improve oxygenation, enhance carbon dioxide elimination, and establish ventilation at optimal FRC (and thereby with the least barotrauma and volutrauma) are listed in Fig. 5.2a–d.
B. The clinically relevant interventional strategies are crucial to achieve optimal gas exchange.
C. It is also valuable to be reminded that in a healthy newborn gas tensions are maintained in a narrow range by exquisitely sensitive feedback mechanisms of chemoreceptors and stretch receptors.
D. Moreover, during fetal development the maternal physiology is significantly altered to maintain fetal normocapnia and neutral acid–base status.
E. Thus, as clinicians assume control of the newborn's ventilation with supportive technologies, the road map for optimal pulmonary gas exchange needs to be "quality controlled" from physiologic perspectives and with the least amount of barotrauma and volutrauma.

Oxygen Therapy

6

Win Tin

I. Introduction
   A. *"The clinician must bear in mind that oxygen is a drug and must be used in accordance with well recognized pharmacologic principles; i.e., since it has certain toxic effects and is not completely harmless (as widely believed in clinical circles) it should be given only in the lowest dosage or concentration required by the particular patient."* [*Julius Comroe, 1945*]
   B. Oxygen is the most commonly used therapy in neonatal intensive care units, and oxygen toxicity in newborns (cicatricial retinopathy or retrolental fibroplasia as it was known) was first described more than 60 years ago.
   C. The ultimate aim of oxygen therapy is to achieve adequate tissue oxygenation, but without creating oxygen toxicity and oxidative stress.
II. Physiological Considerations
   A. Tissue oxygenation depends on:
      1. Fractional inspired oxygen (FiO_2)
      2. Gas exchange mechanism within the lungs
      3. Cardiac output (and the effects of shunts)
      4. Oxygen-carrying capacity of the blood. Approximately 97 % of oxygen transported to the tissue is carried by hemoglobin and 3 % is dissolved in plasma.
      5. Altitude
      6. Local tissue edema or ischemia
   B. Fetal oxygen transport and postnatal changes
      1. Fetal hemoglobin (HbF) has higher oxygen affinity and lower P_{50} (oxygen tension at which 50 % of hemoglobin is saturated at standard pH and temperature). This favors oxygen uptake from the placenta to the fetus as adequate transfer of oxygen is achieved at relatively low PO_2.
      2. High oxygen affinity of HbF, however, has disadvantage in oxygen delivery to the fetal tissue, but this is offset by the fact that the fetal oxygen–hemoglobin saturation curve is

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much steeper. Therefore, adequate dissociation of oxygen from hemoglobin can occur with a relatively small decrease in oxygen tension at the tissue level.

3. The newborn infant needs more oxygen than the fetus (oxygen consumption of most animal species increases by 100–150 % in the first few days of life); therefore, P_{50} which is adequate for tissue oxygenation in a fetus is not enough in a newborn.
4. Changes in both oxygen affinity and oxygen carrying capacity occur postnatally, and in an infant born at term, P_{50} reaches adult levels by about 4–6 months of age.

C. Indices of oxygenation

1. *Alveolar–arterial oxygen pressure difference* [$P(A-a)O_2$]*:* The difference in partial pressure of oxygen between alveolar and arterial levels correlates well with ventilation–perfusion (V/Q) mismatch. In a newborn who is breathing room air, this value can be as high as 40–50 Torr, and may remain high (20–40 Torr) for days. The increase in $P(A-a)O_2$ is generally caused by:
   a. Block of oxygen diffusion at alveolar–capillary level
   b. V/Q mismatch in the lungs (from either increase in physiologic dead space or intrapulmonary shunting)
   c. Fixed right-to-left shunt (intracardiac shunting)
2. *Oxygenation Index (OI)*: This is most frequently used clinically as well as in clinical research studies because of its ease of calculation, and is felt to be a more sensitive indicator for severity of pulmonary illness as mean airway pressure (Pāw) is taken into its calculation

   $$OI = P\bar{a}w \times FiO_2/PaO_2 \times 100$$

3. Arterial-to-alveolar oxygen tension ratio (a/A ratio)
4. There is no significant difference in the performance of these indices in predicting death and adverse respiratory outcome.

D. PaO_2 and O_2 saturation

1. Several clinical studies have shown that fractional O_2 saturation above 92 % can be associated with PaO_2 values of 80 mmHg (10.7 kPa) or even higher (Fig. 6.1)
2. Although PaO_2 and O_2 saturation are directly related to each other, this correlation is influenced by several physiologic changes (quantity and quality of Hb, temperature, acid-base status, PCO_2, and concentration of 2–3 DPG).

III. Monitoring Oxygen Therapy

A. Continuous, Non-invasive monitoring

1. Pulse oxygen saturation (Pulse oximetry, SpO_2): This is the most user friendly method and therefore most widely used for monitoring oxygen therapy, but it has limitations, mainly the failure to detect hyperoxia (Chap. 19).
2. Transcutaneous PO_2 ($TcPO_2$): This is the preferred method by some clinicians, particularly for monitoring in the early life of newborn infants. The accuracy depends on skin thickness and perfusion status and sensor temperature. There is a risk of local skin burns in very premature infants.

B. Continuous, Invasive monitoring (via indwelling arterial catheters)

1. Arterial PO_2
2. Blood gas analysis

C. Intermittent Monitoring

1. Arterial PO_2 (via umbilical or peripheral arterial catheters)
2. Mixed central venous PO_2. This value, if taken from a catheter placed in the inferior vena cava reflects the oxygen tension of the blood that has equilibrated with the tissues, and therefore can be a useful indicator of tissue oxygen delivery.

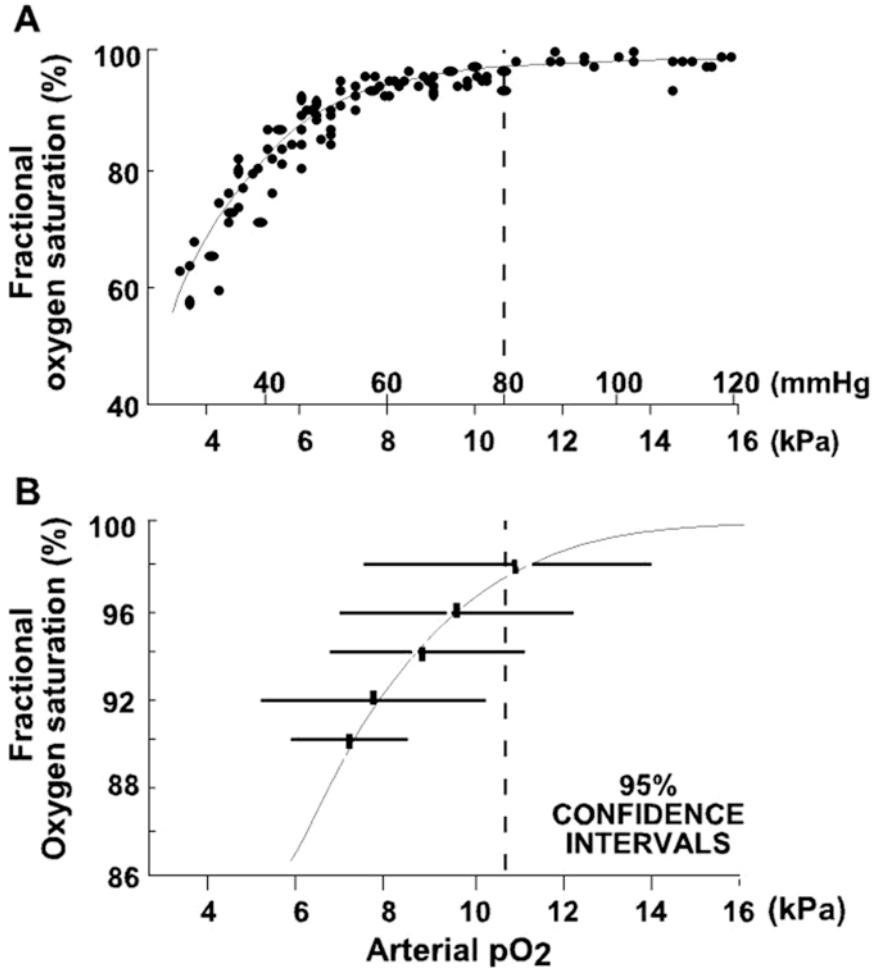

Fig. 6.1 The relation between fractional O_2 saturation measured with a pulse oximeter and arterial partial pressure (reproduced with permission from BMJ Books). The *dashed line* marks the TcO_2 above which there was an increased risk of ROP in the study reported by Flynn in 1992. The *bars* in figure (**b**) show the range within which 95 % of all measures of partial pressure varied) when oximeter read 90 %, 92 %, 94 %, 96 %, and 98 % in the study reported by Brockway and Hay in 1998

IV. Oxygen Toxicity (Chap. 7)
   A. Experimental and research work over more than a century has shown that oxygen can be toxic, and it is now much clearer that preterm infants are more vulnerable to harmful effects of free oxygen radicals and oxidative stress (defined as an imbalance between pro-oxidant and antioxidant forces).
   B. Oxygen and retinopathy of prematurity (ROP, Chap. 83): The retina is completely avascular in early fetal life. New vessels grow outward from the center around the optic nerve, controlled by vascular endothelial growth factor (VEGF), released from normally hypoxic retinal tissue, and this process is completed in utero by about 36 weeks of gestation. Treatment with supplemental oxygen in premature infants, who have incompletely vascularized retinas, may cause hyperoxia and vasoconstriction. This in turn leads to local hypoxia, abnormally high secretion of VEGF, and excessive proliferation of new vessels and fibrous tissue that invades the

vitreous. Contraction of fibrous tissue may result in retinal detachment and visual loss. Although retinal detachment can be prevented by ablative surgery (cryo or laser therapy), the risk of significant visual impairment remains high among infants who develop "threshold ROP."

C. Oxygen and bronchopulmonary dysplasia (BPD, Chaps. 77–79): Direct oxygen toxicity from high concentrations of inspired oxygen is an important cause of BPD. Even if inspired oxygen concentrations are not high, oxidative stress can occur and contribute to tissue injury.

D. Oxygen and brain injury (Chap. 84): Oxidative stress and damage to pre-myelinating oligodendrocytes in cerebral white matter has been proposed as a mechanism of periventricular leukomalacia, increasing the risk of cerebral palsy and cognitive deficit in preterm infants.

V. Clinical Evidence for Monitoring Oxygen Therapy

A. There is no clear evidence to date to suggest what the optimal SpO_2 or PaO_2 values are in premature infants (who receive supplemental oxygen therapy) in order to avoid potential oxygen toxicity while providing adequate oxygen delivery to tissues.

B. Pulse oximetry is more widely used (and is often used solely) as continuous, noninvasive monitoring for oxygen therapy, yet there remains a wide variation in SpO_2 monitoring policies among neonatologists.

C. Several observational studies in the past have suggested that accepting lower arterial oxygen saturation (measured by pulse oximetry) in the neonatal period of preterm infants was associated with lower rates of severe ROP and other neonatal complications including BPD.

D. The STOP-ROP Trial, showed that keeping saturation above 95 % in very premature infants (mean gestational age 25.4 weeks) when they were found to have developed pre-threshold ROP (mean postmenstrual age 35 weeks) slightly reduced the risk of the disease progressing to severe ROP needing retinal surgery, but the benefit was only seen in those without "plus disease." However, this study also suggested that aiming to keep higher oxygen saturation was associated with significantly increased adverse pulmonary outcomes, without any benefit in growth or the eventual retinal outcome as assessed 3 months after the expected date of delivery.

E. The BOOST trial also showed that aiming to keep high oxygen saturation in chronically oxygen dependent babies, born before 30 weeks' gestation was not associated with improvement in growth and development at 1 year, but was associated with increase in duration of oxygen therapy and the utilization of health care resources.

VI. Emerging Evidence from the "Oxygen Saturation Targeting Trials"

A. Five masked randomized controlled trials (with a planned prospective meta-analysis) have been conducted recently to compare the clinical outcomes (primary outcome being death and severe disability) of targeting a "low" oxygen saturation range of 85–89 % versus a "high" range of 91–95 % in preterm infants of <28 weeks' gestation.

B. Meta-analysis of the masked oxygen saturation targeting trials showed that targeting the higher range (91–95 %), compared to the lower range (85–89 %) reduces the risk of mortality and necrotizing enterocolitis but increases the risk of severe ROP.

C. More information will be available when the all the trials report the primary outcome of death and severe disability and the prospective meta-analysis is completed. However, clinicians should be aware that the current oxygen trials may not resolve the questions and controversies on "oxygen"—a powerful and the most commonly used "drug" in neonatal medicine.

Suggested Reading

Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen saturation targets and outcomes in extremely preterm infants. N Engl J Med. 2003;349:959–67.

Askie LM, Brocklehurst P, Darlow DA, Finer N, Schmidt B, Tarnow-Mordi W. NeOproM: neonatal oxygenation prospective meta-analysis collaboration study protocol. BMC Pediatr. 2011. doi:10.1186/1471-2431-11-6.

Brockway J, Hay WW. Prediction of arterial partial pressure of oxygen with pulse oxygen saturation measurements. J Pediatr. 1998;133:63–6.

Delivoria-Papadopoulos M, McGowan JE. Oxygen transport and delivery. In: Polin RA, Fox WW, Abman SH, editors. Fetal and neonatal physiology. Philadelphia: Saunders; 2004.

Saugstad OD. Bronchopulmonary dysplasia—oxidative stress and antioxidants. Semin Neonatol. 2003;8:39–49.

Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation studies. Neonatology. 2014;105:55–63.

Schmidt B, Whyte RK, Asztaols E, Moddemann D, Poets C, Rabi Y, et al. Effects of targeting higher versus lower arterial oxygen saturations on death or disability in extremely preterm infants. JAMA. 2013;309(20):2111–20.

Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. Pediatrics. 2004;113:394–6.

Smith LE. Pathogenesis of retinopathy of prematurity. Semin Neonatol. 2003;8:469–73.

Stop ROP Investigators. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomised controlled trial.1: primary outcomes. Pediatrics. 2000;105:295–310.

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010; 362:1959–69.

The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368:2094–104.

Tin W, Gupta S. Optimum oxygen therapy in preterm babies. Arch Dis Child. 2007;92:F143–7.

Tin W, Carlo WA, Gupta S. Oxygenation targeting and outcomes in preterm infants: the new evidence. In: Bancalari E, Polin R, editors. The newborn lung: neonatology questions and controversies. Philadelphia: Elsevier; 2012.

Weis CM, Cox CA, Fox WW. Oxygen therapy. In: Spitzer AR, editor. Intensive care of the fetus and newborn. St. Louis: Mosby; 1996.

Oxygen Toxicity

7

Ola Didrik Saugstad

I. Oxygen Toxicity in the Newborn Period
   A. Historical Aspects
      1. Oxygen was discovered independently by Scheele and Priestly in 1772 and 1774, respectively. However, already in 1604 a Polish alchemist had described oxygen as vital air.
      2. Lavoisier coined the term oxygen in 1775. Only 5 years later oxygen was used to treat newborns. In 1928, Flagg published in the Journal of the American Medical Association (JAMA) a method to resuscitate newborns with oxygen and CO_2.
      3. Already Priestly understood that oxygen might be toxic and during the nineteenth century more and more information was collected showing its toxic effects.
      4. In the early 1950s, oxygen was associated with development of retrolental fibroplasia today called retinopathy of prematurity (ROP), and at the end of the 1960s oxygen toxicity was associated with development of bronchopulmonary dysplasia (BPD).
      5. Some years later it was hypothesized oxygen might be toxic during resuscitation and in 2010 international guidelines were changed recommending starting resuscitation of term late preterm infants with air instead of oxygen. Still the optimal FiO_2 for extremely low birth weight (ELBW) infants is not defined.
   B. Evolutionary Aspects
      1. Life developed in an oxygen-free and reducing atmosphere.
      2. The so-called Last Universal Common Ancestor was probably resistant to oxygen toxicity and it is hypothesized that this was due to the fact that primitive organisms were forced through a "radiation bottleneck" making life resistant both to radiation injury and oxygen toxicity.
      3. This prepared eukaryotes for a life in a high oxygen atmosphere.
   C. Basic Mechanisms
      1. In 1891, the Scottish chemist sir James Dewar discovered that oxygen is paramagnetic. This is caused by spin of unpaired electrons in the outer electron orbit and this makes it difficult for oxygen to form new chemical bonds.

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2. In order to complete electron pairing oxygen can only receive single electrons with antiparallel spin. Accepting electrons stabilizes the oxygen molecule.
3. During oxidative phosphorylation in the mitochondria single electrons escape and join with 1–2 % of the total oxygen consumed by the cells to form superoxide radicals. By adding another 1, 2, or 3 electrons hydrogen peroxide, hydroxyl radicals, and finally water are formed.
4. Oxygen free radicals or reactive oxygen species (ROS) have the capability to oxidize unsaturated free fatty acids, protein and DNA. They are also important as signaling substances and therefore regulating physiologic processes as circulatory aspects as well as growth and development. Therefore, it is important for the organism to control the redox status and oxidative stress tightly; even short deviations in oxidative stress indicators may trigger long-term effects.

D. Defense Mechanisms
1. The body has a number of antioxidants both intracellular and extracellular. In fetal life the intracellular antioxyenzymes such as superoxide dismutases, catalases, and glutathione peroxidases are low and increase toward term.
2. Extracellular defense is not so low in the premature and after birth, for instance, vitamin C is high. Another important antioxidant in this period of life is bilirubin and also uric acid.
3. The premature baby has less capacity to bind free iron, and thus these babies are more susceptible to damage through Fenton reaction producing hydroxyl radicals.
4. DNA is protected against oxygen toxicity by a series of glycosylases. Base cutting repair is the most important cellular mechanism for repairing oxidative DNA injury. This repair is initiated by DNA glycosylases, which recognize and repair DNA base injuries. A number of glycosylases have been described as Neill 3, hMUTY, hOgg1, and others.

E. Control Mechanisms
1. HIF-1α is an important transcription factor which is activated in hypoxia and closed down by normoxia and hyperoxia. HIF-1α transcribes a series of genes such as vascular endothelial growth factor (VEGF) and erythropoietin, which increases oxygen utilization and reduces oxygen consumption/demand.
2. A number of other transcription factors are involved in hyperoxia.
   a. Nrf2 (NF-erythroid 2-related factor) is activated by hyperoxia and activates ARE (antioxidant response element) and regulates detoxifying and antioxidant enzymes and increases expression of antioxidant enzymes. It is cytoprotective in type II cells of the lung and ameliorates O_2 induced lung injury in mice.
   b. AP-1 controls genes regulating apoptosis, inflammation, and oxidative stress.
   c. NF-kB activates genes regulating apoptosis, inflammation, and oxidative stress. It is activated by endotoxins and oxidative stress via toll like receptors in the cell membrane.
   d. P53 regulates expression of target genes related to cell cycle arrest, cell death and DNA repair.
   e. CEBP (ccat/enhancer binding protein) regulates cell proliferation and tissue development and is increased in the lung of rats exposed to hyperoxia.
   f. STATs are polypeptides participating in signaling pathways and may be protective to hyperoxia by induction of heme-oxygenase which is a cytoprotective enzyme highly inducible following exposure to hyperoxia.

II. Potential Risks of Hyperoxia and Oxygen Toxicity
   A. Brain
      1. The neonatal brain is susceptible to hyperoxia because of a high content of unsaturated free fatty acids which are easily exposed to peroxidation, the presence of free iron, low antioxidant enzymes, and vulnerable oligodendrocytes. These brains are often also exposed to hyperoxia as well as inflammations which increases oxidative stress.
      2. Premature and immature oligodendrocytes are especially vulnerable to hyperoxia and oxidative stress.
      3. This vulnerability is probably time dependent. The vulnerability of the brain to hyperoxia seems in rodents to be confined to a short window postpartum especially in the first week of life. Whether such a vulnerable window exists in humans is not clear.
      4. Microglia which peak in white matter in third trimester, when activated generate free radicals and secrete cytokines
   B. Retina
      1. The transition from intrauterine to extrauterine life increases oxygen tension and decreases VEGF not only in the retina but also in other tissues.
      2. In the retina of the immature baby angiogenesis is halted, however after a few weeks, typically after 32 weeks' post-conceptional age the retina becomes hypoxic due to its increase in size without angiogenesis and consequently VEGF increases. This may lead to an uncontrolled vessel growth and development into the second phase of ROP.
      3. In order for VEGF to be active insulin like growth factor must reach a threshold level. Thus, the genesis of ROP is complex both dependent on hyperoxia and on a number of other non-hyperoxic factors related to growth.
      4. Several studies including one meta-analysis indicate that severe ROP can be significantly reduced by keeping the arterial oxygen saturation not too high and avoiding fluctuations.
   C. Lungs
      1. Oxidative stress generally induces apoptosis in a relatively short period of time (hours).
      2. Hyperoxia predominantly induces non-apoptotic cell death over a longer period of time (days).
      3. Hyperoxia induced lung injury is initially characterized by necrosis and swelling of capillary endothelial cells. Later the epithelial cells are affected.
      4. Hyperoxia induced lung injury is also characterized by inflammation, destruction of the alveolar–capillary barrier, impaired gas exchange, and pulmonary edema.
      5. Hyperoxia and ROS lead to increased release of chemo attractants and other proinflammatory cytokines promoting leukocyte recruitment to the lung. These activated leukocytes produce ROS, thus a vicious circle is established.
      6. Hyperoxia activates caspases 3 and 9 as well as proinflammatory cytokines as IL-1, IL-6, Il-8, TGFβ, TNFα, and VEGF.
      7. Hyperoxia reduces protein synthesis. This seems to be mediated via mTOR pathways. Hyperoxia inhibits translation of mRNA.

III. Clinical Implications
   A. Oxygenation in the Delivery Room
      1. Term and late pre-term infants. Recent international guidelines recommend starting resuscitation with air instead of supplemental oxygen. This is based on animal studies and 10 clinical studies including more than 2000 babies resuscitated with either 21 or 100 % oxygen. It seems that the use of 100 % oxygen increases time to first breath approximately 30 s, and reduces Apgar score and heart rate at 90 s of life. More importantly is that resuscitation with air reduces relative risk of neonatal mortality approximately 30 %. It is therefore

recommended to start ventilation with air, and if possible have a blender so oxygen could be given in case the baby does not respond adequately. A proper ventilation strategy to open the lungs is essential before oxygen is supplemented.

2. In babies with nonhealthy lungs (for instance after meconium aspiration) oxygen supplementation may be needed, and no clinical data exist regarding optimal FiO_2 for such babies. In the rare event of the need of chest compressions (<1/1000 term or late preterm babies) it is not known which FiO_2 should be used although animal studies suggest air is as good as pure oxygen even in this group. It is generally recommended to start with 100 % O_2 and wean down as quickly as possible.
3. If a pulse oximeter is available arterial oxygen saturations should aim at the 10th–50th percentile of the normal saturation limits recently published.
4. ELBW infants. Fewer data are available regarding how to oxygenate these babies in the delivery room. There are, however, data from smaller studies indicating that one should avoid starting with FiO_2 90–100 %. Until more data are collected one advice, which is based on recent meta-analysis and not on large randomized trials, is to start ventilation with 21 or 30 % oxygen and adjust FiO_2 to reach an arterial oxygen saturation between 10th to the 50th percentile of the normal values recently published.

B. Oxygenation Beyond the Delivery Room to 36–40 Weeks' post-conceptional age

1. Term babies should be weaned to air as quickly as possible, and this is often not difficult since their lungs are mature.
2. The optimal SpO_2 target of ELBW infants is not known. Some studies indicate that especially severe ROP is reduced by keeping the SpO_2 between 85 and 89 % and avoiding fluctuations. On the other hand, recent data indicate that this saturation target perhaps increases mortality as well as necrotizing enterocolitis compared to a target of 91–95 %. SpO_2 > 95 % should be avoided and a histogram to monitor the distribution of SpO_2 is often useful to minimize too low and too high levels.

IV. Prevention of Hyperoxia and Hyperoxic Injury

A. The best prevention of hyperoxic injury of the newborn is to avoid hyperoxia and inflammation, especially the combination of these.

B. Beta-carotene and vitamin A in one study was lower in preterm babies developing BPD. Postnatal vitamin A supplementation in a US multicenter trial reduced BPD (RR 0.89, 95 % confidence interval 0.80–0.99, number needed to treat = 14–15).

C. Antioxidant enzymes, such as superoxide dismutase, as well as antioxidants such as vitamin E, have so far not been convincingly successful in preventing hyperoxic injury in newborn infants.

D. Early routine use of inhaled nitric oxide (iNO) in preterm infants with respiratory disease does not improve survival without BPD.

E. A number of different antioxidants such as allopurinol and erythropoietin have been tested with some protective effects. Nutrients such as omega-3 fatty acids, especially docosahexaenoic acid, may have antioxidant properties in the newborn.

F. In the future new and more powerful antioxidants may be developed giving clinical effects when administrated both prenatally and postnatally.

Suggested Reading

Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2010;12, CD000509.

Bhandari V. Molecular mechanisms of hyperoxia-induced acute lung injury. Front Biosci. 2008;13:6653–61.

Bhandari V. Hyperoxia-derived lung damage in preterm infants. Semin Fetal Neonatal Med. 2010;15:223–9.

Chen J, Smith LE. Retinopathy of prematurity. Angiogenesis. 2007;10:133–40.
Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. Pediatrics. 2010;125:e1483–92.
Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, Davis PG, Morley CJ. Defining the reference range for oxygen saturation for infants after birth. Pediatrics. 2010;125:e1340–7.
Dennery PA. Oxidative stress in development: nature or nurture? Free Radic Biol Med. 2010;49:1147–51.
Dennery PA, Buonocore G, Saugstad OD, editors. Oxidative stress in applied basic research and clinical practice. Perinatal and prenatal disorders. New York: Humana Press; 2014.
Gerstner B, DeSilva TM, Genz K, Armstrong A, Brehmer F, Neve L, Felderhoff-Mueser U, Volpe JJ, Rosenberg PA. Hyperoxia causes maturation-dependent cell death in the developing white matter. J Neurosci. 2008;28:1236–45.
Haynes RL, Baud O, Li J, Kinney HC, Volpe JJ, Folkerth DR. Oxidative and nitrative injury in periventricular leukomalacia: a review. Brain Pathol. 2005;15:225–33.
Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. Arch Dis Child Fetal Neonatal Ed. 2008;93:F153–61.
Lane N. Oxygen: the molecule that made the world. Oxford: Oxford University Press; 2002.
Manja V, Lakshminrusimha S, Cook DJ. Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis. JAMA Pediatr. 2015;169:332–40.
Saugstad OD. Oxidative stress in the newborn—a 30-year perspective. Biol Neonate. 2005;88:228–36.
Saugstad OD. Oxygen and oxidative stress in bronchopulmonary dysplasia. J Perinat Med. 2010;38:571–7.
Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology. 2014;105:55–63.
Saugstad OD, Aune D, Aguar M, Kapadia V, Finer N, Vento M. Systematic review and meta-analysis of optimal initial fraction of oxygen levels in the delivery room at ≤32 weeks. Acta Paediatr. 2014;103:744–51.
Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, Stoll BJ, Lemons JA, Stevenson DK, Bauer CR, Korones SB, Fanaroff AA. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med. 1999;340:1962–8.
Vento M, Saugstad OD. Oxygen supplementation in the delivery room: updated information. J Pediatr. 2011;158(2 Suppl):e5–7.
Volpe JJ, Kinney HC, Jensen FE, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. Int J Dev Neurosci. 2011;29:423–40.
Wright CJ, Dennery PA. Manipulation of gene expression by oxygen: a primer from bedside to bench. Pediatr Res. 2009;66:3–10.

Pulmonary Mechanics and Energetics

8

Anton H.L.C. Van Kaam and Vinod K. Bhutani

I. Introduction
   A. Lung function is often compromised in preterm infants because of structural (lung parenchyma, airways, chest wall) and sometimes biochemical (surfactant deficiency) immaturity of the respiratory system.
   B. This can result in significant alterations in pulmonary mechanics, a low functional residual capacity (FRC) and an increased work of breathing (WOB). Clinically this will translate into impaired gas exchange and (the risk of) respiratory failure.
   C. The only preventive measure is antenatal steroids, which can ameliorate both the structural and biochemical immaturity of the preterm lungs. Treatment mainly consists of respiratory support and exogenous surfactant.
   D. The basic aim is to restore pulmonary mechanics and FRC, thereby normalizing WOB and gas exchange. Knowledge of respiratory physiology is essential in selecting the optimal mode and level of respiratory support.

II. Getting air in and out the lung
   A. In order to establish adequate gas exchange, air needs to move in and out of the lungs. Inhalation or inflation is, in terms of energetics, an active process which requires a pressure difference between the airway opening and the alveolar space.
   B. During spontaneous breathing diaphragmatic contraction results in a negative alveolar pressure and as a result air will enter via the airway opening (ambient pressure) and move down the conducting airways.
   C. During mechanical ventilation air flow is achieved by creating a positive airway pressure at the airway opening compared to ambient pressure outside the chest. Under normal conditions exhalation is a passive process as a result of the created pressure difference and depends on the elastic and resistive properties of the lung.

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III. Elastic Properties
   A. The elastic properties of the lung parenchyma are dependent upon the elasticity of pulmonary tissues, gas exchange spaces, smooth muscle, connective tissue, and the vascular tissue. Equally important as tissue elasticity is the recoil effect from surface tension forces at the alveolar air-liquid interface, especially during a state of surfactant deficiency or inactivation. The elastic properties of the airway depend upon the smooth muscle, tissue properties, and fibrocartilaginous structure, whereas the elastic properties of the thorax depend on the rib cage, intercostal muscle, the diaphragm, and tissues of the chest wall. These forces are interdependent, maintain a complex balance, and are influenced by the respiratory cycle and position of the body.
   B. Elasticity is the property of matter such that if a system is disturbed by stretching or expanding it, the system will tend to return to its original position when all external forces are removed. Like a spring, the tissues of the lungs and thorax stretch during inspiration, and when the force of inspiration (respiratory muscular effort) is removed, the tissues return to their resting position. The resting position or lung volume is established by a balance of elastic forces. At rest, the elastic recoil forces of the lung tissues exactly equal those of the chest wall and diaphragm. This occurs at the end of every normal expiration, when the respiratory muscles are relaxed, and the volume remaining in the lungs is the FRC.
   C. The visceral pleura of the lung is separated from the parietal pleura of the chest wall by a thin film of fluid creating a potential space between the two structures. In a normal newborn at the end of expiration, the mean pressure in this space (intrapleural pressure) is 3–6 cm H_2O below atmospheric pressure. This pressure results from the equal and opposite retractile forces of the lungs and chest wall and varies during the respiratory cycle, becoming more negative during active inspiration and more positive during expiration. During normal breathing the pressure within the lungs is dependent upon the airway and tissue frictional resistive properties in response to airflow. Because there is no net movement of air at end-expiration and at end-inspiration, pressure throughout the lung at these times is in equilibrium with atmospheric air.
   D. Pressure–Volume curve of the lungs
      1. One way to characterize the elastic recoil forces of the lungs is to reconstruct a pressure–volume curve.
      2. Starting at residual lung volume, a known volume of air is stepwise injected into the lungs in an incremental manner, until total lung capacity is reached.
      3. By simultaneously measuring the resulting airway pressure at each step, the inflation limb of the pressure–volume curve can be reconstructed. This usually contains a lower and an upper inflection point (Fig. 8.1).
      4. Between these points the pressure–volume relationship is linear.
      5. By stepwise removing volume from the lung, the deflation limb of the pressure–volume curve, starting at total lung capacity, can be reconstructed. The deflation limb also has an upper inflection point. Under most conditions the deflation limb is situated at a higher lung volume than the inflation limb and has more stability in terms of lung volume when the pressure decreases.
      6. The volume difference between the inflation and the deflation limb at similar airway pressures is called lung hysteresis.
      7. Elastic recoil forces will have a significant impact on the volumes and shape of the pressure–volume curves (Fig. 8.2).

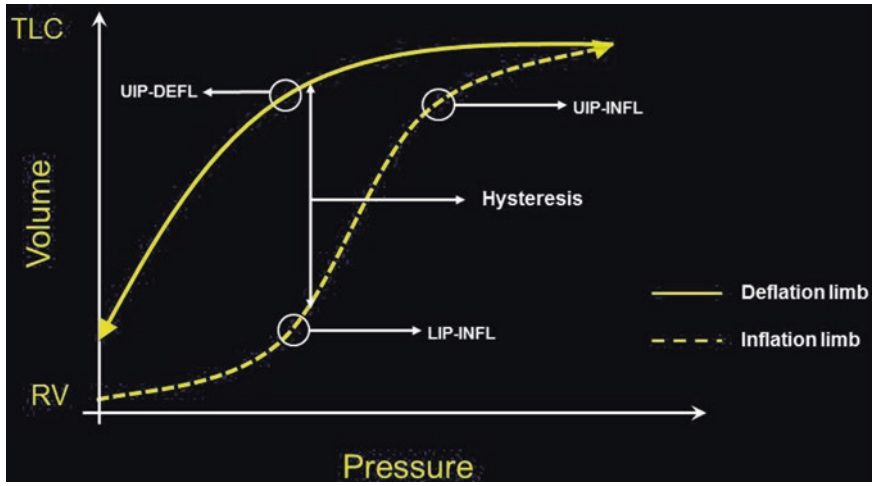

Fig. 8.1 Pressure–volume relationship of the lung inflated from residual volume (RV) to total lung capacity (TLC). Both the inflation limb (*interrupted line*) and the deflation limb (*solid line*) are displayed. Note the difference in lung volume between the inflation and deflation limb at similar pressures (hysteresis). The lower inflection point of the inflation limb (LIP-INFL), the upper inflection point of the inflation limb (UIP-INFL), and the upper inflection point of the deflation limb (UIP-DEFL) are indicated

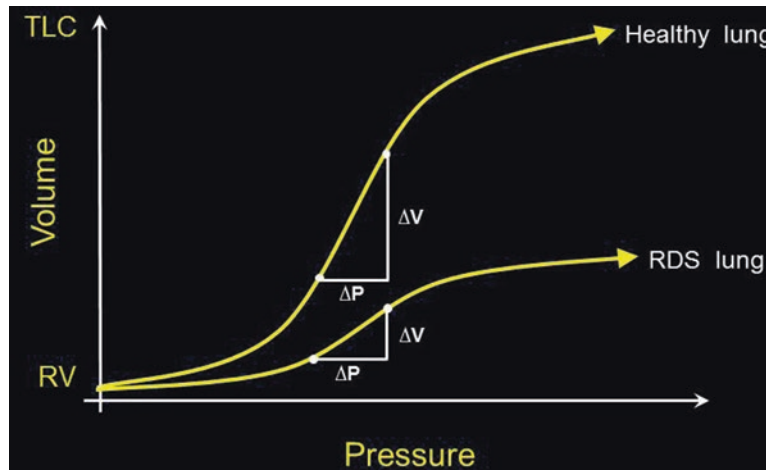

Fig. 8.2 The inflation limb of the pressure–volume relationship of a healthy lung and a surfactant deficient lung due to neonatal respiratory distress syndrome (RDS), inflated from residual volume (RV) to total lung capacity (TLC). Note the clear difference in shape and lung volumes. Per pressure unit, less volume enters the RDS lung than the healthy lung, i.e., lung compliance is lower in the RDS lung

E. Lung Compliance

Although very informative, the pressure–volume curve is not very practical to characterize the elastic properties of the lung. Patients do not breathe in from residual volume to total lung capacity. Instead, tidal breathing is situated somewhere in the pressure–volume envelope, ideally starting inspiration at FRC.

1. The ratio of change in lung volume to change in distending pressure during normal breathing defines the compliance of the lungs:

   Lung Compliance = change in lung volume/change in transpulmonary pressure

   where transpulmonary pressure (P_{TP}) is the net driving pressure to expand the lungs only and is defined as the difference between alveolar pressure and intrapleural pressure.

Intrapleural pressure cannot easily be measured directly, but it can be approximated by measuring the intraesophageal pressure.

2. By definition, lung compliance is a static characteristic obtained while the respiratory system is in a passive state and there is no airflow.
   a. This can be achieved in infants by numerous, well-proven, static techniques.
   b. Using special dynamic techniques, lung compliance can also be measured during uninterrupted spontaneous breathing or mechanical ventilation.
   c. Compliance obtained in this manner is termed dynamic compliance.
3. In case tidal breathing takes place on the linear part of the pressure–volume relationship of the lung, the compliance (of slope $\Delta V/\Delta P$) is maximal and stable over the normal range of tidal volumes beginning at FRC (Fig. 8.3f). Thus, for a given change in pressure, tidal volume will increase in proportion to lung compliance, or $\Delta V = C/\Delta P$.
   a. As lung compliance is decreased, the lungs are stiffer and more difficult to expand.
   b. When lung compliance is increased, the lung becomes easier to distend, and is thus more compliant.
4. It is important to acknowledge that end-expiratory lung volumes below or above the linear part of the pressure–volume relationship will compromise compliance of the lung. In other words, the maximum lung compliance is not reached at suboptimal end-expiratory lung volumes (Fig. 8.3f).
5. Lung compliance and pressure–volume relationships are determined by the interdependence of elastic tissue elements and alveolar surface tension. Tissue elasticity is dependent upon the elastin and collagen content of the lung.
6. A typical value for lung compliance in a young healthy newborn is 1.5–2.0 mL/cm H_2O/kg.
   a. This value is dependent upon the size of the lung (mass of elastic tissue).
   b. As may be expected, the compliance of the lung increases with development as the tissue mass of the lung increases.
   c. When comparing values between different subjects, lung compliance should be normalized for lung volume by dividing by the functional residual capacity. This ratio is called the specific lung compliance. Specific compliance of a newborn infant is similar to that of an adult.
7. The surface-active substance (surfactant, Chap. 58) lining the alveoli of the lung has a significant physiologic function.
   a. Surfactant lowers surface tension inside the alveoli, thereby reducing elastic recoil forces and contributing to lung stability by reducing the pressure necessary to expand the alveoli.
   b. Alveolar type II cells contain osmophilic lamellar bodies that are associated with the transformation of surfactant.
   c. Impaired surface activity, as occurs in those premature infants with respiratory distress syndrome (RDS), typically results in lungs that are stiff (low compliance) and prone to collapse (atelectasis) (Fig. 8.2).
8. In bronchopulmonary dysplasia, the areas of fibrosis and scarring lead to a reduction in the lung compliance. In these conditions, the baby has to generate a higher driving pressure to achieve a similar tidal volume or else hypoventilation will occur.

F. Chest Wall Compliance
   1. Like the lung, the chest wall is elastic.

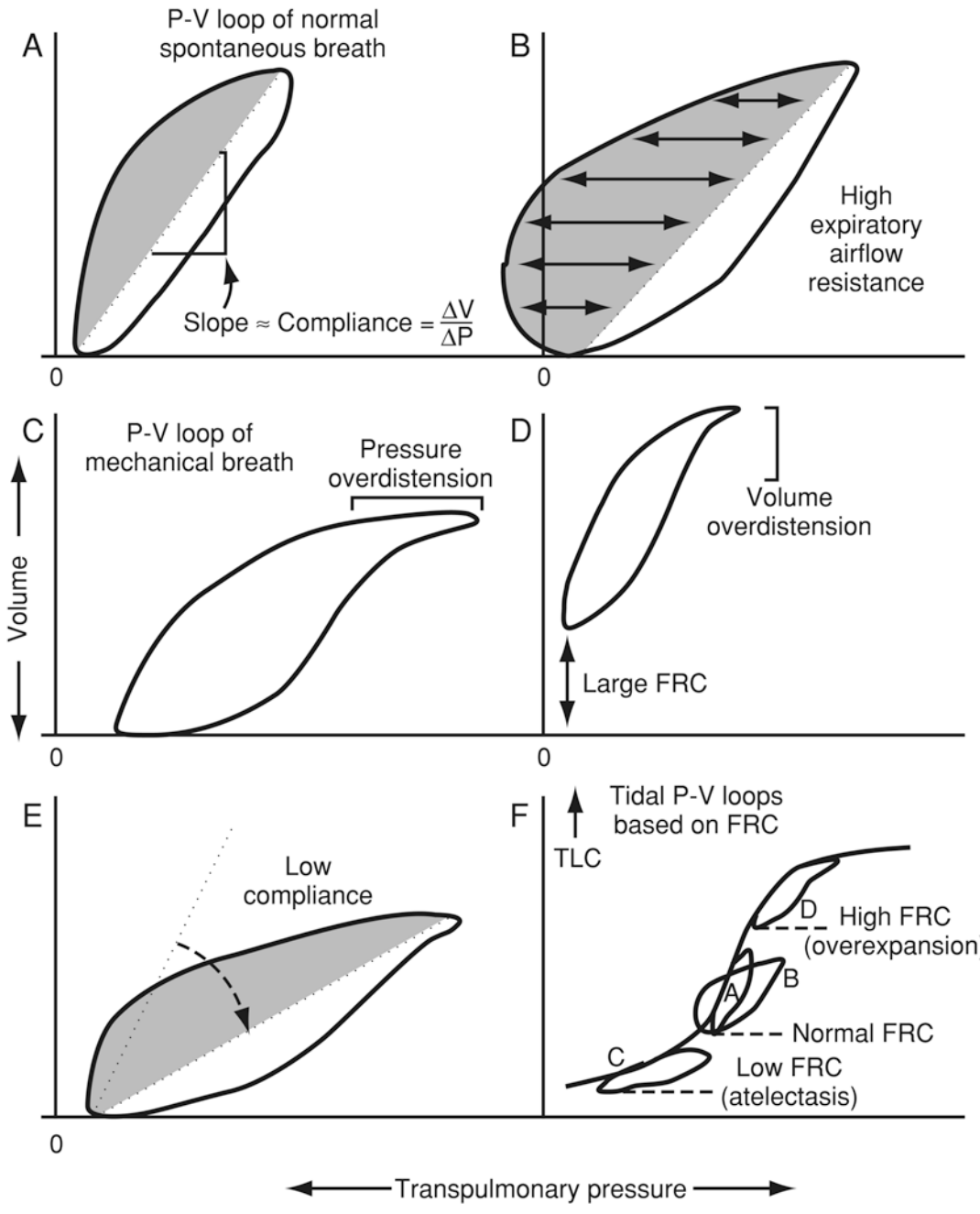

Fig. 8.3 Pressure–volume curves demonstrating elastic behavior of the lungs. (**a**) Normal spontaneous breath. (**b**) High expiratory airflow resistance. (**c**) Mechanical breath with pressure overdistension. (**d**) Mechanical breath with volume overdistension and large functional residual capacity. (**e**) Low compliance with clockwise shift of axis. (**f**) Tidal pressure–volume loops based on the functional residual capacity (Modified from Bhutani VK, Sivieri EM: Physiological principles for bedside assessment of pulmonary graphics. In Donn SM [Ed.]: *Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications.* Armonk, NY, Futura Publishing Co., 1998, p. 70, with permission.)

2. If air is introduced into the pleural cavity, the lungs will collapse inward and the chest wall will expand outward.

   Chest wall compliance = volume change/change in intrathoracic pressure

   where the intrathoracic pressure is the pressure differential across the chest wall to the atmosphere.
3. In the newborn, the chest wall compliance is significantly higher than that of an adult (Fig. 8.4).
4. The chest wall becomes more compliant at earlier stages of gestation.
5. Even if the lungs have a normal elastic recoil and compliance, the FRC will be lowered because the chest wall is unable to balance the elastic forces.
6. The high chest wall compliance in preterm infants may result in the so-called paradoxical or asynchronous breathing: during an inspiratory effort the abdominal compartment moves outward while the (compliant) chest wall moves inward. This results in less efficient gas exchange compared to synchronous breathing (both the abdomen and chest move outward during inspiration).

G. Total Respiratory System Compliance

1. If the driving pressure is measured across the entire respiratory system (the transthoracic pressure), then for a given volume change we obtain the compliance of the combined lung and chest wall together:

   Total Compliance = change in lung volume/change in transthoracic pressure

   where, in a passive respiratory system, transthoracic pressure is the differential between alveolar and atmospheric pressure.
2. Because compliance is the reciprocal of elastance and

   Elastance of the Respiratory System = Elastance of Lungs + Elastance of chest wall.

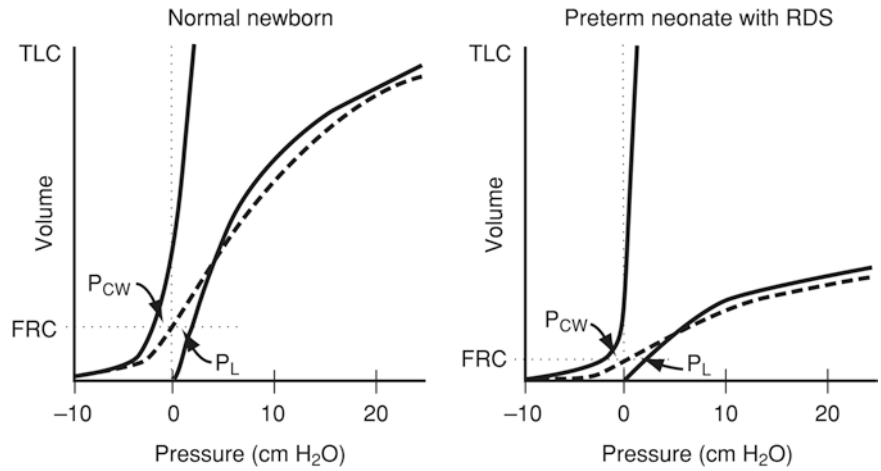

Fig. 8.4 Balance of elastic recoil at rest to maintain stable functional residual capacity. *Left*. Normal newborn; chest wall compliance is higher than that of the adult. *Right*. Preterm newborn with RDS. Chest wall is even more compliant and aggravated by disease state, FRC is lower (Modified from Bhutani VK, Sivieri EM: Physiological principles for bedside assessment of pulmonary graphics. In Donn SM [Ed.]: *Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications.* Armonk, NY, Futura Publishing Co., 1998, p. 72, with permission.)

this also means that

1/Total Respiratory System Compliance = 1/Lung Compliance + 1/Chest Wall Compliance

3. Because the chest wall compliance is extremely high compared to the lung compliance in a preterm infant, respiratory system compliance is considered equal to lung compliance.

IV. Resistive Properties
   A. Non-elastic properties of the respiratory system characterize its resistance to motion.
   B. Since motion between two surfaces in contact usually involves friction or loss of energy, resistance to breathing occurs in any moving part of the respiratory system.
   C. These resistances would include frictional resistance to airflow, tissue resistance, and inertial forces.
      1. Lung resistance results predominantly (80 %) from airway frictional resistance to airflow.
      2. Tissue resistance (19 %) and inertia (1 %) also influence lung resistance.
   D. Airflow through the airways requires a driving pressure generated by a pressure difference between the airway opening and the alveolar space.
   E. When alveolar pressure is less than atmospheric pressure (during spontaneous inspiration), air flows into the lung; when alveolar pressure is greater than atmospheric pressure, air flows out of the lung.
   F. By definition, resistance to airflow is equal to the resistive component of driving pressure (P_R) divided by the resulting airflow ($\dot{V}$), thus:

$$\text{Resistance} = P_R / \dot{V}$$

   G. When determining pulmonary resistance (tissue and airway), the resistive component of the measured transpulmonary pressure is used as the driving pressure (Fig. 8.5).
   H. To obtain airway resistance alone, the differential between alveolar pressure and atmospheric pressure is used as the driving pressure.
   I. Under normal tidal breathing conditions, there is a linear relationship between airflow and driving pressure.
      1. The slope of the flow vs. pressure curve changes as the airways narrow, indicating that the patient with airway obstruction has a greater resistance to airflow.
      2. The resistance to airflow is greatly dependent on the size of the airway lumen.
      3. According to Poiseuille's law, the pressure (ΔP) required to achieve a given flow ($\dot{V}$) for a gas having viscosity η and flowing through a rigid and smooth cylindrical tube of length L and radius r is given as:

$$P = \left(\dot{V} 8 \eta L\right) / \left(\pi r^4\right)$$

Therefore, Resistance to airflow is defined as:

$$P / \dot{V} = \left(8 \eta L\right) / \left(\pi r^4\right)$$

      4. Thus, the resistance to airflow increases by a power of four with any decrease in airway diameter.
      5. Because the newborn airway lumen is approximately half that of the adult, the neonatal airway resistance is about 16-fold that of the adult. Normal airway resistance in a term newborn is approximately 20–40 cm H_2O/L/s (adults 1–2 cm H_2O/L/s).

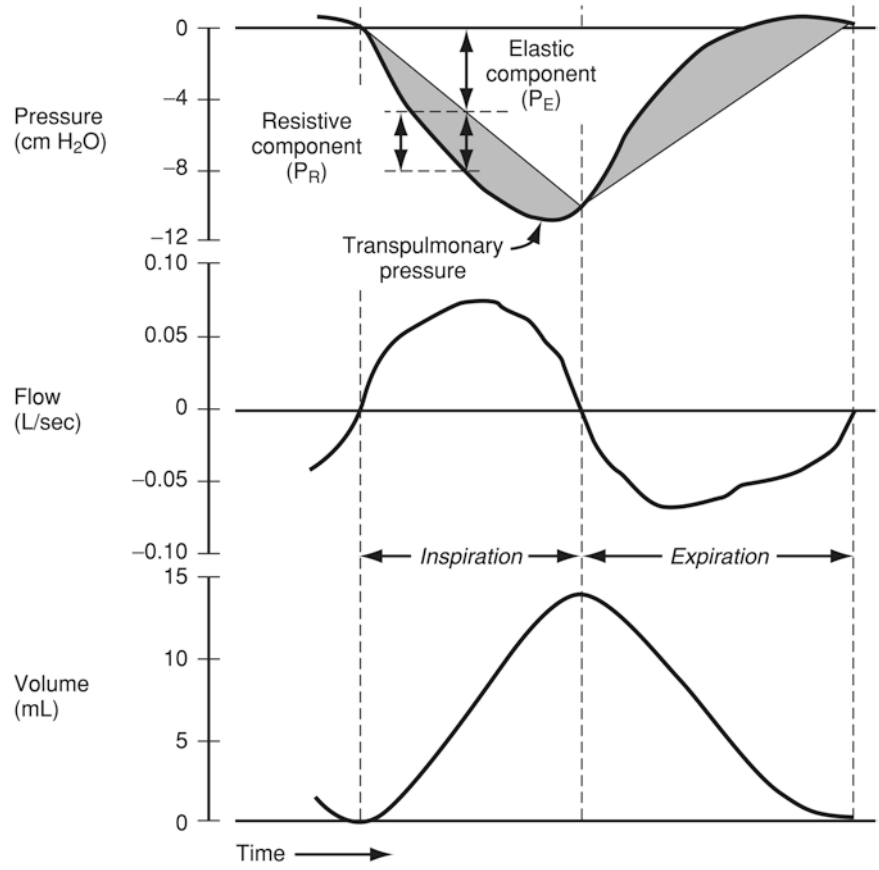

Fig. 8.5 The relative elastic and resistive components of transpulmonary pressure recorded from a typical single spontaneous breath. Pulmonary resistance is determined from simultaneous measures of the resistive component of pressure and the flow signal

J. Nearly 80 % of the total resistance to airflow occurs in large airways up to about the fourth to fifth generation of bronchial branching.
   1. The patient usually has large airway disease when resistance to airflow is increased.
   2. Since the smaller airways contribute a small proportion of total airway resistance, they have been designated as the "silent zone" of the lung in which airway obstruction can occur without being readily detected.

K. Airway resistance is also dependent upon lung volume. With increasing lung volume, the airway diameter increases and the resistance decreases. The converse is true for decreasing lung volumes.

L. It is important to realize that most interfaces of respiratory support, such as an endotracheal tube, will increase airway resistance significantly.

V. Inertial Properties

Inertial forces are generally considered negligible for normal tidal breathing and when considering a linear model of respiration. However, with use of high airflow mechanical ventilation, high frequency ventilation, and in severe airway disease, inertial forces need to be considered.

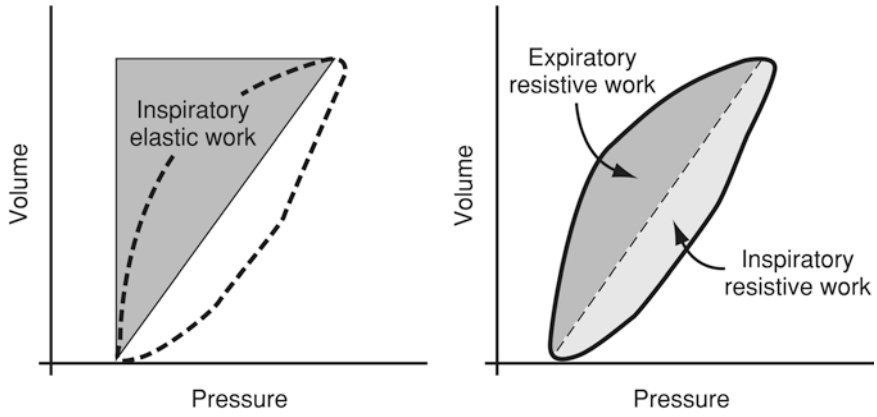

Fig. 8.6 Work of breathing is calculated as the area under the pressure versus volume curve (*shaded areas*)

VI. Work of Breathing
   A. True work of breathing may be expressed as the energy required by the respiratory muscles in moving a given tidal volume of air into and out of the lungs. For obvious reasons, this type of work is difficult to determine accurately, whereas, the actual mechanical work done by or on the lungs is much easier to measure. The mechanical work expended in compressing or expanding a given volume is obtained from the integral product of the applied pressure and the resulting volume change or:

$$\text{Work} = \int P \mathrm{d}V$$

   B. This value is simply the area under the applied pressure vs. volume curve for any gas. Therefore, by integrating the transpulmonary pressure curve over volume, the pulmonary work of breathing is easily calculated (Fig. 8.6). This mechanical work can be partitioned into elastic and resistive components:
      1. Elastic work is that portion needed to overcome elastic resistance to inflate the lungs. Under normal conditions this work is stored as potential energy and is used in restoring the system to its resting volume.
      2. Resistive work is that portion needed to overcome airway and tissue frictional resistances. The hysteresis of the pressure–volume relationship represents the resistive work of breathing and can be further partitioned into inspiratory and expiratory components.
   C. Normally, the elastic energy stored during inspiration is sufficient to provide the work needed to overcome expiratory frictional resistance.
      1. In babies with obstructive airway disease, the expiratory component of resistive work of breathing is increased (Fig. 8.3b).
      2. The units of work of breathing correspond to the units of pressure times volume (cm $H_2O \bullet L$), or equivalently, force times distance (kg•m), and is usually expressed as the work per breath or respiratory cycle.

VII. Functional Residual Capacity
   A. The volume remaining in the lungs after a normal passive expiration is called the FRC, estimated at 20–30 mL/kg in a normal newborn.
   B. Preterm infants are prone to a low FRC, and this will have the following effects on lung physiology:
      1. Decreased compliance of the respiratory system (Fig. 8.3f)
      2. Increased airway resistance
      3. Increased work of breathing

Table 8.1 Calculated respiratory parameters

	Units	Adult	Newborn	Newborn RDS	Newborn BPD
Pulmonary compliance	mL/cm H_2O/kg	2.5–3	2–2.5	<0.6	<1.0
Chest wall compliance	mL/cm H_2O	<1	>4	–	–
Pulmonary resistance	cm H_2O/L/s	1–2	20–40	>40	>150
Resistive work	gm cm/kg	<10	20–30	30–40	>40

Table 8.2 Mean normal values of neonatal pulmonary function during the first month

Authors	Study year	GA (wks)	Age (days)	V_T (mL/kg)	FRC (mL/kg)	C_{DYN} (mL/cm H_2O)	R (cm H_2O/L/s)
Berglund /Karlberg	1956	Term	7		27		
Cook et al.	1957	Term	1–6	5.3		5.2	29
Swyer et al.	1960	Term	1–11	6.7		4.9	26
Polgar	1961	Term	1–17		52.6	5.7	18.8
Strang/McGrath	1962	Term	1–6		49.5		
Nelson et al.	1963	Preterm	1–16		38.7		
		Term	2–4		27		
Feather/Russell	1974	Term	1–3			3.7	42
Ronchetti et al.	1975	34	4–28		29.5		
Taeusch et al.	1976	Term	4–6	7.2		3.7	
Adler/Wohl	1978	Term	2–5			3.5	
Mortola et al.	1984	Term	1–4	6.2		3.8	
Taussig et al.	1982	Term	1–9		31.4		
Migdal et al.	1987	34	1–28			2.4	
		Term	1–29			3.2	
Anday et al.	1987	28–30	2–3	5.9		2.0	50 exp
			5–7	6.6		2.3	70 exp
Gerhardt et al.	1987	31–36	3–30		16.7	2.2	87 exp
		Term	6–16		17.1	3.6	58 exp
Abbasi/Bhutani	1990	28–34	2–3	6.3		2.4	54
Sivieri et al.	1995	27–40	2–30		23.4		
		26–37	2–30		21.5 RDS		
		23–32	1–22		18.9 BPD		

GA gestational age, *VT* tidal volume, *FRC* functional residual capacity, C_{DYN} dynamic lung compliance, *R* pulmonary resistance, *exp* expiratory, *RDS* infants with respiratory distress syndrome, *BPD* infants who developed bronchopulmonary dysplasia

4. Increased intrapulmonary right-to-left shunt
5. Increased pulmonary vascular resistance
6. Impaired gas exchange

VIII. Some Reference Values

A. Calculated values of both elastic and resistive properties determined in adult and term newborns are listed in Table 8.1. These are compared to values obtained in infants with RDS and BPD.

B. Table 8.2 lists values of neonatal pulmonary function parameters during the first month from several investigators collected over several decades of work in this area.

C. Pulmonary mechanics and energetics at age <3 days for infants with RDS who received surfactant replacement immediately after birth (Table 8.3).

Table 8.3 Pulmonary mechanics and energetics at age <3 days for infants with RDS who received surfactant replacement immediately after birth

Infants grouped by GA at birth	≤26 weeks ($n=38$)	27–28 weeks ($n=50$)	29–30 weeks ($n=48$)	≥31 weeks ($n=63$)
Tidal volume (mL/kg)	6.1 ± 1.7	5.7 ± 1.5	5.1 ± 1.2	5.2 ± 0.8
Pulmonary compliance (mL/cm H_2O/kg)	0.27 ± 0.18	0.35 ± 0.22	0.40 ± 0.23	0.77 ± 0.75
Pulmonary resistance (cm H_2O/L/s)	194 ± 161	139 ± 117	101 ± 64	87 ± 76
Flow-resistive work (g cm/kg)	38 ± 29	28 ± 17	21 ± 14	15 ± 1.2

Table 8.4 Predicted probability of BPD based on pulmonary mechanics and gestational age based on a predictive model for the study infants with RDS categorized by birth weight

Birth weight (g)	Gestational age (week)	Pulmonary compliance (mL/cm H_2O/kg)	Pulmonary resistance (cm H_2O/L/s)	Likelihood ratio for BPD	Percent predicted probability
500–750	26 ± 0.4	0.3 ± 0.03	102 ± 16	537 ± 171	93 ± 3 %
751–1000	28 ± 0.3	0.5 ± 0.05	176 ± 24	76 ± 35	73 ± 5 %
1001–1250	29 ± 0.3	1.0 ± 0.2	96 ± 11	5.5 ± 1.8	42 ± 7 %
1251–1500	31 ± 0.3	1.5 ± 0.2	69 ± 8	0.8 ± 0.3	15 ± 5 %
1501–2000	32 ± 0.3	1.8 ± 0.3	69 ± 11	0.3 ± 0.1	8 ± 3 %

Predicted probability and likelihood ratio (LR) of BPD evaluated on the previously reported predictive model based on GA and pulmonary mechanics: $LR = \exp\{33.6 - 1.13GA - 0.93C_l/kg - 0.001R_t\}$

Table 8.5 Pulmonary mechanics and energetics at term PMA of surviving infants with RDS who received surfactant replacement immediately after birth

Surviving infants grouped by GA at birth	≤26 weeks ($n=25$)	27–28 weeks ($n=35$)	29–30 weeks ($n=38$)	≥31 weeks ($n=59$)
Term PMA (mean values) (weeks)	38.7	38.8	39.9	38.0
Tidal volume (mL)	13.3 ± 4.1	14.3 ± 4.2	15.2 ± 4.4	14.4 ± 4.7
Pulmonary compliance (mL/cm H_2O)	2.6 ± 0.9	2.4 ± 0.8	2.6 ± 1.3	2.1 ± 0.6
Pulmonary resistance (cm H_2O/L/s)	61 ± 41	59 ± 31	57 ± 31	40 ± 20
Flow-resistive wort (g cm/kg)	29 ± 19	29 ± 20	30 ± 19	25 ± 18

D. Predicted probability of BPD based on pulmonary mechanics and gestational age from a predictive model for the study infants with RDS categorized by birth weight (Table 8.4)
E. Pulmonary mechanics and energetics at term post-menstrual age of infants surviving RDS, who received surfactant replacement immediately after birth (Table 8.5)

Suggested Reading

Bancalari E. Pulmonary function testing and other diagnostic laboratory procedures in neonatal pulmonary care. In: Thibeault DW, Gary GA, editors. Neonatal pulmonary care. 2nd ed. East Norwalk, CT: Appleton-Century Crofts; 1986. p. 195–234.

Bhutani VK, Sivieri EM. Physiological principles for bedside assessment of pulmonary graphics. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics. Principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1998. p. 57–79.

Bhutani VK, Shaffer TH, Vidyasager D, editors. Neonatal pulmonary function testing: physiological, technical and clinical considerations. Ithaca, NY: Perinatology Press; 1988a.

Bhutani VI, Sivieri EM, Abbasi S. Evaluation of pulmonary function in the neonate. In: Polin RA, Fox WW, editors. Fetal and neonatal physiology. 2nd ed. Philadelphia: WB Saunders Co.; 1988b. p. 1143–64.

Comroe JH. Physiology of respiration. 2nd ed. Chicago: Year Book Medical Publishers; 1974.
Comroe JH, Forster RE, Dubois AB, et al. Clinical physiology and pulmonary function tests. 2nd ed. Chicago: Year Book Medical Publishers; 1971.
Polgar G, Promadhat V. Pulmonary function testing in children. Philadelphia: WB Saunders Co.; 1971.
Rodarte JR, Rehder K. Dynamics of respiration. In: Geiger SR, editor. Handbook of physiology, Section 3: The respiratory system. Macklem PT, Mead J (Volume Eds.), Volume III, Mechanical of breathing, Part I, Fishman AP (Section Ed.). Bethesda: American Physiological Society; 1986. p. 131–44.
Stocks J, Sly PD, Tepper RS, Morgan WJ, editors. Infant respiratory function testing. New York: Wiley-Liss; 1996.
West JB. Respiratory physiology: the essentials. Oxford: Blackwell Scientific Publications; 1974.

Basic Principles of Mechanical Ventilation

9

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I. The ventilatory needs of a patient depend largely on the mechanical properties of the respiratory system and the type of abnormality in gas exchange.
II. Pulmonary Mechanics (Fig. 9.1)
   A. The mechanical properties of the lungs determine the interaction between the ventilator and the infant.
   B. A pressure gradient between the airway opening and alveoli drives the flow of gases during inspiration and expiration.
   C. The pressure gradient necessary for adequate ventilation is largely determined by the compliance and resistance (see below).
III. Compliance
   A. Compliance describes the elasticity or distensibility of the lungs or respiratory system (in neonates the chest wall is very distensible and in general does not contribute substantially to compliance).
   B. It is calculated as follows:

$$\text{Compliance} = \frac{\Delta\text{Volume}\left(\text{mL}\right)}{\Delta\text{Pressure}\left(\text{cm}\,\text{H}_2\text{O}\right)}$$

   C. Compliance in infants with normal lungs ranges from 3 to 5 mL/cm H_2O/kg.
   D. Compliance in infants with respiratory distress syndrome (RDS) is lower and often ranges from 0.1 to 1 mL/cm H_2O/kg.
IV. Resistance
   A. Resistance describes the ability of the gas conducting parts of the lungs or respiratory system (lungs plus chest wall) to impede airflow.

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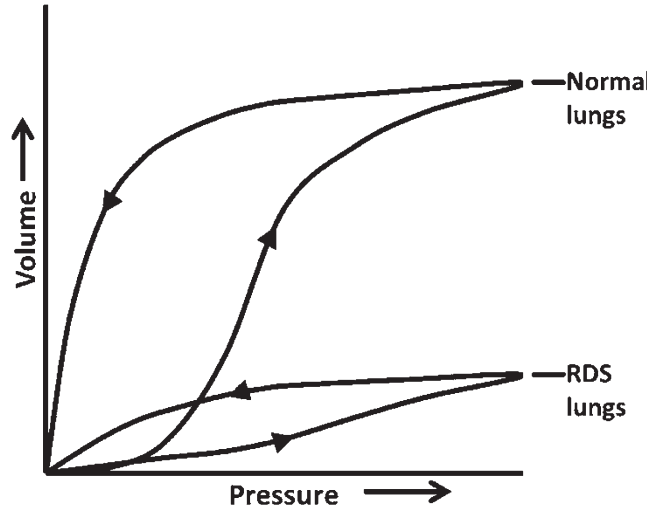

Fig. 9.1 Representation of pressure–volume relationship of the lungs for an infant with normal lung compliance and an infant with respiratory distress syndrome (RDS). The decreased lung compliance manifests as a decreased volume change for a given change in pressure

B. Pressure is needed to force gas through airways (airways resistance) and to exceed the viscous resistance of the lung tissue (tissue resistance).
C. It is calculated as follows:

$$\text{Resistance} = \frac{\Delta\text{Pressure}\left(\text{cm}\,\text{H}_2\text{O}\right)}{\Delta\text{Flow}\left(\text{L}/\text{s}\right)}$$

D. Resistance in infants with normal lungs ranges from 25 to 50 cm H_2O/L/s. Resistance is not markedly altered in infants with respiratory distress syndrome or other acute pulmonary disorders, but can be increased to 100 cm H_2O/L/s or more by small endotracheal tubes (Poiseuille's Law: Resistance ∞ $L\eta/r^4$, where L = length, η = viscosity, and r = radius; it is good practice to use appropriately sized endotracheal tubes and to cut tubes as short as practical after insertion).

V. Time Constant
A. The time constant is a measure of the time (expressed in seconds) necessary for the alveolar pressure (or volume, or flow) to reach 63 % of its steady state value in response to a step change in airway pressure (Fig. 9.2).
B. It is calculated as follows:

$$\text{Time constant} = \text{Compliance} \times \text{Resistance}$$

For example, if an infant has lung compliance of 2 mL/cm H_2O (0.002 L/cm H_2O) and a resistance of 40 cm H_2O/L/s, time constant is calculated as follows:

$$\text{Time constant} = 0.002\text{L}/\text{cm}\,\text{H}_2\text{O} \times 40\text{cm}\,\text{H}_2\text{O}/\text{L}/\text{s}$$
$$\text{Time constant} = 0.080\text{s}$$

(Note that in the calculation of the time constant, compliance is not normalized by body weight.)

C. A duration of inspiration or expiration equivalent to 3–5 time constants is required for a relatively complete inspiration or expiration, respectively. Once pressure is equilibrated, there will be no more air flow or volume change. Little further equilibration occurs beyond 3–5 time constants. Thus, in the infant described above, inspiratory and expiratory duration should be around 240–400 ms each (or 0.24–0.4 s).

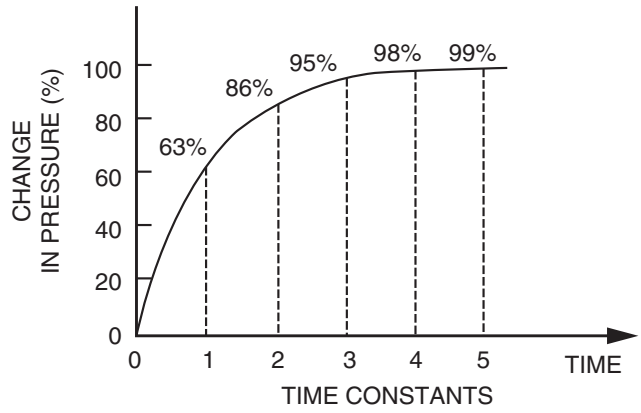

Fig. 9.2 Percentage change in pressure in relation to the time (in time constants) allowed for equilibration. As a longer time is allowed for equilibration, a higher percentage change in pressure will occur. The same rules govern the equilibrium for step changes in volume. Changes in pressure during inspiration and expiration are illustrated (Modified from Carlo WA, Chatburn RL: Assisted ventilation of the newborn. In Carlo WA, Chatburn RL (Eds.): Neonatal Respiratory Care, 2nd Edition. Chicago, Year Book Medical Publishers, 1988, p. 323, with permission)

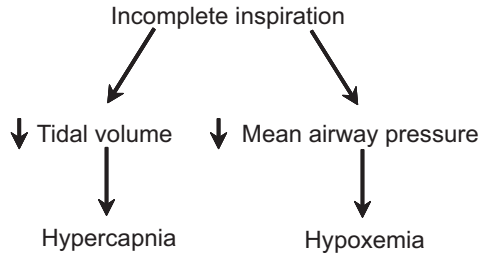

Fig. 9.3 Effect of incomplete inspiration on gas exchange (From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (Eds.): New Therapies for Neonatal Respiratory Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994, p. 137, with permission)

D. The time constant will be shorter if compliance is decreased (e.g., in patients with respiratory distress syndrome) or if resistance is decreased. The time constant will be longer if compliance is high (e.g., large infants with normal lungs) or if resistance is high (e.g., infants with chronic lung disease or airway obstruction).
E. Patients with a short time constant ventilate well with short inspiratory and expiratory times and high ventilatory frequency, whereas patients with a long time constant require longer inspiratory and expiratory times and lower rates.
F. If inspiratory time is too short (i.e., a duration shorter than approximately 3–5 time constants), there will be a decrease in tidal volume delivery (Fig. 9.3).
G. If expiratory time is too short (i.e., a duration shorter than approximately 3–5 time constants), there will be gas trapping and inadvertent positive end expiratory pressure (autoPEEP) (Fig. 9.4). The presence of autoPEEP decreases the driving pressure between airway opening and the alveoli, thus decreasing the tidal volume.
H. While the respiratory system is often modeled as being composed of a single constant compliance and a single constant resistance, it is known that the mechanical properties vary with changes in lung volume, even within a breath. Furthermore, the mechanical characteristics of the respiratory system change somewhat between inspiration and expiration. In addition, lung disease can be heterogeneous, and thus, different areas of the lungs can have varying mechanical characteristics.

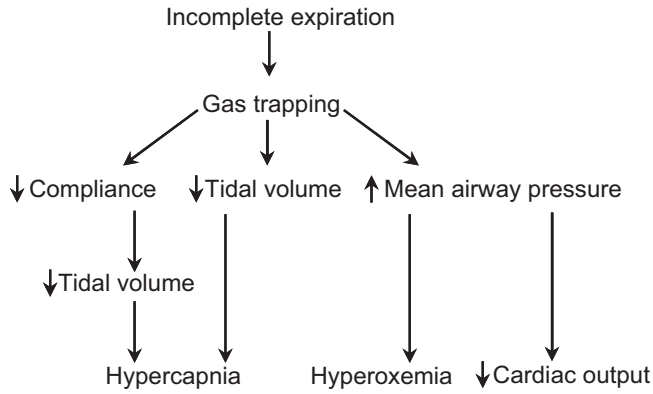

Fig. 9.4 Effect of incomplete expiration on gas exchange (From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (Eds.): New Therapies for Neonatal Respiration Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994. p. 137, with permission)

VI. Equation of Motion
   A. The pressure necessary to drive the respiratory system is the sum of the elastic, resistive, and inertial components and can be calculated as follows:

$$P = \frac{1}{C}V + R\dot{V} + I\ddot{V}$$

   Where P is pressure
   C is compliance
   V is volume
   R is resistance
   $\dot{V}$ is flow
   $\ddot{V}$ is the rate of change in flow
   I is inertance
   B. Because the inertial component is small at physiologic flows, the last component ($\ddot{V}$) can be neglected
   C. The equation of motion can be used to derive estimates of compliance and resistance. For example, between points of $\dot{V} = 0$ (points of no flow), the pressure gradient results from compliance only (some ventilators can calculate static compliance between inspiratory and expiratory pauses). Between points of equal volume (e.g., inspiration vs. expiration), the pressure gradient results from resistance only. Alternatively, dynamic compliance can be calculated by fitting the equation of motion to multiple measurements of pressure, volume, and flow (e.g., collected every 20 min during inspiration or expiration).

VII. Gas Exchange
   A. Hypercapnia and/or hypoxemia occur during respiratory failure.
   B. Although impairment in CO_2 elimination and oxygen uptake and delivery may coexist, some conditions may affect gas exchange differentially.

VIII. Gas Exchange During Transition to Extrauterine Life
   A. Hemodynamic changes during transition to extrauterine life
      1. Systemic vascular resistance increases.
      2. Pulmonary vascular resistance decreases.
      3. Pulmonary blood flow increases.

B. Blood gas values in the perinatal period

	At birth	10 min of age
PaO_2 (Torr)	15–20	46–57
$PaCO_2$ (Torr)	49–76	40–47
pH	7.10–7.24 (normalizes by 3–5 h after birth)	

IX. Determinants of Pulmonary Gas Exchange
  A. Composition and volume of alveolar gas
  B. Composition and volume of mixed venous blood
  C. Ratio of ventilation to perfusion in the lungs
  D. Mechanisms of gas exchange

X. Composition of Inspired and Alveolar Gases
  A. Partial pressure of oxygen in dry air

Partial pressure of O_2 = fractional content × total gas pressure

If barometric pressure = 760 mmHg, then

$$PO_2 = 0.21(760\text{mmHg})$$
$$PO_2 = 160\text{mmHg}$$

  B. Partial pressure of oxygen in humidified air is affected by humidification because water vapor also exerts a partial pressure.

Partial pressure O_2 = fractional content × (total gas pressure − water vapor pressure)

$$PiO_2 = 0.21(760 - 47\text{mmHg})$$
$$PiO_2 = 149\text{mmHg}$$

  C. Alveolar Air Equation. Partial pressure of oxygen in humidified alveolar gas is further affected by the presence of carbon dioxide continuously diffusing from capillary blood.

Partial pressure of alveolar $O_2 = PiO_2 - PACO_2\,(FiO_2 + [1 - FiO_2]/R)$

Where $PACO_2$ is alveolar PCO_2 and R is the respiratory quotient. R represents the ratio of CO_2 elimination to O_2 uptake and has a typical value of 0.8. Because CO_2 diffuses very well through the alveoli, $PACO_2 \approx PaCO_2$. If barometric pressure = 760 mmHg and water vapor pressure is 47 mmHg, if $FiO_2 = 100$, then $PiO_2 = 713$.

If FiO_2 is 1.00, $(FiO_2 + [1 - FiO_2]/R) = 1.0$, then $PAO_2 = 713 - 40 = 673$ mmHg.

If FiO_2 is 0.21, then $PAO_2 = 0.21 \times (760 - 47) - 40 \times (0.21 + [1 - 0.21]/0.8) = 102$ mmHg.

XI. Composition of Mixed Venous Blood
  A. Mixed venous PO_2 (PvO_2) depends on arterial O_2 content, cardiac output, and metabolic rate.
  B. Oxygen content of blood per 100 mL is the sum of blood dissolved in the plasma (minor component) and oxygen bound to hemoglobin.

Dissolved $O_2 = 0.003$ mL O_2 per mmHg of PaO_2

Hemoglobin bound O_2 = O_2 Sat × 1.34/g hemoglobin × hemoglobin concentration

For example, 1 kg infant (blood volume ≈ 100 mL) with $PaO_2 = 100$ mmHg (O_2 sat = 100 %, or 1.0), and hemoglobin = 17 mg/dL

$$O_2\text{content} = \text{hemoglobin bound}\,O_2 + \text{dissolved}\,O_2$$
$$O_2\text{content} = 1.00 \times 1.34 \times 17 + 0.003 \times 100$$
$$O_2\text{content} = 22.78 + 0.3\text{mL}\,O_2$$
$$O_2\text{content} = 23.08\text{mL}\,O_2$$

C. CO_2 content of blood

CO_2 is carried in three forms: (1) dissolved in plasma (main component) and red cells; (2) as bicarbonate; and (3) bound to hemoglobin as carbamine compounds.

XII. Hypoxemia

The pathophysiologic mechanisms responsible for hypoxemia are in order of relative importance in newborns: ventilation–perfusion (V/Q) mismatch, shunt, hypoventilation, and diffusion limitation (Figs. 9.5, 9.6, and 9.7):

A. V/Q mismatch

An important cause of hypoxemia in newborns. Supplemental oxygen can largely overcome the hypoxemia resulting from V/Q mismatch by displacing nitrogen from the alveoli.

B. Shunt

Shunt is a common cause of hypoxemia in newborns. A shunt may be physiologic, intracardiac (e.g., PPHN, congenital cyanotic heart disease), or pulmonary (e.g., atelectasis). It can be thought of as a $V/Q=0$ and supplemental O_2 cannot reverse the hypoxemia caused by a large shunt (>30 %).

C. Hypoventilation

Hypoventilation results from a decrease in minute alveolar ventilation such that the metabolic consumption of oxygen exceeds the supply from breathing. Thus, alveolar PO_2 falls and PaO_2 decreases. It can be thought of as low V/Q and supplemental O_2 can overcome the hypoxemia easily (see alveolar air equation). Causes of hypoventilation include: depression

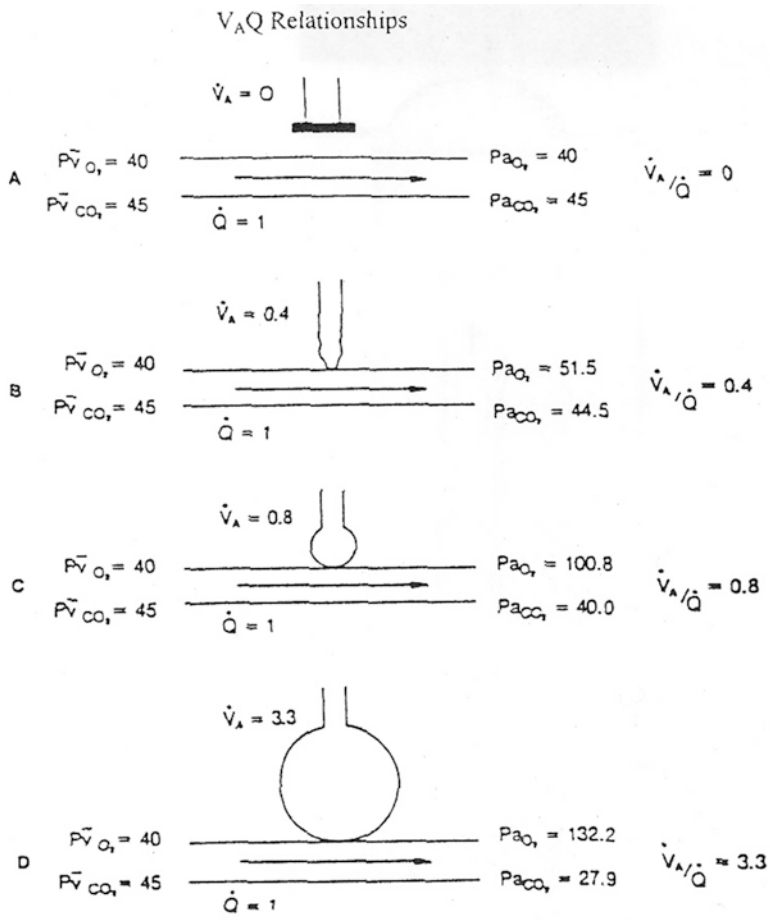

Fig. 9.5 Effects of various ventilation–perfusion ratios on blood gas tensions. (**a**) Direct venoarterial shunting ($VA/Q=0$). (**b**) Alveolus with a low VA/Q ratio. (**c**) Normal alveolus. (**d**) Underperfused alveolus with VA/Q ratio (From Krauss AN: Ventilation-perfusion relationships in neonates. In Thibeault DW, Gregory GA (Eds.): Neonatal Pulmonary Care, 2nd Edition. Norwalk, CT, Appleton-Century-Crofts, 1986, p. 127, with permission)

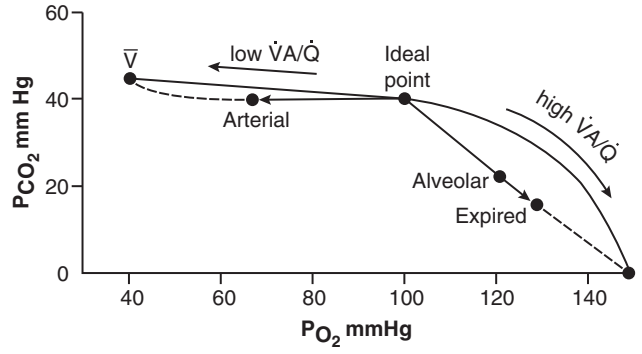

Fig. 9.6 O_2–CO_2 diagram showing the arterial, ideal, alveolar, and expired points. The *curved line* indicates the PO_2 and PCO_2 of all lung units having different ventilation–perfusion ratios (From West JB: Gas exchange. In West JB (Ed.): Pulmonary Pathophysiology: The Essentials. Baltimore, Williams & Wilkins, 1977, p. 27, with permission

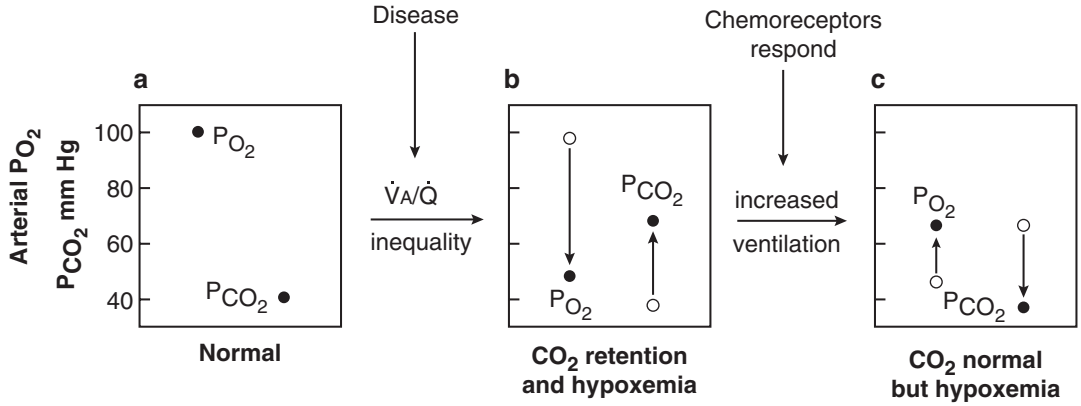

Fig. 9.7 PO_2 and PCO_2 in different stages of ventilation–perfusion inequality. Initially, there must be both a fall in oxygen and a rise in carbon dioxide tensions. However, when the ventilation to the alveoli is increased, the PCO_2 returns to normal, but the PO_2 remains abnormally low (From West JB: Gas exchange. In West JB (Ed.): Pulmonary Pathophysiology: The Essentials. Baltimore, Williams & Wilkins, 1977, p. 30, with permission)

of respiratory drive, weakness of the respiratory muscles, restrictive lung disease, and airway obstruction.

D. Diffusion limitation
Diffusion limitation is an uncommon cause of hypoxemia, even in the presence of lung disease. Diffusion limitation occurs when mixed venous blood does not equilibrate with alveolar gas. Supplemental O_2 can overcome hypoxemia secondary to diffusion limitation.

XIII. Oxygenation During Assisted Ventilation

A. Oxygenation may be increased by increasing the concentration gradient (FiO_2), by optimizing lung volume (surface area), which in turn depends on mean airway pressure (Fig. 9.8), or by maximizing pulmonary blood flow (decreasing shunts).

B. Mean airway pressure is the average pressure to which lungs are exposed during the respiratory cycle. Graphically, it is equivalent to the area between the airway pressure vs. time curve, for one cycle, divided by the cycle time (i.e., inspiratory time plus expiratory time)

C. During pressure control ventilation, any of the following will increase mean airway pressure: increasing inspiratory flow (i.e., if it is adjustable and it indirectly decreases the pressure rise time), increasing peak inspiratory pressure (PIP), increasing the inspiratory to

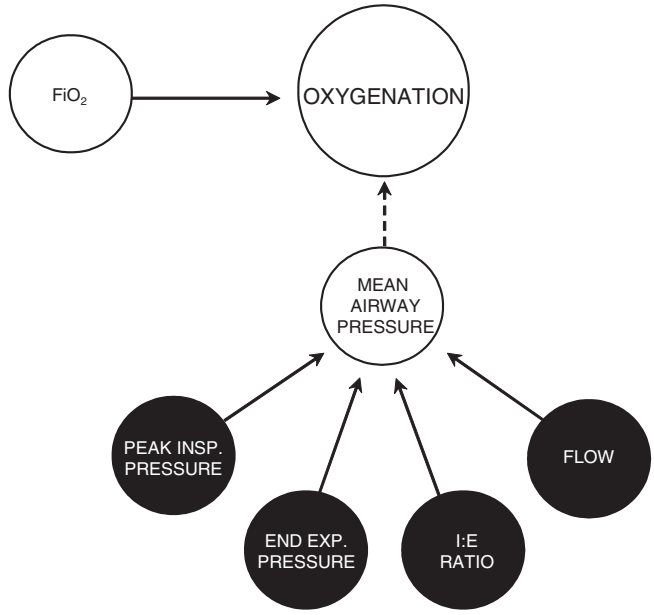

Fig. 9.8 Determinants of oxygenation during pressure-limited, time-cycled ventilation. *Shaded circles* represent ventilator-controlled variables. *Solid lines* represent the simple mathematical relationships that determine mean airway pressure and oxygenation, whereas *dashed lines* represent relationships that cannot be quantified (From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (eds.): New Therapies for Neonatal Respiration Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994, p. 134, with permission)

expiratory (I:E) ratio, or PEEP. Decreasing the pressure rise time (when the control is available) also has a small effect of increasing mean airway pressure.

D. Mean airway pressure maybe calculated as follows:

$$\text{Mean airway pressure} = K\left(\text{PIP} - \text{PEEP}\right)\left[T_{\text{I}} / \left(T_{\text{I}} + T_{\text{E}}\right)\right] + \text{PEEP}$$

where K is a constant that depends on the rate of rise of the early inspiratory part of the airway pressure curve; (K ranges from approximately 0.8–0.9 during pressure control ventilation): T_{I} is inspiratory time; T_{E} is expiratory time.

For the same change in mean airway pressure, increases in PIP and PEEP increase oxygenation more.

E. The relationship of mean airway pressure to oxygenation is not linear. A very high mean airway pressure transmitted to the intrathoracic structures may increase pulmonary vascular resistance and increase right-to-left shunting causing decreased left atrial filling and decreased oxygen transport despite adequate PaO_2.

XIV. Hypercapnia

The pathophysiologic mechanisms responsible for hypercapnia are V/Q mismatch, shunt, hypoventilation, and increased physiologic dead space. The physiologic dead space results in part from areas of inefficient gas exchange because of low perfusion (wasted ventilation). Physiologic dead space includes ventilation to conducting airways and alveolar spaces not perfused (i.e., anatomical dead space).

XV. CO_2 Elimination During Assisted Ventilation

A. CO_2 diffuses easily into the alveoli and its elimination depends largely on the total amount of gas that comes in contact with the alveoli (alveolar ventilation). Minute alveolar ventila-

tion is calculated from the product of the frequency (number of breaths per minute) and the alveolar tidal volume (tidal volume minus dead space).

$$\text{Minute alveolar ventilation} = \text{frequency} \times (\text{tidal volume minus dead space})$$

Anatomical dead space is relatively constant. Therefore, changes in tidal volume and frequency increase alveolar ventilation.

B. During volume controlled ventilation (i.e., preset tidal volume and inspiratory flow), the desired delivered volume is preset. During pressure control ventilation, the tidal volume depends on the pressure gradient between the airway opening and the alveoli; this is peak inspiratory pressure (PIP) minus the positive end expiratory pressure (PEEP), or amplitude (ΔP).

C. Depending on lung compliance and resistance, and hence the time constant of the respiratory system (and the expiratory path of the patient circuit of the ventilator), a very short inspiratory time (T_I) may reduce the tidal volume, and a very short expiratory time (T_E) may cause gas trapping and inadvertent PEEP, and consequently may also reduce tidal volume (see above).

D. Figure 9.9 illustrates the relationships among ventilator controls, pulmonary mechanics, and minute ventilation. Ventilator controls are shown in shaded circles.

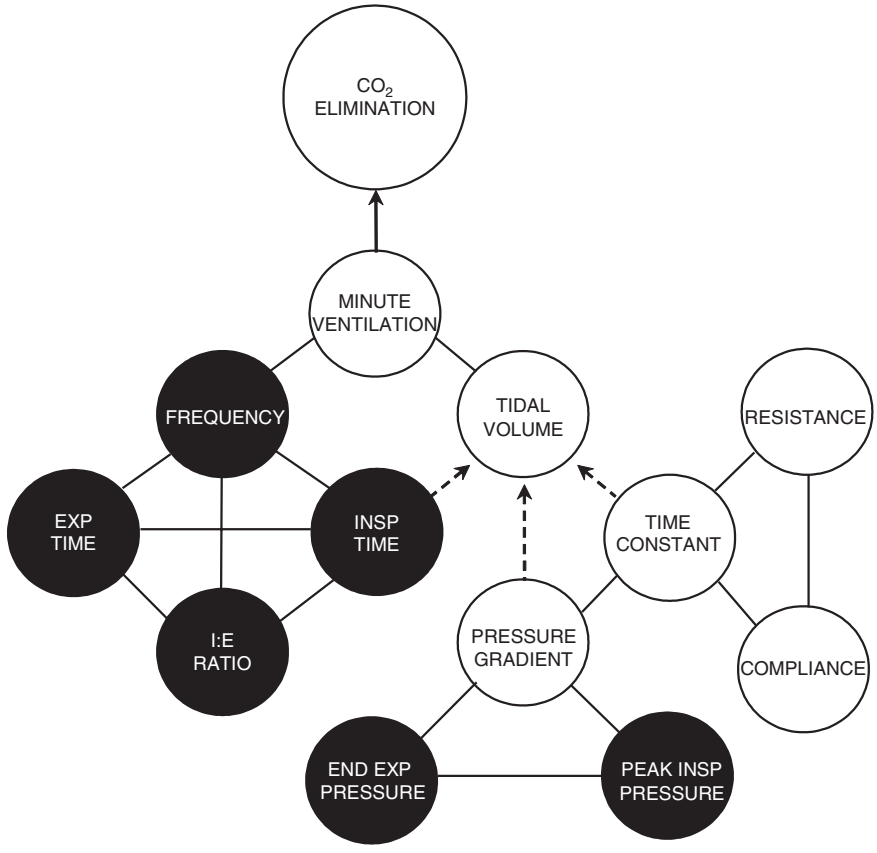

Fig. 9.9 Relationships among ventilator-controlled variables (*shaded circles*) and pulmonary mechanics (*unshaded circles*) that determine minute ventilation during time-cycled, pressure-limited ventilation. Relationships between *circles* joined by *solid lines* are mathematically derived. The *dashed lines* represent relationships which cannot be precisely calculated without considering other variables such as pulmonary mechanics. Alveolar ventilation can be calculated from the product of tidal volume and frequency when dead space is subtracted from the former (From Carlo WA, Greenough A, Chatburn RL: Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH (Eds.): New Therapies for Neonatal Respiration Failure: A Physiologic Approach. Cambridge, Cambridge University Press, 1994. p. 133, with permission)

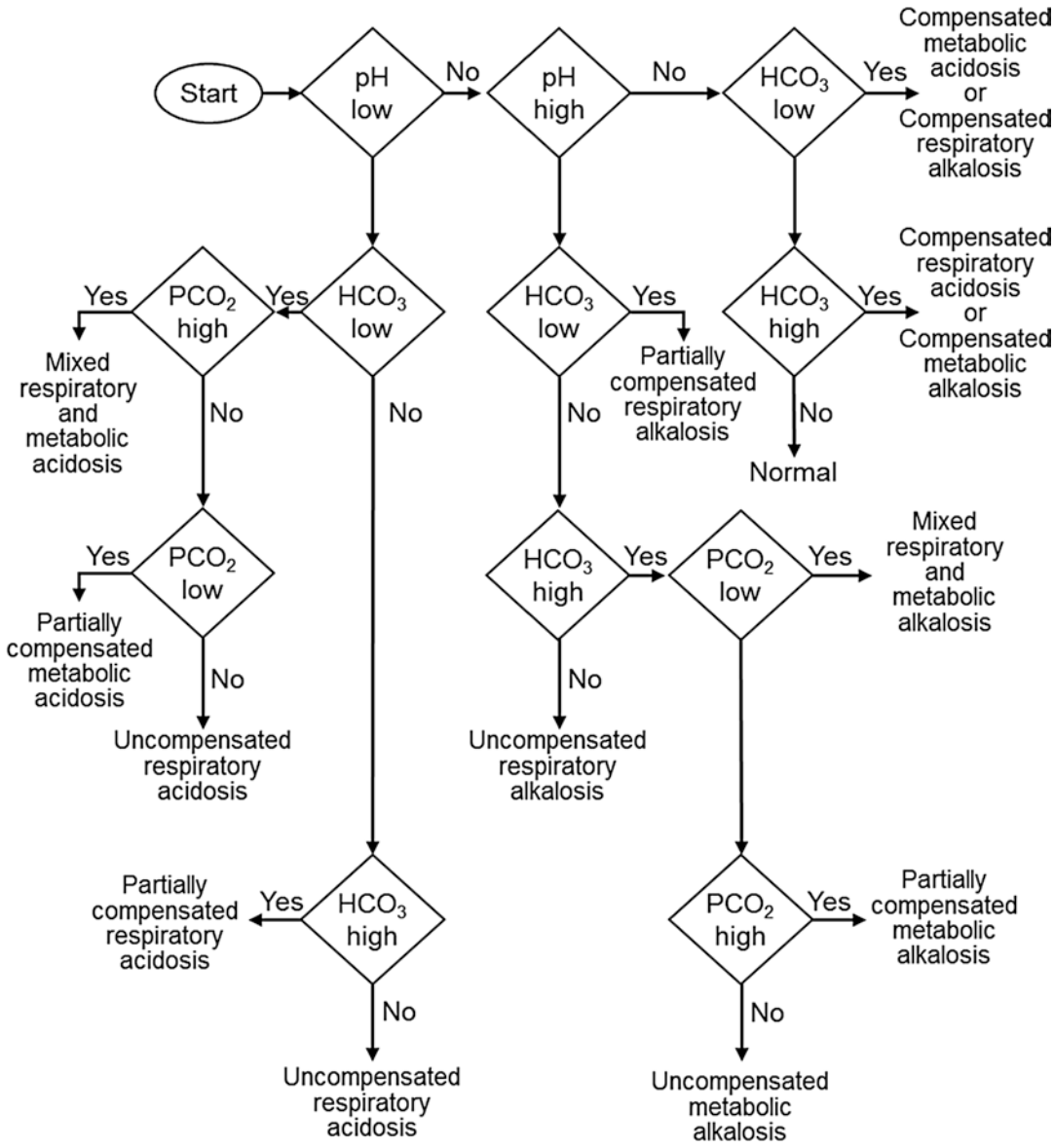

Fig. 9.10 A flowchart illustrating the algorithm through which a set of arterial blood gas values may be interpreted (From Chatburn RL, Carlo WA: Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL [eds]: Neonatal Respiratory Care, 2nd ed. Chicago, Year book Medical Publishers, 1998, p 56, with permission)

E. Adequate PEEP prevents alveolar collapse and maintains lung volumes at end expiration. Mechanical ventilation without PEEP causes surfactant inactivation, decreased lung compliance, and atelectrauma from recurrent shear forces from reopening of collapsed terminal airways. However, use of excessive PEEP may decrease lung compliance and decrease tidal volume for a given ΔP without substantially improving oxygenation.

XVI. Blood Gas Analysis

A careful interpretation is essential for appropriates respiratory care (Table 9.1, Figs. 9.10 and 9.11, Chap. 20).

Table 9.1 Blood gas classifications[a]

Classification	pH	$PaCO_2$	HCO_3^-	BE
Respiratory disorder				
Uncompensated acidosis	↓	↑	N	N
Partly compensated acidosis	↓	↑	↑	↑
Compensated acidosis	N	↑	↑	↑
Uncompensated alkalosis	↑	↓	N	N
Partly compensated alkalosis	↑	↓	↓	↓
Compensated alkalosis	N	↓	↓	↓
Metabolic disorder				
Uncompensated acidosis	↓	N	↓	↓
Partly compensated acidosis	↓	↓	↓	↓
Uncompensated alkalosis	↑	N	↑	↑
Partly compensated alkalosis	↑	↑	↑	↑
Compensated alkalosis	N	↑	↑	↑

[a]*Arrows* = elevated or depressed values; N = normal; BE = base excess

From Carlo WA, Chatburn RL: Assessment of Neonatal Gas Exchange. In Carlo WA, Chatburn RL [eds.]: *Neonatal Respiratory Care*, 2nd Edition. Chicago, Year Book Medical Publishers, 1988, p. 51, with permission

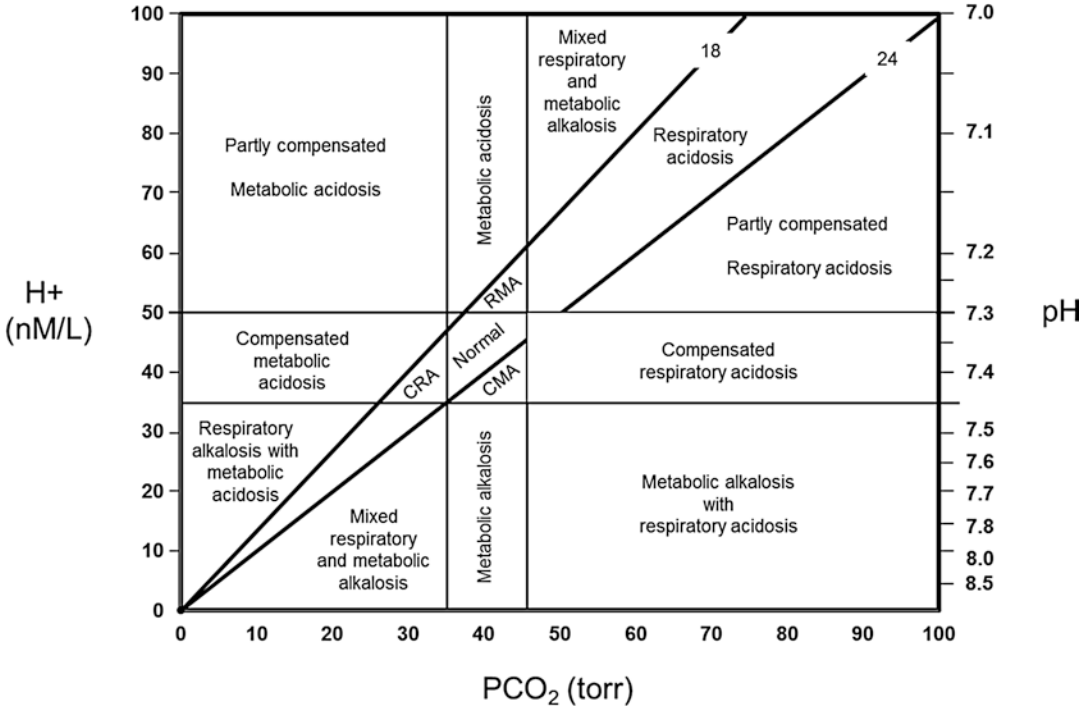

Fig. 9.11 A neonatal acid–base map. *CRA* compensated respiratory acidosis, *CMA* compensated metabolic acidosis, *RMA* mixed respiratory and metabolic acidosis (From Chatburn RL, Carlo WA: Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL [eds]: Neonatal Respiratory Care, 2nd ed. Chicago, Year book Medical Publishers, 1998, p 58, with permission)

A. Respiratory acidosis (low pH, high $PaCO_2$, normal HCO_3^-)
   1. From *V*/*Q* mismatch, shunt and/or hypoventilation
   2. Secondary renal compensation
      a. Reduction in bicarbonate excretion
      b. Increased hydrogen ion excretion
B. Respiratory alkalosis (high pH, low $PaCO_2$, normal HCO_3^-)
   1. From hyperventilation
   2. Secondary renal compensation
      a. Increased bicarbonate excretion
      b. Retention of chloride
      c. Reduced excretion of acid salts and ammonia
C. Metabolic acidosis (low pH, normal $PaCO_2$, low HCO_3^-)
   1. From increased acid production or impaired acid elimination
   2. Secondary pulmonary compensation—hyperventilation with decreased $PaCO_2$
D. Metabolic alkalosis (high pH, normal $PaCO_2$, high HCO_3^-)
   1. From excessive $NaHCO_3$ administration, diuretic therapy, and loss of gastric secretions
   2. Secondary pulmonary compensation—hypoventilation

Suggested Reading

Carlo WA, Chatburn RL. Assisted ventilation of the newborn. In: Carlo WA, Chatburn RL, editors. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers; 1988. p. 320–46.

Carlo WA, Greenough A, Chatburn RL. Advances in conventional mechanical ventilation. In: Boynton BR, Carlo WA, Jobe AH, editors. New therapies for neonatal respiratory failure: a physiologic approach. Cambridge, UK: Cambridge University Press; 1994. p. 131–51.

Chatburn RL, Khatib ME, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1997.

Greenough A, Milner AD, editors. Neonatal respiratory disorders. London: Arnold Publishers; 2003.

Krauss AN. Ventilation-perfusion relationship in neonates. In: Thibeault DW, Gregory GA, editors. Neonatal pulmonary care. 2nd ed. Norwalk, CT: Appleton; 1986. p. 127.

Mariani GL, Carlo WA. Ventilatory management in neonates. Clin Perinatol. 1998;25:33–48.

Spitzer AR, Clark RH. Positive-pressure ventilation in the treatment of neonatal lung disease. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: W.B. Saunders Co; 2011. p. 163–85.

West JB. Gas exchange. In: West JB, editor. Pulmonary pathophysiology—the essentials. 6th ed. Baltimore: Williams & Wilkins; 2003.

Classification of Mechanical Ventilation Devices

10

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I. Ventilators, or more precisely, the modes they deliver, can be classified by the variables that are controlled (e.g., pressure or volume), as well as those that start (or trigger), sustain (or limit), and end (cycle) inspiration and those that maintain the expiratory support (or baseline pressure). Microprocessor and sensor technology has increased the quality and quantity of ventilator output feedback available (Fig. 10.1). These advances in technology have led to several different targeting schemes that warrant further classification (Chap. 44).

II. Breath Control Variables. A mode of ventilation can be classified as either a form of pressure control or volume control, meaning that either pressure or volume are used as feedback control variables by the mechanism that controls breath delivery. The theoretical foundation for identifying a control variable is the equation of motion for the respiratory system. A simple version for this purpose (representing a passive patient) is as follows:

$$P_{\text{vent}} = E \times V(t) + R \times \dot{V}(t)$$

Where P_{vent} is the pressure generated by the ventilator to drive inspiration, E = elastance ($\Delta P/\Delta V$), $V(t)$ = volume as a function of time (t), and $\dot{V}(t)$ is flow as a function of time. If the ventilator controls the left hand side of the equation, i.e., the pressure waveform parameters are preset, then the mode is pressure control. This includes modes for which the peak inspiratory pressure is preset or it is automatically adjusted by the ventilator to be proportional to the patient's inspiratory effort. If the ventilator controls the right hand side of the equation, i.e., both tidal volume and inspiratory flow are preset, the control variable is volume.

A. Pressure control

To deliver pressure control modes, the ventilator controls the airway pressure waveform such that: (1) airway pressure, making it rise above the body surface pressure (i.e., positive pressure ventilator); or (2) body surface pressure, making it fall below the airway pressure

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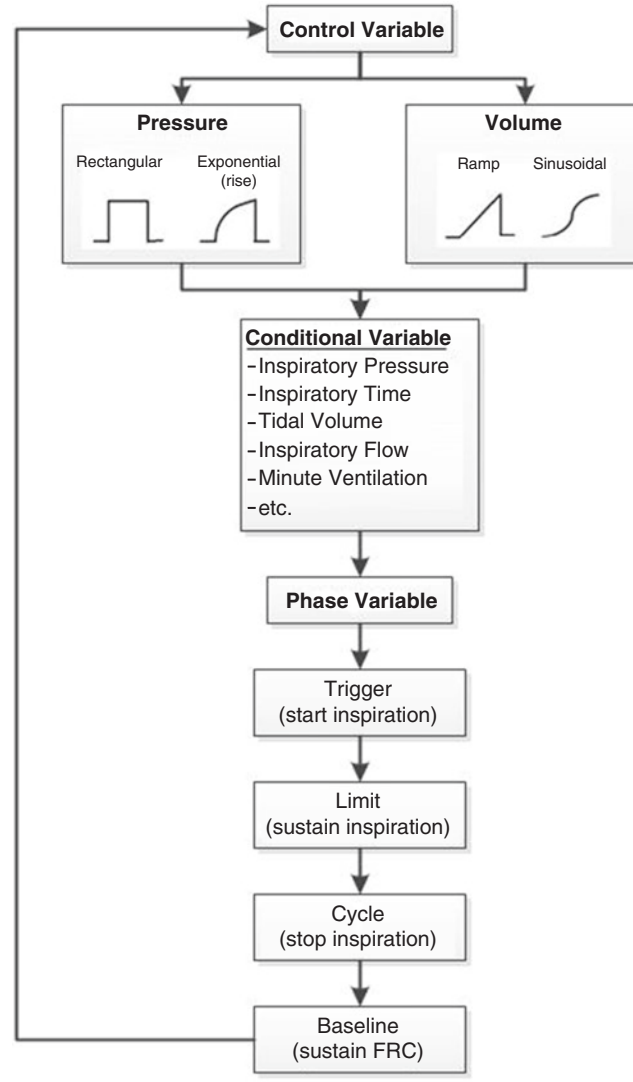

Fig 10.1 Application of the equation of motion to the respiratory system. A common waveform for each control variable is shown. Pressure, volume, flow, and time are also used as phase variables that determine the characteristics of each ventilator cycle (e.g., trigger sensitivity, inspiratory time, baseline pressure). This emphasizes that each control variable may have a different set of control and phase variables, depending on the mode of ventilation desired (Adapted from Chatburn RL. Classification of mechanical ventilator. In: Branson RD, Huess DR, Chatburn RL, editors. Respiratory care equipment. Philadelphia: JB Lippincott; 1995. P. 280, with permission)

(i.e., negative pressure ventilation); or (3) inspiratory pressure is made to be proportional to inspiratory effort, as sensed by the ventilator, as a signal generated by the diaphragm (e.g., flow or electrical voltage). As the equation of motion indicates, pressure is the independent variable, while volume and flow are dependent variables, whose values are determined by elastance (or compliance) and resistance.

B. Volume control

To deliver volume control, the ventilator regulates flow according to a preset value (in a variety of preset flow waveforms) for a preset time, yielding a preset tidal volume. As the equation of motion indicates, flow (and volume, as it is simply the integral of flow) are the independent variables, and thus airway pressure depends upon elastance (or compliance) and resistance. Control of tidal volume can be useful in circumstances of rapidly changing lung mechanics.

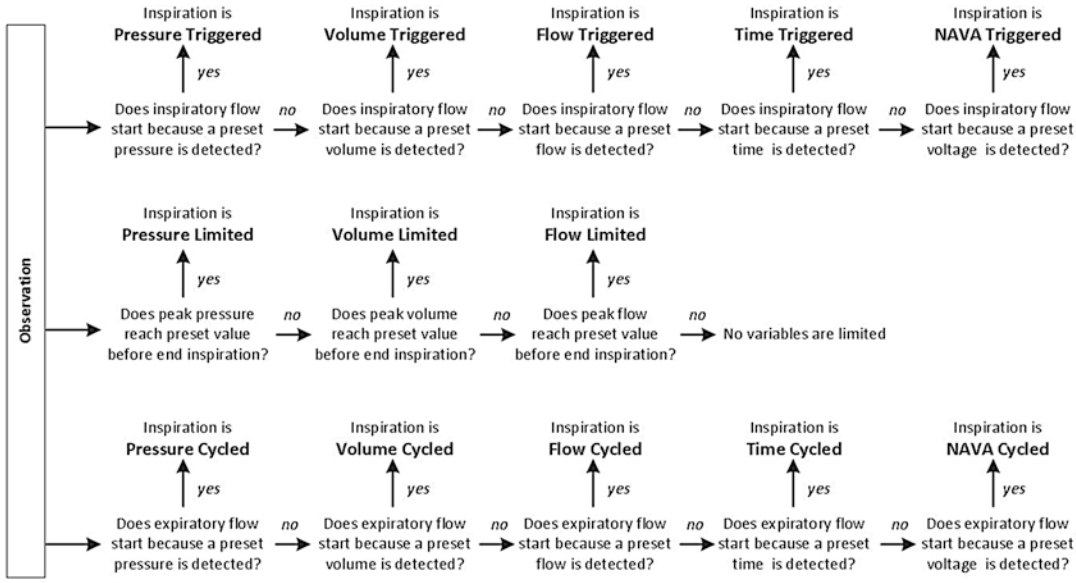

Fig. 10.2 Criteria for determining the phase variables during a ventilator-supported breath (Adapted from Chatburn RL. Classification of mechanical ventilator. In: Branson RD, Huess DR, Chatburn RL, editors. Respiratory care equipment. Philadelphia: JB Lippincott; 1995. P. 280, with permission)

C. Time control

There are modes of ventilation for which neither pressure nor flow/volume is preset. All that is preset are the inspiratory and expiratory times. Hence, we say the control variable is time and the mode is a form of time control (vs. volume or pressure control). High frequency oscillatory ventilation and intrapulmonary percussive ventilation are examples of modes classified as time control.

III. Ventilator Cycle Phase Variables

The ventilatory cycle has four phases: (1) the change from expiration to inspiration (trigger); (2) inspiratory limit; (3) the change from inspiration to expiration (cycle); and (4) expiration (baseline pressure) (Fig. 10.2). With spontaneous breaths, the start and end of inspiration are determined by the patient independent of any ventilator settings. Spontaneous breaths may be assisted (as in pressure support) or unassisted. With mandatory breaths, the patient does not control the timing of the entire breath. A mandatory breath is by definition assisted.

A. Trigger

1. Inspiration begins when one or more monitored variables in the equation of motion (i.e., pressure, volume, flow, and time) reaches a preset threshold.
2. Trigger events may be either patient-initiated or ventilator-initiated.
3. The most common trigger variables are time (i.e., after a pre-defined time, the ventilator is triggered to start inspiration, as in intermittent mandatory ventilation) and pressure (i.e., when an inspiratory effort is detected as a change in the end expiratory pressure, the ventilator is triggered to start inspiration as in patient-triggered ventilation). Flow-triggering involves less patient effort and is more commonly used in neonatal/infant ventilators. Neurally adjusted ventilatory assist (NAVA, Chap. 50) triggers a ventilator breath by monitoring electrical signals from the diaphragm.

B. Limit
   1. Pressure, volume, and flow increase during inspiration.
   2. A limit variable restricts the inspiratory increase to a pre-set value but does not limit the duration.
   3. Many modes delivered by neonatal ventilators are pressure-limited.

C. Cycle
   1. Inspiration stops (or is cycled off) when a monitored variable reaches a pre-set threshold.
   2. Cycling events may be either patient-initiated or ventilator-initiated.
   3. Many neonatal ventilators, including high-frequency ventilators, are time-cycled (ventilator-initiated).
   4. Changes in airway pressure, volume, flow, or electrical signals from the diaphragm may also be used to terminate the inspiratory phase (patient-initiated).

D. Baseline
   The baseline variable maintains expiratory pressure and expiratory lung volume (e.g., positive end expiratory pressure).

IV. Ventilatory Modes

Because neonatal ventilators now offer dozens of modes, it is necessary to have a classification system (taxonomy, Chap. 44) to understand ventilator capabilities. Modes are classified using three basic characteristics. First is the control variable (described above). Second is the "breath sequence" or pattern of mandatory and/or spontaneous breaths. If all breaths are mandatory we say the breath sequence is continuous mandatory ventilation (CMV). If spontaneous breaths are possible between mandatory breaths, the sequence is intermittent mandatory ventilation (IMV). Finally, if all breaths are spontaneous, the sequence is continuous spontaneous ventilation (CSV) (Table 10.1). The third component of a mode classification system adds detail that allows us to distinguish among similar modes. This is the targeting scheme (described below). Thus, to classify a mode, we specify the control variable, the breath sequence, and the targeting scheme. For example, the most common mode use with neonates has historically been called "time cycled, pressure limited." Formally, this mode is classified as pressure control intermittent mandatory ventilation with set-point targeting, appreciated as PC-IMVs.

V. Targeting Scheme (Fig. 10.3)

A target is a pre-determined goal of ventilator output. The targeting scheme describes the relationship between the selected ventilator settings and the ventilator output as detected by feedback control systems. Targets can be set between-breaths or within-breaths. Within each ventilatory mode there are also several targeting schemes that can be distinguished, although some ventilators use more than one targeting scheme. The currently available targeting schemes and their abbreviations (in parentheses) are as follows:

A. Set-point (s)
   Operator sets all the parameters of the pressure wave form or volume and flow waveforms.

B. Dual (d)
   Switches between volume control and pressure control during a single inspiration.

C. Servo (r)
   Ventilator output (pressure or volume) automatically follows a varying input (inspiratory effort).

D. Adaptive (a)
   Ventilator automatically sets one target (pressure) in order to achieve another monitored target (volume).

Table 10.1 Targeting schemes

Name	Abbreviation	Description	Advantage	Disadvantage	Example mode name
Set-point	s	The operator sets all parameters of the pressure waveform (pressure control modes) or volume and flow waveforms (volume control modes)	Simplicity	Changing patient condition may make settings inappropriate	Volume Control Continuous Mandatory Ventilation
Dual	d	The ventilator can automatically switch between volume control and pressure control during a single inspiration	Can adjust to changing patient condition and assure either a preset tidal volume or peak inspiratory pressure, whichever is deemed most important	Complicated to set correctly and needs constant readjustment	Volume Control
Servo	r	The output of the ventilator (pressure/volume/flow) automatically follows a varying input	Support by the ventilator is proportional to inspiratory effort	Requires estimates of artificial airway and/or respiratory system mechanical properties	Proportional Assist Ventilation Plus
Adaptive	a	The ventilator automatically sets target(s) between breaths in response to varying patient conditions	Can maintain stable tidal volume delivery with pressure control for changing lung mechanics or patient inspiratory effort	Automatic adjustment may be inappropriate if algorithm assumptions are violated or they do not match physiology	Pressure Regulated Volume Control
Bio-variable	b	The ventilator automatically adjusts the inspiratory pressure or tidal volume randomly	Simulates the variability observed during normal breathing and may improve oxygenation or mechanics	Manually set range of variability may be inappropriate to achieve goals	Variable Pressure Support
Optimal	o	The ventilator automatically adjusts the targets of the ventilatory pattern to either minimize or maximize some overall performance characteristic (e.g., work rate of breathing)	Can adjust to changing lung mechanics or patient inspiratory effort	Automatic adjustment may be inappropriate if algorithm assumptions are violated or they do not match physiology	Adaptive Support Ventilation
Intelligent	i	Targeting scheme that uses artificial intelligence programs such as fuzzy logic, rule based expert systems, and artificial neural networks	Can adjust to changing lung mechanics or patient inspiratory effort	Automatic adjustment may be inappropriate if algorithm assumptions are violated or they do not match physiology	SmartCare/PS IntelliVent-ASV

PS pressure support, *ASV* adaptive support ventilation

Adapted from Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respiratory Care. 2014;59(11):1747–63, with permission from the American Academy of Respiratory Care

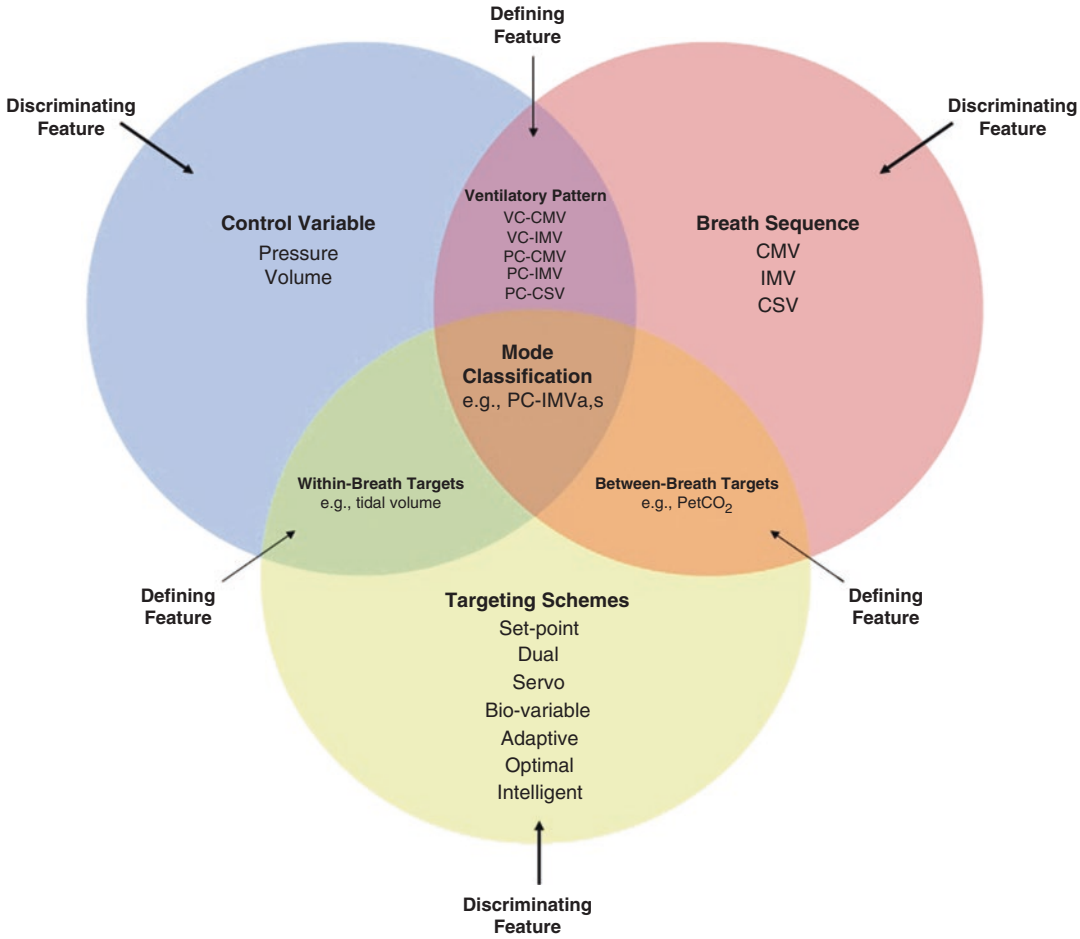

Fig. 10.3 Venn diagram illustrating how the mode taxonomy can be viewed in terms of discriminating features and defining features (From Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respiratory Care. 2014;59(11):1747–63, with permission from the American Academy of Respiratory Care). *CMV* conventional mandatory ventilation, *IMV* intermittent mandatory ventilation, *CSV* continuous spontaneous ventilation, *VC* volume control, *PC* pressure control, $P_{et}CO_2$ end-tidal partial pressure of carbon dioxide, *a* adaptive targeting, *s* set-point targeting

E. Bio-variable (b)
   Ventilator randomly selects inspiratory pressure or volume to mimic the variability of normal breathing.
F. Optimal (o)
   Ventilator automatically adjusts the targets of the ventilatory pattern to either minimize or maximize a monitored target (e.g., work of breathing).
G. Intelligent (i)
   Ventilator automatically adjusts the targets of the ventilatory pattern using artificial intelligence programs.

Suggested Reading

Carlo WA, Greenough A, Chatburn RL. Advances in conventional mechanical ventilation. In: Boynton BR, Carlo WA, Jobe AH, editors. New therapies for neonatal respiratory failure: a physiologic approach. Cambridge, England: Cambridge University Press; 1994. p. 131–51.

Chatburn RL. Classification of mechanical ventilators. In: Branson RD, Hess DR, Chatburn RL, editors. Respiratory care equipment. Philadelphia: J. B. Lippincott Company; 1995. p. 264–93.

Chatburn RL. Understanding mechanical ventilators. Expert Rev Respir Med. 2010;4(6):809–19.

Chatburn RL, Mireles-Cabodevila E. Closed-loop control of mechanical ventilation: description and classification of targeting schemes. Respir Care. 2011;56(1):85–102.

Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

Ventilator Parameters

11

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I. Peak Inspiratory Pressure (PIP)
   A. Physiologic effects
      1. PIP (peak inspiratory pressure relative to atmospheric pressure) in part determines the pressure gradient between the onset and end of inspiration ($\Delta P = \text{PIP} - \text{PEEP}$), and thus affects the tidal volume and minute ventilation.
      2. During volume-targeted ventilation an increase in tidal volume corresponds to an increase in PIP during pressure ventilation. If tidal volume is not measured, initial PIP can be selected based on observation of the chest wall movement and magnitude of the breath sounds.
   B. Gas exchange effects
      1. An increase in PIP will increase tidal volume, and thus increase CO_2 elimination, and decrease $PaCO_2$.
      2. An increase in PIP will increase mean airway pressure, and thus improve oxygenation.
   C. Side effects
      1. An elevated PIP may increase the risk of ventilator-induced lung injury, from barotrauma/volutrauma, and thereby increase the risk of pulmonary air leaks and bronchopulmonary dysplasia.
      2. There is evidence that ventilator-induced lung injury is primarily caused by excessive tidal volume delivery (volutrauma) and lung overdistention rather than high peak pressures in the absence of excessive tidal volumes (barotrauma).
      3. It is important to adjust PIP based on lung compliance and ventilate with relatively small tidal volumes (e.g., 3–5 mL/kg). Adjustment of PIP is particularly important in the setting of rapidly changing lung compliance (e.g., post-surfactant treatment).

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II. Positive End Expiratory Pressure (PEEP)
   A. Physiologic effects
      1. PEEP in part determines lung volume during the expiratory phase, improves *V*/*Q* mismatch, and prevents alveolar collapse.
      2. PEEP contributes to the pressure gradient between the onset and end of inspiration ($\Delta P = \text{PIP} - \text{PEEP}$), and thus affects the tidal volume and minute ventilation.
      3. At least a minimum "physiologic" PEEP of 2–3 cm H_2O should be used in most intubated newborns to improve lung compliance and reduce the risk of atelectrauma from ventilation below the opening pressure of the terminal airways.
   B. Gas exchange effects
      1. An increase in PEEP increases expiratory lung volume (functional residual capacity) during the expiratory phase, and thus improves *V*/*Q* matching and oxygenation in patients whose disease state reduces expiratory lung volume.
      2. An increase in PEEP will increase mean airway pressure, and thus improve oxygenation in patients with respiratory distress syndrome (RDS).
      3. The lowest pulmonary vascular resistance as well as the best lung compliance is found when the lung is neither underinflated nor overinflated. Adequate PEEP improves lung compliance and may allow the use of lower peak pressures to achieve the same tidal volume. Adequate PEEP also maximizes oxygenation for a given mean airway pressure.
   C. Side effects
      1. An elevated PEEP may overdistend the lungs and lead to decreased lung compliance, decreased tidal volume for a given ΔP, and impaired CO_2 elimination.
      2. A very high PEEP may increase pulmonary vascular resistance and decrease cardiac output and oxygen transport.

III. Frequency (or rate)
   A. Physiologic effects
      1. The ventilator frequency (or rate) in part determines minute ventilation ($\text{MV} = f \times V_T$), and thus CO_2 elimination. Ventilation at high rates ($\geq$60/min) frequently facilitates synchronization of the ventilator with spontaneous breaths.
      2. Spontaneous breathing rates are inversely related to gestational age and weight and the time constant of the respiratory system. Thus, infants with smaller and less compliant lungs (RDS) tend to breathe faster based on the principle of minimal work. When the spontaneous respiratory rate is low, excessive work has to be generated by the respiratory muscles to overcome lung and chest wall elastic forces to achieve larger tidal volumes. Therefore, more metabolically efficient alveolar ventilation can be achieved by the brain's respiratory center increasing the respiratory rate rather than increasing the tidal volume.
   B. Gas exchange effects. Very high frequencies as used in mid-frequency ventilation and high-frequency ventilation permit adequate minute ventilation while using lower peak inspiratory pressures and tidal volumes.
   C. Side effects. Use of very high ventilator frequencies may lead to insufficient inspiratory time and decreased tidal volume or insufficient expiratory time and gas trapping, which can negatively affect ventilation by decreasing lung compliance especially in infants with long time constants (established bronchopulmonary dysplasia, BPD). Gas trapping also decreases the pressure gradient between the airway opening and the lungs during pressure control ventilation, thus decreasing V_T.

IV. Inspiratory Time (T_I), Expiratory Time (T_E), and Inspiratory to Expiratory Ratio (*I*:*E* Ratio)
   A. Physiologic effects

1. The effects of the T_I and T_E are strongly influenced by the relationship of those times to the inspiratory and expiratory time constants.
2. A T_I as long as 3–5 time constants allows relatively complete inspiration.
3. T_I of 0.2–0.5 s is usually adequate for newborns with RDS.
4. Infants with a long time constant (e.g., BPD) may benefit from a longer T_I (up to approximately 0.6–0.8 s).

B. Gas exchange effects
1. Changes in T_I, T_E, and *I*:*E* ratio generally have modest effects on gas exchange.
2. A sufficient T_I is necessary for adequate tidal volume delivery and CO_2 elimination.
3. Use of relatively long T_I or high *I*:*E* ratio may improve oxygenation slightly.

C. Side effects
1. Use of a longer T_I (>0.5 s) generally does not improve ventilation or gas exchange and may lead to ventilator asynchrony and an increased risk of pulmonary air leak.
2. A very short T_I will lead to incomplete inspiration and decreased tidal volume.
3. A very short T_E or high *I*:*E* ratio can lead to incomplete expiration and increase gas trapping which can decrease lung compliance, decrease V_T, and impair cardiac output.

V. Inspired Oxygen Concentration (FiO_2)

A. Physiologic effects
1. Changes in FiO_2 alter alveolar oxygen pressure, and thus oxygenation.
2. Because both FiO_2 and mean airway pressure determine oxygenation, the most effective and less adverse approach should be used to optimize FiO_2.
3. When FiO_2 is above 0.6–0.7, increases in mean airway pressure are generally warranted.
4. When FiO_2 is below 0.3–0.4, decreases in mean airway pressure are generally preferred.

B. Gas exchange effects. FiO_2 directly determines alveolar PO_2 and thus PaO_2.

C. Side effects. A very high FiO_2 can damage the lung tissue, but the absolute level of FiO_2 that is toxic has not been determined.

VI. Flow

1. Inspiratory flow is directly set during volume control modes. The higher the flow for a given V_T, the shorter the T_I.
2. Inspiratory flow is indirectly set during pressure control modes and is a function of the set ΔP and the pressure rise time, for a given value of respiratory system time constant. Peak inspiratory flow decreases as respiratory system resistance increases or the pressure rise time increases.
3. Historically, infant ventilators were designed to deliver pressure limited breaths by diverting a pre-set constant flow through a pressure pop-off valve. This is referred to as the "time cycled, pressure limited" mode. At least one modern ventilator (AVEA, CareFusion) still offers this modality. In this scenario, changes in the pre-set constant circuit flow rate affect the airway pressure rise time during inspiration (i.e., the higher the set flow, the faster the pressure rise and the higher the peak inspiratory flow). This phenomenon has not been well studied in infants, but it probably affects arterial blood gases minimally as long as a sufficient flow is used.
4. Inadequate flow (i.e., long pressure rise time and low peak inspiratory flow) may contribute to air hunger, asynchrony, and increased work of breathing if effective opening pressure is not reached within an appropriate time.
5. Higher flow rates and steeper inspiratory pressure slopes (short pressure rise times) may be needed at high ventilator rates with short T_I to maintain adequate flow for complete inspiration.

6. Excessive flow may contribute to turbulence, inefficient gas exchange, and inadvertent PEEP.

VII. In summary, depending on the desired change in blood gases, the following ventilator parameter changes can be performed (Table **11.1**).

VIII. Suggested Management Algorithm for RDS (Fig. **11.1**) Table **11.2** lists abbreviations and symbols seen in the figure.

Table 11.1 Desired blood gas goal and corresponding ventilator parameter changes

Desired goal	PIP	PEEP	Frequency	*I*:*E* ratio	Flow
Decrease $PaCO_2$	↑	↓	↑	–	±↑
Increase $PaCO_2$	↓	↑	↓	–	±↑
Decrease PaO_2	↓	↓	–	↓	±↑
Increase PaO_2	↑	↑	–	↑	±↑

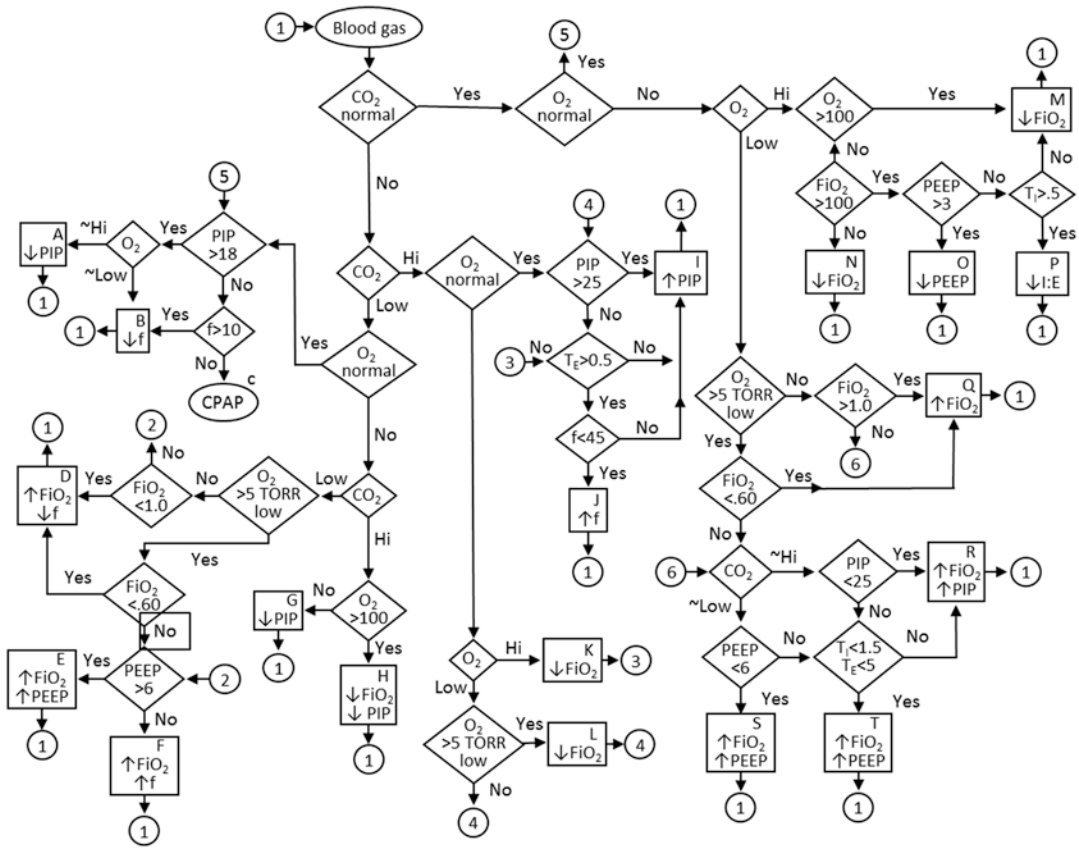

Fig. 11.1 Flowchart illustrating simplified version of ventilator algorithm. Symbols: I, calls for decisions; O, type and direction of ventilator setting changes. Abbreviations: CO_2 arterial carbon dioxide tension (mmHg), O_2 arterial oxygen tension (mmHg), FiO_2 fraction of inspired oxygen, *PIP* peak inspiratory pressure (cm H_2O), *PEEP* positive end-expiratory pressure (cm H_2O), *CPAP* continuous positive airway pressure (cm H_2O), *I:E* ratio of inspiratory to expiratory time, *f* ventilator frequency (breaths per minute), T_I inspiratory time (s), T_E expiratory time (s), *HI* variable in decision symbol is above normal range, *LOW* variable in decision symbol is below normal range, *~HI* variable in decision symbol is at high side of normal, *~LOW* variable in decision symbol is at low side of normal

Table 11.2 Abbreviations and symbols used in the flowchart in figure

CO_2	Arterial carbon dioxide tension (mmHg)
O_2	Arterial oxygen tension (mmHg)
F_iO_2	Fraction of inspired oxygen
PIP	Peak inspiratory pressure (cm H_2O)
Paw	Mean airway pressure (cm H_2O)
PEEP	Positive end-expiratory pressure (cm H_2O)
CPAP	Continuous positive airway pressure without mechanical ventilation (cm H_2O)
I:*E*	Ratio of inspiratory to expiratory time
f	Ventilator frequency (breaths/min). Unless otherwise specified, a change in frequency should be accompanied by a change in *I*:*E* to maintain the same T_I, so that tidal volume remains constant
T_I	Inspiratory time (s)
T_E	Expiratory time (s)
HI	The variable in the decision symbol is above normal range
LOW	The variable in the decision symbol is below normal range
≈HI	The variable in the decision symbol is at the high end of normal
≈LOW	The variable in the decision symbol is at the low end of normal
↑	Increase
↓	Decrease
>	Greater than
<	Less than
Torr	Unit of pressure; 1 Torr–1 mmHg

From Carlo WA, Chatburn RL: Assisted Ventilation of the Newborn. In Carlo WA, Chatburn RL [Eds.]: *Neonatal Respiratory Care*, 2nd edition. Chicago, Year Book Medical Publishers, 1988 p. 339, with permission.)

Suggested Reading

Chatburn RL, Volsko TA. Documentation issues for mechanical ventilation in pressure-control modes. Respir Care. 2011;55(12):1705–16.

Davis GM, Bureau MA. Pulmonary and chest wall mechanics in the control of respiration in the newborn. Clin Perinatol. 1987;14(3):551–79.

Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1997.

Greenough A. Respiratory support. In: Greenough A, Roberton NRC, Milner AD, editors. Neonatal respiratory disorders. New York: Oxford University Press; 1996. p. 115–51.

Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev. 2008;1, CD000456.

Kamlin C, Davis PG. Long versus short inspiratory times in neonates receiving mechanical ventilation. Cochrane Database Syst Rev. 2004;4, CD004503.

Mariani GL, Carlo WA. Ventilatory management in neonates. Controversies in Neonatal Pulmonary Care. 1998;25:33–48.

Mireles-Cabodevila E, Chatburn RL. Mid-frequency ventilation: unconventional use of conventional mechanical ventilation as a lung-protection strategy. Respir Care. 2008;53(12):1669–77.

Spitzer AR, Clark RH. Positive-pressure ventilation in the treatment of neonatal lung disease. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: W.B. Saunders Co.; 2011. p. 163–85.

Walsh BK, Craig N, Betit P, Thompson JE, Arnold JH. Respiratory distress associated with inadequate mechanical ventilator flow response in a neonate with congenital diaphragmatic hernia. Respir Care. 2010;55(3):342–5.

Respiratory Gas Conditioning and Humidification

12

Andreas Schulze

I. Introduction
   A. Inadequate humidification and warming of respiratory gas may lead to adverse effects within minutes to hours in infants with an artificial airway through various mechanisms.
      1. Impaired mucociliary clearance with subsequent retention of inspissated secretions, inhaled particles, and microorganisms. Associated risks are airway clogging, atelectasis, and air leak syndromes.
      2. Inflammatory and necrotic injury to the bronchial epithelium
      3. Heat loss
   B. Humidifier malfunction may also impose risks.
      1. Flushing of contaminated condensate into the airways with subsequent pneumonia
      2. Thermal injury to airways
      3. Over-hydration
      4. Airway occlusion ("Artificial noses," also called Heat and Moisture Exchangers)

II. Physiology: Structure and Function of the Airway Lining
   A. Three layers cover the luminal surface of most of the upper respiratory tract and the entire tracheobronchial tree as far as the respiratory bronchioles. These layers constitute the mucociliary clearance function.
      1. A basal cellular layer of mainly ciliated epithelial cells. A variety of other cell types in this layer may each be concerned with a specific function. Serous cells, brush cells, and Clara cells produce and reabsorb aqueous fluid; goblet cells and submucosal mucous glands secrete mucous globules.
      2. An aqueous (sol) layer
      3. A viscoelastic gel (mucus) layer at the luminal surface of the airway. Neighboring cilia beat in a coordinated fashion so that waves of aligned cilia move through the airway-lining fluid, propelling the mucus and entrapped particles in a cephalad direction. Dry inspired gas may dehydrate the mucus, decrease the depth of the aqueous layer, and change the viscosity gradient across the layers, all of which impair the function of the mucociliary elevator.

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B. The respiratory tract functions as a counter current heat and moisture exchanger.
   1. The inspired air gains heat and water vapor from the upper airway lining, which is partly recovered when the expired gas loses heat, and water condenses on the airway surface. This recovery occurs because the upper airway temperature remains lower than core body temperature during expiration under physiologic circumstances. Breathing is associated with a net loss of heat and water when the expired air temperature is higher than the ambient temperature. The greater the difference in temperature between the inspired and expired gases, the greater the losses. They must be replenished by the airway epithelium, which in turn is supplied by the bronchial circulation. It is unclear under which circumstances the capacity of the airway lining to humidify cold and dry gas becomes overcharged. This capacity is likely different in health than in disease.
   2. The level at which the inspired air reaches core body temperature and full saturation with water vapor is called the isothermic saturation boundary. It is located at the level of the main bronchi during normal quiet breathing. Its position will move distally when frigid dry gas is inhaled, when minute ventilation is high, or when the upper airway is by-passed (e.g., use of a tracheostomy tube). Overall, however, under normal physiologic circumstances, only a small segment of the airway surface is exposed to a temperature below core body temperature and to less than full saturation.
   3. Damage to the airway epithelial cells and their luminal coverage deprives the system of its function as a heat and moisture exchanger. Loss of this function may in turn induce structural damage in a vicious cycle that leads to penetration of the injury into the periphery of the bronchial tree.

III. Basic Physics of Humidity and Heat

A. Air can accommodate water in two different ways.
   1. Nebulized water (aerosol) is a dispersion of droplets of water in air. They are visible because they scatter light (clouds) and may carry infectious agents. Deposition occurs along the tracheobronchial tree by impaction and sedimentation. The smaller the particles, the better they penetrate into more peripheral areas of the lung.
   2. Vaporized water is a molecular (i.e., gaseous) distribution of water in air. It is invisible and unable to carry infectious agents. The gaseous partial pressure of water vapor is 47 mmHg when air is fully saturated (100 % relative humidity) at 37 °C. This corresponds to 44 mg of water per liter of gas (absolute humidity). The term absolute humidity (AH) is defined as the amount of water vapor (mg) per gas volume (mL) at a given temperature.
   3. Relative humidity (RH) is the actual amount of water (mg) in a given gas volume relative to the amount of water content (mg) in this same gas volume at the same temperature at full saturation.
   4. There is a fixed relationship between AH, RH, and temperature (Fig. 12.1).

B. Air can accommodate heat in two distinct variants. The total heat content determines the capacity of inspired gas to cool or overheat the airway.
   1. The air temperature represents sensible heat. Increasing the air temperature alone without adding water vapor adds very little to the total energy content of the gas. Therefore, if the respiratory gas leaves the humidifier chamber fully saturated at 37 °C and is subsequently dry-heated to 40 °C within the inspiratory limb of the ventilator circuit, it does not entail the risk of overheating or thermal injury to the airway.
   2. The water vapor mass reflects the latent heat content. Changes in humidity represent major changes in total energy content compared to changes in air temperature alone. Therefore, vaporization consumes much energy, and thus vaporization of water from the airway lining

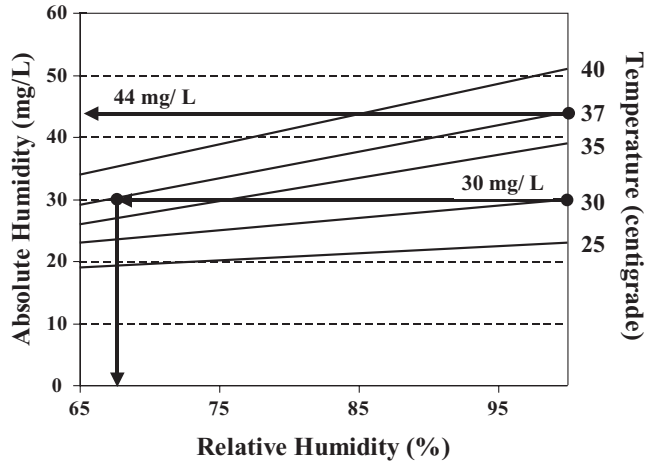

Fig. 12.1 Relationship between absolute humidity, relative humidity, and temperature of gases. The relative humidity depends on the absolute water content and the temperature of the gas. At 37.0 °C and 100 % relative humidity, the respiratory gas has 44 mg/L absolute water content. If the gas is saturated (100 % relative humidity) at 30.0 °C, its water content will be only 30 mg/L. When the gas is then warmed to 37.0 °C, its relative humidity will fall to below 70 %

fluid for humidification of dry inspiratory gas has a strong capacity to cool the airway, even if warm gas enters the airway. Conversely, rainout (condensation of water vapor) generates energy. If it occurs inside the inspiratory limb of the ventilator circuit, the tubing may feel "nice and warm" even though the gas loses the required energy (and water vapor) content.

IV. Inspired Gas Conditioning Devices and Procedures. Medical-grade compressed gases from cylinders or central supply systems have virtually negligible water content. It is rational to deliver the inspiratory gas at or close to core body temperature and close to full saturation with water vapor to infants with an artificial airway (nasal or pharyngeal prongs or cannula, endotracheal tube, or tracheostomy tube).
   A. Heated humidifiers.
      1. The respiratory gas is warmed inside the humidification chamber to a set target temperature, and water vapor is added from the heated water reservoir.
      2. Heated-wire inspiratory circuit tubing is then used to maintain or slightly raise the gas temperature so as to prevent rainout before the gas reaches the infant. Heated humidifiers are safe and effective respiratory gas conditioning devices for short-term and long-term application in infants. However, their technology is complex and device malfunction is not always immediately obvious. Consideration should be given to basic principles of operation common to all types of heated humidifiers.
         a. The target respiratory gas condition is a temperature close to core temperature with nearly full water vapor saturation. To achieve this target, the gas must be loaded with nearly 44 mg of water/L.
         b. Knowing the circuit flow rate of the ventilator, the minimum water consumption rate of the humidifier chamber to meet this target can easily be estimated and can be used to check the function of the humidifier (Fig. 12.2).
         c. Rainout in the inspiratory limb of the ventilator does not prove that there is proper humidification. Major circuit condensation usually indicates a moisture loss that leads to under-humidification of the respiratory gas. This may occur if the maximum heating

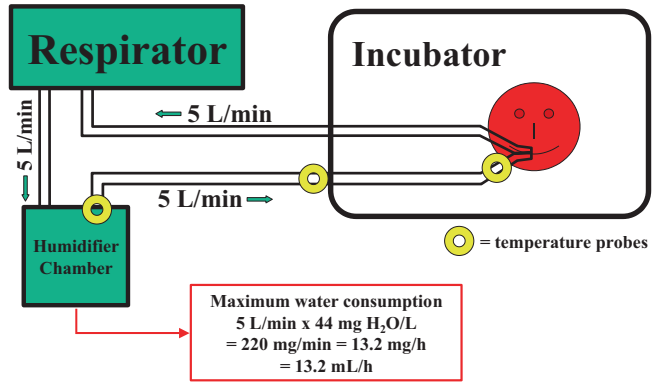

Fig. 12.2 Position of three temperature probes of a heated-wire humidification system for infants. The user sets the target temperature to be reached at the endotracheal tube adaptor. This temperature is commonly set at or slightly above 37.0 °C. The temperature inside the humidifier chamber must be high enough to vaporize an amount of water near the absolute water content of gas saturated at 37 °C (44 mg/L). The water consumption rate of a humidifier chamber required to reach a target respiratory gas humidity can be calculated from the circuit flow rate. Observation of this water consumption rate can be employed as a simple test of the efficiency of a humidifier

capacity of the heated circuit wire cannot meet requirements under specific conditions such as drafts around the tubing (air-conditioned rooms), low room temperatures, or a large outer surface area of small diameter tubing (particularly if corrugated).

d. Rainout should also be avoided for other reasons: condensate is easily contaminated, may be flushed down the endotracheal tube with risks of airway obstruction and nosocomial pneumonia, and may disturb the function of the ventilator (particularly autocycling in patient-triggered ventilators). Binding the inspiratory and expiratory limbs of the tubing closely may obviate the problem.

3. The temperature probe close to the patient connection serves to monitor the respiratory gas temperature. It is commonly part of a servo-control aimed at maintaining the set gas temperature at the wye adapter by controlling the heated-wire power output.
   a. If the temperature probe is in the presence of a heated field (incubator or radiant warmer), it may register a temperature higher than the actual respiratory gas temperature as a result of radiation or convection from the warmer environment. This may cause the servo-control to decrease the heating output of the ventilator circuit and may lead to loss of gas temperature and rainout.
   b. Insulating the temperature probe by a light reflective patch or other material can improve the performance of the system.
   c. Another way to alleviate this problem is to place the temperature probe just outside the heated field and use an unheated extension adapter tubing to carry the gas through the heated field to the infant. The extension tube does not need to incorporate heated wires because its temperature is maintained by the heated field.
   d. If cooler incubator temperatures are employed, as for older preterm infants, rainout will occur in the unheated segment, particularly at low circuit gas flow rates. A circuit should then be used that is equipped with a heated wire along the entire length of its inspiratory limb.
   e. Another suitable type of circuit is one with two temperature probes, one outside the heated field and another one close to the wye adapter. These circuits can perform well

over a range of incubator temperatures above and below the target respiratory gas temperature, because the heated-wire servo-control can be programmed to select the lower of the two recorded temperatures to drive the power output.

B. Artificial noses.
   1. Working principle: Heat and moisture exchangers (HMEs) recover part of the heat and moisture contained in the expired air. A sponge material of low thermal conductivity inside the clear plastic housing of these devices absorbs heat and condenses water vapor during expiration for subsequent release during inspiration.
   2. Different brands may vary widely in performance characteristics. Device performance has improved, and further advances can be expected to facilitate neonatal applications.
      a. Some HMEs are additionally coated with bacteriostatic substances and equipped with bacterial or viral filters.
      b. Hygroscopic condenser humidifiers (HCH) use hygroscopic compounds, such as $CaCl_2$, $MgCl_2$, and LiCl to increase the water retention capacity.
   3. Application
      a. These devices are appropriate for short-term conventional and high-frequency mechanical ventilation in infants, such as during transport or surgical procedures.
      b. The safety and effectiveness of HME/HCH for long-term mechanical ventilation is controversial in adults and has not been established in infants.
      c. HMEs/HCHs must not be used in conjunction with heated humidifiers, nebulizers, or metered dose inhalers. This may cause a hazardous increase in device resistance and/ or leaching of the hygroscopic coating.
   4. Advantages of HMEs/HCHs
      a. Simplification of the ventilator circuit
      b. Passive operation without requirement of external energy and water sources
      c. No ventilator circuit condensate
      d. Low risk of circuit contamination
      e. Low expense
   5. Potential risks and drawbacks of HMEs/HCHs
      a. Depending upon the actual water load, these devices add a variable resistance and dead space to the circuit.
      b. A risk of airway occlusion from clogging with secretions or from a dislodgement of internal components has been reported for infants, even during short-term application.
      c. An expiratory air leak will impair the barrier effect of any HMEs/HCH against moisture loss.
   6. Measures of effectiveness of HMEs/HCHs
      a. Performance is not reliably reflected by indirect clinical measures, such as the occurrence of nosocomial pneumonia, number of endotracheal tube occlusions, or frequency of suctioning.
      b. Visual evaluation of the amount of moisture in the adapter segment between the endotracheal tube and the HME/HCH was found to closely correlate with objective measurements of the delivered humidity.

C. Aerosol application for respiratory gas conditioning. Water or normal saline nebulization offer no significant benefits for inspiratory gas conditioning compared to the use of heated humidifiers. It may entail a risk of over-humidification.
   1. With appropriate use of heated humidifiers, the isothermic saturation boundary is close to the tip of the endotracheal tube. Downstream of this, aerosol particles cannot be eliminated

through evaporation and exhalation. They will therefore become a water burden to the mucosa.
   a. The surplus water needs to be absorbed by the airway epithelium in order to maintain an appropriate periciliary fluid depth.
   b. An increase in depth of the airway lining fluid's aqueous layer may make it impossible for the cilia to reach the mucous layer and thus impair mucus transport.
   c. Furthermore, if the aerosol deposition rate exceeds absorption capacity, this may lead to increased airway resistance and possibly narrowing or occlusion of small airways.
   d. Severe systemic over-hydration subsequent to ultrasound aerosol therapy has been described in the term newborn and in adults.
2. If an aerosol stream meets the airway proximal to the isothermic saturation boundary, the particulate water can theoretically contribute to the gas conditioning process by evaporation before and after deposition. The droplets, however, contain sensible heat only, and the mucosa needs to supply most of the latent heat for vaporization. This will cool the airway.

D. Irrigation of the airway.
1. It is a common clinical practice to instill small amounts (0.1–0.5 mL/kg) of water, normal saline solution, or diluted sodium bicarbonate periodically into the endotracheal tube prior to suctioning procedures in the belief that this provides moisture and loosens tenacious secretions.
2. The safety and efficacy of this practice has not been established.

V. Inspiratory Gas Conditioning and the Nosocomial Infection Risk
A. There is no evidence that appropriate warming and humidifying of respiratory gases increase the risk of nosocomial pneumonia in infants with an artificial airway.
B. The incidence of nosocomial pneumonia in adults was not increased when ventilator circuits were changed less frequently than every 24 h or even between patients only.
C. The optimal rate of ventilator circuit changes for infants is unknown. Changing a ventilator circuit may disrupt ventilation in a potentially dangerous way, and medical personnel may become a vector for cross-contamination between patients. Weekly circuit changes or no circuit changes at all except between patients appears to be a rational (though unproven) approach.

Suggested Reading

Kelly M, Gillies D, Todd DA, Lockwood C. Heated humidification versus heat and moisture exchangers for ventilated adults and children. Cochrane Database Syst Rev 2010; CD004711.

Kollef MH, Shapiro SD, Boyd V, et al. A randomized clinical trial comparing an extended-use hygroscopic condenser humidifier with heated-water humidification in mechanically ventilated patients. Chest. 1998; 113:759.

Lellouche F, Taillé S, Lefrançois F, Deye N, Maggiore SM, Jouvet P, Ricard JD, Fumagalli B, Brochard L, Groupe de travail sur les Respirateurs de l'AP-HP. Humidification performance of 48 passive airway humidifiers: comparison with manufacturer data. Chest. 2009;135:276.

Nakagawa NK, Macchione M, Petrolino HM, et al. Effects of a heat and moisture exchanger and a heated humidifier on respiratory mucus in patients undergoing mechanical ventilation. Crit Care Med. 2000;28:312.

Ricard JD, Le Miere E, Markowicz P, et al. Efficiency and safety of mechanical ventilation with a heat and moisture exchanger changed only once a week. Am J Respir Crit Care Med. 2000;161:104.

Schiffmann H, Rathgeber J, Singer D, et al. Airway humidification in mechanically ventilated neonates and infants: a comparative study of a heat and moisture exchanger vs. a heated humidifier using a new fast-response capacitive humidity sensor. Crit Care Med. 1997;25:1755.

Schulze A. Respiratory gas conditioning in infants with an artificial airway. Semin Neonatol. 2002;7:369.

Shelly MP, Lloyd GM, Park GR. A review of the mechanisms and methods of humidification of inspired gases. Intensive Care Med. 1988;14:1.

Siempos II, Vardakas KZ, Kopterides P, Falagas ME. Impact of passive humidification on clinical outcomes of mechanically ventilated patients: a meta-analysis of randomized controlled trials. Crit Care Med. 2007;35:2843.

Williams RB. The effects of excessive humidity. Respir Care Clin N Am. 1998;4:215.

Williams R, Rankin N, Smith T, et al. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. Crit Care Med. 1996;24:1920.

Section III

Procedures and Techniques

Cardiorespiratory Examination

13

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I. Normal Physical Findings
   A. Respiratory rate 40–60/min
      1. Irregular with pauses ≤5 s in rapid eye movement (REM) sleep
      2. Regular in non-REM sleep, rate 5–10 breaths/min slower than in REM sleep or when awake
      3. Comfortable (no dyspnea)
      4. No chest retractions (subcostal or intercostal)
      5. No flaring of nostrils
      6. No grunting
   B. Pulse rate 120–160 beats/min (but may go as low as 80 during sleep)
      1. Sinus arrhythmia rare in the newborn
      2. Pulses easy to feel;
         a. Femoral pulses may be decreased in the first 48 h
         b. Femoral pulses may be impalpable, reduced or delayed with coarctation of the aorta. In any infant with suspected heart disease, blood pressure should be measured in all four limbs. A difference of >15 mmHg between the upper (higher) and lower extremities is significant.
         c. Bounding pulses are characteristic of a patent ductus arteriosus
      3. Interpreting the heart rate is best done in conjunction with the respiratory rate and oxygen saturation.
         a. Episodes of desaturation are mostly transient or from movement artifact, but if more severe and prolonged will be accompanied by bradycardia.
         b. An increase in heart rate may be observed with movement/crying, respiratory distress, anemia, hypovolemia, fever, infection, pain, fluid overload, or arrhythmias
         c. Slowing of the heart is seen with hypoxia, hypothermia, seizures, heart block, and (rarely) increased intracranial pressure.

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d. Monitor artifacts may also produce bradycardia. The clinical diagnosis of neonatal sepsis is preceded by abnormal heart rate characteristics of transient decelerations and reduced variability. (HERO system)

C. First and second heart sounds are often single; S_2 splits by 48 h in 75 % of infants.
D. Murmurs are common in first few days (1–2 % of normal infants).
E. Blood pressure (see below)

II. Clinical Examination of Cardiorespiratory System
A. The four classic components should be followed.
1. Observation
2. Palpation
3. Percussion
4. Auscultation. Murmurs are common in healthy newborns. Their source may be pulmonary branch stenosis, patent ductus arteriosus, tricuspid regurgitation, or other congenital cardiac lesions.

B. In the newborn, careful visual as well as auditory observation is important.
C. Cardinal signs of respiratory distress
1. Intercostal, subcostal, and substernal *retractions* (use of accessory muscles)
2. Nasal *flaring* (decreases airway resistance)
3. Expiratory *grunting* (increases positive end expiratory pressure)
4. *Tachypnea* >60/min
5. *Cyanosis*
a. Peripheral cyanosis (extremities) is common in normal infants.
b. Central cyanosis (lips and tongue) signifies >5 g/dL of desaturated hemoglobin and is significant ($SpO_2 < 90\,\%$).
c. The commonest causes of cyanosis are heart disease, pulmonary disease, and methemoglobinemia. The underlying cause of cyanosis must be determined. If cyanosis is relieved by oxygen administration, the most likely cause is pulmonary disease.

III. Observation
A. Respiratory Rate
1. Rates >60 breaths/min are abnormal.
2. Very fast rates may have a better prognosis as they occur in more mature babies with a good respiratory pump able to sustain the tachypnea.
3. Slow irregular rates <30 breaths/min with or without gasping are ominous as are apneic periods in term infants.
4. Remember that tachypnea is a very nonspecific finding and can be caused by:
a. Pulmonary disease
b. Cardiac disease
c. Sepsis
d. Anemia
e. Metabolic acidemia of any cause
f. Fever
g. CNS pathology
h. Stress (e.g., after feeding or crying)

IV. Dyspnea
A. Distortion of the chest by the powerful attempts of the muscles of respiration to expand noncompliant lungs is one of the most significant findings in parenchymal lung disease.
B. With anemia, acidemia, cyanotic heart disease, or fever, there is often tachypnea without dyspnea (“comfortable tachypnea”).

C. Preterm babies (<1.5 kg) in non-REM sleep when muscle tone is low often show mild intercostal and subcostal retractions.
D. Other features of dyspnea include:
   1. Flaring of the alae nasi. By enlarging the nostrils there is a reduction in nasal resistance enhancing air flow.
   2. "See-saw" respiration; abdominal expansion (from diaphragmatic contraction) at the same time as sternal retractions.
   3. Intercostal and subcostal retractions
   4. Retractions (suprasternal, intercostals, and subcostal) result from the compliant rib cage being drawn in on inspiration by the diaphragm as the infant attempts to generate high intrathoracic pressures in order to ventilate poorly compliant lungs.

V. Interaction with Positive Pressure Ventilation
A. In the early stages of severe lung disease, especially respiratory distress syndrome (RDS), the baby may breathe out of phase with the ventilator. This compromises oxygenation and increases the risk of air leaks. Synchronization of the ventilator to the baby's own respiratory effort has been shown to decrease time on the ventilator and assists weaning.
B. In both situations it is important to be aware of the ventilator rate as well as the baby's spontaneous ventilation rate (total respiratory rate).
C. If the baby's condition has deteriorated rapidly, is the chest moving at all with the ventilator? It if is not, it may suggest a blocked or dislodged endotracheal tube. Always consider a pneumothorax in an infant whose condition has deteriorated rapidly.

VI. Apnea and Gasping
When counting the respiratory rate note if there are any pauses lasting more than 20 s, or if there are any gasping respirations (both very abnormal), as opposed to normal sighs (deep inspirations against the normal background respiratory pattern).

VII. General Appearance
A. Does the baby look ill or well? Multiple factors to assess are:
   1. Color (pallor, cyanosis, plethora)
   2. Level of activity and overall tone
   3. Cry
   4. Eye opening
   5. Posture
   6. Edema
   7. Perfusion
   8. Dysmorphic features
B. Edema—leaky capillaries in ill babies lead to subcutaneous edema as well as pulmonary edema.
C. Perfusion
   1. Pallor (capillary refill time >3 s)
   2. Nonspecific illness
   3. Anemia
   4. Hypotension
   5. Shock (septic or other)
   6. Visible veins in skin (especially in preterm)
      a. Hypercapnia
      b. Nonspecific severe illness with shock (e.g., extensive hemorrhage)

D. Cyanosis
1. Assessed from lips, mucous membranes (acrocyanosis is peripheral cyanosis of hands and feet; it is common and rarely significant). May be difficult to see in non-white races (even in mucosa)
2. Cyanosis results from >5.0 g/dL desaturated hemoglobin.
   a. Seen in normally oxygenated polycythemic babies
   b. Difficult to detect in very anemic babies
3. In an oxygen-enriched environment, oxygen may be absorbed through the skin making the baby look pink although central cyanosis may be present.

E. Saturation (Chaps. 18 and 19):
1. Because clinical signs of hypoxemia are unreliable, if in doubt initially check oxygen saturation (SpO_2) by oximetry (quick and easy) and if necessary confirm hypoxemia by arterial blood gas analysis.
2. An arterial oxygen tension of 60–90 Torr results in a saturation of 94–98 % and changes of 1–2 % usually reflect a PaO_2 change of 6–12 Torr. Below 40 Torr the saturation falls below 90 %.
3. Saturations above 95 % are normal in term babies.
4. Note that SpO_2 does not correct for abnormal hemoglobin as in methemoglobinemia—baby is blue but saturation is high.

VIII. Clubbing (rarely seen in newborns)

IX. Venous Pressure
A. Observe venous pulsation in the neck for evidence of congestive heart failure.
B. Prominent pulsation in the neck may be observed with Vein of Galen arteriovenous malformation.
C. Auscultation of the head will reveal a bruit.

X. Other Systems
A. Abdomen
1. Distention
   a. Large amount of gas in stomach after positive pressure ventilation, especially with mask and bag
   b. Enlarged liver from heart failure, hepatitis, or metabolic disorder; liver is normally 1–2 cm below the costal margin
   c. Liver may be displaced caudally by hyperinflated chest or tension pneumothorax.
   d. Enlarged spleen, kidneys, or other abdominal mass
   e. Retention of urine secondary to drugs, CNS disease
   f. Tense distended abdomen, which transilluminates with perforated viscus and free air in abdomen (Fig. 13.1)
2. Scaphoid abdomen strongly suggests congenital diaphragmatic hernia

B. Central Nervous System
1. Seizures
2. Tense fontanelle when the newborn is not crying suggests increased intracranial pressure.
3. Abnormal tone
4. Abnormal level of consciousness (e.g., irritability, lethargy, coma)

XI. Auditory Observations
A. Listen to the baby. If he/she is crying vigorously, he/she is unlikely to be seriously ill.

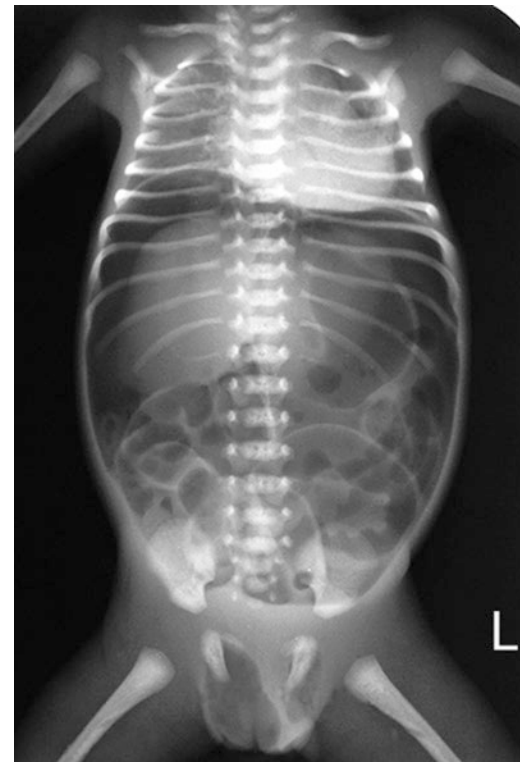

Fig. 13.1
Pneumoperitoneum—ruptured viscus. Extensive free air under diaphragm with liver surrounded by large collection of air

B. Three important auditory clues:
   1. Grunting—a pathognomonic feature of neonatal lung disease—expiration against a partially closed glottis traps alveolar air and maintains functional residual capacity (FRC).
   2. Stridor, usually inspiratory
      a. Upper airway problems (e.g., laryngomalacia is the commonest)
      b. Glottic and subglottic injury or post-intubation edema
      c. Local trauma following over-vigorous laryngeal instrumentation
      d. Congenital subglottic stenosis
      e. Vascular rings, hemangiomas, hamartomas (rare)
   3. "Rattle"—the bubbling of gas through secretions in the oropharynx. Often an ominous sign in a baby with severe CNS injury as well as lung disease.
   4. Excessive drooling with choking and cyanosis suggests esophageal atresia (diagnose by placing an orogastric tube and chest radiograph; if present, tube will end in esophageal pouch; a stomach bubble indicates a fistula)

XII. Palpation
   A. Not usually of great help. The following may be noted:
      1. Mediastinal shift (trachea, apical beat) with air leak, diaphragmatic hernia, collapse (consolidation)
      2. Tense abdomen (tension pneumothorax or pneumoperitoneum)

3. Subcutaneous emphysema following air leaks creates crepitus
4. Pulses
   a. Should be checked in all four limbs if there is any suspicion of cardiac disease and documented by blood pressure measurements
   b. Bounding pulses are a feature of increased cardiac output often with a left-to-right shunt. In the preterm infant this may be the first sign of a PDA.
5. Cardiac precordial activity
6. Thrills are very rare in the neonatal period; if present, always significant.

XIII. Percussion
   A. Increased resonance may be seen with a pneumothorax and occasionally with severe pulmonary interstitial emphysema (PIE).
   B. Decreased resonance accompanies pleural effusions.
   C. Decreased resonance with marked collapse/consolidation
      1. Pneumonia
      2. Endotracheal tube in one bronchus
   D. Decreased resonance with congenital diaphragmatic hernia

XIV. Auscultation
   A. Always use the small neonatal stethoscope. It can be difficult to apply to the chest of a preterm newborn in a way that excludes extraneous noise, and trial and error will identify whether the bell or diaphragm is best in a given situation. Use whichever gives the best acoustic seal.
   B. Another problem is that babies, particularly preterm ones, wiggle when the stethoscope is placed on the chest making cardiac examination difficult. The trick is to hold the prewarmed stethoscope in the same place and after 10–15 s the baby habituates to the stimulus and lies still.
   C. Breath sounds are widely conducted through the upper torso of the newborn, and the smaller the baby, the greater the conduction. Even with the neonatal stethoscope head it is difficult to be certain about where air is going. Two common (and very serious) auscultation mistakes:
      1. Failing to realize during mechanical ventilation that air is going in and out of the stomach rather than the lungs.
      2. Failing to realize that only one lung is being ventilated (particularly if there is some mediastinal shift).

XV. Air Entry
   A. The breath sounds in newborns with normal lungs can be heard in both inspiration and expiration, being slightly louder and longer in inspiration. In other words, part of the expiratory phase, which is physiologically longer, is silent.
   B. A general reduction in air entry is heard with:
      1. Any severe lung disease (e.g., RDS)
      2. Occluded endotracheal tube
   C. Unilateral decrease in air entry—any unilateral lung disease, which will usually require a chest radiograph for further evaluation.
      1. Pneumonia
      2. Air leak
      3. Pleural effusion
      4. Misplaced endotracheal tube/spontaneous extubation
      5. Unilateral pulmonary atresia (rare)

XVI. Other Sounds

A. There should be no rales or crepitations (discontinuous sounds) and no rhonchi (continuous sounds). The other common sound heard on auscultating the chest of a preterm baby is condensed water bubbling in the ventilator circuit or endotracheal tube. Clearly, it is impossible to do a successful clinical examination under these circumstances. The tubing should be transiently disconnected from the ventilator circuit and emptied.

B. Crepitations occur in:
   1. Pneumonia
   2. Aspiration
   3. Heart failure (PDA and other)
   4. Massive pulmonary hemorrhage
   5. Bronchopulmonary dysplasia (BPD)
   6. Meconium aspiration (stickier and louder)

C. Rhonchi occur with:
   1. Retained secretions during mechanical ventilation
   2. Meconium aspiration
   3. BPD

D. *None of these findings is specific*. They indicate a lung disease that requires further evaluation, initially by radiography.

E. Bowel sounds in the chest are a specific finding of congenital diaphragmatic hernia.

XVII. Cardiac Auscultation

A. Heart sounds—the ready availability of echocardiography has blunted the need for sophisticated auscultatory diagnostic skills for the newborn. The following, however, should always be noted:
   1. S_1 and S_2 are usually single in the first 24–48 h, with splitting of S_2 being present in 75 % of babies by 48 h.
   2. A gallop rhythm (S_3 and S_4) is always abnormal, usually indicating heart failure.

B. Innocent murmurs are very common in the first 24–48 h; characteristics:
   1. Grade 1–2/6 mid-systolic at the left sternal edge
   2. No ejection clicks
   3. Occur in babies with normal pulses (especially femoral; document by blood pressure measurements)
   4. Occur in babies with an otherwise normal clinical examination

C. Significant murmurs are more likely to be heard >48 h of age; their features include:
   1. Pansystolic ± diastolic ± thrills
   2. Grade 3/6 or more and harsh
   3. Best heard at upper left sternal edge (e.g., PDA)
   4. Abnormal S_2 (not splitting) ± gallop rhythm
   5. Early or mid-systolic click
   6. Decreased femoral pulses with murmur heard at back
   7. Other signs of illness (heart failure, shock, and cyanosis)

D. Any baby with these features needs urgent evaluation (radiography, electrocardiography, and echocardiography). The absence of murmurs or auscultatory abnormality in the first 48–72 h does not exclude serious or even lethal heart disease.

XVIII. Transillumination (Chap. 24)

A. A bright light source applied to the chest wall can be a very useful and effective way of detecting a collection of intrapleural air, typically a pneumothorax, but large cysts, severe PIE, or marked lobar emphysema may also transilluminate. To be effective the light source has to be very bright (ideally a fiber-optic source), the room around the baby needs to be very dark, time for adaptation to the dark, and some experience is required to differentiate the normal 0.5–0.1 cm halo of light around the probe from increased transillumination from a small collection of air. In cases where the whole hemithorax lights up, the diagnosis is easy.

B. The technique is more useful in smaller babies in whom the light is transmitted into the pleural cavity much more easily than with term babies with a thick layer of subcutaneous fat.

XIX. Blood Pressure (Chap. 56)

A. The readily available automatic blood pressure recording devices now mean that this is a routine part of the assessment of all newborns.

B. Attention to the following details is important:

1. Baby quiet and not recently crying
2. Cuff covers 75 % of the distance between the axilla and the elbow.
3. Bladder virtually encircles the arm
4. A similar cuff size if appropriate for the upper arm and the calf.

C. In ill preterm babies, the oscillometric device may over-estimate the true blood pressure, and if there is any doubt about systolic pressure accuracy, direct measurement from an indwelling arterial catheter may be indicated.

D. In summary, in the newborn the circulation is assessed by:

1. Blood pressure measurement. Normative values are available for term infants, but there are less reliable data for extremely low birth weight infants (Fig. 13.2). BP may correlate poorly with systemic blood flow and circulating volume. Cerebral blood flow is critical.
2. Heart rate. Tachycardia from hypovolemia is common, and bradycardia is a late sign of shock.
3. Temperature difference (between abdomen and toes) >2 °C may suggest shock. Also caused by a cold environment and infection without shock.
4. Capillary refill time >3 s is abnormal.
5. Acid–base status (increased lactate with circulatory insufficiency)
6. Echocardiographic evaluation of cardiac function
7. Urine output (after the first 24 h.)

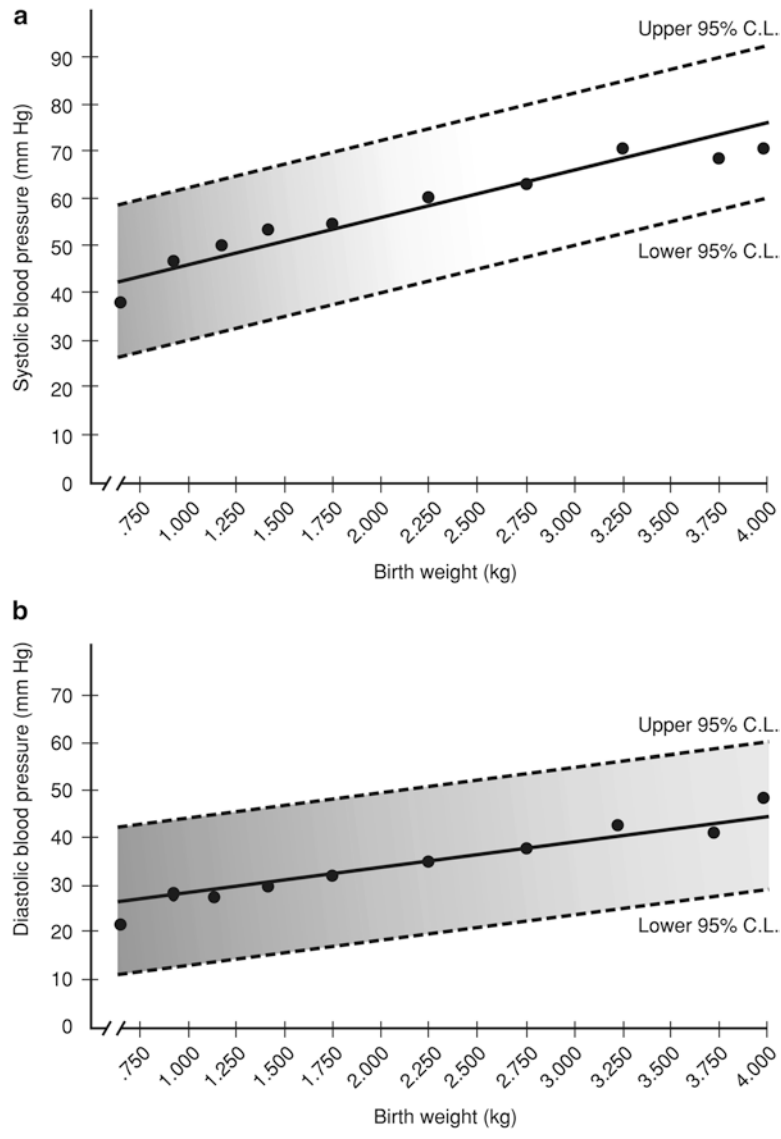

Fig. 13.2 Linear regression of mean (**a**) and diastolic (**b**) blood pressure on birth weight in 329 infants admitted to the NICU on day 1 of life is plotted. *C.L.* confidence limits. (From Zubrow AB, Hulman S, Kushner H, et al.: Determination of blood pressure in infants admitted to neonatal intensive care units. A prospective multicenter study. J Perinatol 1995; 15:470–479. Copyright, the Nature Publishing Group, reprinted with permission.)

Suggested Reading

Arlettaz R, Archer N, Wilkinson AR. Natural history of innocent heart murmurs in newborn babies: controlled echocardiographic study. Arch Dis Child Fetal Neonatal Ed. 1998;78:F166–70.

Barrington K. Neonatal screening for life threatening congenital heart disease. BMJ. 2009;338:a2663.

Coggins SA, Weitkamp JH, Grunwald L, Stark AR, Reese J, Walsh W, Wynn JL. Heart rate characteristic index monitoring for bloodstream infection in an NICU: a 3-year experience. Arch Dis Child Fetal Neonatal Ed. 2016; 10:F329–32.

Frommelt MA. Differential diagnosis and approach to a heart murmur in term infants. Pediatr Clin North Am. 2004;51:1023–32.

Greenough A, Greenall F. Observation of spontaneous respiratory interaction with artificial ventilation. Arch Dis Child. 1988;63:168–71.

Yi MS, Kimball TR, Tsevat J, Mrus JM, Kotagal UR. Evaluation of heart murmurs in children: cost-effectiveness and practical implications. J Pediatr. 2002;141:504–11.

Neonatal Resuscitation

14

Gary M. Weiner

I. Anticipating resuscitation. Most newborns make the fetal-to-neonatal transition without intervention. When any risk factor from a candidate list of potential moderate and high risk factors was present, 20 % of newborns required positive-pressure ventilation (PPV) to aerate their lungs. Given the large number of births each year, this represents a relatively frequent emergency. With appropriate attention to identifiable risk factors, most neonatal resuscitations can be anticipated before birth, however; even in the complete absence of risk factors a small proportion (0.2–7 %) will require PPV. Achieving the best outcome requires an organized and efficient response from a highly reliable team. Because the need for resuscitation cannot always be predicted, every birth should be attended by at least one qualified individual with neonatal resuscitation skills, including basic airway management and positive-pressure ventilation, whose only responsibility is providing care for the newly born infant. If risk factors are identified, additional personnel should be present at the time of birth. A team with advanced airway and vascular access skills should be identified and immediately available for resuscitation. Risk factors include:
   A. Preterm delivery
   B. Category 2 or 3 fetal heart rate pattern
   C. Chorioamnionitis
   D. Maternal hypertension
   E. Vaginal breech delivery
   F. Obstetrical emergencies (shoulder dystocia, cord prolapse)
   G. Maternal opiate administration in labor
   H. Meconium-stained amniotic fluid
   I. Oligohydramnios
   J. Fetal anomalies
II. Normal postnatal transition.
   A. The first breath generates a large negative pressure that inflates the lungs and clears liquid.

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B. Subsequent short, deep inspirations followed by exhalation against a closed or partially closed glottis results in a larger volume of air inspired than expired and rapidly establishes functional residual capacity (FRC).
C. Carbon dioxide is exhaled.
D. Pulmonary vascular resistance decreases allowing pulmonary blood flow to increase. Pulmonary venous return fills the left atrium and ventricle.
E. Flow through the ductus arteriosus changes from right-to-left to left-to-right.

III. Neonatal resuscitation equipment
A. Preheated radiant warmer and warm towels/blankets in a warm, well lit area
B. Stethoscope
C. Bulb syringe
D. Positive-pressure ventilation device (self-inflating bag, flow-inflating bag, or T-piece resuscitator). All devices should be equipped with manometers and suitable pressure regulators. If using a flow-inflating bag or T-piece, a self-inflating bag must be available as a back-up if gas pressure is lost.
E. Compressed gas source (air and oxygen) with adjustable flowmeter and blender
F. Face masks for term and preterm newborns
G. Orogastric feeding tube (8 F) and syringe
H. Pulse oximeter with neonatal sensor
I. Electronic cardiac (ECG) monitor and leads (chest or limb)
J. Laryngoscopes (blade size-0 and size-1, size-00 optional) with backup bulbs and batteries
K. Endotracheal tubes (sizes 2.5, 3.0, 3.5) and (optional) stylet
L. Suction device with a range of catheter sizes (10–12 F)
M. Colorimetric carbon dioxide detector or capnometer
N. Measuring tape
O. Waterproof tape and scissors or endotracheal tube securing device
P. Emergency umbilical venous catheter supplies
Q. Epinephrine (1:10,000) and normal saline
R. Personal protective supplies (gloves, gowns, masks)
S. Special equipment for premature births
1. Polyethylene plastic bag/wrap, hat, and thermal mattress
2. Servo-controlled temperature sensor
3. Pre-warmed transport incubator
4. Surfactant
T. Special equipment for difficult airways and emergency vascular access
1. Laryngeal mask or other supraglottic device
2. Oral (Guedel) airway
3. Intraosseous needle

IV. Preparation
A. Complete a pre-resuscitation briefing (“time-out”).
1. Review the pregnancy/labor history and evaluate risk factors.
2. Establish the plan for timing of umbilical cord clamping with the obstetric provider.
3. Assign roles and responsibilities.
B. Check equipment and supplies using a standardized checklist.

V. Initial Steps (Fig. 14.1)
A. Rapidly evaluate gestational age, tone, and respiratory effort.
1. If no contraindication, delay cord clamping for 30–60 s.
2. Vigorous term newborns should be placed skin-to-skin on mother’s chest or abdomen to monitor transition.

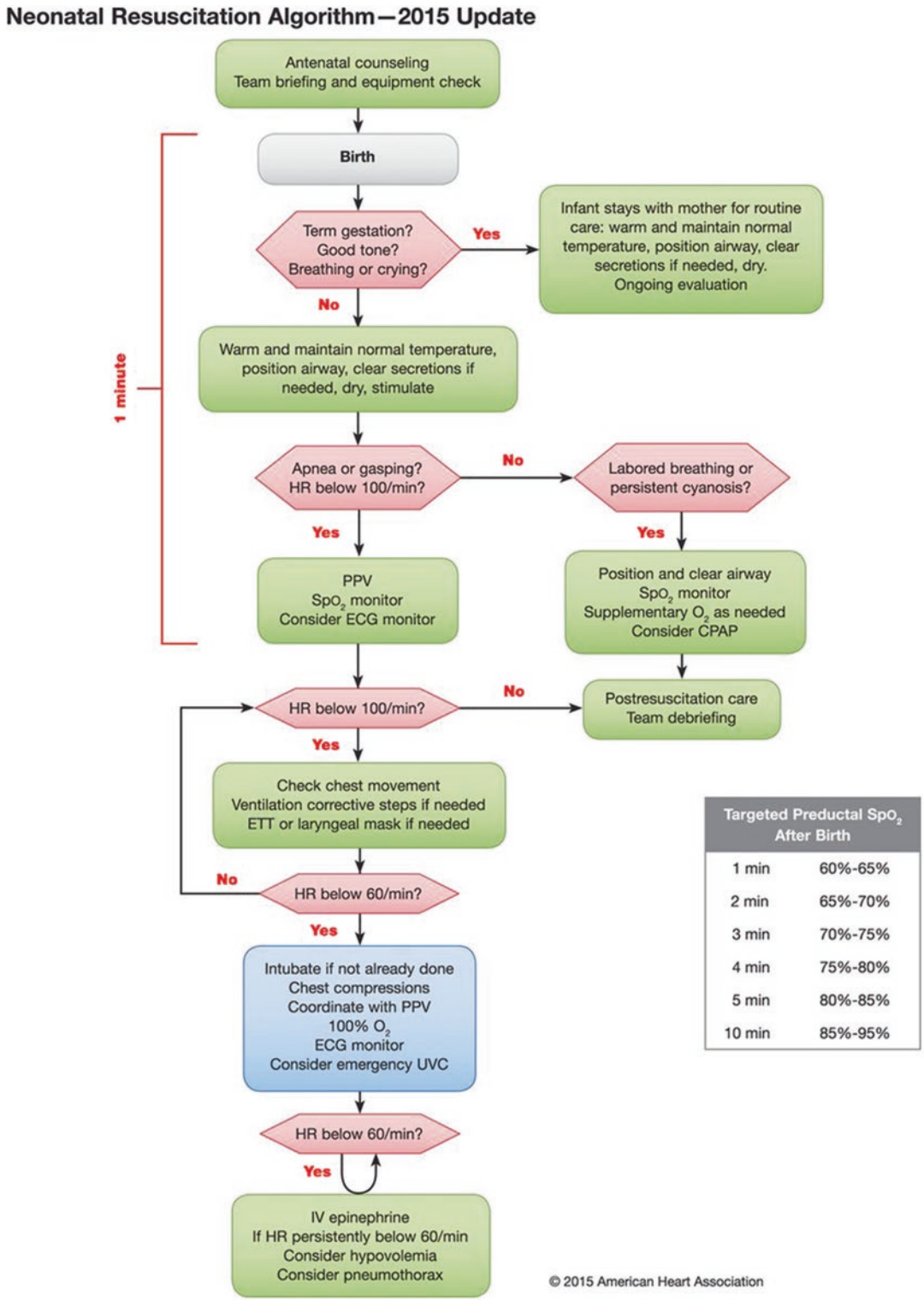

Fig. 14.1 Neonatal resuscitation algorithm. Wyckoff MH et al. Circulation. 2015;132:S543–S560

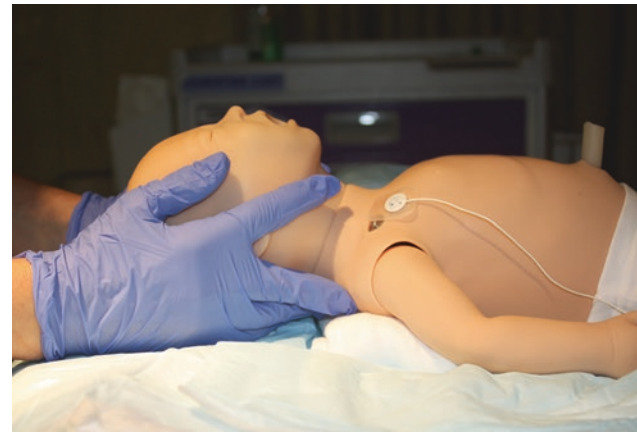

Fig. 14.2 Sniffing position

3. Preterm and non-vigorous newborns should be carried to a radiant warmerbed.

B. Remove wet towels and dry with warm towels/blanket.

C. Establish an open airway. Position the neck neutral or slightly extended in the "sniffing the morning air" position (Fig. 14.2).

D. Gently suction the mouth and nose with a bulb syringe if meconium stained fluid is present, the baby is not breathing, or the baby is having difficulty breathing. Routine suctioning and aggressive pharyngeal suctioning are not recommended.

E. Rub the back or extremities, as necessary, to stimulate breathing.

F. Evaluate response to the initial steps. Is the newborn breathing or crying? Is the heart rate (HR) at least 100 bpm?

1. If the baby is not breathing or the HR is <100 bpm by 1 min of age, proceed to positive-pressure ventilation
2. If the baby is breathing and the HR is at least 100 bpm, but central cyanosis persists, use pre-ductal pulse oximetry (right hand) to assess the need for supplemental oxygen.
3. Heart rate is most accurately assessed by auscultation at the cardiac apex or by using an ECG monitor. Palpation of the umbilical pulse is unreliable and often inaccurate.

VI. Positive-pressure ventilation.

Most newborns requiring resuscitation will improve when their lungs are effectively aerated and ventilated.

A. Place the baby supine. Consider placing a small, rolled towel or blanket under the baby's shoulders to prevent the prominent occiput from flexing the neck.

B. Standing at the head of the bed, hold the baby's head and neck in the sniffing position, and apply an appropriate size mask to the baby's face. The mask should not cover the eyes or extend beyond the chin. Use a one-hand (Fig. 14.3) or two-hand hold to ensure an airtight seal.

C. Begin PPV.

1. Inflate the lungs with 20–25 cm H_2O pressure. The first breaths may require higher pressure (30–40 cm H_2O). PEEP (5 cm H_2O) helps to establish and maintain FRC.
2. The ventilation rate is 40–60 breaths per minute.
3. Initiate ventilation with 21 % oxygen (room air) for term babies and 21–30 % oxygen for babies less than 35 weeks' gestation.
4. Use pre-ductal pulse oximetry (right hand) during PPV to evaluate oxygenation and adjust the oxygen concentration (F_iO_2). Use a target oxygen saturation table to guide supplemental oxygen.

Fig. 14.3 Face-mask with one-hand hold and CO_2 detector

D. The baby's HR should promptly increase with PPV.
   1. As soon as PPV is started, an assistant should monitor the HR response. Consider using an ECG monitor for accurate assessment of HR during PPV.
   2. If HR rapidly improves, continue PPV until the HR is at least 100 bpm and the baby is breathing effectively.
   3. If the HR does not increase within approximately 15 s, it is likely because effective ventilation has not been achieved. Ensure there is chest movement with PPV. If chest movement is absent or inconsistent, sequentially perform corrective steps until there is consistent chest movement.
   4. Corrective steps include repositioning the mask and neck, suctioning the airway, opening the mouth, and increasing the ventilating pressure. Consider placing a carbon dioxide (CO_2) detector between the PPV device and ventilation mask to monitor exhaled CO_2 as an additional indicator of effective ventilation.
   5. If the baby's HR is not improving and chest movement cannot be achieved with face-mask ventilation, insert an alternative airway (tracheal tube or laryngeal mask).
   6. If tracheal intubation is performed, select the correct tube size, confirm intubation with capnography, estimate the insertion depth using the nasal-tragus length (NTL), and confirm equal breath sounds with ventilation. The location of the vocal cord guide on the tracheal tube varies by manufacturer and is not a reliable indicator of correct insertion depth.
   7. If the HR remains <60 bpm after 30 s of effective ventilation through a properly placed endotracheal tube or laryngeal mask, increase the F_iO_2 to 100 % and proceed to chest compressions

VII. Chest compressions. Few newborns (approximately 1 in 1000) require chest compressions. The vast majority of babies requiring resuscitation will improve with effective ventilation alone.
   A. Chest compressions should be performed if the HR remains <60 bpm despite at least 30 s of ventilation that effectively aerates the lungs as indicated by consistent chest movement.
      1. Chest compressions should not be started until effective ventilation has been established.
      2. In most cases, a baby that requires compressions should be intubated.
   B. Encircle the chest with both hands, at the level of the lower third of the sternum, and compress the middle of the sternum with the thumbs (Fig. 14.4).
      1. Compress the chest by one third of the anteroposterior diameter.
      2. Compress at a rate of 90 compressions per minute.

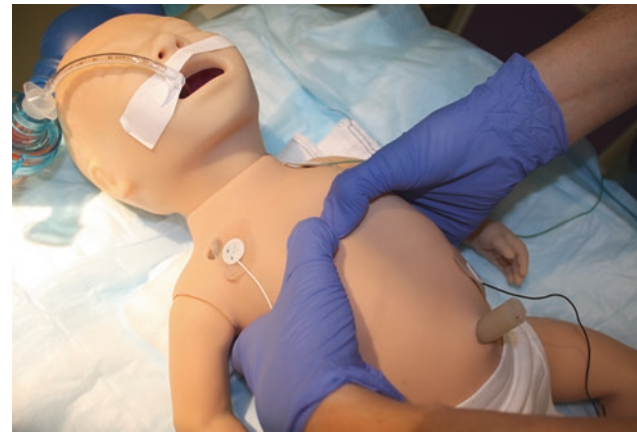

Fig. 14.4 Hand placement for chest compressions. Hands encircle the chest with two thumbs placed on the sternum

Fig. 14.5 Chest compressions from the head of the bed

3. PPV must continue during compressions. At present, synchronous chest compressions and ventilations are recommended. Give one lung inflation after every third compression (a ratio of 3:1) resulting in 90 compressions and 30 ventilations per minute.
4. Once the alternative airway is secured, the compressor should stand at the head of the bed with the ventilator at the side (Fig. 14.5). This improves ergonomics and allows space for another provider to obtain emergency vascular access.

C. Check the HR response after 60 s of compressions using an ECG monitor to improve accuracy and limit the "thumbs-off-chest" time.
1. When compressions are stopped for a pulse check, the perfusion pressure within the coronary arteries decreases and may delay the return of circulation.
2. If the baby's HR remains less than 60 bpm despite compressions and effective ventilation, proceed to emergency medications.

VIII. Drugs. If chest compressions are required, it indicates that the myocardium is severely depressed and will likely require epinephrine, and possibly volume expansion, to achieve a sufficient coronary artery perfusion pressure to restore effective circulation. Once compressions start, another provider should rapidly secure central venous access with an umbilical venous catheter (UVC) or intraosseous needle (ION).

A. Epinephrine (adrenaline)
   1. Indication: HR <60 bpm despite 60 s of compressions and effective ventilation (preferably by endotracheal tube)
   2. Preparation: 1:10,000 (0.1 mg/mL)
   3. Route: UVC or ION, rapidly infused
   4. Dose: 0.1–0.3 mL/kg, repeated every 3–5 min, if needed
   5. Endotracheal absorption is less reliable and likely to be less effective. If the endotracheal route is used, while vascular access is being obtained, a higher dose (epinephrine 1:10,000; 0.3–0.5 mL/kg) is recommended. This larger dose should not be administered intravenously. Repeated endotracheal administration is not recommended.

B. Volume expansion. Routine volume expansion during and after resuscitation is not recommended.
   1. Indication: Insufficient response to the previous steps of resuscitation with signs of shock or a history of acute blood loss
   2. Preparation: Normal saline (0.9 % NaCl) or type-O, Rh-negative blood
   3. Route: UVC or ION
   4. Dose: 10 mL/kg

IX. Failure to Respond to Resuscitation.

A. If the baby does not respond to resuscitation measures, examine the baby, ensure effective ventilation and chest compressions, intubate if not already done, consider obtaining a chest X-ray, and evaluate each of the following:
   1. Is the endotracheal tube in the esophagus?
   2. Is there a leak in the ventilation system or has it become disconnected?
   3. Is the airway obstructed?
   4. Is there a tension pneumothorax?
   5. Is there a pleural or pericardial effusion?
   6. Is there evidence of pulmonary hypoplasia, a congenital diaphragmatic hernia, a pulmonary embolism, or septic/hemorrhagic shock?

B. Discontinuing resuscitation.
   1. Absent heart rate (asystole): The decision to stop should be individualized, and variables to consider include uncertainty about the duration of asystole, whether the resuscitation interventions were optimal, the baby's gestational age, the etiology and timing of the perinatal events leading to cardiorespiratory arrest, the availability of advanced therapies (therapeutic hypothermia), and the family's desires and values. Although previous case series have indicated that confirmed absence of a HR after 10 min is a strong predictor of mortality or serious morbidity in late preterm and term newborns, recent reports from therapeutic hypothermia trials suggest that outcomes may not be as poor as previously reported. Given the limitations of the current evidence and the difficulty of assessing key variables during the time pressure of a complex resuscitation, in most circumstances it seems reasonable to continue resuscitative efforts for up to 20 min as more information is obtained.
   2. Prolonged bradycardia (HR <60 bpm) without improvement: Assuming that prolonged bradycardia reflects cardiorespiratory compromise (not congenital heart block) and resuscitative efforts have been optimized, there is currently insufficient evidence to make a specific recommendation when to discontinue resuscitative efforts.

X. Special considerations

A. Prematurity
   1. Careful attention to thermal management is particularly important and multiple methods may be required to avoid hypothermia. For preterm newborns <32 weeks' gestation,

increase the room temperature to 23–25 °C (74–77 °F); use a polyethylene plastic bag to wrap the newborn, without drying, from feet to neck; place a cap on the head; use an exothermic (warming) mattress; use a servo-controlled radiant warmer. The goal is to maintain an axillary temperature 36.5–37.5 °C.

2. PPV devices capable of providing PEEP or continuous positive airway pressure (CPAP) are preferred (T-piece or flow-inflating bag).
3. Resuscitation of newborns <35 weeks' gestation begins with 21–30 % oxygen.
4. Decisions regarding resuscitation at the edge of viability should involve shared decision-making with the parents and medical providers using all available prognostic information (Chap. 91).

B. Congenital diaphragmatic hernia
   1. Avoid prolonged face-mask ventilation.
   2. Promptly intubate the trachea and place a large double-lumen orogastric sump tube (Replogle) to prevent gaseous distention of herniated bowel.

XI. Controversies in resuscitation
   A. The role of delayed cord clamping or cord milking for babies requiring resuscitation
   B. The role of tracheal suction among non-vigorous newborns with meconium stained amniotic fluid
   C. The optimum pressure and inspiratory time for initial inflating breaths with PPV
   D. The optimal saturation targets and F_iO_2 for PPV in preterm newborns
   E. Tools and educational methods to improve intubation success
   F. Synchronous (coordinated) or asynchronous ventilations during chest compressions
   G. The role of pulmonary function monitoring during neonatal resuscitation
   H. When to discontinue resuscitation with unresponsive asystole and bradycardia
   I. Educational methods to address skill decay among resuscitation providers

Suggested Reading

Perlman JM, Wyllie J, Kattwinkel J, et al. 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Part 7: Neonatal resuscitation. Circulation. 2015;132:S204–41.

Weiner G, editor. Textbook of neonatal resuscitation. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, Simon WM, Weiner GM, Zaichkin JG. Part 13: Neonatal resuscitation. 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132:S543–60.

Wyllie J, Bruinenberg J, Roehr CC, Rudiger M, Trevisanuto D, Urlesberger B. European Resuscitation Council guidelines for resuscitation 2015. Section 7. Resuscitation and support of transition of babies at birth. Resuscitation. 2015;95:249–63.

Laryngoscopy and Endotracheal Intubation

15

Steven M. Donn

I. Indications for Intubation
   A. Need for prolonged positive pressure ventilation for respiratory failure
   B. Inability to provide effective bag and mask ventilation
   C. Administration of surfactant
   D. Apnea, either central or obstructive
   E. Airway maintenance
      1. Anatomic anomalies of the airway such as choanal atresia, micrognathia, laryngomalacia, laryngeal web, or vocal cord paralysis
      2. Compressive lesions on the airway, such as cystic hygroma or hemangioma
      3. Airway protection in cases of congenital neuromuscular disorders or other neurologic injury
   F. Congenital diaphragmatic hernia. Avoidance of mask ventilation and delivery of air into the gastrointestinal tract is critical, and immediate intubation should be performed.

II. Endotracheal Tube Diameter
   A. Size of tube (internal diameter, mm):

Up to 1000 g	2.5
1001–2000 g	3.0
2001–3000 g	3.5
>3000 g	3.5–4.0

   B. Depth of insertion may be estimated by measuring the distance from the nose to the tragus (X), in cm.
      1. Orotracheal route: Depth = 0.91 X + 1.8 cm
      2. Nasotracheal route: Depth = 1.1 X + 1.3 cm

III. Use of Pre-medication
   A. Anesthesia or analgesia should be provided except in emergency situations.

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B. Can help attenuate the adverse physiologic effects of intubation. When practical, premedication prior to intubation in the newborn offers the following potential advantages:
   1. Increased hemodynamic stability
   2. Faster intubation
   3. Less hypoxemia
   4. Less rise in intracranial pressure

C. Pre-medication regimens (see Chaps. 59 and 62)
   1. Pain relief (e.g., morphine)
   2. Sedation (e.g., midazolam)
   3. Paralytic agent (e.g., succinylcholine, atracurium, rocuronium). Muscle relaxants should only be used with an experienced neonatologist present. Do not paralyze the baby unless you are confident the airway can be maintained and adequate manual ventilation provided.
   4. Adjunctive or reversal agents
      a. Atropine: can be given prior to anesthesia to reduce secretions and prevent bradycardia and hypotension. Intravenous bolus will produce an effect in 30 s that will last for up to 12 h.
      b. Neostigmine: reverses the effects of non-depolarizing muscle relaxants.

IV. Laryngoscopy and Oral Intubation (Fig. 15.1)

A. Place all the equipment you need close by and prepare a means of securing the tracheal tube once it is in place.

B. Position the baby on a firm flat surface. Place a small roll or blanket under the baby's shoulders so as to lift the shoulders (not the head) about 1.5 in. (3 cm) off the surface. Extend the baby's neck *slightly* beyond the neutral position.

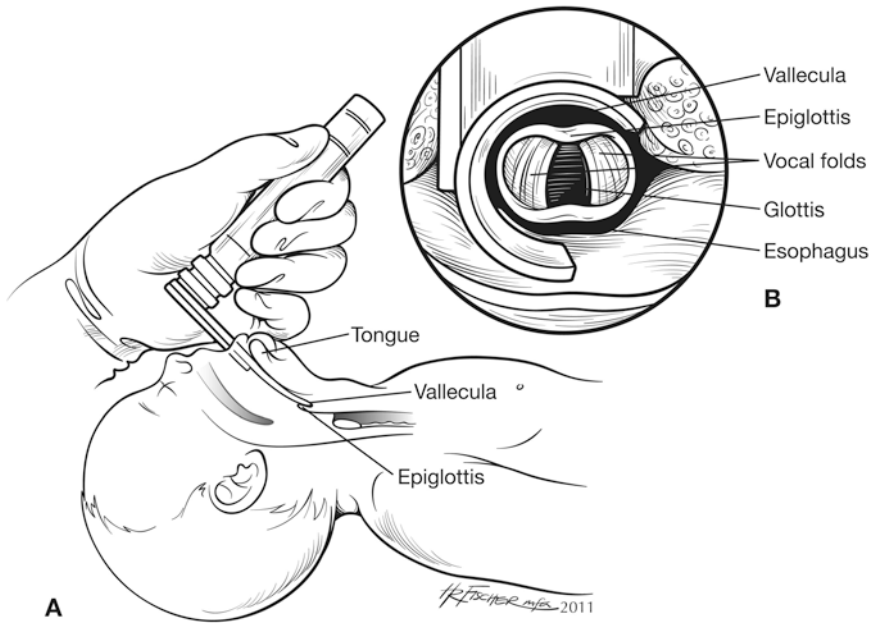

Fig. 15.1 Demonstration of technique of laryngoscopy and visualization of the airway

C. Open the baby's mouth with the index finger of your right hand. Holding the laryngoscope in your left hand, insert the blade carefully into the right side of the baby's mouth while looking along the blade.
D. Move the laryngoscope into the center by pushing the tongue over to the left side of the mouth.
E. Position yourself so you can see comfortably along the laryngoscope blade. If the blade is pushed in too far, all you will see is the esophagus; you must then withdraw the blade slightly to allow the larynx to drop into view from above. Alternatively, if the blade is not in far enough you may see little except the tongue and the roof of the mouth: you must advance the blade gently until you can see the epiglottis.
F. Once you have found the epiglottis, place the tip of the blade at the base where it meets the tongue (the vallecula). Lift the laryngoscope gently upward. This will open the mouth further and gently compress the tongue and will bring the larynx into view from behind the epiglottis. Slight external downward pressure on the cricoid should bring the larynx into the center of the field of view. Do not lever the end of the laryngoscope blade forward by pressing backward on the baby's upper jaw, as this may damage the alveolus and developing teeth.
G. Bring the endotracheal tube (ETT) in from the right hand corner of the mouth and keep the curve of the tube horizontal so as not to obscure the view of the larynx. Visualize the vocal cords through the groove in the laryngoscope blade. If necessary, wait for the cords to relax. Insert the tube 1–2 cm through the cords. Several commercially available tubes have markings to indicate where the ETT should align with the vocal cords.
H. Tape the tube in place immediately while it is still optimally positioned. Most tubes are marked in centimeters from the tip; make a note of the length at the upper lip.
I. Inflate the lung using a controlled inflation device. Watch the chest to check that it is moving appropriately and listen at the mouth to check that there is no significant leak around the ETT.
J. Placement of a gastric tube (e.g., nasogastric or orogastric tube) is recommended to decompress the stomach.

V. Oral Intubation Without a Laryngoscope: Oral intubation using a finger rather than a laryngoscope is possible. Skilled practitioners can place a tube in a baby with normal anatomy in 3–5 s (Fig. 15.2).
A. Insert the index finger of the nondominant hand into the baby's mouth, with the palmar surface sliding along the tongue. Use the little finger if the baby is small.
B. Slide the finger along the tongue until it meets the epiglottis. This feels like a small band running across the root of the tongue.
C. Slide the finger a little further until its tip lies behind and superior to the larynx and the nail touches the posterior pharyngeal wall.
D. Using your dominant hand, slide the tube into the mouth between your finger and the tongue until the tip lies in the midline at the root of the distal phalanx of your finger.
E. At this point, place the thumb of your nondominant hand on the baby's neck just below the cricoid cartilage in order to grasp the larynx between the thumb on the outside and the fingertip on the inside.
F. While the thumb and finger steady the larynx, the dominant hand advances the tube a short distance, about 1–2 cm.
G. A slight give can sometimes be felt as the tube passes into the larynx *but no force is needed for insertion.*
H. When the tube is in the trachea, the laryngeal cartilages can be felt to encircle it. If it has passed into the esophagus it can be felt between the finger and the larynx.

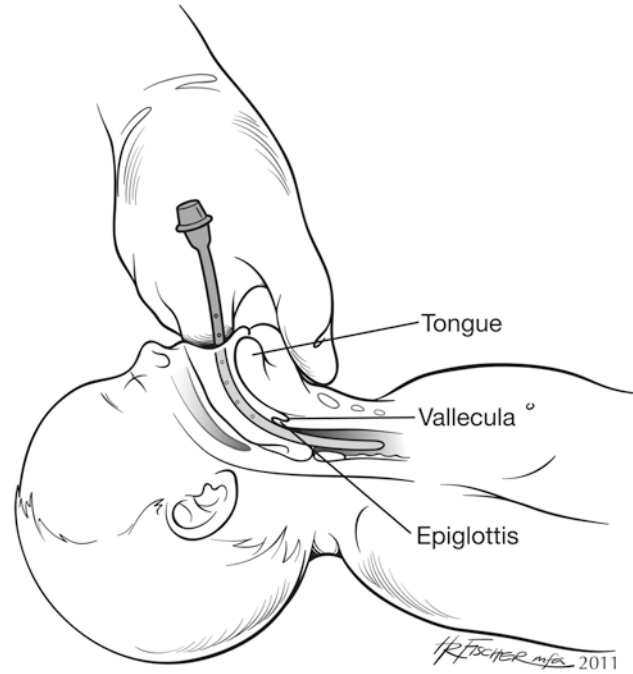

Fig. 15.2 Demonstration of technique of manual intubation

VI. Nasotracheal intubation: Nasal intubation is not normally used for emergency intubation but many neonatologists prefer this route. Nasal intubation is most commonly an elective procedure in an orally intubated baby.
   A. Get the baby well oxygenated in preparation for the procedure.
   B. Use premedication (see Section III, above).
   C. Position the baby supine with the shoulders supported on a small towel roll (see above) with the neck *slightly* extended beyond the neutral position.
   D. Take a small feeding tube, narrow enough to fit inside the intended ETT, remove the flared end and lubricate the other end. Lift up the tip of the nose and pass the tube into one nostril, directing it towards the back of the mouth until it has passed through the nose into the nasopharynx. Remember that the nasal passages follow the line of the palate and not the line of the nasal bone.
   E. Choose an appropriately sized tube, cut it to an appropriate length (see chart above) and attach the appropriate connector.
   F. Lubricate the end of the tracheal tube, thread it over the feeding tube and insert it through the nostril and into the nasopharynx.
   G. Remove the feeding tube.
   H. Loosen the attachments of the oral tube and have an assistant prepare to remove it when requested.
   I. Visualize the larynx with the oral tube in place using a laryngoscope. Identify the nasal tube within the nasopharynx.
   J. Ask an assistant to remove the oral tube. Grasp the nasal tube with a small pair of Magill or crocodile forceps and position the end of the tube into the laryngeal opening.
   K. It may not be possible to advance the tip of the nasal tube directly into the larynx because the nasal tube, approaching from the nasopharynx rather than the oropharynx, is likely to be at an angle to the line of the trachea. Gently flexing the neck while advancing the tube into

the nose may suffice to correct this. Alternatively, take hold of the tube connector at the nose and gently twist it clockwise 120° while maintaining some forward pressure and the tube will slip gently through the vocal cords.

L. Fix the tube in place and continue ventilation.

VII. Confirming Tube Position

A. Clinically
   1. Equality of breath sounds
   2. Absence of phonation
   3. Good chest excursions, symmetrical
   4. Appropriate physiologic responses (HR, RR, SpO_2)

B. Radiologic
   1. Should always be obtained for initial intubation
   2. Obtain with head and neck in *neutral* position.
   3. Optimal position is midway between glottis and carina.

C. Capnography may also be helpful.
   1. Disposable end-tidal CO_2 detectors are now available to confirm that the tube is in the trachea.
   2. The color changes from purple to yellow in the presence of exhaled CO_2.
   3. False negative results may occur with reduced pulmonary blood flow (e.g., after cardiopulmonary resuscitation, cardiac anomalies) or with severe airway obstruction.

VIII. Replacing the Endotracheal Tube

A. Despite meticulous post-extubation care, use of methylxanthines, and a trial of CPAP, about 20–25 % of babies require re-intubation. The immediate goal is to re-intubate and provide assisted ventilation in order to stabilize their cardiopulmonary status.

B. The following factors, singularly or in combination should alert the caregiver that a trial of extubation is failing.
   1. Clinical manifestation of respiratory muscle fatigue, such as progressive respiratory distress (increased work of breathing), or apnea
   2. Cardiovascular collapse
   3. Increasing base deficit and developing respiratory or metabolic acidosis
   4. Increasing FiO_2 requirement to achieve reasonable PaO_2 or SpO_2

C. Suggested protocol for re-intubation
   1. Stabilization with pre-oxygenation and bag and mask ventilation
   2. Select optimal size (and length) of the ETT.
   3. Use of premedication (see Section III)
   4. Insert ETT by previously described techniques.
   5. Before fixation determine for correct placement by assessing air entry, chest wall movement, and improvement in oxygenation saturation and heart rate. If in doubt, obtain a chest radiograph.

D. Changing an indwelling tube
   1. Prepare new ETT and adjunctive equipment (e.g., tape, stylet, adhesives).
   2. Remove tape and adhesive from existing ETT, but stabilize tube position manually while doing so.
   3. Visualize the glottis by direct laryngoscopy.
   4. Hold new tube in the right hand.
   5. Ask assistant to remove old ETT and quickly insert new ETT to desired depth.
   6. Secure new ETT when successful placement is confirmed clinically.
   7. A radiograph is necessary only if there is a question of suitable placement.

Suggested Reading

Donn SM, Blane CE. Endotracheal tube movement in the preterm infant: oral versus nasal intubation. Ann Otol Rhinol Laryngol. 1985;94:18–20.

Donn SM, Engmann C. Neonatal resuscitation: special procedures. In: Donn SM, editor. The Michigan manual—a guide to neonatal intensive care. 3rd ed. Philadelphia, PA: Hanley & Belfus; 2003. p. 33–4.

Donn SM, Kuhns LR. Mechanism of endotracheal tube movement with change of head position in the neonate. Pediatr Radiol. 1980;9:37–40.

Hancock PJ, Peterson G. Finger intubation of the trachea in newborns. Pediatrics. 1992;89(2):325–7.

Kempley ST, Moreiras JW, Petrone FL. Endotracheal tube length for neonatal intubation. Resuscitation. 2008;77:369–73.

Sarkar S, Schumacher RE, Baumgart S, Donn SM. Are newborns receiving premedication before elective intubation? J Perinatol. 2006;26(5):286–9.

Shukla HJ, Hendricks-Munoz KD, Atakent Y, Rapaport SJ. Rapid estimation of insertional length of endotracheal intubation in newborn infants. Pediatrics. 1997;131:561–4.

Whyte KL, Levin R, Powls A. Clinical audit: optimal positioning of endotracheal tubes in neonates. Scott Med J. 2007;52:25–7.

Woody NC, Woody HB. Direct digital intubation for neonatal resuscitation. J Pediatr. 1968;73:903–5.

Vascular Access

16

Steven M. Donn

I. Umbilical Artery Catheterization (UAC)
   A. Indications
      1. Monitoring arterial blood gases
         a. $FiO_2 \geq 0.4$
         b. Unreliable capillary samples
         c. Need for continuous monitoring
      2. Need for invasive blood pressure monitoring
   B. Procedure
      1. *Elective* procedure
      2. Use sterile technique
      3. Catheterize vessel after cutdown technique using 3.5 F (<1500 g) or 5 F catheter
      4. Preferred position of tip
         a. High (T_7–T_{10})
         b. Low (L_3–L_4)
      5. Confirm position radiographically
      6. Secure with tape bridge and (optional) sutures
   C. Complications
      1. Blood loss
      2. Infection
      3. Thromboembolic events
         a. Digit necrosis
         b. NEC
         c. Renal artery thrombosis
         d. Spinal cord injury (rare, but reported)
      4. Vasospasm
      5. Vessel perforation
      6. Air embolus
      7. Hypertension (renal artery thrombosis)

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D. Removal
   1. When $FiO_2 < 0.4$ and decreasing
   2. When noninvasive blood pressure monitoring is adequate
   3. At first signs of complication

E. Comments
   1. Confirm position. A malpositioned UAC can have life-threatening consequences.
   2. Remember that samples obtained from the UAC are post-ductal.
   3. Never infuse pressor agents through a UAC.
   4. When removing, withdraw last 5 cm *very* slowly, no faster than 1 cm/min. Watch for pulsations to stop.
   5. Controversy still exists regarding infusion of TPN and certain medications through a UAC.
   6. Inadequate line clearing prior to sampling may result in spurious laboratory results.

II. Umbilical Vein Catheterization

A. Indications
   1. Emergent need for vascular access (i.e., resuscitation)
   2. Need for central venous line
      a. Pressure monitoring
      b. TPN or hypertonic glucose administration
      c. Frequent blood sampling in unstable patient without other access
   3. Exchange transfusion

B. Procedure
   1. Sterile technique should be used.
   2. Direct cutdown approach
   3. Use umbilical catheter (5.0 F; 8.0 F for exchange transfusion in term infant); do not use feeding tube except as last resort.
   4. Preferred positions
      a. Low: insert 4–6 cm to achieve blood return if using for resuscitation or exchange transfusion.
      b. High: tip should be above diaphragm and below right atrium in the vena cava for indwelling use.
   5. Confirm position radiographically.
   6. Secure with tape and (optional) sutures.

C. Complications
   1. Blood loss
   2. Infection
   3. Vessel perforation. Commercially available exchange transfusion kits contain catheters with side holes to decrease resistance. These should not be left in situ, as they may injure the intima.
   4. Thromboembolic events
   5. Air embolus
   6. Liver necrosis (see below)
   7. NEC (may be more related to procedures such as exchange transfusion than to catheter itself)

D. Removal
   1. When no longer needed or when other central venous access is achieved
   2. At first signs of complications
   3. When procedure is completed
   4. May be pulled directly.

E. Comments
1. Avoid infusion or injection of hypertonic solutions (e.g., sodium bicarbonate) unless catheter tip is above diaphragm. This may cause hepatic necrosis.
2. CVP monitoring may provide useful trend data regarding intravascular fluid status and hemodynamics.
3. Recent trend in increased longer-term use in ELBW infants
4. Inadequate line clearing prior to sampling may result in spurious laboratory results.

III. Peripheral Artery Catheterization
A. Indications generally same as for UAC when umbilical access is unavailable or cannot be achieved.
B. Procedure
1. Preferred sites
a. Radial artery
b. Posterior tibial artery
2. Assess for adequate collateral circulation (i.e., Allen's test).
3. Prepare site thoroughly using antiseptic solution.
4. Cannulate vessel percutaneously. Transillumination may be helpful in locating vessel.
5. Secure catheter with tape.
6. Check for blood return, pulse waveform, and adequacy of distal circulation.
C. Complications
1. Infection
2. Blood loss
3. Thromboembolic events
4. Vasospasm, ischemic injury
D. Removal
1. At first sign of complications
2. When no longer indicated
E. Comments
1. Transillumination may be very helpful in locating vessel.
2. Keep patency by infusing continuously, but slowly. Use low tonicity fluid (e.g., 0.45% sodium chloride). Many centers prefer use of low-dose heparin (0.5–1.0 units/mL) to decrease risk of clotting.
3. Brachial artery should not be cannulated (inadequate collateral circulation) and femoral artery should be used only as a last resort.
4. Cerebral infarction has been reported following superficial temporal artery cannulation and thus this vessel is also not used. However, it is not clear whether this was causally related or just an association.

IV. Peripheral Intravenous Catheters
A. Indications
1. To provide partial or total fluids and/or nutrition when gastrointestinal nutrition is not possible
2. Used when central access is unnecessary or unattainable
B. Procedure
1. Visualize, palpate, and/or use transillumination to select vessel for cannulation. Suggested order of preference for vessels to cannulate:
a. Dorsal venous plexus of back of hand
b. Median antebrachial, accessory, or cephalic veins of forearm
c. Dorsal venous plexus of foot

   d. Basilic or cubital veins of antecubital fossa
   e. Small saphenous, or great saphenous veins of ankle
   f. Supratrochlear, superficial temporal, or posterior auricular veins of scalp
2. Apply tourniquet if placing in extremity.
3. Clean area with antiseptic.
4. Attach syringe to cannula and fill with saline, then detach syringe.
5. Hold needle parallel to vessel, in direction of blood flow.
6. Introduce needle into skin a few millimeters distal to the point of entry into the vessel. Introduce needle into the vessel until blood flashback appears in the cannula.
7. Remove stylet and advance needle into vessel.
8. Remove tourniquet.
9. Infuse a small amount of saline to assure patency then attach IV tubing.

C. Special considerations
1. Placement should not be near area of skin loss or infection, or across joints, if possible, because of problems with joint immobilization.
2. Care should be taken to assure that vessel is actually a vein and not an artery.
   a. Note color of blood obtained from vessel and if pulsations are present
   b. Look for blanching of skin over vessel when fluid is infused suggesting arterial spasm.
   c. When attempting scalp vein cannulation, shave area of head where IV is to be placed. Avoid sites beyond hairline.

D. Complications
1. Phlebitis
2. Infection
3. Hematoma
4. Embolization of formed clot with vigorous flushing
5. Air embolus
6. Infiltration of subcutaneous tissue with IV fluid. Infiltration may cause:
   a. Superficial blistering
   b. Sloughing of deep layers of skin that may require skin grafting
   c. Subcutaneous tissue calcification from infiltration of calcium-containing IV solutions

Suggested Reading

Donn SM. Vascular catheters. In: Donn SM, editor. The Michigan manual of neonatal intensive care. 3rd ed. Philadelphia, PA: Hanley & Belfus Publishing Col; 2003. p. 46–9.

Feick HJ, Donn SM. Vascular access and blood sampling. In: Donn SM, Faix RG, editors. Neonatal emergencies. Mt. Kisco, NY: Futura Publishing Co.; 1991. p. 31–50.

Workman EL, Donn SM. Intravascular catheters. In: Donn SM, Fisher CW, editors. Risk management techniques in perinatal and neonatal practice. Armonk, NY: Futura Publishing Co.; 1996. p. 531–49.

Tracheostomy

17

Steven M. Donn

I. Description: Creation of an artificial airway through the trachea for the purposes of establishing either airway patency below an obstruction or an airway for prolonged ventilatory support.
II. Indications
  A. Emergent
    1. Upper airway malformations
    2. Upper airway obstructions
  B. Elective
    1. Prolonged ventilatory support
      a. Chronic lung disease
      b. Neurologic or neuromuscular dysfunction
    2. Subglottic stenosis following endotracheal intubation
III. Preparation
  A. Rare need for emergent tracheostomy because of obstructive lesion which precludes performing endotracheal intubation first
  B. Baby should be intubated.
  C. Should generally be performed in operating room because of availability of:
    1. General anesthesia
    2. Optimal lighting
    3. Available suction
    4. Proper exposure
    5. All necessary personnel and equipment
IV. Technique
  A. Baby placed supine with head and neck maximally extended. Use towel roll or sandbag.
  B. Cricoid cartilage is identified by palpation of tracheal rings.
  C. Short (1.0 cm) transverse skin incision made over second tracheal ring
  D. Incision dilated with hemostat
  E. Incision deepened by needle point cautery

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F. Maintain meticulous hemostasis.
G. Strap muscles separated by fine hemostat
H. Trachea exposed by dividing isthmus of thyroid gland by cautery, if necessary
I. Longitudinal incision made in trachea (by cautery) through second and third tracheal rings. Do not excise tracheal cartilage, which would lead to loss of tracheal support and stricture formation.
J. Place silk ties on each side to facilitate placement of tracheostomy tube and postoperative replacement.
K. Withdraw endotracheal tube until it is visualized just proximal to incision.
L. Insert tracheostomy tube. Choose a size that requires minimal pressure to insert; avoid metal tubes. Remove endotracheal tube.
M. Assess proper fit by manual ventilation through tracheostomy tube. If leak is large, replace with bigger tube.
N. Secure tube with tapes around neck. These should be padded and can be tightened during neck flexion.
O. Trachea may be irrigated with 2.0 mL saline and suctioned.
P. Auscultate chest; obtain radiograph.

V. Postoperative Care
A. Minimize movement of head and neck for 3–5 days to establish stoma. Sedation and analgesia strongly recommended. Occasionally, skeletal muscle relaxants are required.
B. Frequent suctioning and humidification required until stoma established
C. Caretakers must know how to replace tube if it becomes dislodged or occluded.
D. Removal should be accomplished in intensive care unit setting.

VI. Ex Utero Intrapartum Treatment (EXIT) Procedure
A. Performed in selected centers to manage various forms of fetal airway obstruction
1. Neck masses
2. Congenital high airway obstruction syndrome (CHAOS)
3. Intrathoracic masses
4. Unilateral pulmonary agenesis and diaphragmatic hernia
B. Procedure
1. Requires multidiscipline team
a. Obstetrics
b. Neonatology
c. Pediatric surgery
d. Pediatric anesthesiology
e. Radiology
f. Nursing
2. Tocolytic (e.g., indomethacin) given to mother
3. Maternal rapid sequence intubation after anesthesia
4. Maintain uterine relaxation and maternal blood pressure
a. Inhalational agents
b. Terbutaline or intravenous nitroglycerine
5. Fetal anesthesia with pancuronium and Fentanyl
6. Maternal laparotomy
7. Ultrasound to map placental borders
8. Hysterotomy
9. Exposure of fetal head

10. Attempt intubation
11. Clamp and cut cord, deliver infant
12. EXIT to ECMO has also been successfully reported.

Suggested Reading

Coran AG. Tracheostomy. In: Donn SM, Faix RG, editors. Neonatal emergencies. Mount Kisco, NY: Futura Publishing Co.; 1991. p. 247–51.

Coran AG, Behrendt DM, Weintraub WH, et al. Surgery of the neonate. Boston: Little, Brown and Company; 1978. p. 31–5.

Hirose S, Harrison MR. The ex utero intrapartum treatment (EXIT) procedure. Semin Neonatol. 2003;8:207–21.

Section IV

Monitoring the Ventilated Patient

Continuous Monitoring Techniques

18

Christian F. Poets

I. Transcutaneous partial pressure of oxygen ($TcPO_2$) monitoring
   A. Principle of operation
      Electrodes consist of a platinum cathode and silver reference anode, encased in an electrolyte solution and separated from the skin by an O_2-permeable membrane. Electrodes are heated to improve oxygen diffusion and to arterialize the capillary blood. Oxygen is reduced at the cathode, generating an electric current proportional to the O_2 concentration in the capillary bed underneath the sensor. Sensors require a 10–15 min warm-up period after application and have to be calibrated every 4–8 h.
   B. Factors influencing measurements
      1. Sensor temperature. Good agreement with PaO_2 only at 44 °C, but then frequent (2–4 hourly) re-siting necessary. At lower sensor temperatures, increasing PaO_2–$TcPO_2$ difference with increasing PaO_2.
      2. Probe placement. $TcPO_2$ will underread PaO_2 if sensor is placed on bony surface, if pressure is applied on sensor, or if too much contact gel is used. With patent ductus arteriosus and right-to-left shunt, $TcPO_2$ will be higher on upper than on lower half of thorax.
      3. Peripheral perfusion. $TcPO_2$ depends on skin perfusion. If the latter is reduced, e.g., from hypotension, anemia, acidosis (pH <7.05), hypothermia, or marked skin edema, $TcPO_2$ will be falsely low. If underreading of PaO_2 occurs, check patient for the above conditions.
      4. Skin thickness. Close agreement with PaO_2 only in neonates; beyond 8 weeks of age, $TcPO_2$ will usually only be 80 % of PaO_2.
      5. Response times. In vivo response time to a sudden fall in PaO_2 is 16–20 s.
   C. Detection of hypoxemia and hyperoxemia
      Sensitivity to these conditions (at 44 °C sensor temperature) is approximately 85 %.
II. Pulse oximetry (SpO_2)
   A. Principle of operation

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The ratio of the absorbances of red and infrared light sent through a tissue correlates with the ratio of oxygenated to deoxygenated hemoglobin in the tissue. First-generation oximeters determine the arterial component within this absorbance only by identifying the peaks and troughs in the absorbance over time, thereby obtaining a "pulse-added" absorbance that is independent of the absorbance characteristics of the non-pulsating parts of the tissue. Current instruments use additional techniques. For example, they scan through all red-to-infrared ratios found in the tissue, determine the intensity of these and choose the right-most peak of these intensities, which will correspond to the absorbance by the arterial blood in the tissue. Some instruments also use frequency analysis, time domain analysis and adaptive filtering to establish a noise reference in the detected physiological signal, thereby improving the ability to separate between signal and noise. All instruments have built-in calibration algorithms to associate their measured light absorbances with empirically determined arterial oxygen saturation (SaO_2) values.

B. Factors influencing measurements
   1. Probe placement. Light receiving diode must be placed exactly opposite emitting diode; both must be shielded against ambient light and not be applied with too much pressure. Light bypassing the tissue can cause both falsely high and falsely low values. Sensor site must be checked 6–8 hourly. Highly flexible sensors (usually disposable) provide better skin contact and thus better signal-to-noise ratio.
   2. Peripheral perfusion. Most oximeters require a pulse pressure above 20 mmHg or a systolic blood pressure above 30 mmHg to operate reliably; performance at low perfusion is substantially better with current, i.e., next-generation instruments.
   3. Response and averaging times. The former largely depends on the latter. Longer averaging times may reduce alarm rates but will increase response time and will hide true severity of short-lived hypoxemic episodes. The relationship between desaturation rate and averaging time can be described mathematically, so that rates observed with one averaging time can be translated into those that would have been obtained with another averaging time.
   4. Movement artifact. Most frequent cause of false alarms. Has been reduced with next-generation instruments, but potentially at the expense of an unreliable detection of true alarms. May be identified from analysis of the pulse waveform signal or via a signal quality indicator displayed by some instruments.
   5. Other hemoglobins and pigments. Methemoglobin (MetHb) will cause SpO_2 readings to tend towards 85 %, independent of SaO_2. Carboxyhemoglobin (COHb) will cause overestimation of SaO_2 by 1 % for each percent COHb in the blood. Fetal hemoglobin (HbF) and bilirubin do not affect pulse oximeters, but may lead to an underestimation of SaO_2 by co-oximeters. In patients with dark skin, SpO_2 values may be falsely high, particularly during hypoxemia.
   6. Calibration algorithms. These may vary between brands and even between different software versions from the same manufacturer. Recently, the discovery of a shift in the in-built calibration curve used in one manufacturer's instruments revealed a reduction in the number of SpO_2 readings between 87 and 90 % and was subsequently corrected by the manufacturer. Also, some instruments subtract a priori the typical levels of COHb, MetHb etc. in healthy nonsmoking adults from their measurements and will thus display SpO_2 values that are 2–3 % lower than those displayed by other instruments.

C. Detection of hypoxemia and hyperoxemia (Fig. 18.1)
   In the absence of movement, pulse oximeters have a high sensitivity for the detection of hypoxemia. Due to the shape of the O_2 dissociation curve, they are less well suited for

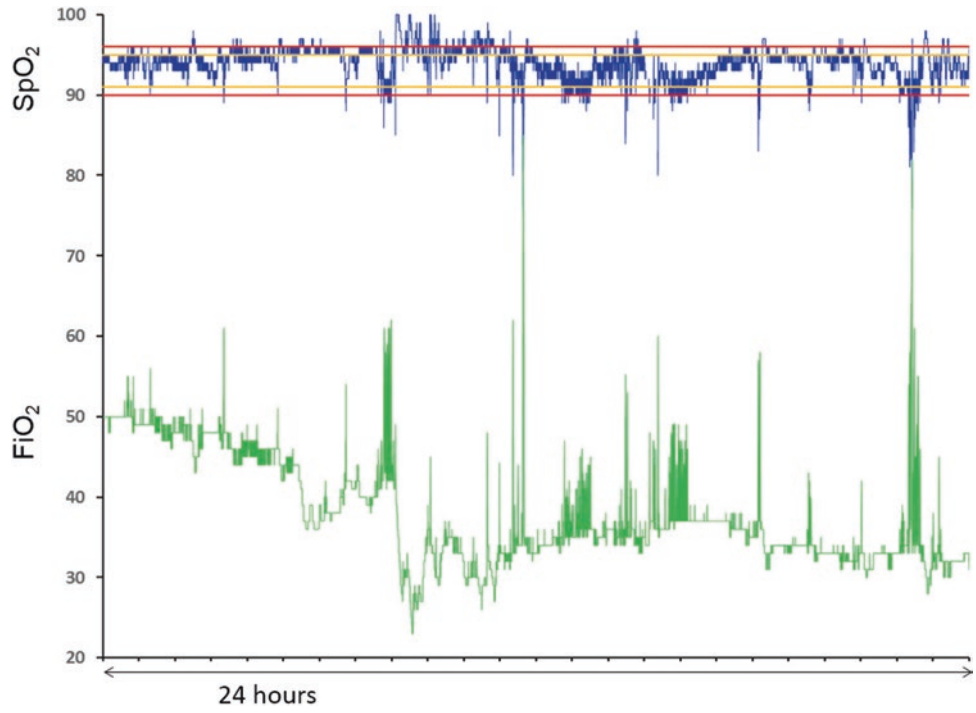

Fig. 18.1 Twenty-four hours recording showing relationship of inspired oxygen concentration and pulse oximetry values

detecting hyperoxemia. The upper alarm setting at which a $PaO_2 > 80$ mmHg can be reliably avoided varies between 88 and 95 % with different instruments, although it is at the upper end of this range with most next-generation instruments.

III. Transcutaneous partial pressure of carbon dioxide ($TcPCO_2$) monitoring

A. Principle of operation

$TcPCO_2$ sensor consists of a pH-sensing glass electrode and a silver-silver chloride reference electrode, covered by a hydrophobic CO_2-permeable membrane from which they are separated by a sodium bicarbonate-electrolyte solution. As CO_2 diffuses across the membrane there is a pH change of the electrolyte solution ($CO_2 + H_2O \rightarrow HCO_3^- + H^+$), which is sensed by the glass electrode. All instruments have built-in correction factors since their uncorrected measurements will be 50 % higher than arterial PCO_2. They must also be calibrated at regular intervals and require a 10–15 min run-in time following resiting.

B. Factors influencing measurements

1. Sensor temperature. Optimal sensor temperature is 42 °C, but if sensors are used in combination with a $TcPO_2$ sensor, a sensor temperature of 44 °C can be used without jeopardizing the precision of the $TcPCO_2$ measurement.
2. Sensor placement and skin thickness. $TcPCO_2$ measurements are relatively independent of sensor site or skin thickness, but $TcPCO_2$ may be falsely high if pressure is applied onto the sensor.
3. Peripheral perfusion. $TcPCO_2$ may be falsely high in severe shock. Precision may already be affected if $PaCO_2$ is >45 mmHg and/or arterial pH is <7.30, but there is no systematic over- or underestimation of $PaCO_2$ under these conditions.
4. Response times. 90 % response time to a sudden change in $PaCO_2$ is between 30 and 50 s.

C. Detection of hypocarbia and hypercarbia
Sensitivity to both hypocarbia and hypercarbia is 80–90 %.

IV. End-tidal carbon dioxide ($ETCO_2$) monitoring (Capnometry)
A. Principle of operation
An infrared beam is directed through a gas sample and the amount of light absorbed by the CO_2 molecules in the sample measured; this is proportional to the CO_2 concentration in the sample.
B. Factors influencing measurements
1. Gas sampling technique. Two approaches exist: (1) with mainstream capnometers, the CO_2 analyzer is built into an adapter which is placed in the breathing circuit. Advantage: fast response time (10 ms), therefore reliable even at high respiratory rates. Disadvantage: 1–10 mL extra dead space; risk of tube kinking. (2) Sidestream capnometers aspirate the expired air via a sample flow. Advantages: no extra dead space; can be used in non-intubated patients. Disadvantages: risk of dilution of expired gas by entrainment of ambient air at the sampling tube–patient interface; longer response time; falsely low values at high respiratory rates (>60/min).
2. Influence of V/Q mismatch. $ETCO_2$ will only approximate $PaCO_2$ if (1) CO_2 equilibrium is achieved between end-capillary blood and alveolar gas, (2) $ETCO_2$ approximates the average alveolar CO_2 during a respiratory cycle, and (3) ventilation–perfusion relationships are uniform within the lung. These conditions are rarely achieved in patients with respiratory disorders. The reliability of an $ETCO_2$ measurement can be assessed from the expiratory signal: this must have a steep rise, a clear end-expiratory plateau, and no detectable CO_2 during inspiration.

V. Chest wall movements
A. Impedance plethysmography. Changes in the ratio of air to fluid in the thorax, occurring during the respiratory cycle, create changes in transthoracic impedance. Cannot be used to quantify respiration. May be heavily influenced by cardiac and movement artifacts.
B. Inductance plethysmography. Changes in the volume of the thoracic and abdominal compartment create changes in inductance, which is registered via abdominal and thoracic bands. The sum of these changes is proportional to tidal volume, and several methods have been developed to calibrate the systems so that tidal volume can be quantified. This, however, only works as long as the patient does not shift position.
C. Strain gauges (usually mercury in silicon rubber) sense respiratory efforts by measuring changes in electrical resistance in response to stretching. These measurements, however, are not reproducible enough to quantify tidal volume.
D. Pressure capsules detect movements of an infant's diaphragm by means of an air-filled capsule that is taped to the abdomen and connected to a pressure transducer via a narrow air-filled tube. The outward movement of the abdomen during inspiration compresses the capsule to produce a positive pressure pulse that is interpreted as a breath. The technique is predominantly used in apnea monitors and in trigger devices for infant ventilators; it is not suitable for quantifying tidal volume.

VI. Electrocardiography (ECG)
The ECG records electrical depolarization of the myocardium. During continuous monitoring, only heart rate can be determined with sufficient precision; any analysis of P and T waves, axis, rhythm, or QT-times requires a printout and/or a 12-lead ECG.

Suggested Reading

Poets CF. Monitoring in the NICU. In: Mathew OP, editor. Respiratory control and its disorders in the newborn. New York: Marcel Dekker, Inc; 2003. p. 217–36.

Poets CF, Bassler D. Providing stability in oxygenation for preterm infants: is transcutaneous oxygen monitoring really better than pulse oximetry? Arch Dis Child Fetal Neonatal Ed. 2008;93:F330–1.

Poets CF, Southall DP. Non-invasive monitoring of oxygenation in infants and children: practical considerations and areas of concern. Pediatrics. 1994;93:737–46.

Raju TN, Stevenson DK, Higgins RD, Stark AR. Safe and effective devices and instruments for use in the neonatal intensive care units: NICHD Workshop summary. Biomed Instrument Technol. 2009;43:308–18.

Clinical Controversies: Pulse Oximetry

19

Win Tin and Samir Gupta

I. Introduction
   A. Noninvasive monitoring of oxygenation has become a standard procedure in neonatology.
   B. Pulse oximetry (SpO_2) is based on using the pulsatile variations in optical density of tissues in the red and infrared wavelengths to compute arterial oxygen saturation without the need for calibration.
   C. The method was invented in 1972 by Takuo Aoyagi, and its clinical application was first reported in 1975 by Susumu Nakajima, a surgeon, and his associates.
   D. There is a small discrepancy between SaO_2 and the SpO_2. The SaO_2 denotes measurement of arterial oxygen saturation by invasive methods and SpO_2 by pulse oximetry.

II. Advantages
   A. Saturation is a basic physiologic determinant of tissue oxygen delivery.
   B. High sensitivity to detect hypoxemia
   C. No warm-up or equilibration time
   D. Immediate and continuous readout
   E. Pulse-by-pulse detection of rapid or transient changes in saturation
   F. Substantially lower maintenance
   G. Skin burns from probe are very rare compared to transcutaneous monitoring.
   H. Minimal effect of motion, light, perfusion, and temperature with the advent of "signal extraction technology" in pulse oximetry

III. Disadvantages
   A. Failure to detect hyperoxia at functional saturation of more than 94% and may impede weaning of oxygen as high PaO_2 is not recognized
   B. Not reliable in cases of severe hypotension or marked edema
   C. May provoke unnecessary evaluation of transient clinically insignificant desaturation events with older pulse oximeters

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D. Pulsatile veins may cause falsely low SpO_2 readings because the oximeter cannot differentiate between venous and arterial pulsations (e.g., in newborns with hyperdynamic circulation).

IV. Terminology in Pulse Oximetry

A. Functional and fractional saturation.

1. Functional saturation—Any forms of hemoglobin in the sample which do not bind oxygen in a reversible way are not included in calculating functional hemoglobin saturation. Pulse oximetry can measure functional saturation from only two forms of hemoglobin, oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb), which is calculated by

$$\text{Functional saturation} = \frac{HbO_2}{HbO_2 + Hb} \times 100$$

2. Fractional saturation—The fractional saturation is defined as the ratio of the amount of hemoglobin saturated with oxygen to all other forms of hemoglobin, including dyshemoglobin (CoHb and MetHb). The co-oximeters used in blood gas laboratories measure fractional saturation, as they use many wavelengths of light and are thus able to measure all types of hemoglobin present:

$$\text{Functional saturation} = \frac{HbO_2}{HbO_2 + Hb + CoHb + MetHb} \times 100$$

3. Pulse oximeters can measure only functional saturation. Some instruments display fractional saturation measurements, which are derived by subtracting 2 % from the functional saturation. It is important to be aware of what the instrument is reading.

B. Bias and precision

Normal level of dyshemoglobin is <2 %. The mean of the difference (error) between oxygen saturation and oxyhemoglobin (SpO_2 and HbO_2) measured by a co-oximeter is called *bias* and the standard deviation of this is called *precision*.

V. Practical Considerations

A. Oxyhemoglobin dissociation curve and pulse oximetry (Chap. 6)

B. Presence of abnormal hemoglobins (dyshemoglobin):

1. Carboxyhemoglobin—SpO_2 is overestimated in the presence of CoHb (e.g., neonatal jaundice, hemolysis).
2. Methemoglobin—SpO_2 decreases in proportion to the percentage of MetHb present.

C. Reduced perfusion states

1. Hypothermia: Does not cause problem if the temperature is >30 °C.
2. Hypovolemia: Loss of signal (but presence of signal does not indicate adequate perfusion).

D. Anemia: Does not cause problem as long as Hb is >5 g/dL.

E. Effect of dyes

1. Bilirubin: Has no influence except if there is acute hemolysis (CoHb).
2. Meconium staining of skin can cause falsely low SpO_2 readings.

F. Venous pulsations (e.g., tricuspid regurgitation) may cause falsely low SpO_2 readings.

G. Abnormal absorption spectrum of hemoglobin (e.g., Hb Köln) may affect the reliability of pulse oximetry but is extremely rare.

VI. Technical Considerations

A. Calibration and accuracy

1. Quality of signal: Before interpreting an SpO_2 reading, the quality of signal received by probe should be confirmed by a good plethysmographic waveform and/or heart rate similar to that on ECG monitor.
2. Differing software among brands: There are small differences between the measurements obtained with different brands of pulse oximeters.
3. Inaccuracy increases when saturation is <75–80 %. The bias and precision between SpO_2 and HbO_2 measured by co-oximetry:
   a. 0.5 % and 2.5 %, respectively, when SpO_2 is >90 %
   b. 1.9 % and 2.7 %, respectively, when SpO_2 is 80–90 %
   c. 5.8 % and 4.8 %, respectively, when SpO_2 is <80 %

B. Delay of response
1. Response time is faster if probe is centrally placed, 50–60 % earlier detection by sensors placed centrally (ear, cheek, tongue) than by sensors placed peripherally (finger, toe).
2. Depends on averaging time. The shortest averaging time should be selected, although this usually increases sensitivity to motion.

C. Motion artifact. The performance of pulse oximeters is affected by motion. To overcome this several brands of pulse oximeters are now equipped with new algorithms that cancel noise signal that is common to both wavelengths.

D. Interference from other light sources
1. Fluctuating light sources. Shielding the probe with cloth or opaque material can overcome the problem of light interference.
2. Incorrectly placed probe (optical shunt or penumbra effect). Part of the light is transmitted without any tissue absorption. This is particularly so if too large a probe is used.

E. Electrical or magnetic interface
1. When using pulse oximetry in MRI suite, care should be taken to use specially designed equipment in order to avoid interference with SpO_2 or even burns from ferrous metals.
2. Electrocautery can also cause failure of pulse oximetry.

VII. Clinical Use of Pulse Oximetry

A. Optimizing oxygen therapy. Meta-analysis of the oxygen saturation target studies concluded that, within the widely used SpO_2 target range of 85–95 %, targeting the "lower" range (85–89 %) compared to the "higher" range (91–95 %) for preterm infants <28 weeks' gestation significantly increased the relative risks of mortality and necrotizing enterocolitis, and significantly reduced the risk of severe ROP.

B. Delivery room stabilization/resuscitation. Pulse oximetry during resuscitation provides real-time clinical information about heart rate and oxygen saturation, and facilitates important decision-making related to interventions such as positive pressure ventilation, cardiac compression, and oxygen titration.

C. Newborn screening. Pulse oximetry has now been accepted as a standard screening tool for early detection of cyanotic congenital heart disease and is increasingly adopted by pediatric societies around the world as part of the routine newborn evaluation.

VIII. Rules for the Optimal Use of Pulse Oximetry

A. Verify probe integrity before use.
B. Avoid mixing probes and monitors of different brands.
C. Check the quality of signal received by the probe (good waveform or true heart rate).
D. Maintain probe positioning under direct visual control.
E. Consider physiologic limitations of SpO_2 and interpret accordingly.
F. In case of doubt, check patient's condition.
G. Check arterial blood gas if saturation is persistently below 80 %.
H. Remember that high SaO_2 may indicate significant hyperoxemia.

Suggested Reading

Dawson JA, Kamlin CO, Vento M, Wong C, Cole TJ, Donath SM, et al. Defining the reference range for oxygen saturation for infants after birth. Pediatrics. 2010;125:e1340–7.

Hay Jr WW, Rodden DJ, Collins SM, et al. Reliability of conventional and new pulse oximetry in neonatal patients. J Perinatol. 2002;22:360–6.

Morgan C, Newell SJ, Ducker DA, et al. Continuous neonatal blood gas monitoring using a multiparameter intra arterial sensor. Arch Dis Child. 1999;80:F93–8.

Moyle JTB, Hahn CEW, Adams AP, editors. Principles and practice series: pulse oximetry. London: BMJ Books; 1998.

Poets CF, Southhall DP. Noninvasive monitoring of oxygenation in infants and children: practical considerations and areas of concern. Pediatrics. 1994;3:737–46.

Richardson DK, Eichenwald EC. Blood gas monitoring and pulmonary function tests. In: Cloherty JP, Stark AR, editors. Manual of neonatal care. New York: Lippincott-Raven; 1998. p. 354–5.

Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation studies. Neonatology. 2014;105(1):55–63.

Thangaratinam S, Brown K, Zamora J, Khan KS, Ewer AK. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. Lancet. 2012;379:2459e64.

Tin W, Lal M. Principles of pulse oximetry and its clinical application in neonatal medicine. Semin Fetal Neonatal Med. 2015;20:192–7.

Veyckemans F. Equipment, monitoring and environmental conditions. In: Bissonnette B, Dalens BJ, editors. Pediatric anesthesia—principles and practice. New York: McGraw-Hill; 2002. p. 442–5.

Interpretation of Blood Gases

20

Steven M. Donn

I. Physiology of Gas Exchange
   A. Oxygenation. The movement of O_2 from the alveolus into the blood is dependent upon the matching of ventilation and perfusion. Ventilation/perfusion matching is abnormal if:
      1. Pulmonary blood flows past unventilated alveoli, causing an *intrapulmonary* right-to-left shunt. In newborns, this is typically caused by atelectasis. The treatment for atelectasis is positive pressure, which opens previously unventilated alveoli and decreases intrapulmonary shunting.
      2. Blood flows right-to-left through the foramen ovale or patent ductus arteriosus, causing an extrapulmonary right-to-left shunt. This sort of *extrapulmonary* shunt is typically caused when pulmonary vascular resistance is high and pulmonary pressure is greater than systemic blood pressure.
      3. Oxygenation depends on the pulmonary surface area available for gas exchange. This in turn is proportional to mean airway pressure.
   B. Ventilation. Ventilation is the removal of CO_2 from the blood.
      1. During spontaneous breathing or conventional mechanical ventilation, the movement of CO_2 from the blood into the alveolus is dependent upon the amount of gas that flows past the alveoli, or alveolar ventilation. Alveolar ventilation is the product of alveolar volume and respiratory rate. Thus, any change in ventilatory strategy, which results in an increase in alveolar volume and/or respiratory frequency, will increase ventilation and decrease P_aCO_2. Minute ventilation is the amount of CO_2 removed in 60 s.
      2. During high-frequency ventilation, gas exchange between the alveolus and the upper airway is predominantly a consequence of mixing, rather than bulk flow. Because of this, CO_2 removal during high-frequency ventilation is proportional to:
         (Frequency) × (Volume of the high-frequency "breaths")^2
   C. Acid-base status (Table 20.1)
      1. The pH of arterial blood is determined primarily by:
         a. P_aCO_2

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Table 20.1 Recommended ranges of blood gases in the first week of life for preterm babies with RDS

Arterial	pH	7.25–7.35
	P_aCO_2	35–45
	P_aO_2	50–70
Capillary	pH	7.20–7.30
	PCO_2	40–50
	PO_2	<50
Venous	pH	7.20–7.30
	PCO_2	40–50
	PO_2	<50

   b. Lactic acid, produced by anaerobic metabolism
   c. Buffering capacity, particularly the amount of bicarbonate in the blood and concentration of hemoglobin
2. Respiratory acidosis occurs when an increase in P_aCO_2 causes a decrease in pH. Respiratory alkalosis occurs when a decrease in P_aCO_2 causes an increase in pH.
3. Metabolic acidosis occurs when there is either an excess of lactic acid, or a deficiency in the buffering capacity of the blood, resulting in a decrease in pH. It is reflected by an increased base deficit, also termed a decreased base excess.
4. If P_aCO_2 remains persistently elevated, the pH will gradually return to normal as a result of a slow increase in bicarbonate in the blood, termed a compensatory metabolic alkalosis. Conversely, a patient with a persistently low P_aCO_2 will gradually develop a compensatory metabolic acidosis.
5. In patients with intact respiratory drive, a persistent metabolic acidosis will result in hyperventilation (sustained tachypnea), termed a compensatory respiratory alkalosis.
6. Most extremely low-birth-weight infants have immature renal tubular function in the first week of life and spill bicarbonate in the urine, contributing to a metabolic acidosis. Administration of extra base in the intravenous fluids may prevent and/or correct this metabolic acidosis.
7. If an infant has severe hypoxemia and/or decreased tissue perfusion, anaerobic metabolism causes the production and accumulation of lactic acid, and results in a metabolic acidosis. *This should be treated by improving the underlying problem, rather than by administering additional base (bicarbonate).* Lactic acid can be directly measured by most blood gas machines, and is a useful tool for tracking the development and resolution of impaired perfusion (e.g., in patients with septic or cardiogenic shock).

II. Oxygen Content of Blood
   A. Oxygen is carried in the blood in two ways.
      1. Bound to hemoglobin (97 %). The amount of O_2 that is carried in the blood bound to hemoglobin is dependent upon both the hemoglobin concentration and the hemoglobin saturation (S_aO_2). In the normal infant with a hemoglobin level of 15 g/100 mL and S_aO_2 of 100 %, approximately 20 mL O_2 is bound to the hemoglobin in 100 mL of blood.
      2. Dissolved in plasma (3 %). In the normal infant (or adult), the amount of oxygen dissolved in plasma is trivial compared to the amount of oxygen that is bound to hemoglobin (Hb). Approximately 0.3 mL of O_2 is dissolved in 100 mL plasma per 100 Torr O_2 partial pressure.
   B. Significantly increasing P_aO_2 beyond that which is needed to fully saturate Hb will slightly increase the amount of O_2 dissolved in plasma, but will not increase the amount of O_2 bound to Hb.

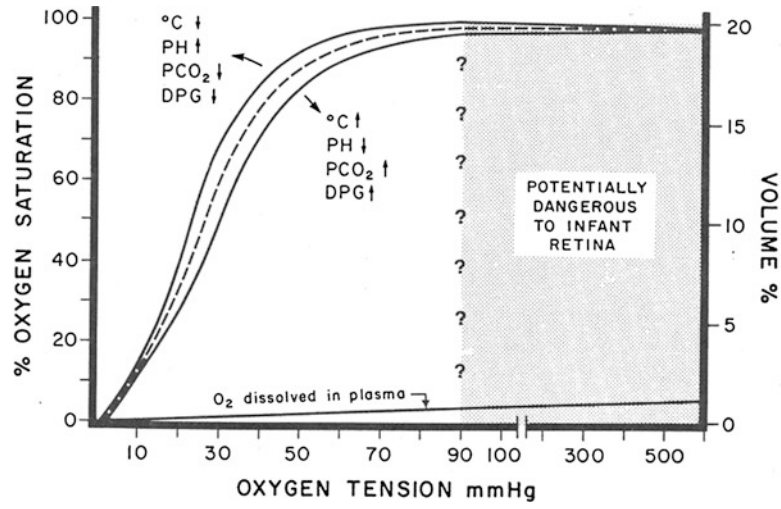

Fig. 20.1 The oxyhemoglobin dissociation curve (from Klaus MH, Fanaroff AA: *Care of the High Risk Neonate*. Philadelphia, WB Saunders CO., 1986, p. 173. Used by permission)

C. The P_aO_2 that is required to fully saturate Hb is dependent upon the oxygen-hemoglobin dissociation curve (Fig. 20.1). This curve is affected by many factors, including the relative amount of fetal Hb in the blood (fetal Hb is fully saturated at a lower P_aO_2 than is adult Hb). For this reason, arterial saturation (S_aO_2) is a better indicator of the amount of oxygen in the blood than is P_aO_2.

III. Oxygen Delivery and Mixed Venous Oxygen Saturation

A. The amount of oxygen delivered to the tissues depends on the amount of oxygen in the blood (C_aO_2) and cardiac output (CO). Oxygen delivery is the product of oxygen content and blood flow.

1. Assume that an average infant has a C_aO_2 of 20 mL O_2/100 mL blood and a cardiac output of 120 mL/kg/min.
2. Therefore, the amount of oxygen available for delivery to the body can be calculated as the product of C_aO_2 and CO.
3. (20 mL O_2/100 mL blood) × (120 mL/kg/min) = 24 mL O_2/kg/min available for delivery to tissues.

B. Under stable conditions, oxygen consumption for the average infant is approximately 6 mL/kg/min.

C. If an infant is delivering oxygen to the systemic circulation at a rate of 24 mL/kg/min and is utilizing oxygen at a rate of 6 mL/kg/min, 25 % of the oxygen in the blood is utilized by tissues; 75 % of the oxygen (18 mL/kg/min) is not utilized by the tissues, so blood returning to the right atrium from the systemic circulation is 75 % saturated. This is the normal mixed venous saturation (S_vO_2) in a healthy infant.

1. Mixed venous saturation (S_vO_2) is the saturation of blood as it enters the pulmonary artery. It is referred to as "mixed" venous blood, because it represents the average of the blood returning to the right atrium from the superior vena cava and from the inferior vena cava. S_vO_2 can be measured directly with a pulmonary artery catheter, or can be approximated by a sample of blood from the right atrium, but this is of course impractical in most neonatal clinical contexts.
2. S_vO_2 is an important measurement in patients with questionable cardiac output. A low S_vO_2 (<75 %) means that an unusually large fraction of the available oxygen has been

extracted by the tissues. This usually indicates inadequate delivery of oxygen to the tissues, but it may represent increased oxygen consumption in states such as sepsis.

3. Causes of low S_vO_2 include inadequate oxygenation of the blood, anemia, or low cardiac output. The presence of low S_vO_2 in a patient with normal S_aO_2 and normal Hb is diagnostic of cardiac output inadequate to meet tissue oxygen demands.
4. S_vO_2 is typically used to monitor the adequacy of tissue perfusion in patients receiving ECMO (Chap. 64) and can be useful in any patient where adequacy of cardiac output is uncertain, but it is generally not available in neonatal intensive care beyond ECMO.

IV. Arterial, Capillary, and Venous Blood
   A. As blood flows through the systemic capillary bed, O_2 is extracted and CO_2 and lactic acid are added to it. Thus, venous blood has a lower PO_2, a lower pH, and a higher PCO_2 than arterial blood. Unfortunately, the size of the PO_2, PCO_2, and pH gradients between arterial and venous blood is dependent upon multiple factors (including Hb, cardiac output, and metabolic demand). Essentially, the only useful information from a venous blood sample (other than a mixed venous sample) is that the P_aCO_2 is lower than the P_vCO_2.
   B. Capillary blood gases are typically "arterialized" samples, where the capillary bed has been warmed to increase blood flow. The assumption is that increased blood flow leads to decreased exchange of O_2, CO_2, and lactic acid between the tissue bed and the capillaries. However, this is not a consistent effect, and the correlation between capillary and arterial values is poor. In addition, capillary sampling is painful and usually causes infants to cry and change their respiratory pattern, raising the question of how reflective of baseline state a capillary sample truly is. In general, capillary blood gases should be used only to provide a rough approximation of arterial CO_2, with the understanding that they may over-estimate P_aCO_2 by 5–10 Torr (or more). Technique is critical and values tend to be less reliable with increasing postnatal age.

V. Noninvasive Estimation of Blood Gases (Chaps. 18 and 19)
   A. Pulse oximeters are the clinical "gold standard" for measuring oxygenation.
   B. Transcutaneous monitors provide an estimate of P_aO_2 and P_aCO_2. They can be cumbersome to use, and both the adhesives used to attach the probes to the skin and the elevated temperature at which their function can cause skin injury to extremely preterm infants. However, they are a useful tool for continuously monitoring critically ill infants, or infants with labile P_aCO_2. In general, transcutaneous CO_2 monitors are as accurate as capillary blood gas samples. They are especially useful when switching an infant from conventional to high-frequency ventilation to avoid hypocapnia.
   C. End-tidal CO_2 monitors (capnometry) can provide useful information about P_aCO_2 in some infants. The concentration of CO_2 at the end of exhalation is close to P_aCO_2 in patients with healthy lungs and low respiratory rates. This makes end-tidal CO_2 monitoring a useful tool for term post-operative babies, or other larger babies with only minimal lung disease. For patients who are small, and tachypneic, or have severe lung disease, end-tidal monitoring can provide a useful measure of trends in P_aCO_2, although not an accurate measure of absolute P_aCO_2 values. Capnography is discussed in detail in Chap. 21.

VI. Errors in Blood Gas Measurements
   A. An air bubble in a blood gas sample will cause the blood to equilibrate with room air.
      1. P_aCO_2 will be artificially lowered.
      2. P_aO_2 will move closer to the partial pressure of O_2 in room air (approximately 140 Torr or 18.7 kPa, depending on altitude and humidity).
   B. Dilution of a blood gas sample with IV fluid of any sort will cause both CO_2 and O_2 to diffuse from the blood into the diluting fluid.
      1. P_aO_2 will be artificially lowered.
      2. P_aCO_2 will be artificially lowered.

3. Because of the buffering capability of the blood, pH will not change as much as will P_aCO_2. The combination of relatively normal pH and decreased P_aCO_2 will appear to be a respiratory alkalosis with metabolic acidosis.

C. If a blood gas sample is left for too long a period at room temperature, the blood cells will continue to metabolize oxygen and produce CO_2 and metabolic acids.

D. Most blood gas machines calculate S_aO_2 from P_aO_2, assuming that all of the Hb is adult Hb. In an infant with a significant amount of fetal Hb, this calculated value will be much lower than the actual measured S_aO_2.

E. Capillary blood gas values are frequently assumed to approximate arterial blood gas values. However, there is marked variation in the correlation of capillary and arterial values. Capillary blood gases should always be interpreted with caution.

F. Blood gases obtained by arterial puncture or capillary stick are painful and disturb the infant, frequently causing agitation, desaturation, or hyperventilation. They should be interpreted with caution.

VII. Clinical Interpretation of Blood Gases. Blood gas values, by themselves, convey relatively little information; they must always be interpreted in a clinical context. When interpreting blood gas results, a number of other factors must also be assessed.

A. How hard is the infant working to breathe?

1. A normal blood gas in an infant who is clearly struggling to breathe is not necessarily reassuring. It reflects compensation "at a price."
2. An elevated P_aCO_2 in an infant with BPD, who is comfortable, is not necessarily concerning.

B. Does a recent change in blood gas values represent a change in the patient, or is it an artifact?

C. If a blood gas result is used to make decisions about ventilator strategy, how much of the total respiratory work is being done by the patient, and how much is being done by the ventilator?

D. Where is the patient in the course of the disease? A P_aCO_2 of 65 Torr (8.7 kPa) may be very concerning in an infant in the first few hours of life, but perfectly acceptable in an infant with BPD.

E. When deciding whether to obtain a blood gas sample, ask yourself whether you will learn anything from it that you cannot learn from a clinical examination of the patient. Clinical or ventilator-derived information includes:

1. Respiratory rate
2. Minute volume (ventilation)
3. Lung compliance and resistance
4. Hemodynamic status (heart rate, blood pressure, perfusion)

VIII. Target Ranges for Blood Gases. A wide range of blood gas values are seen in newborn infants, depending upon their gestational age, postnatal age, and disease state. In most infants with a respiratory disease, the goal is not to make blood gases entirely normal, but to keep them within an acceptable "target range." There are little controlled data to guide the choice of these "target ranges;" instead they have gradually evolved, and are continuing to evolve.

A. pH. In most newborns, the goal is to keep the arterial pH between 7.25 and 7.40. However, in some patients it is appropriate to allow a lower arterial pH. An alkalotic pH (>7.40) should almost always be avoided.

B. P_aCO_2. In the healthy term newborn, the normal P_aCO_2 is approximately 35–40 Torr.

1. Infants with any significant lung disease will exhibit alveolar hypoventilation and develop an elevated P_aCO_2 and respiratory acidosis.

2. Over the last two decades, there has been a gradual shift toward tolerating higher P_aCO_2 levels ("permissive hypercapnia").
3. Partially because of the data suggesting a potential link between hypocarbia and decreased cerebral blood flow and brain injury, P_aCO_2 levels much below 40 Torr should be avoided.
4. With time, respiratory acidosis will be matched by a compensatory metabolic alkalosis, and the arterial pH will move toward the normal range.
5. Because of the complex interaction of disease severity, ventilatory support, and duration of hypercapnia, many clinicians find it easier to define a "target pH" rather than a "target P_aCO_2."

C. P_aO_2. P_aO_2 is not nearly as important a physiologic parameter as S_aO_2, and because of the variable amount of fetal Hb in an infant's blood, it is also widely variable. Many neonatologists think of oxygenation only in terms of S_aO_2, not in terms of P_aO_2.

D. S_aO_2. In the healthy-term infant S_aO_2 is close to 100 %. However, the oxygen content of blood is adequate for tissue oxygen delivery at much lower levels of S_aO_2. In patients with cyanotic heart disease S_aO_2 of 70–75 % is sufficient to ensure adequate tissue oxygenation. Because of the association between high S_aO_2 with an increased risk of both retinopathy of prematurity and BPD, most premature infants should be managed with $S_aO_2 \leq 95\,\%$. The ideal target range for S_aO_2 remains uncertain, and is the subject of ongoing controversy.

E. Base Deficit.
1. In the healthy-term infant, the base deficit is usually around 3–5 mEq/L.
2. Base deficit is a calculated value, and can vary significantly.
3. In most patients with a base deficit between 5 and 10 mEq/L, assuming good tissue perfusion on clinical examination, no acute intervention is needed. A base deficit in this range in a very preterm infant may suggest renal bicarbonate wasting, and may prompt an increase in the amount of base administered in the maintenance fluids.
4. A base deficit of more than 10 mEq/L should prompt a careful examination of the infant for signs of under-perfusion. In the patient with a significant base deficit and clinical under-perfusion, correcting the cause of the under-perfusion should be the primary goal. In most cases, correcting the underlying cause of metabolic acidosis is far more effective than is administering extra base.

F. Caveats
1. Trends are usually more important than singular values.
2. Blood gas results must always be reconciled with the clinical status of the baby.
3. Blood gas targets must also take into account the baby's disease status and the gas exchange capability of the lungs. "Normal" blood gases in a baby with severe BPD, for example, would represent iatrogenic overventilation.
4. Remember to interpret blood gas results according to clinical contexts. A baby who has received a lot of transfused blood has a higher concentration of adult hemoglobin with a different P50 and will supply more oxygen to tissues than a baby with more fetal hemoglobin, all other things being equal.

Suggested Reading

Ambalavanan N, Carlo W. Hypocapnia and hypercapnia in respiratory management of newborn infants. Clin Perinatol. 2001;28:517–31.

Aschner JL, Poland RL. Sodium bicarbonate: basically useless therapy. Pediatrics. 2008;122:831–5.

Chen ML, Guo L, Smith LEH, Dammann CEL, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. Pediatrics. 2010;125:e1483–92.
Courtney SE, Weber KR, Breakie LA, et al. Capillary blood gases in the neonate: a reassessment and review of the literature. Am J Dis Child. 1990;144:168–72.
Dennis RC, Ng R, Yeston NS, Statland B. Effect of sample dilutions on arterial blood gas determinations. Crit Care Med. 1985;13:1067–8.
Dudell G, Cornish JD, Bartlett RH. What constitutes adequate oxygenation? Pediatrics. 1990;85:39–41.
Molloy EJ, Deakins K. Are carbon dioxide detectors useful in neonates? Arch Dis Child Fetal Neonatal Ed. 2006;91:F295–8.
SUPPORT Study Group. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362:1959–69.
Tobias JD. Transcutaneous carbon dioxide monitoring in infants and children. Paediatr Anaesth. 2009;19:434–44.

Volumetric Capnography in Critically Ill Neonates and Children

21

Joachim Zobel, Klaus Pfurtscheller, and Gerfried Zobel

I. Definitions
   A. Time-based capnography. Expired CO_2 concentration is plotted against time.
   B. Volume-based capnography. Expired CO_2 concentration is plotted against the expired gas volume of a single breath (SBT-CO_2).
II. General Information
   A. It shows airway integrity and alveolar ventilation.
   B. It indicates pulmonary perfusion.
   C. It provides noninvasive breath-by-breath assessment of ventilation.
   D. It shows airway dead space and allows calculation of physiologic and alveolar dead spaces.
III. Mainstream Technology for Gas Measurement
   A. Infrared (IR) absorption technique
   B. Capnostat 5 sensor
      1. Consists of an IR source and IR detector
      2. The beam of IR radiation passes through the cuvette and the fraction of IR radiation absorbed is measured by the detector.
   C. Airway adapters
      1. Infants (dead space <1 mL)
      2. Children/adults (dead space 6 mL)
   D. The airway adapters are placed between the endotracheal tube and the flow sensor of the respiratory circuit.
IV. Graphical User Interfaces (GUI)
   A. Modern ventilators have touch screen interfaces with color displays.
   B. Neonatal-capable ventilators with integral volumetric capnography
      1. Hamilton S1, C2, and T1 (Hamilton Medical, Reno, NV)
      2. Draeger VN 500 (Draeger, Telford, PA)
      3. Avea (CareFusion, Yorba Linda, CA)
      4. Servo-i (Maquet Critical Care, Wayne, NJ)

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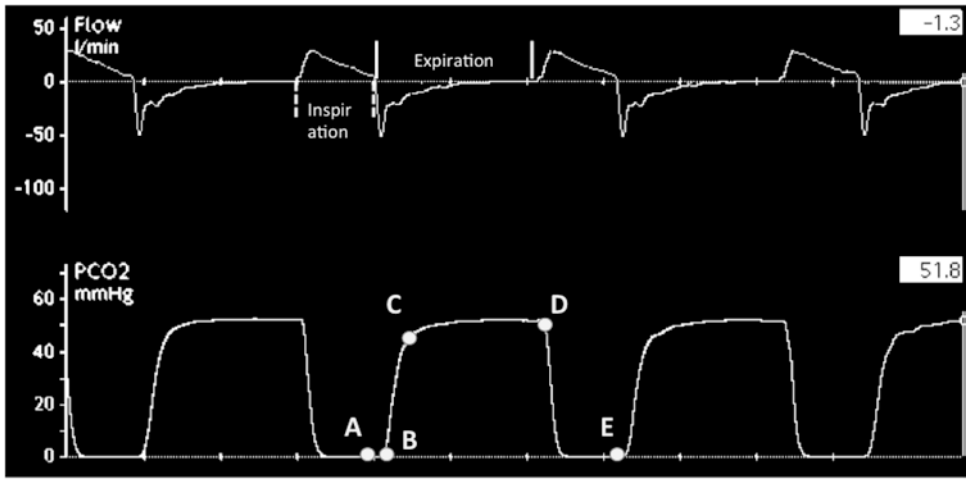
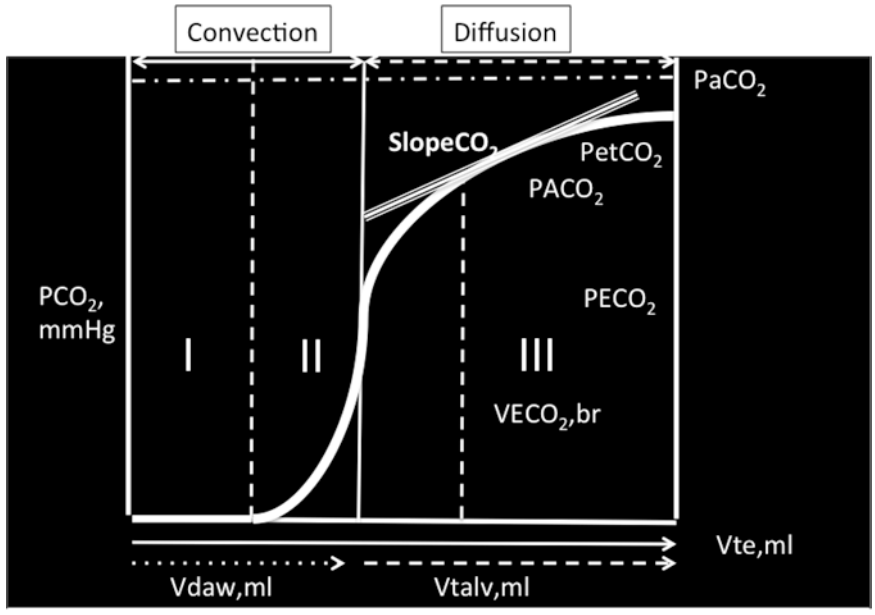


A-B: Early stage of expiration (CO_2-free air of the upper respiratory tract)
B-C: Mixed air of the lower respiratory tract and the early emptying alveolar units
C-D: CO_2 rich air of the alveolar units
D: Partial pressure of endexpiratory CO_2
D-E: Inspiration

Fig. 21.1 Time-based capnography

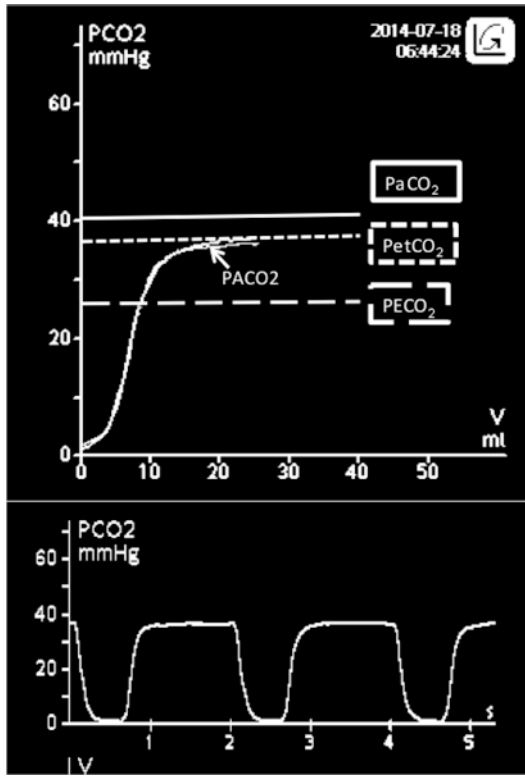
V. Graphic Waveforms
   A. Time-based waveform (Fig. 21.1)
      1. A–B: Early phase of expiration (CO_2-free air of the upper respiratory tract)
      2. B–C: Mixed air of the lower respiratory tract and early-emptying alveolar units
      3. C–D: CO_2-rich air of the alveolar units
      4. D: Partial pressure of end-tidal CO_2.
      5. D–E: Inspiration.
   B. Volume-based waveform (Figs. 21.2 and 21.3):
      1. Phase I: Represents the first portion of the expired air and is therefore more or less free of CO_2.
      2. Phase II: Represents the mixed air of the convective airways and the alveolar units. Furthermore, this phase represents the transition between the terminal airways and the early-emptying alveoli. The ascent of the tracing of this phase of the capnogram is normally very steep, because more and more CO_2 streams out of the alveolar units.
      3. Phase III: Represents the CO_2-rich air of the alveolar units, the tracing reaches a plateau with its highest value at the end of expiration ($etCO_2$).
      4. SlopeCO_2: The slope of phase III (S III) represents the mean value of the ascent of phase III. Phase III is divided into three parts; in the middle part ten equidistant points are determined and the mean value of these ten points is used to calculate the mean value of S III. It is a simple and noninvasive method to detect inhomogeneities in ventilation and perfusion (Figs. 21.4, 21.5, 21.6, 21.7, 21.8, and 21.9).

VI. Dynamic Measurements/Calculations
   A. PetCO_2 (mm Hg) is the end-tidal partial pressure of CO_2 in the expired air.



Phase I: CO_2-free gas
Phase II: Represents the mixed air of convective airways and alveolar units
Phase III: Alveolar gas with a slow increase of partial pressure of CO_2 associated with an increase in the expired CO_2 volume ($VECO_2$,br)

Fig. 21.2 Volume-based capnography



$PaCO_2$,torr	**40**
$PetCO_2$,torr	37
$PECO_2$,torr	27.5
$PACO_2$,torr	36.4
Pa-$etCO_2$,torr	3
Pa-ACO_2,torr	3.6
Slope,%CO_2/L	38.8
VD_{aw},%	0.231
VD_{alv},%	0.081
VD_{physBE},%	0.32
SpO_2,%	99
Vte,ml	27
$VECO_2$,ml	1.0

Fig. 21.3 Time- and volume-based capnography in a neonate with normal cardiorespiratory function

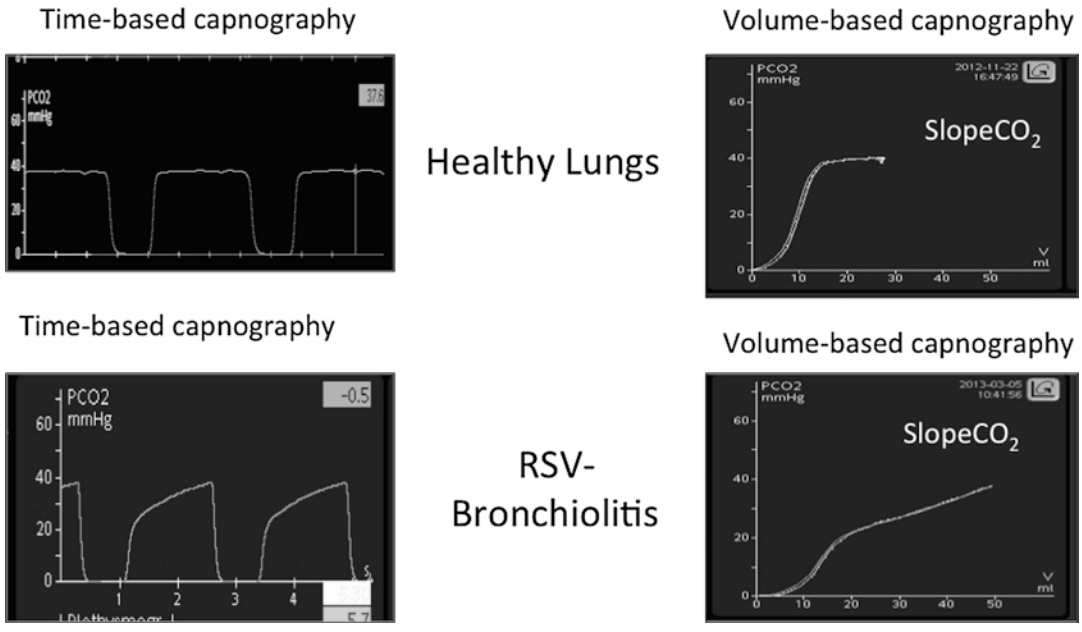


Fig. 21.4 Time- and volume-based capnography in an infant with healthy lungs and an infant with severe RSV-bronchiolitis. In severe RSV-bronchiolitis phase II is elongated and the ascent is not so steep as in normally ventilated lungs. The transition between phases II and III is difficult to determine and in phase III the tracing does not reach its typical plateau. These changes are caused by significant ventilation/perfusion mismatches and peripheral airway obstruction

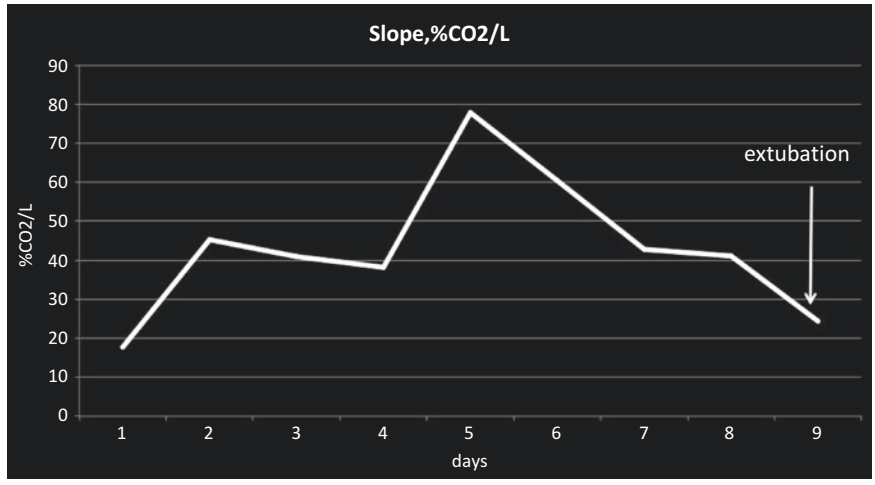


Fig. 21.5 The course of slopeCO_2 (vol%/L) in an infant with severe RSV bronchiolitis on invasive mechanical ventilation. The course of slopeCO_2 in an infant with severe RSV bronchiolitis shows that the maximum slopeCO_2 will be reached within 4–6 days. When peripheral airway obstruction improves over time, slopeCO_2 decreases

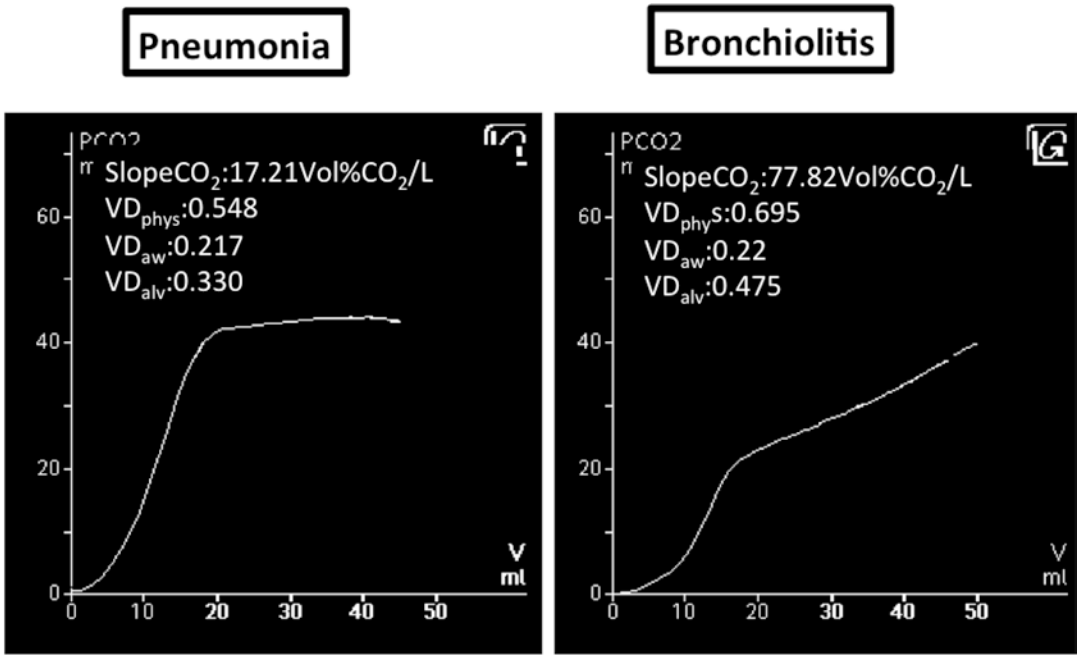
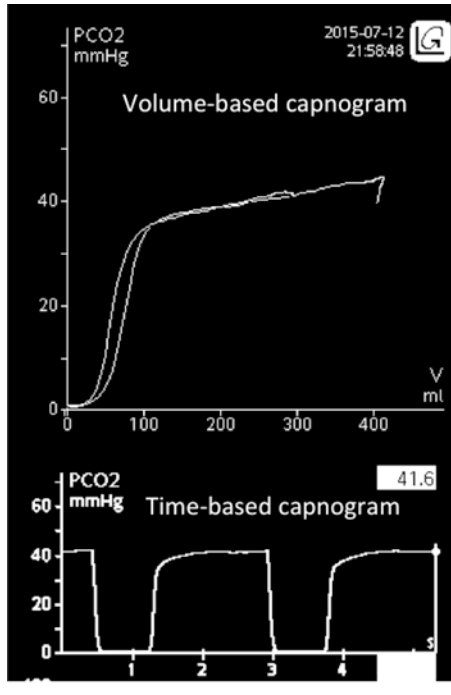


Fig. 21.6 Volume-based capnography to define severe respiratory RSV infection. Whereas volume-based capnogram looks normal in an infant with severe RSV pneumonia, there are significant changes in phases II and III in an infant with severe RSV bronchiolitis



PEEP,mbar	12
FiO_2	0.65
$PaCO_2$,mmHg	48.3
$PetCO_2$,mmHg	43
Pa-$etCO_2$,mmHg	5.3
Pa-ACO_2,mmHg	16.8
$SlopeCO_2$,vol%/L	4.9
VD_{aw},%	0.23
VD_{phys},%	0.48
VD_{alv},%	0.25
SpO_2/FiO_2,%	146
OSI	12.3

Fig. 21.7 Pre- and postoperative time- and volume-based capnography in an infant with tetralogy of Fallot. Improved postoperative pulmonary perfusion can be seen on both time- and volume-based capnograms

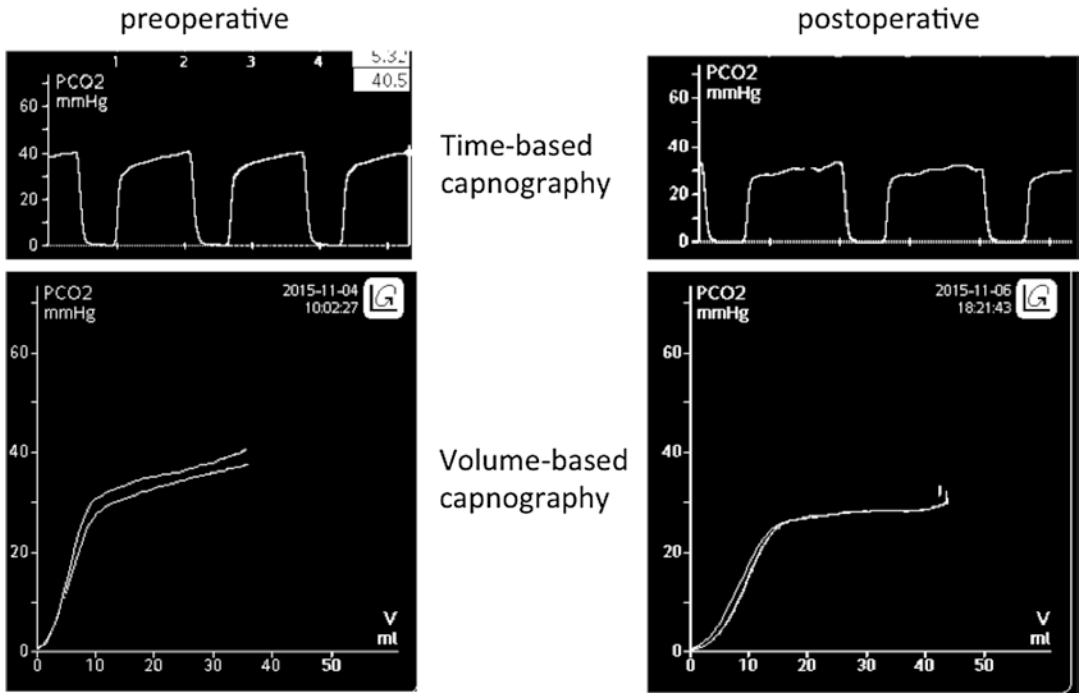


Fig. 21.8 Time- and volume-based capnography in a patient with ARDS. PEEP can be titrated to optimize alveolar dead space fraction (VD_{alv}/Vte,%) and the differences between arterial and end-tidal CO_2 (Pa-etCO_2) or arterial to alveolar CO_2 (Pa-ACO_2)

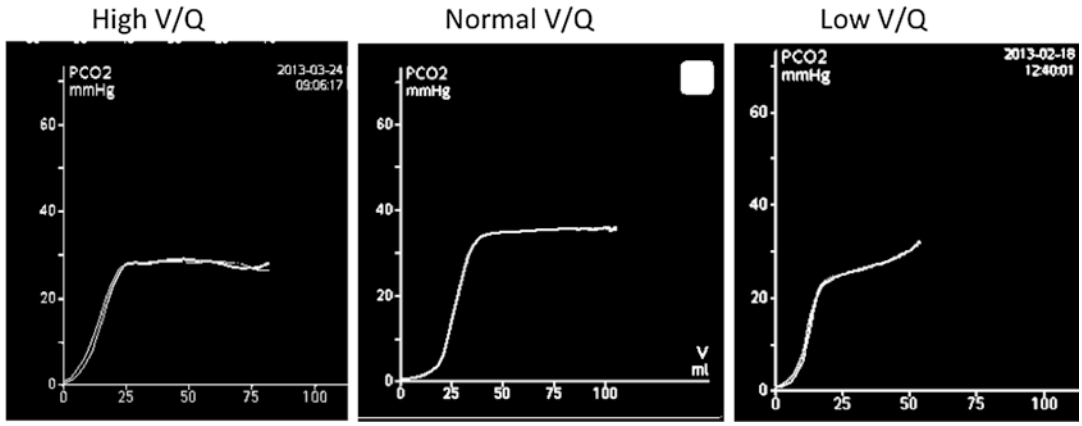


Fig. 21.9 Volume-based capnography and ventilation-perfusion matching. Three different volume-based capnograms with high, normal, and low ventilation-perfusion matching

B. $PECO_2$ (mm Hg) represents the mixed-expired partial pressure of CO_2, which is used to calculate the physiologic dead space.
   Bohr equation: $(PA\text{-}ECO_2)/PACO_2$.
C. $PACO_2$ (mm Hg) is the mean alveolar partial pressure of carbon dioxide, used in the Bohr.
D. VCO_2 (mL/min) represents the volume of CO_2 eliminated per minute. In steady-state conditions VCO_2 is equal to metabolic CO_2 production.

E. $VECO_2$ (mL) is the breath-by-breath elimination of CO_2.
F. $SlopeCO_2$ (CO_2 vol%/L) represents the mean value of the ascent of phase III of the volumetric capnogram.
G. Dead spaces:
   1. Airway dead space fraction (VD_{aw}/Vte,%)
   2. Physiologic dead space fraction (VD_{phys}/Vte.%)
      a. $VD_{phys}/Vte = VD_{aw}/Vte + VD_{alv}/Vte$
      b. Bohr-Enghoff equation: $(PaCO_2 - PECO_2)/PaCO_2$
   3. Alveolar dead space fraction (VD_{alv}/Vte,%)
H. Pa-$etCO_2$ (mmHg) represents the arterial-to-end tidal gradient for PCO_2 and is an index for gas exchange (normal value 3–5 mmHg). Some investigators use this index as a parameter for the alveolar dead space fraction.
I. Pa-ACO_2 (mmHg) represents the gradient between arterial-to-alveolar PCO_2. It is a more accurate index for gas exchange than Pa-$etCO_2$. Normal values are from 4 to 8 mmHg.

VII. Indications
A. Endotracheal intubation
   Shows expiratory gas flow immediately after endotracheal intubation, confirming the tube placement.
B. Optimizing ventilatory parameters
   1. Respiratory rate (RR)
   2. Peak inspiratory pressure (PIP)
   3. Positive end expiratory pressure (PEEP)
   4. Inspiratory time (Ti)
   5. Synchronization
C. Evaluation of infant's spontaneous effort
   1. Respiratory pattern
   2. Readiness for extubation
D. Therapeutic response to pharmacologic agents
   1. Bronchodilators
   2. Inhaled pulmonary vasodilators
   3. Surfactant
E. Disease evaluation
   1. Restrictive
   2. Obstructive
   3. Severity
   4. Recovery

Suggested Reading

Almeida-Junior AA, Nolasco da Silva MT, Almeida CCB, et al. Relationship between physiologic deadspace/tidal volume ratio and gas exchange in infants with acute bronchiolitis on invasive mechanical ventilation. Pediatr Crit Care Med. 2007;8:372–7.

Bhalla AK, Belani S, Leung D, et al. Higher dead space is associated with increased mortality in critically ill children. Crit Care Med. 2015;43:2439–45.

Fletcher R, Jonson B, Cumming G, et al. The concept of deadspace with special reference to the single breath test for carbon dioxide. Br J Anaesth. 1981;53:77–88.

Ghuman AK, Newth CJL, Khemani RG. The association between the end tidal alveolar dead space fraction and mortalitiy in pediatric acute hypoxemic respiratory failure. Pediatr Crit Care Med. 2012;13:11–5.

Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med. 2002;346:1281–6.

Ong T, Stuart-Killion RB, Daniel BM, et al. Higher pulmonary dead space may predict prolonged mechanical ventilation after cardiac surgery. Pediatr Pulmonol. 2009;44:457–63.

Raurich JM, Vilar M, Colomar A, et al. Prognostic value of the pulmonary deadspace fraction during the early and intermediate phases of acute respiratory distress syndrome. Respir Care. 2010;55:282–7.

Ream RS, Schreiner MS, Neff JD, et al. Volumetric capnography in children. Anesthesiology. 1995;82:64–73.

Sinha P, Flower O, Soni N. Deadspace ventilation: a waste of breath! Intensive Care Med. 2011;37:735–46.

Suarez-Sipmann F, Bohm SH, Tusman G. Volumetric capnography: the time has come. Curr Opin Crit Care. 2014;20:333–9.

Tusman G, Boehm SH, Suarez-Sipmann F, et al. Lung recruitment and positive end-expiratory pressure have different effects on CO_2 elimination in healthy and sick lungs. Anesth Analg. 2010;111:968–77.

Tusman G, Suarez-Sipmann F, Bohm SH, et al. Capnography reflects ventilation/perfusion distribution in a model of acute lung injury. Acta Anaesthesiol Scand. 2011;55:597–606.

Tusman G, Sipmann FS, Boehm SH. Rationale of dead space measurement by volumetric capnography. Anesth Analg. 2012;114:866–74.

Zobel J. Volumetric capnography and slope-CO_2 in mechanically ventilated infants and children under the age of 36 months. Diplomarbeit, Medical University of Graz; 2015. https://qline.medunigraz.at

Neonatal Pulmonary Graphics

22

Mark C. Mammel and Steven M. Donn

I. Indications
   A. Optimizing mechanical ventilation parameters
      1. Peak inspiratory pressure (PIP)
      2. Positive end expiratory pressure (PEEP)
      3. Inspiratory and expiratory tidal volume (V_{TI} or V_{TE})
      4. Inspiratory time (T_I)
      5. Expiratory time (T_E)
      6. Flow rate
      7. Synchronization
      8. Compliance
   B. Evaluation of infant's spontaneous effort
      1. Spontaneous V_T
      2. Minute ventilation (MV)
      3. Respiratory pattern
      4. Readiness for extubation
   C. Therapeutic response to pharmacologic agents
      1. Surfactant
      2. Bronchodilators
      3. Diuretics
      4. Steroids

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D. Evaluation of respiratory waveforms, loops, and mechanics
   1. Waveforms
      a. Pressure
      b. Flow
      c. Volume
   2. Loops
      a. Pressure–volume loop
      b. Flow–volume loop
   3. Mechanics
      a. Dynamic compliance (C_D) or static compliance (C_{ST})
      b. Resistance (inspiratory and expiratory)
      c. Time constants

E. Disease Evaluation
   1. Restrictive
   2. Obstructive
   3. Severity
   4. Recovery

II. Graphical User Interfaces

A. Graphical user interfaces (GUI) provide continuous, real-time, breath-to-breath feedback of the interaction between the patient and the ventilator.

B. They are also an excellent teaching tool.

C. Graphics monitors have been available for the last decade as an option that can be added to ventilators; now, the latest generation of ventilators has touch screen interfaces with color displays that are integral to the ventilator.

D. Graphics data collection. Flow sensor location:
   1. Proximal flow sensor positioning, at the airway opening, is critical for accurate waveforms, loops, and data.
   2. Distal flow sensors, within the ventilator or near the tubing exit, produce waveforms, loops, and data that include circuit compliance and resistance. So-called circuit compliance compensation calculations do not accurately correct the data displayed. They should not be used in very preterm babies, where suboptimal volume delivery may promote lung injury.

E. Flow sensors
   1. Heated wire anemometer: Measures the amount of current required to keep a heated wire at a constant temperature as gas flows past the wire and heat is convected. This current can be converted to a flow measurement, and integrated to determine volume.
   2. Differential pressure pneumotachometer: As gas flows through the sensor across an element, a differential pressure is created between the upstream and downstream sensing ports. The change in pressure across the element is proportional to flow.
   3. Diaphragmatic neural sensor: This technique uses a modified feeding tube containing a number of electrode sensors for measurement of diaphragmatic EMG.

F. Neonatal-capable ventilators with integral GUI
   1. Avea (CareFusion, Yorba Linda, CA)
   2. Dräger Babylog VN500, Evita XL, Evita Infinity V500 (Draeger Medical, Inc, Telford, PA)
   3. Puritan Bennett 840 (Covidien-Puritan Bennett, Mansfield, MA)
   4. Servo-i (Maquet Critical Care, Wayne, NJ)
   5. Hamilton C-2 and S-1 (Hamilton Medical, Reno, NV)
   6. SLE 4000 and 5000 (SLE, Ltd., Surrey, UK)

7. Newport e360T and Newport WAVE (if Compass added) (Newport Medical Instruments, Newport Beach, CA)

G. Neonatal-pediatric ventilators that are still in use, but not currently being manufactured
1. VIP BIRD/GOLD with Bird Graphic Monitor (CareFusion Health Care, Yorba Linda, CA)
2. Bear Cub 750 with Ventilator Graphics Monitor (CareFusion Healthcare, Yorba Linda, CA).
3. Dräger Babylog 8000+ (Dräger, Telford, PA)

III. Graphic Waveforms

A. Pressure
1. Pressure waveform (Fig. 22.1, top waveform)
   a. The up-sweep of the waveform represents inspiration and the down-sweep represents expiration.
   b. PIP is the maximum pressure point on the curve (A).
   c. PEEP is the baseline pressure level (B).
   d. The area under the curve represents the mean airway pressure (shaded—Fig. 22.2).
   e. The shape of the curve represents the breath type, e.g., volume (triangular) or pressure (square).

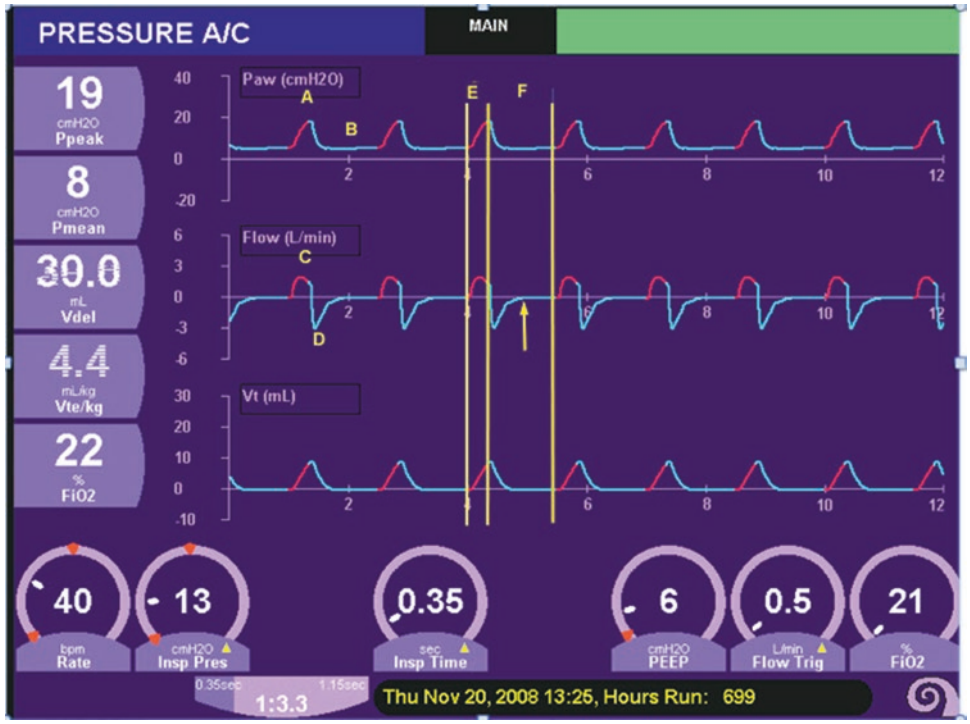

Fig. 22.1 The pressure waveform. See text for full description

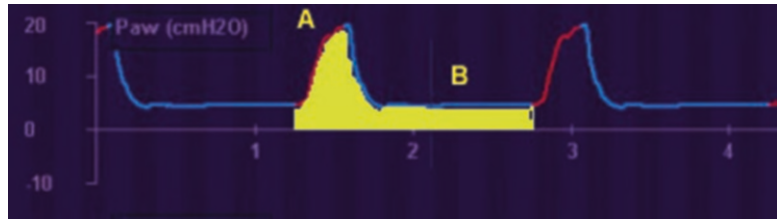

Fig. 22.2 Graphic display of mean airway pressure

Fig. 22.3 Scalar tracing showing the effect of prolonging inspiratory time. Panel (**a**) shows inspiratory time set such that inspiration ends when flow returns to zero. Panel (**b**) shows a prolonged inspiratory time, with a pressure plateau in which no further volume delivery occurs. Mean airway pressure is increased

B. Flow
   1. Flow waveform (Fig. 22.1, center waveform)
      a. Horizontal line is the zero flow point. Up-sweep of the flow waveform above this line is inspiratory flow, and down-sweep is expiratory flow.
      b. Greatest deflection above reference equals peak inspiratory flow (C).
      c. Greatest deflection below reference equals peak expiratory flow (D).
      d. Inspiratory time is measured from the initial flow delivery until expiratory flow begins (E).
      e. At the point on the waveform where flow is zero (Fig. 22.3, arrows), no additional volume can be delivered to the infant. Panel a shows inspiratory time set such that inspiration ends when flow returns to zero. Panel b shows a prolonged inspiratory time, with a pressure plateau in which no further volume delivery occurs. Mean airway pressure is increased.
      f. Flow cycling allows a mechanical breath to be triggered (cycled) into expiration by a specific algorithm (usually 5–25 % of peak inspiratory flow). The ability of a patient to control inspiratory time and cycle a breath to expiration may lead to improved synchronization. This feature is available on the newer generation ventilators and on any ventilator having pressure support (Fig. 22.4; red shows inspiration, blue expiration; arrow shows end-inspiration above zero flow baseline).
      g. Expiratory time is the point where expiratory flow begins until the next inspiration begins (Fig. 22.1F). When expiratory flow returns to zero, lung deflation is complete (Fig. 22.1, arrow).
      h. If flow has not reached zero before the next breath is delivered, gas trapping may occur (Fig. 22.5, arrow).

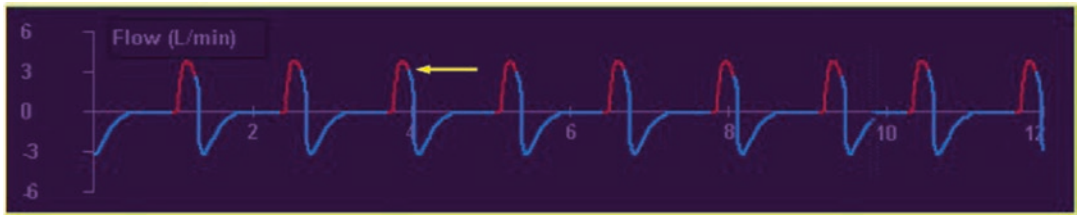

Fig. 22.4 This flow waveform illustrates flow cycling. *Red* shows inspiration, *blue* expiration. *Arrow* shows end inspiration above zero flow baseline

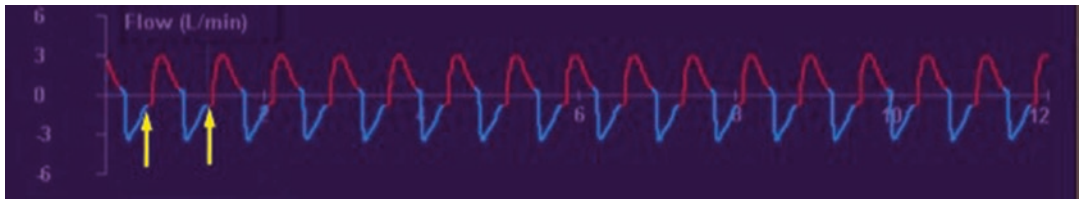

Fig. 22.5 Flow waveform demonstrating gas trapping

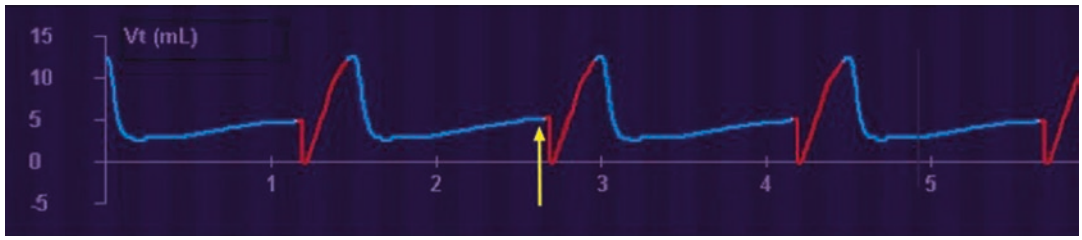

Fig. 22.6 Flow waveform demonstrating an endotracheal tube leak. Note that expiratory flow does not completely return to baseline before the next breath

C. Volume
   1. Volume waveform (Fig. 22.1, bottom waveform)
      a. Inspiration is represented as the waveform sweeps upward and expiration as the waveform sweeps downward.
      b. The red line represents delivered inspiratory tidal volume.
      c. An endotracheal tube leak is observed when the expiratory portion of the waveform fails to return to the zero baseline (Fig. 22.6, arrow).
   2. Traditional volume ventilation produces a square-flow waveform. Some ventilators enable this to be decelerated.

D. Patient-ventilator interaction
   1. Intermittent mandatory ventilation (IMV)
      a. Unsynchronized IMV, the initial form of neonatal ventilation that allowed patients to breath between ventilator cycles, results in machine breaths delivered at various times in the patient effort cycle with deleterious results (Fig. 22.7). Complications include pneumothorax and IVH. Yellow arrows show patient effort augmenting the ventilator breath, with very high Vt. Green arrows show patient beginning exhalation during machine inspiration.
      b. Synchronized IMV (SIMV) synchronizes patient inspiratory effort to mechanical breath delivery (Fig. 22.8). Yellow arrows show a synchronized machine breath, and red arrows show an unaugmented spontaneous breath.

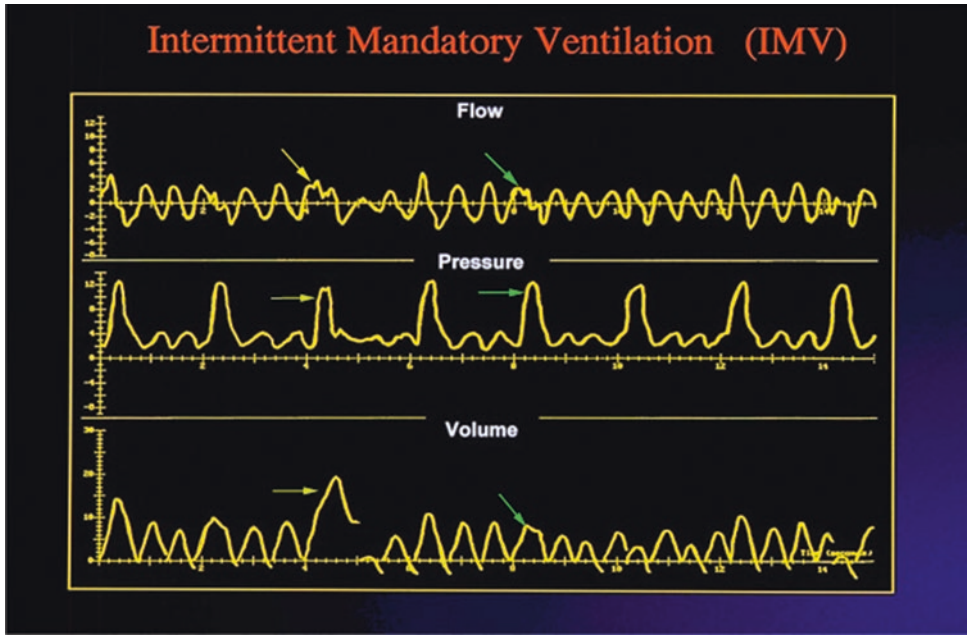

Fig. 22.7 Intermittent mandatory ventilation. *Yellow arrows* show patient effort augmenting the ventilator breath, with very high Vt. *Green arrows* show patient beginning exhalation during machine inspiration

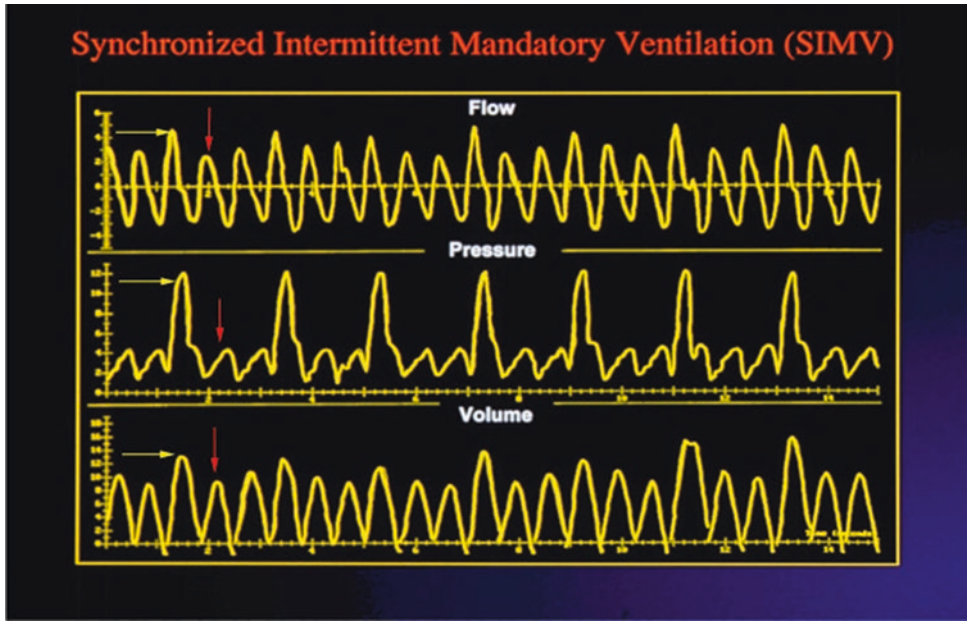

Fig. 22.8 Synchronized IMV. *Yellow arrows* show a synchronized machine breath, *red arrows* show an unaugmented spontaneous breath

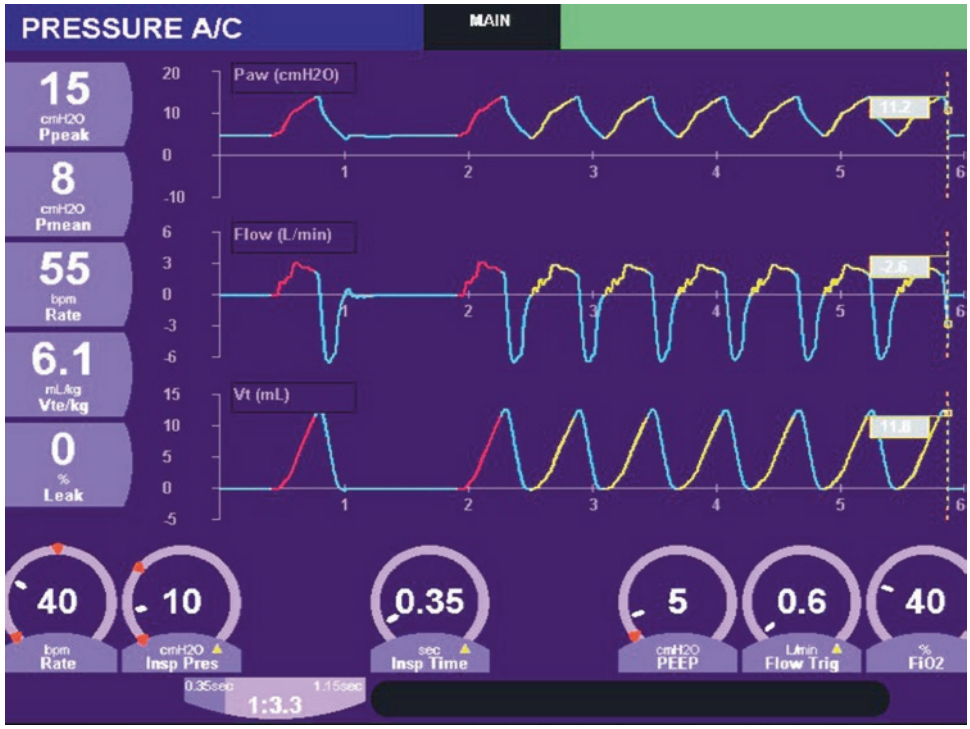

Fig. 22.9 Assist/control. *Red* shows a time-cycled machine delivered breath during apnea, *yellow* shows patient-initiated breaths

2. Assist/control and pressure support
   a. Assist/control (A/C) assists (triggers a machine-delivered inspiration) when the patient initiates a breath, and controls (delivers a time-cycled inspiration) if the patient is apneic or fails to trigger (Fig. 22.9). Red shows a time-cycled machine delivered breath during apnea, and yellow shows patient initiated breaths.
   b. Pressure support is very similar to A/C as all patient-triggered breaths are supported by a set pressure. Unlike A/C, it may be used as a blended mode during SIMV (Fig. 22.10).

IV. Graphic Loops
   A. Pressure–volume (*P-V*) loop (Fig. 22.11)
      1. A pressure–volume loop displays the relationship of pressure to volume.
         a. Pressure is displayed along the horizontal axis and volume is displayed on the vertical axis.
         b. Inspiration is represented by the up-sweep from the baseline (PEEP) terminating at PIP. Expiration is the down-sweep from PIP back to baseline.
         c. A line drawn from each endpoint represents pulmonary compliance ($\Delta V/\Delta P$).
         d. The *P-V* loop may be used to assess adequacy of PEEP, used to maintain end-expiratory lung volume (Fig. 22.12). If the inspiratory limb of the *P-V* curve demonstrates a lower inflection point, identifying opening pressure, PEEP is inadequate.
         e. The *P-V* loop may help identify lung overdistension (Fig. 22.13). If the inspiratory limb flattens at the top, this indicates pressure exposure without further volume delivery. It is measured on most neonatal ventilators as the C_{20}/C ratio.

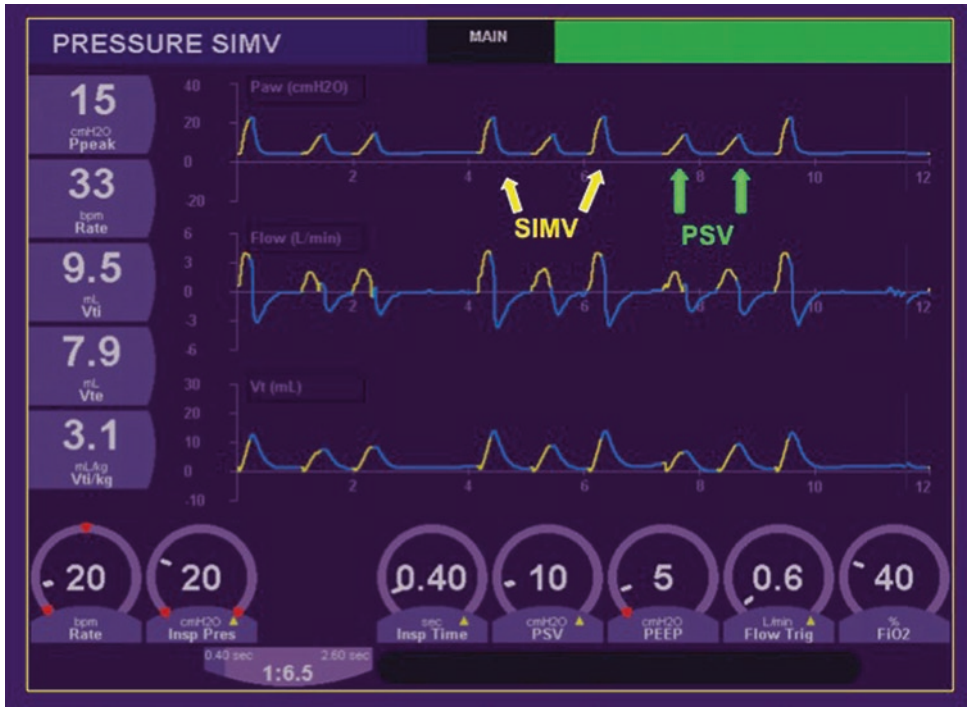

Fig. 22.10 Pressure support during SIMV

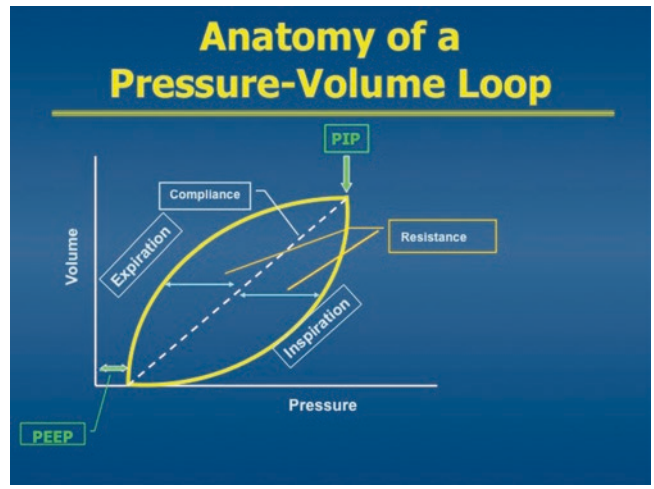

Fig. 22.11 The pressure –volume loop

f. *P-V* loops can help evaluate whether flow delivery from the ventilator is adequate to meet the needs of the patient. Inadequate flow is represented by cusping of the inspiratory portion of the curve. Severe flow limitation may appear as a "figure-8" on the *P-V* loop (Fig. 22.14).

B. Flow-Volume ($\dot{V} - V$) loop (Fig. 22.15)

1. A $\dot{V} - V$ loop displays the relationship between volume and flow. Volume is plotted on the horizontal axis and flow is plotted on the vertical axis. The breath starts at the zero axis

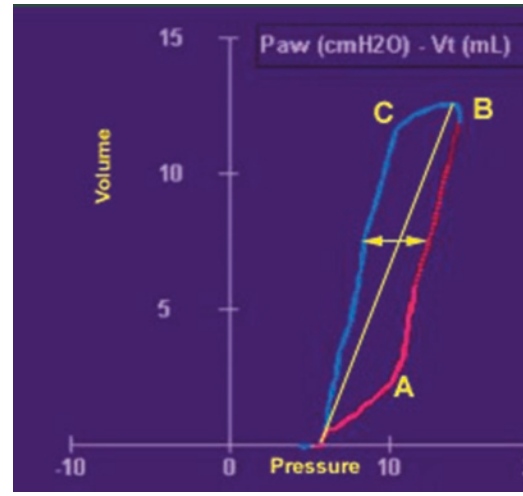

Fig. 22.12 PEEP assessment using the *P-V* loop

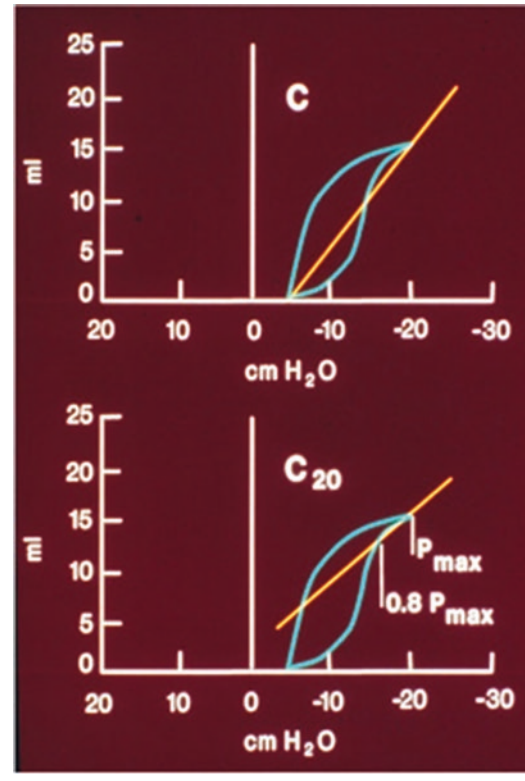

Fig. 22.13 Lung overdistension as assessed by the C_{20}/C ratio

and moves upward and to the right on inspiration, terminating at the delivered inspiratory volume and downward, to the left, back to zero on expiration.

a. The $\dot{V} - V$ loop changes shape when either inspiratory resistance (Fig. 22.16, with flattened inspiratory limb) or expiratory resistance (Fig. 22.17, with flattened expiratory limb) is increased.

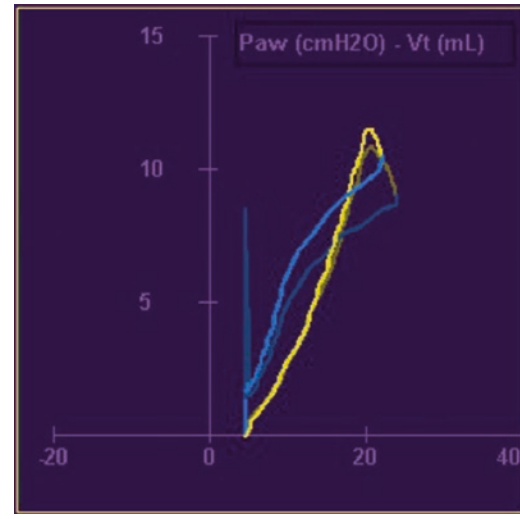

Fig. 22.14 *P-V* loop showing inadequate inspiratory flow resulting in figure 8 appearance

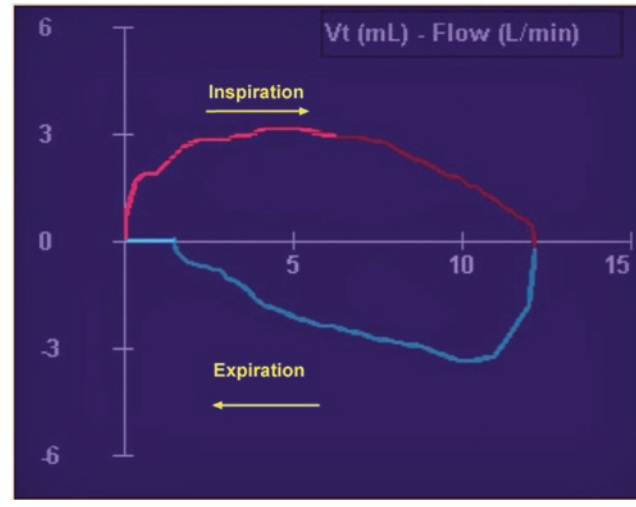

Fig. 22.15 The flow -volume loop

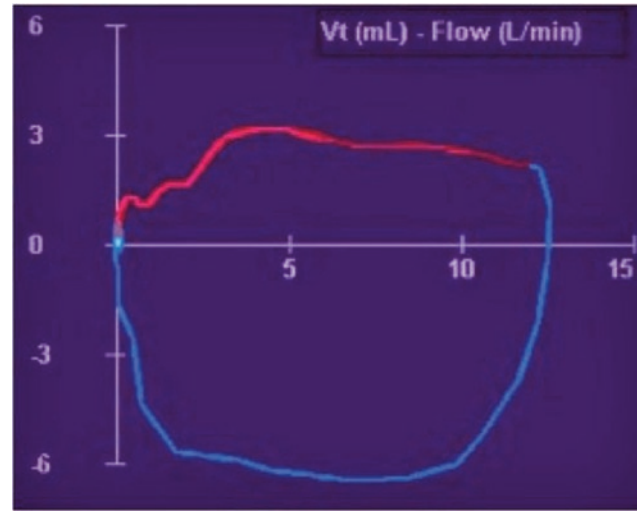

Fig. 22.16 $\dot{V} - V$ loop showing increased inspiratory resistance

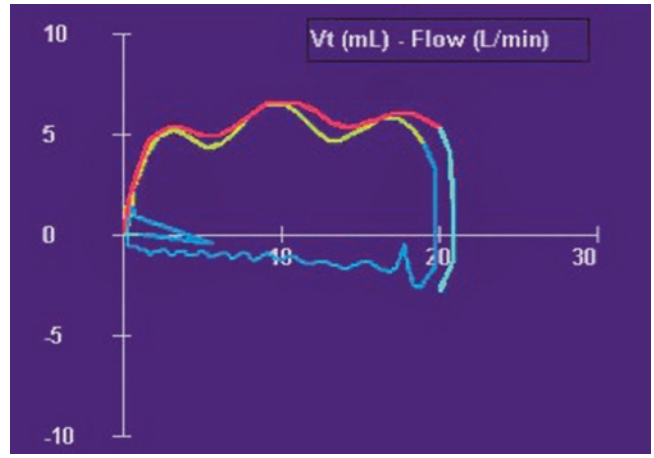

Fig. 22.17 $\dot{V} - V$ loop showing increased expiratory resistance

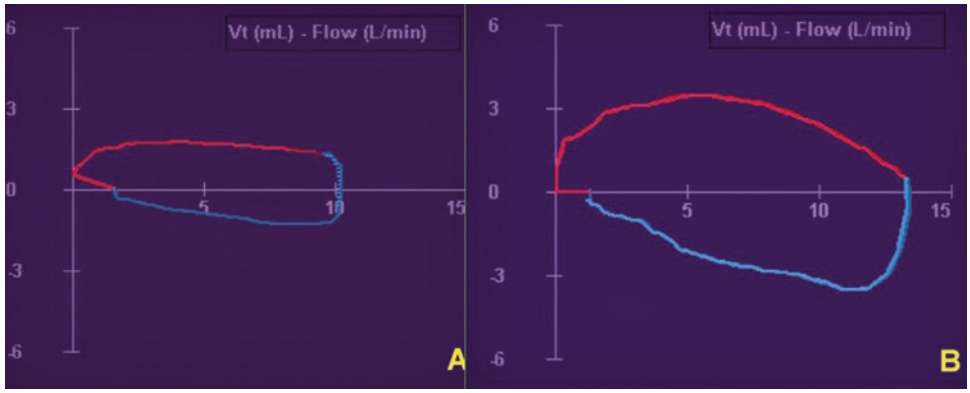

Fig. 22.18 $\dot{V} - V$ loop showing bronchodilator effect. (**a**) Pretreatment. (**b**) Posttreatment

b. The $\dot{V} - V$ loop is useful for evaluating the effectiveness of bronchodilators in treating airway reactivity. In Fig. 22.18, increased inspiratory and expiratory flow is seen in loop B as compared to the loop A.
c. Presence of secretions or water in the ventilator tubing or flow sensor can be seen on the loop displays. Since suctioning should only be performed as indicated, loops are a useful way to evaluate the need for suctioning or draining water from the circuit (Fig. 22.19).

V. Dynamics Measurements/Calculations
A. Tidal volume is measured on inspiration and expiration. Normal delivered V_T is 4–7 mL/kg.
B. Minute ventilation is the product of V_T and respiratory rate. The normal range is 240–360 mL/kg/min.
C. Pressure may be measured as peak inspiratory pressure or static pressure. Static pressure is obtained by doing an inflation hold maneuver, which measures pressure obtained by closing the exhalation valve and stopping flow delivery during a mechanical breath.
D. Compliance is the relationship between a change in volume and a change in pressure.
1. Dynamic compliance (C_D) is the measurement of compliance based on peak pressure:

$$C_D = \frac{V_{Ti}}{PIP - PEEP}$$

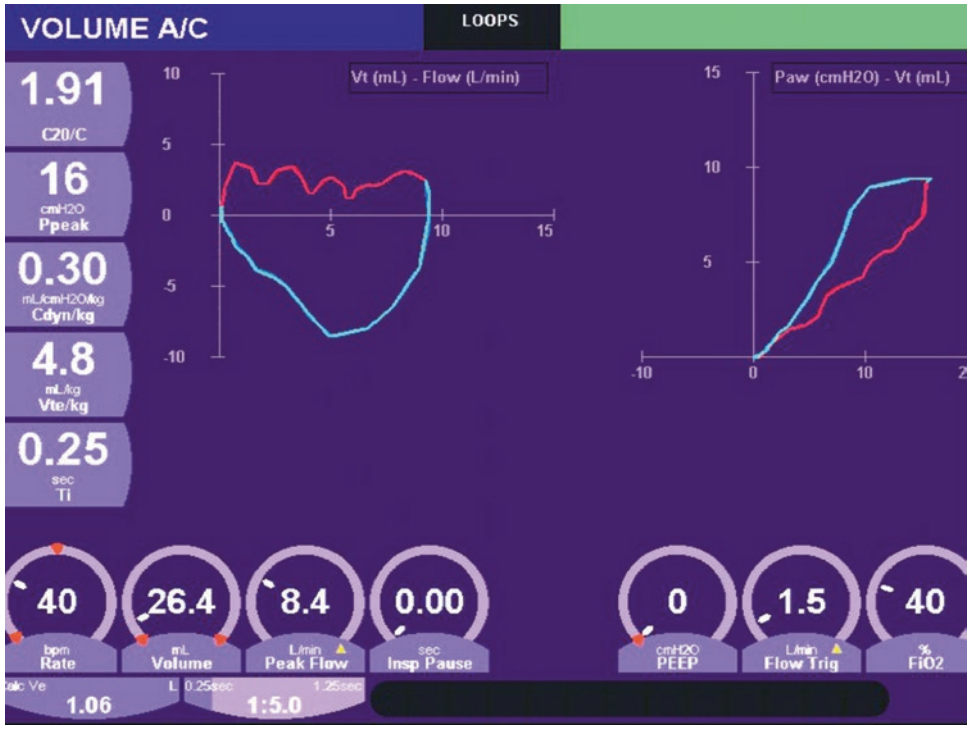

Fig. 22.19 Flow-volume loop on an infant in need of suctioning

2. Static compliance is the measurement based on static pressure:

$$C_{ST} = \frac{V_{Ti}}{P_{ST} - \text{PEEP}}$$

3. C_{20}/C is the ratio of compliance of the last 20 % of the *P-V* curve to the compliance of the entire curve. With overdistension this ratio will be less than 1.0.

E. Resistance is the relationship of pressure to flow. The pressure may be dynamic or static, and flow measurements are taken from various measurements.
1. Peak flow is the maximum flow on either inspiration or expiration.
2. Average flow is based on multiple point linear regression.
3. Mid-volume flow is based on the flow measured at a point of mid-volume delivery.
4. $R_{AW}\left(\text{cm}\,H_2O / L / s\right) = \dfrac{\text{PIP} - \text{PEEP}}{\text{Flow}}$

Suggested Reading

Bhutani VK, Benitz WE. Pulmonary function and graphics. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: W.B. Saunders Co.; 2011. p. 306–20.

Cannon ML, Cornell J, Trip-Hamel D, et al. Tidal volumes for ventilated infants should be determined with a pneumotachometer placed at the endotracheal tube. Am J Respir Crit Care Med. 2000;62:2109–12.

Castle RA, Dunne CJ, Mok Q, et al. Accuracy of displayed values of tidal volume in the pediatric intensive care unit. Crit Care Med. 2002;30:2566–74.

Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1998a.
Donn SM, editor. Neonatal and pediatric pulmonary graphics: a bedside guide. Armonk, NY: Futura Publishing Co.; 1998b.
Donn SM, Mammel MC. Neonatal pulmonary graphics: a clinical pocket atlas. New York: Springer; 2015. ISBN 978-1-4939-2016-7.
Mammel MC. Bedside tidal volume measurements: GIGO? Crit Care Med. 2002;30:2606.
Mammel MC, Donn SM. Real-time pulmonary graphics. Semin Fetal Neonatal Med. 2015;20:181–91.
Nicks JJ. Graphics monitoring in the neonatal intensive care unit: maximizing the effectiveness of mechanical ventilation. Palm Springs, CA: Bird Products Corp.; 1995.
Sinha SK, Nicks JJ, Donn SM. Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. Arch Dis Child. 1996;75:F213–8.
Wilson BG, Cheifetz IM, Meliones JN. Mechanical ventilation in infants and children with the use of airway graphics. Palm Springs, CA: Bird Products Corp.; 1995.

Diagnostic Imaging

23

Ramon Sanchez and Javier Lucaya

I. Introduction
   A. Conventional chest radiography is the primary imaging modality used for the evaluation of the neonatal chest.
   B. Computed tomography (CT), magnetic resonance (MR), ultrasound (US), and fluoroscopy are less frequently used but are extremely important in selected cases.
II. Conventional Radiography
   A. Introduction
      1. With conventional radiography, electrical energy is received and converted into X-rays in a generator tube. These X-rays (electromagnetic radiation) create an image after travelling through an object and reaching a detector.
      2. Chest radiographs are usually done portably at the bedside.
      3. Most incubators incorporate X-ray tray devices into the mattress support where the detector is placed. When available, X-ray tray devices should be used to minimize manipulation of patients and to decrease radiation exposure.
      4. Conventional film screen radiography has largely been replaced by digital radiology systems. This technology allows almost immediate availability of images, and different visualization options, such as magnification, electronic archiving, and transmission in networks, and have the potential to significantly decrease the radiation exposure to the patient without affecting image quality.
      5. The anteroposterior (AP) view is the primary projection used. Lateral and cross-table views can be obtained in selected cases (for example: better delineation of support devices, additional evaluation of pneumothoraces, pneumomediastinum, and pleural effusions).
   B. Common indications
      1. Respiratory distress
      2. Abnormal blood gases

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S.M. Donn, S.K. Sinha (eds.), *Manual of Neonatal Respiratory Care*,
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3. Sepsis and/or pneumonia
4. Cardiac anomalies
5. Suspected congenital anomalies
6. Postsurgical evaluation
7. Assessment of catheters and tubes

III. Computed Tomography (CT)
   A. Introduction. A thin X-ray beam is projected through the body. The radiation is measured by detectors. The X-ray beam and the detectors rotate around the patient while the examination table and patient move through the scanner. Sophisticated computer software reconstructs the images for display on a monitor.
   B. Common indications
      1. Developmental lung anomalies
      2. Cardiovascular anomalies
      3. Vascular rings and slings and tracheal anomalies
      4. Acute or chronic lung parenchyma disease
      5. Postsurgical evaluation
      6. Image guidance for percutaneous procedures
   C. Advantages
      1. Good tissue characterization within the thorax
      2. Newer generation multidetector scanners with short acquisition times have decreased the need for sedation or anesthesia
      3. Multiplanar and 3D capabilities
   D. Disadvantages
      1. Higher dose of ionizing radiation than conventional radiography
      2. Requires transport to the scanner
      3. May require sedation or anesthesia
      4. May require intravenous iodinated contrast administration

IV. Magnetic Resonance Imaging (MRI)
   A. Introduction. MRI makes use of the magnetic properties of protons. Protons of different tissues resonate at different frequencies when subjected to an electromagnetic field. MRI *does not* use ionizing radiation.
   B. Common indications
      1. Pre- and post-surgical evaluation of cardiovascular anomalies incompletely evaluated on echocardiogram including suspected vascular rings
      2. Mediastinal masses
      3. Further characterization of congenital anomalies detected on prenatal US
   C. Advantages
      1. *No ionizing radiation*
      2. Multiplanar and 3D capabilities
      3. Exquisite tissue characterization
      4. Dynamic evaluation (multiple phases of contrast, cardiac motion, functional assessment)
      5. Can be performed *in utero*
   D. Disadvantages
      1. Limited evaluation of lung parenchyma disease
      2. Need for transport, sedation, and/or anesthesia, and in many circumstances intravenous gadolinium-based contrast material
      3. Vital signs may be difficult to monitor during long acquisition time

4. Expensive
5. Not available in all institutions
6. Magnet incompatibility with standard monitor equipment; requires specialized non-ferrous monitors
7. Requires continuous monitoring of patient temperature secondary to environment and length of scan

V. Ultrasound
   A. Ultrasound waves propagate similarly to sound waves through a medium. Transmitted ultrasound waves reflect from interfaces with tissue back to the detection transducer. Different tissues have different acoustic properties. With diagnostic ultrasound, a body part is exposed to sound waves to produce images of the inside of the body. Ultrasound *does not* use ionizing radiation.
   B. Common indications
      1. Pleural or pericardial effusions, and detection of pneumothorax
      2. Intrathoracic and mediastinal masses
      3. Assessment of blood flow
      4. Evaluation of diaphragmatic motion
      5. Guidance for vascular access and other minor procedures
   C. Advantages
      1. *No ionizing radiation*
      2. Can be performed at the bedside
      3. Dynamic evaluation of structures
      4. Does not require sedation or contrast administration
      5. Serial studies can be done
   D. Disadvantages
      1. Operator dependent
      2. Limited value for lung parenchyma disease. There is no transmission of sound waves through well-aerated lung parenchyma
      3. Superimposed structures such as air, dressing, hardware, and osseous structures can limit the field of view and cause imaging artifacts
      4. Incomplete coverage; limited by scan planes and points of access

VI. Fluoroscopy
   A. Introduction: Fluoroscopy provides real-time X-ray images using a continuous X-ray beam (or preferably a pulsed beam to decrease radiation exposure). A television-like system is used to transfer a set of images from the source of the image to a monitor screen.
   B. Common indications
      1. Esophagogram for tracheal, esophageal, or vascular anomalies
      2. Pre- and post-surgical evaluation of tracheo-esophageal anomalies
      3. Evaluation of diaphragmatic motion
      4. Evaluation of impaired swallowing function
   C. Advantages
      1. Dynamic evaluation
      2. Multiplanar capabilities
      3. High contrast resolution
   D. Disadvantages
      1. Ionizing radiation
      2. Cannot be performed at the bedside and requires transport
      3. Requires immobilization
      4. May require administration of contrast material

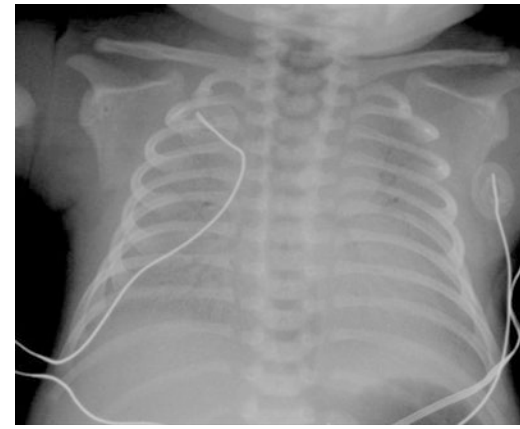

Fig. 23.1 RDS. Frontal chest radiograph shows symmetrically underinflated lungs with bilateral granular opacities and air bronchograms

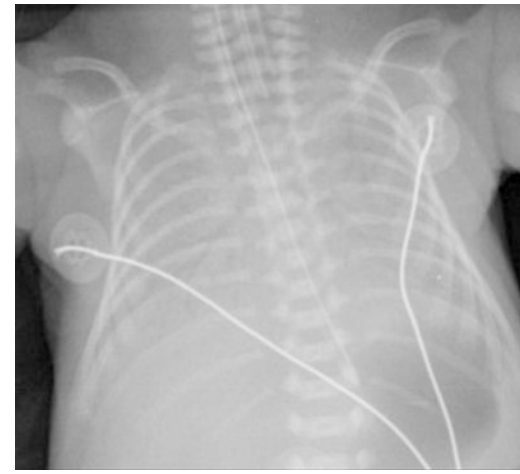

Fig. 23.2 RDS. Frontal chest radiograph shows complete opacification of lungs with indistinctness of the cardiomediastinal silhouette secondary to atelectasis

VII. Common Clinical Applications
- A. Lung disease in the preterm infant
  1. Respiratory distress syndrome (RDS)
     - a. Typical radiographic pattern is a diffuse, bilateral, and symmetric granular pattern with air bronchograms and low lung volumes. This pattern results from a combination of collapsed alveoli and air filling the terminal bronchioles (Fig. 23.1).
     - b. Atelectasis may cause complete whiteout of the lung (Fig. 23.2).
     - c. Assisted ventilation may produce normal aerated lungs (Fig. 23.3).
     - d. Non-homogeneous distribution of surfactant may cause an asymmetric appearance of the typical radiographic pattern (Fig. 23.4).
     - e. A left-to-right shunt from a patent ductus arteriosus (PDA) may cause worsening of the radiologic pattern despite adequate treatment as well as cardiomegaly (Fig. 23.5).
- B. Bronchopulmonary dysplasia (BPD)
  1. A form of chronic lung disease (CLD) common in low-birth-weight premature infants treated with prolonged mechanical ventilation.
  2. The most common radiographic appearance is the presence of diffuse, coarse, bilateral interstitial markings with lung hyperinflation, and parenchymal pseudocysts with little change over the time (Fig. 23.6).
  3. If pulmonary hypertension is present, cardiomegaly can occur.

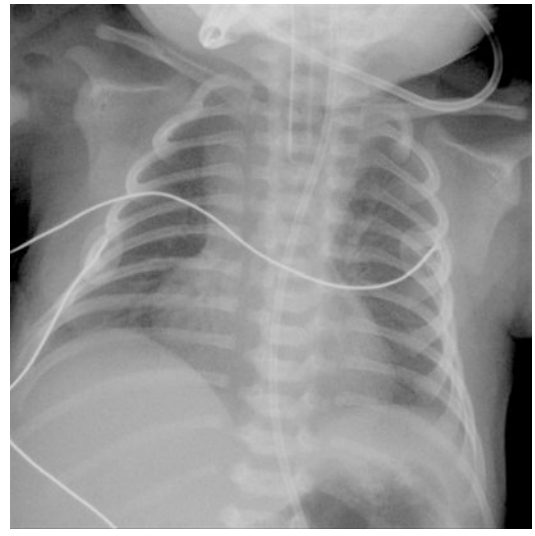

Fig. 23.3 RDS. Frontal chest radiograph preformed 24 h later after endotracheal intubation and surfactant treatment. Lung aeration has improved. Diffuse bilateral granular pattern and air bronchograms persist

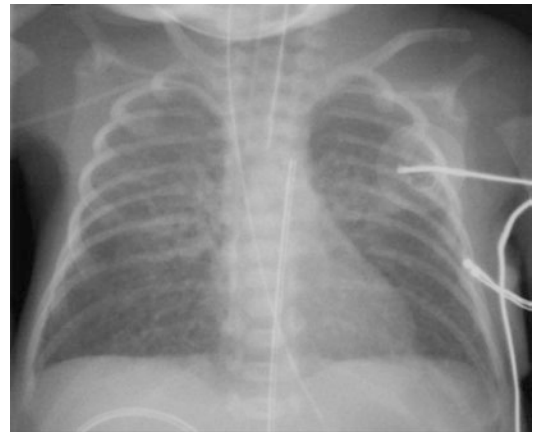

Fig. 23.4 RDS. Note the improved aeration of lower lobes compared to the upper lobes secondary to heterogeneous distribution of surfactant

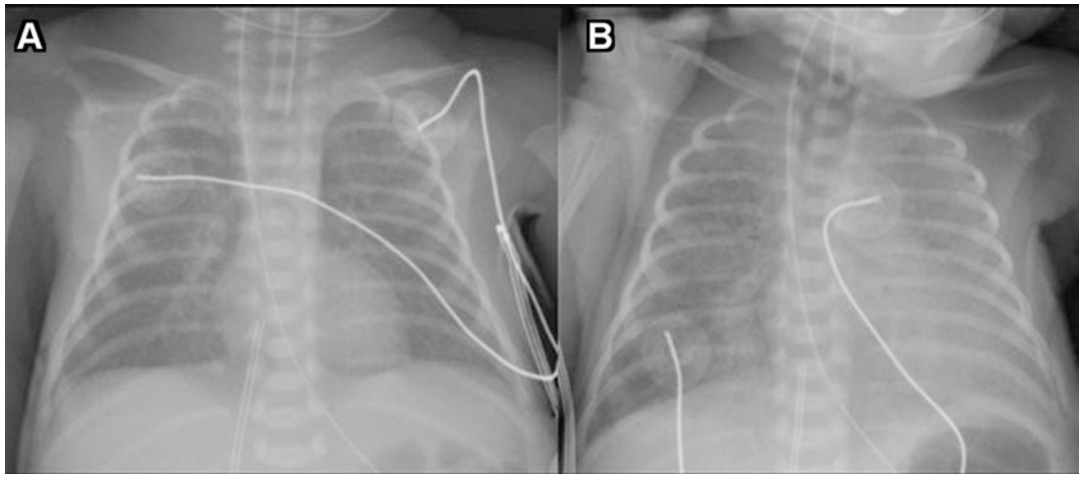

Fig. 23.5 RDS. (**a**) Four-day-old neonate with a diffuse bilateral and symmetrical granular pattern consistent with RDS. (**b**) On day of life eight, there was significant worsening of his respiratory status. Diffuse, bilateral air space opacities and cardiomegaly are noted. The baby had a large PDA with a significant left-to-right shunt

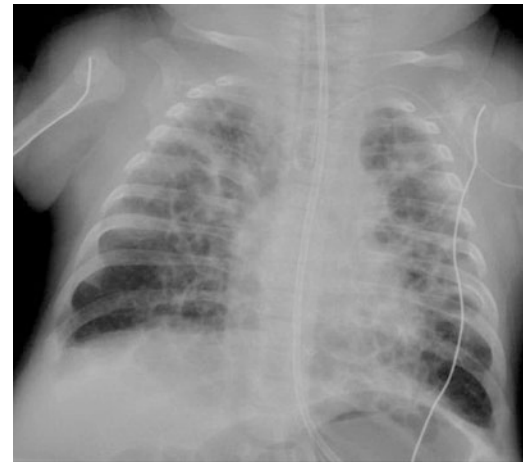

Fig. 23.6 BPD. Hyperventilated lungs with diffuse, bilateral interstitial coarse opacities and pseudocystic changes are the typical radiographic findings

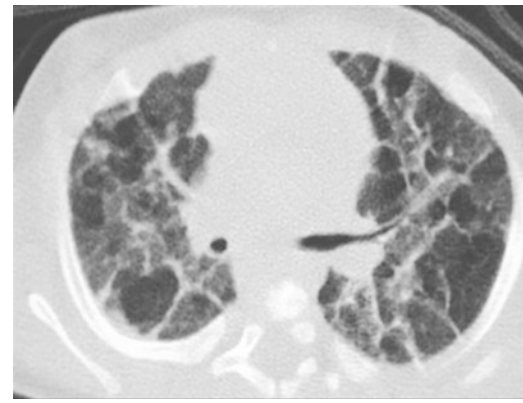

Fig. 23.7 BPD. Axial high-resolution CT performed in a 3-month-old male shows the presence of multiple linear opacities representing septal thickening, parenchymal bands, diffuse ground-glass opacities (*denser areas*), and scattered areas of air trapping (*darker areas*)

4. Early stages simulate and overlap RDS. End-stage disease causes pseudocystic lung changes with linear opacities representing atelectasis, and septal thickening.
5. Limited thin-slice low-dosed high-resolution chest CT can be performed to evaluate the disease. Septal thickening, subpleural, parenchymal bands, scars, atelectasis, and hyperexpanded hyperlucent areas are common findings giving an overall "cobblestone" appearance of the lungs (Fig. 23.7).

VIII. Lung Disease in the Term Infant

A. Transient tachypnea of the newborn (TTN; TTNB)
   1. Typical radiographic findings include mildly overinflated lungs with prominent interstitial markings, pleural thickening, and small pleural effusions. The latter are more common on the right side (Fig. 23.8).
   2. Findings are usually symmetric and the heart may be mildly enlarged.
   3. Radiolographic findings usually resolve in 12–24 h when retained fluid is cleared.

B. Meconium aspiration syndrome
   1. The syndrome consists of aspirated meconium, respiratory distress, and a characteristic chest radiograph.
   2. Aspiration of meconium causes coarse patchy nodular opacities representing atelectasis and lung consolidation (Fig. 23.9).

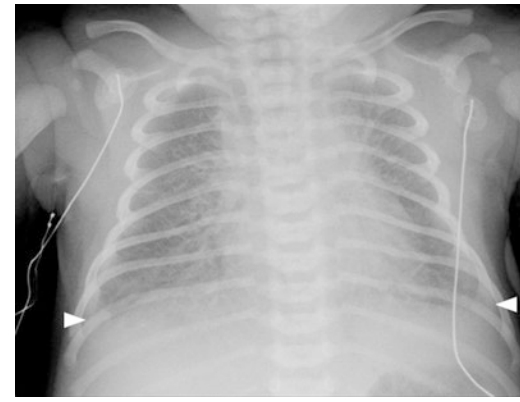

Fig. 23.8 TTNB. Frontal radiograph shows diffuse, bilateral, and symmetrical prominent interstitial markings as well as small pleural effusions, seen as bilateral costophrenic blunting (*arrowheads*). Note mild hyperinflation of the lungs as well as mild cardiomegaly

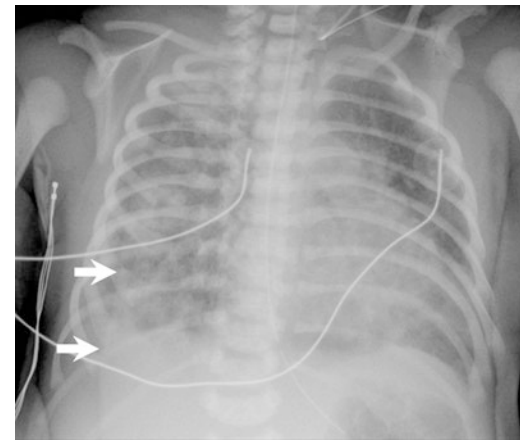

Fig. 23.9 Meconium aspiration. Diffuse, bilateral patchy opacities representing atelectasis and consolidation are seen on this chest radiograph. Note that heart is mildly enlarged. The vertically oriented linear density (*arrows*) projecting over the right hemithorax extending below the diaphragm represents a skin fold mimicking a pneumothorax

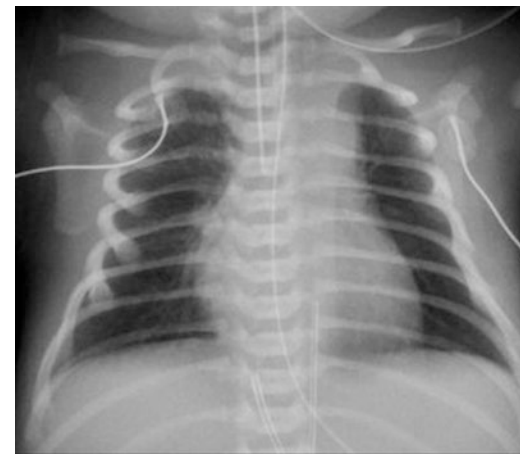

Fig. 23.10 PPHN. Radiograph shows symmetrical hyperlucent lungs and decreased pulmonary vascularity in a 1-day-old neonate

3. Lung hyperinflation, air leaks, pleural effusions, and cardiomegaly can also be present. Meconium aspiration is a common cause of secondary persistent pulmonary hypertension (PPHN).

C. Persistent pulmonary hypertension (PPHN): Idiopathic persistent pulmonary hypertension causes hyperlucent lungs with decreased pulmonary vascularity (Fig. 23.10).

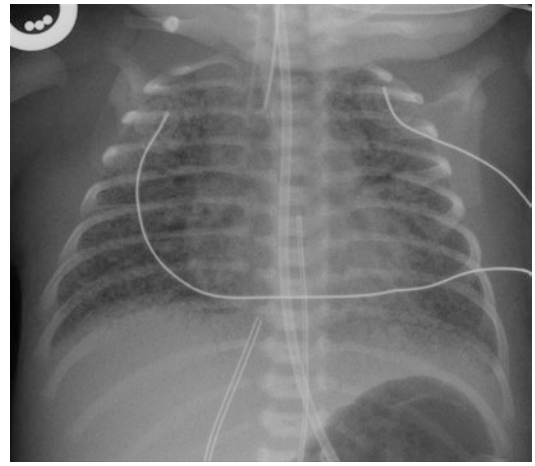

Fig. 23.11 Neonatal pneumonia. Neonate with group B streptococcal pneumonia. Note the diffuse and bilateral mixed interstitial and alveolar opacities. Thickening of the minor fissure is also seen

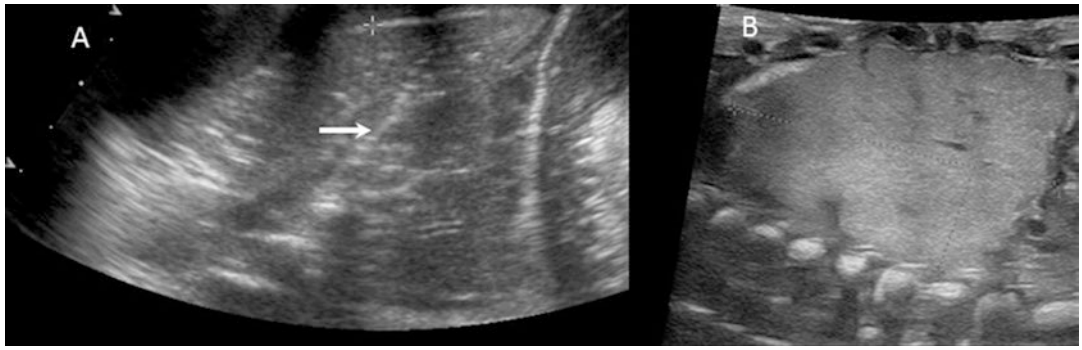

Fig. 23.12 Neonatal pneumonia. Ultrasound findings. (**a**) Ultrasound image shows "hepatization" of the lung parenchyma with air bronchograms (*arrow*). (**b**) Sagittal anterior view through the left hemithorax with large solid homogenous echogenic mass representing a large sequestration

IX. Other Neonatal Respiratory Disorders
   A. Neonatal pneumonia
      1. Radiographic patterns of neonatal pneumonia are nonspecific. Differentiating pneumonia from TTN, RDS, pulmonary edema, and pulmonary hemorrhage can be difficult, if not impossible, without appropriate clinical history.
      2. Common radiographic manifestations are bilateral coarse or scattered mixed air space-interstitial opacities (Fig. 23.11). Lungs are usually normally aerated and pleural effusions may also occur.
      3. Isolated air opacities with air bronchograms are uncommon in this age group but may be seen.
      4. Ultrasound can be used to differentiate focal lung consolidation from other lung parenchymal opacities (Fig. 23.12). Ultrasound also identifies the presence of pleural fluid.
      5. CT may be used in specific circumstances to rule out uncommon complications, such as lung abscesses (Fig. 23.13) and bronchopleural fistula formation.
   B. Atelectasis
      1. Atelectasis may be segmental, lobar, or total. On radiographs, atelectasis is seen as areas of lung opacification with volume loss, fissure displacement, and mediastinal shift proportional to the degree of lung collapse (Fig. 23.14). This is most common with endotracheal tube malposition and after extubation and typically resolves rapidly.

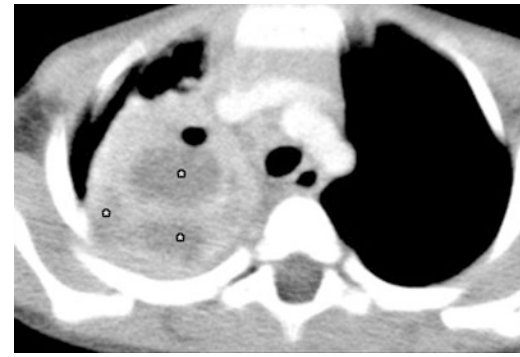

Fig. 23.13 Pneumonia. Axial CT image performed after intravenous contrast administration. Note a right upper lobe air space opacification with non-enhancing areas (*asterisks*) and an air-fluid level representing necrotizing pneumonia

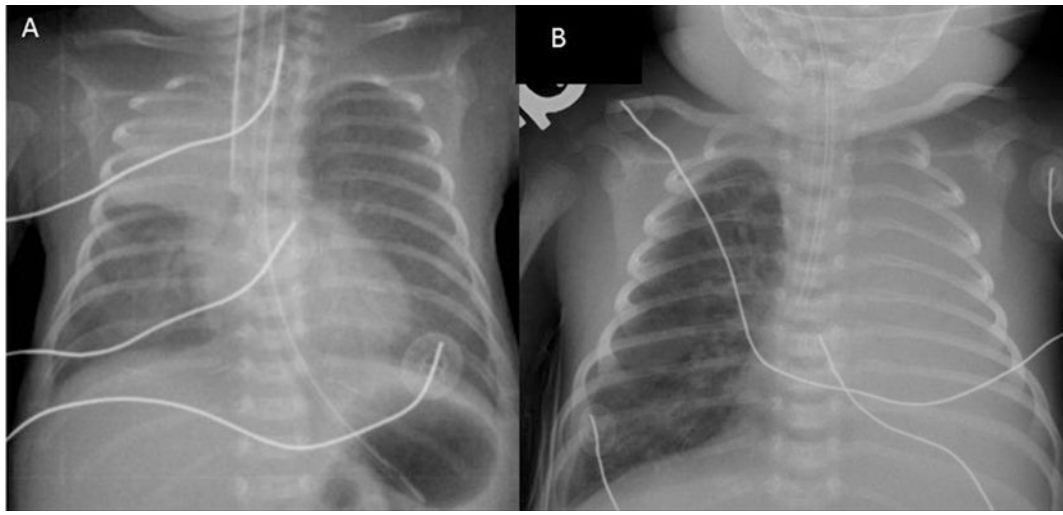

Fig. 23.14 Atelectasis. (**a**) Right upper lobe atelectasis (*arrow*). Note that the trachea is slightly deviated to the right and there is also obscuration of the right upper mediastinum. (**b**) Left lung collapse with complete opacification of the left hemithorax and obscuring of the left heart border and upper mediastinum. Note the position of the endotracheal tube tip below the carina

2. Rapid resolution differentiates atelectasis from other causes of lung opacification.
3. Poor radiographic technique (expiratory images and underexposure) may simulate atelectatic lungs as well as cardiomegaly (Fig. 23.15).
4. A normal thymus may simulate lung atelectasis. Ultrasound has been used to differentiate atelectasis from normal thymus simulating a collapsed lobe (Fig. 23.16).

C. Pleural effusion
1. Large pleural effusions are seen as increased opacification of the ipsilateral hemithorax with adjacent lung collapse and possible contralateral mediastinal shift (Fig. 23.17).
2. Lateral decubitus films may be used to further delineate the presence of a suspected pleural effusion in special circumstances (such as sub-pulmonic location) but do not allow characterization of pleural fluid (Fig. 23.18). Ultrasound is now considered a better imaging modality to detect pleural effusion and should substitute, when available, for the lateral decubitus films.
3. Supine films underestimate the amount of pleural effusion, and small effusions may be subtle on supine films. Increased lung density, blurring of the diaphragm and heart contour, thickening of the fissures, and costophrenic blunting are typical findings. Ultrasound can be used to detect, quantify, and better characterize pleural effusions (Fig. 23.19).

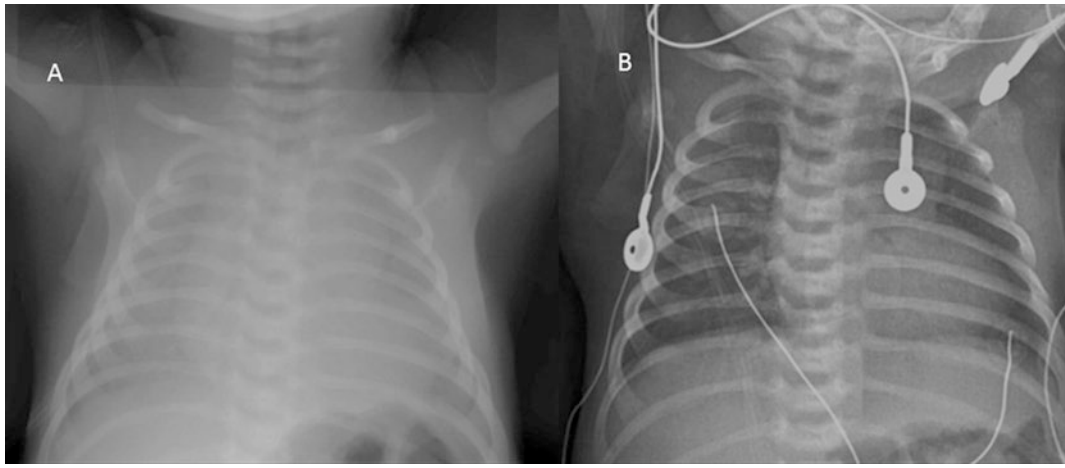

Fig. 23.15 (**a**) Simulated bilateral lung atelectasis and cardiomegaly secondary to expiratory film and underexposure. (**b**) Short-term follow-up X-ray with adequate radiographic technique and degree of inspiration

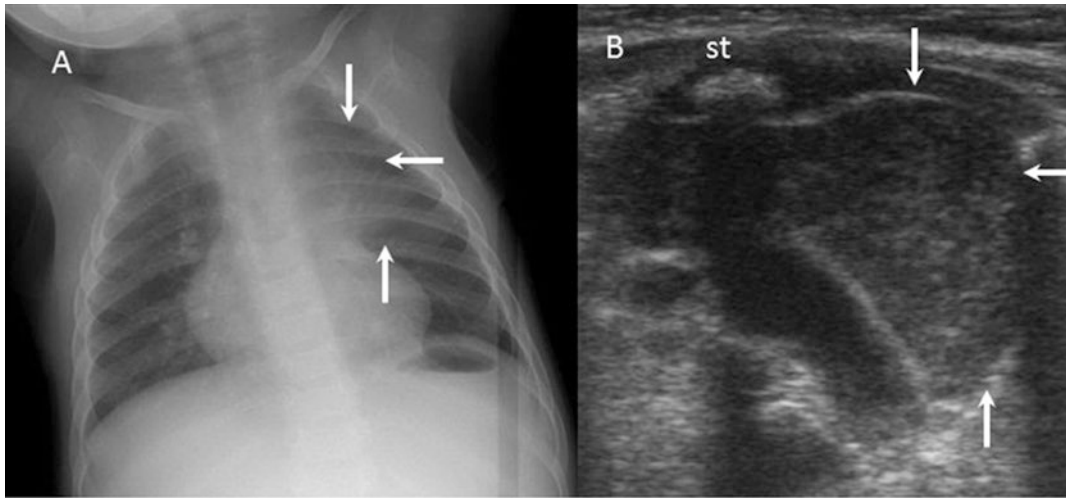

Fig. 23.16 Normal thymus-simulating atelectasis. (**a**) Chest radiograph shows a left upper lobe opacity (*arrows*) mimicking lung collapse. (**b**) Transverse ultrasound image at the level of the upper mediastinum shows that the area of lung opacity on radiograph corresponds to normal thymus (*arrows*). *ST* sternum. On ultrasound the thymus has a homogeneous relatively hypoechoic echotexture with internal echogenic strands

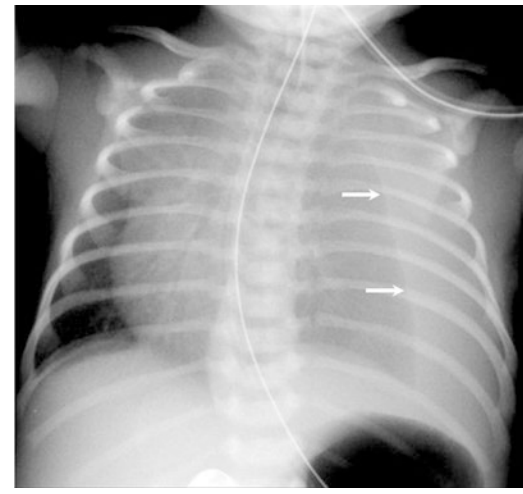

Fig. 23.17 Neonate with large left-sided pleural effusion. Supine radiograph of the chest shows diffuse left lung haziness with a moderate left pleural effusion (*arrows*). Note the contralateral mediastinal shift and the compressive right upper lobe atelectasis

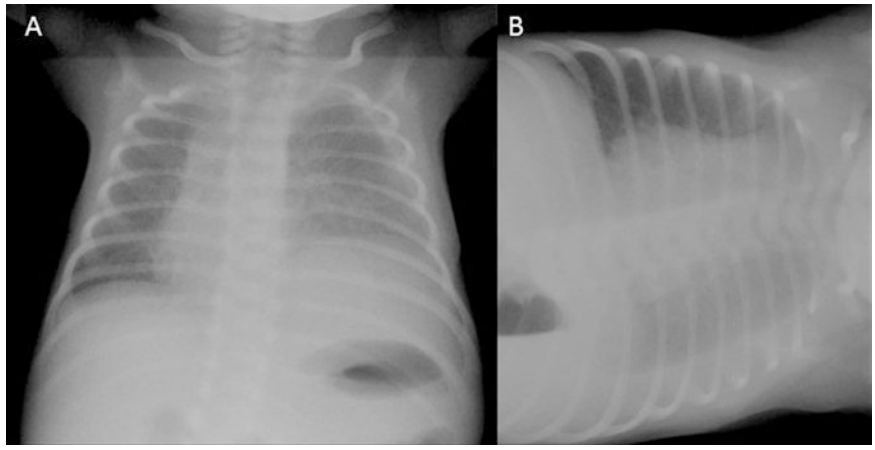

Fig. 23.18 Pleural effusion. Supine view (**a**) shows an underinflated left lung with left lateral pleural thickening, contralateral mediastinal shift, and simulated elevation of the ipsilateral diaphragm (note the increased distance between the gastric bubble and the "pseudo" diaphragm) caused by a large predominantly subpulmonic pleural effusion. Left lateral decubitus film (**b**) better delineates the presence of left-sided pleural effusion

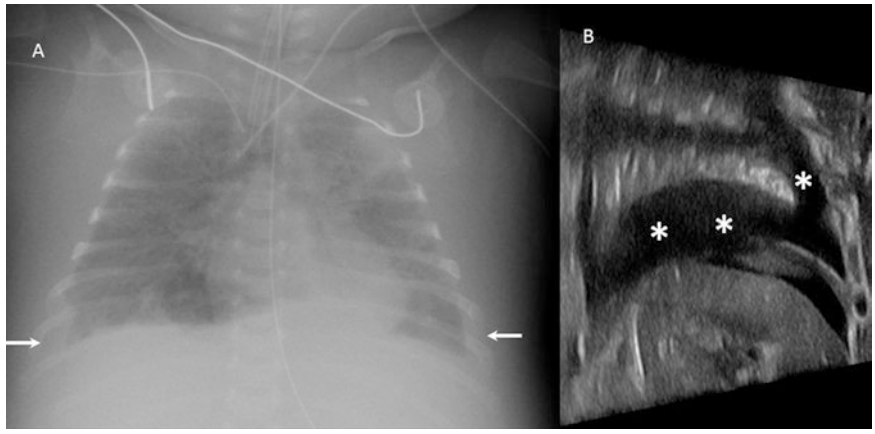

Fig. 23.19 Pleural effusion. (**a**) Supine chest radiograph shows diffuse bilateral lung haziness and bilateral costophrenic blunting (*arrows*). (**b**) Chest ultrasound performed a few minutes after the chest X-ray shows a large amount of anechoic pleural fluid (*asterisks*) surrounding the atelectatic lung

4. Echogenic pleural fluid and septations are seen in complex pleural effusions (Fig. 23.20).

D. Air leaks
   1. Pneumothorax
      a. Imaging appearance depends on the size, location, and projection.
      b. On supine chest radiographs, pneumothoraces are typically seen as radiolucent spaces without associated vascular markings (Fig. 23.21).
      c. Small pneumothoraces can be subtle on supine views, since air accumulates anteriorly, causing increased sharpness of the mediastinal edge and a hyperlucent lung, and occasional mild mediastinal shift (Fig. 23.22a). Medial pneumothorax can be difficult to differentiate from a pneumomediastinum.

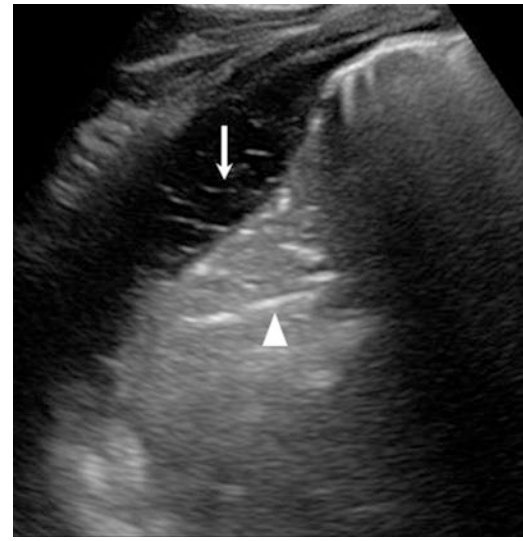

Fig. 23.20 Pleural effusion. Ultrasound image shows a pleural effusion with multiple internal thin septations (*arrow*) representing fibrin bands in a patient with empyema. Note the "hepatization" of the underlying lung with presence of air bronchograms (*arrowhead*)

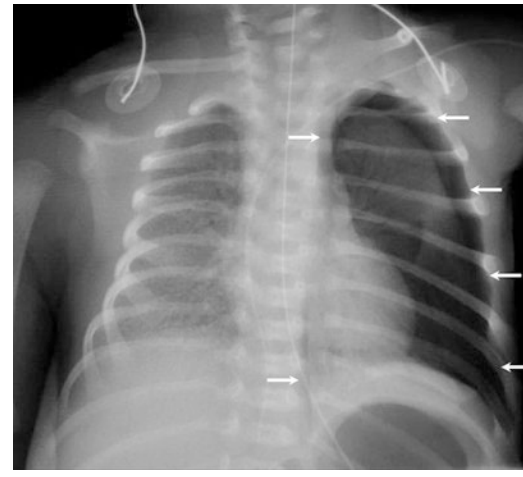

Fig. 23.21 Pneumothorax. Supine view of the chest in a patient with left pneumothorax (*arrows*). The left hemithorax appears hyperlucent compared to the contralateral side. Note the presence of diffuse, bilateral granular opacities and air bronchograms and a left upper extremity PICC extending into the IVC

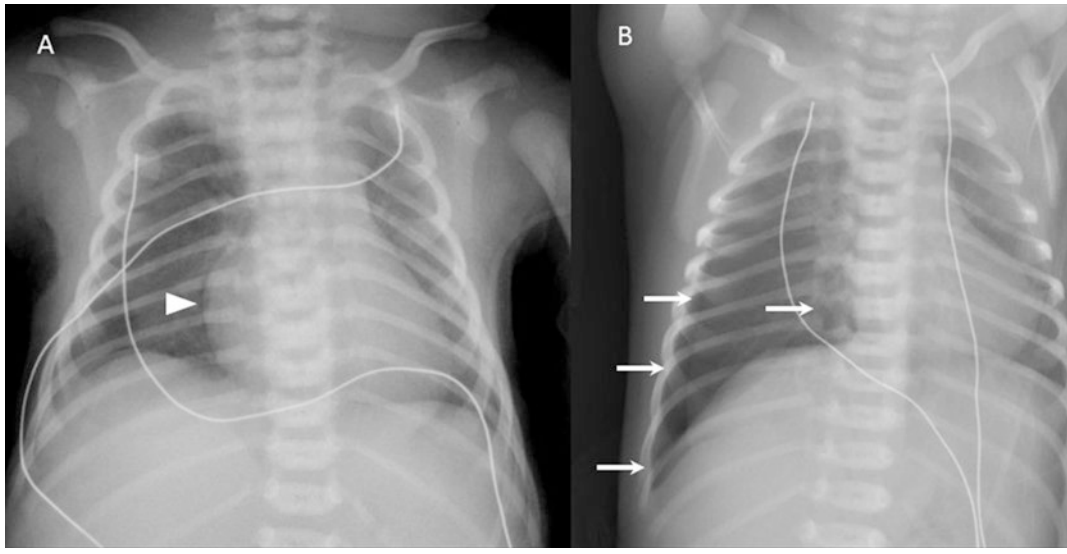

Fig. 23.22 Pneumothorax. (**a**) Supine view of the chest in a patient with right pneumothorax. The right hemithorax appears hyperlucent and there is increased sharpness of the right heart border (*arrowheads*). (**b**) Left lateral decubitus view in the same patient better delineates the presence of a pneumothorax (*arrows*)

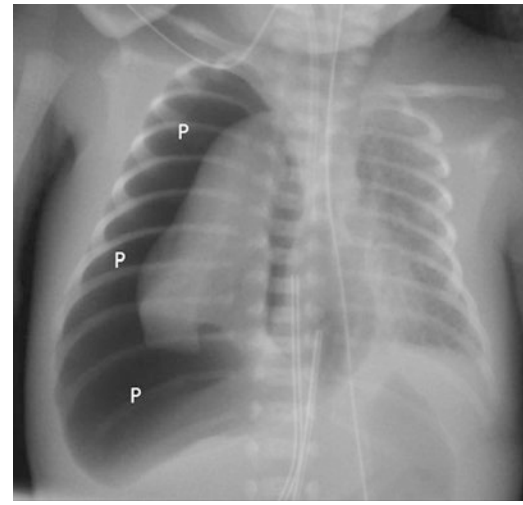

Fig. 23.23 Pneumothorax. Note the presence of a right tension pneumothorax (P), which causes right lung collapse, inversion of the right diaphragm, and mediastinal shift to the left

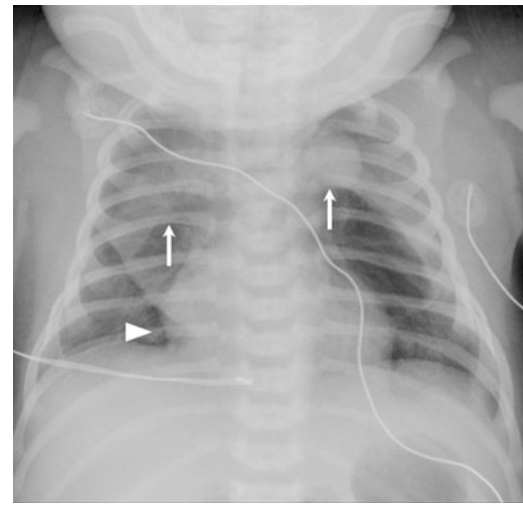

Fig. 23.24 Pneumomediastinum. Air in the mediastinum displaces the thymus ("spinnaker" sign) superiorly (*white arrows*). Associated right pneumothorax is present (*arrowhead*)

d. Decubitus views can be useful in some circumstances and are preferred to cross-table lateral views, which do not differentiate side and are limited by overlying structures (Fig. 23.22b).
e. Normal skin folds may mimic pneumothoraces. Skin folds usually extend beyond the lung edge (Fig. 23.9).
f. Tension pneumothoraces are seen as hyperlucent lungs with lung collapse and mediastinal shift (Fig. 23.23).

2. Pneumomediastinum
   a. Mediastinal air collections tend to occur as a result of hyperventilation, are usually asymptomatic, and almost never require intervention.
   b. Anteriorly located pneumomediastinum usually outlines, delineates or displaces the thymus ("spinnaker" sign) (Fig. 23.24).
   c. Neonatal pneumomediastinum rarely dissects into the subcutaneous tissues of the neck and almost never into the abdomen. When this happens, it is usually in the setting of mechanical ventilation.

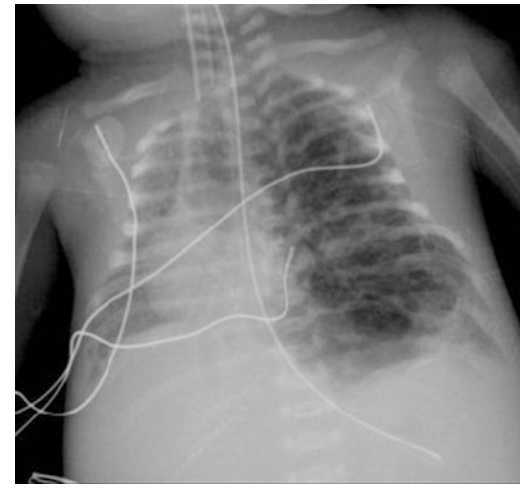

Fig. 23.25 PIE. Multiple linear and cystic lucencies are identified in the entire left lung. Note the hyperexpansion of the left lung with flattening of the diaphragm and mediastinal shift to the right)

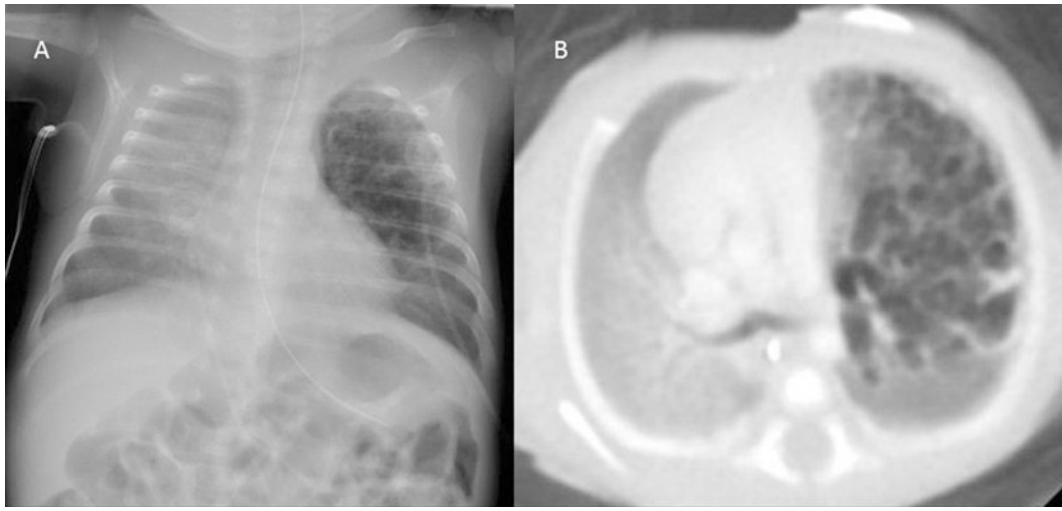

Fig. 23.26 PIE. Chest radiograph (**a**) and axial CT image (**b**) show the presence of localized left upper lobe PIE seen as multiple linear and cystic lucencies, which can mimic CPAM)

3. Pulmonary interstitial emphysema (PIE)
   a. On radiography, PIE is seen as linear and cystic lucencies radiating from the hilum towards the periphery of the lung (Fig. 23.25).
   b. May be localized, unilateral, or bilateral. It may cause significant mass effect and mediastinal shift. Localized PIE may mimic CPAM, and CT can be used to differentiate these two entities (Fig. 23.26). Careful review of prior radiographs and prenatal imaging may be the only way to differentiate CPAM and PIE.
4. Pneumopericardium. Pneumopericardium is recognized by the presence of a curvilinear lucency completely surrounding the heart, which conforms to the pericardial sac (Fig. 23.27).

E. Congenital cardiovascular anomalies
   1. Chest radiography
      a. A cardiothoracic index (ratio of the transverse diameter of the heart to the maximum internal diameter of the thorax) >60 % suggests cardiomegaly (Fig. 23.28a); lateral

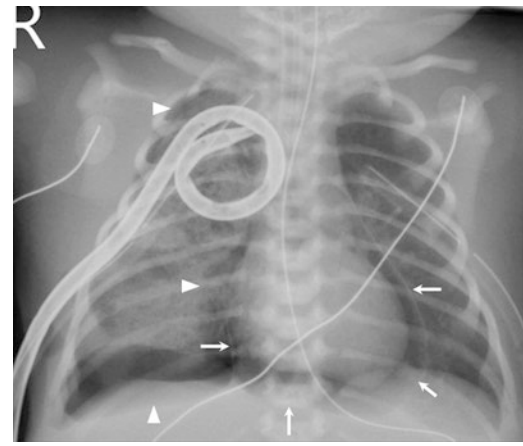

Fig. 23.27 Pneumopericardium. The heart is completely surrounded by air (*white arrows*). Note the presence of an associated right-sided pneumothorax (*arrowheads*)

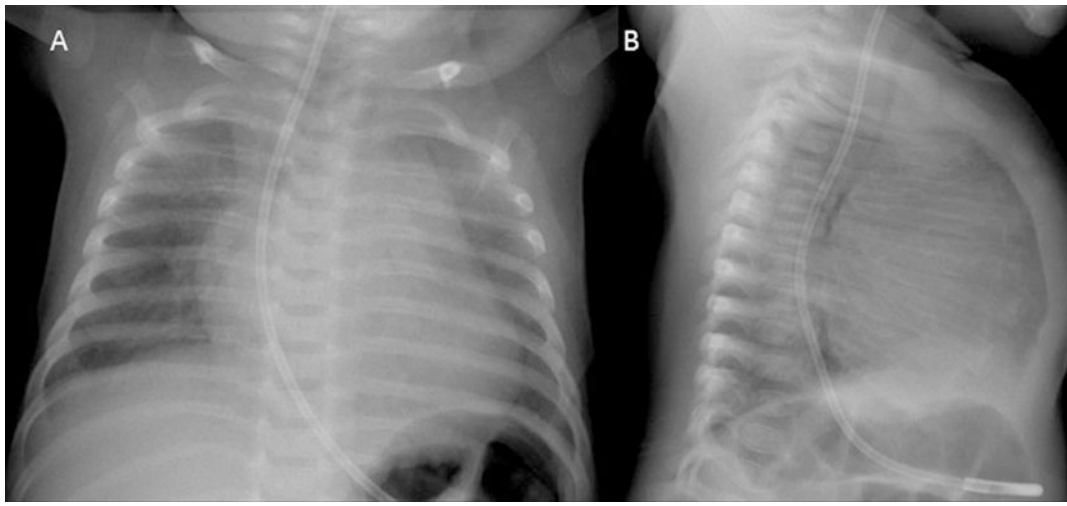

Fig. 23.28 Frontal (**a**) and lateral (**b**) chest radiographs show cardiomegaly. Note on the lateral view the posterior displacement of the esophagus by an enlarged heart, which extends to the level of the spine

views also help to assess heart size (Fig. 23.28b). From radiography, determination of which heart chamber is enlarged is usually not very useful.

b. Expiratory films may simulate cardiomegaly (Fig. 23.15a).
c. A normal thymus can extend inferiorly and may mimic cardiomegaly (Fig. 23.29).
d. The aortic arch may be hidden by the thymus, but the descending aorta is usually visible (Fig. 23.29). Assessment of the aortic arch may be suggested by the position of the trachea, slightly deviated to the right in case of left aortic arch.
e. Left-to-right shunts >2:1 usually cause increased pulmonary vascularity (Fig. 23.30a) and congenital cardiac anomalies such as total anomalous pulmonary venous connections (TAPVR) and cor triatriatum can cause diffuse interstitial edema with normal heart size (Fig. 23.30b). These radiographic changes may not be apparent in the first week of life.
f. Skeletal abnormalities, cardiac position, tracheal position, and abdominal situs should also be assessed.

2. Esophagogram. An esophagogram may be performed when there is a suspicion of a vascular anomaly causing airway compression (Fig. 23.31).

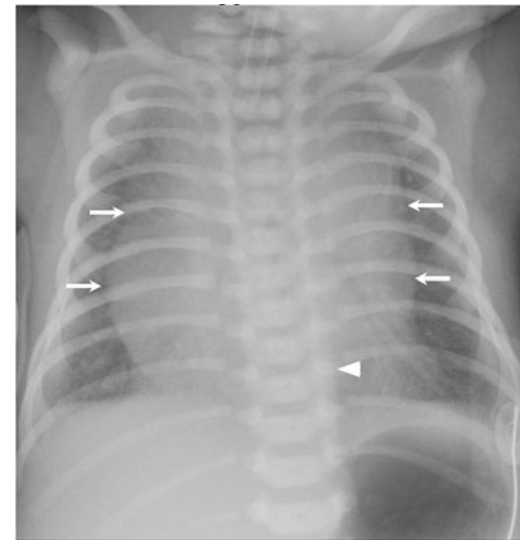

Fig. 23.29 Thymus-simulating cardiomegaly. The heart and mediastinum appear widened secondary to the presence of a prominent thymus. Note the undulating appearance of the lateral aspect of the thymus secondary to the impressions caused by the ribs (*white arrows*). Descending aorta is indicated (*arrowheads*)

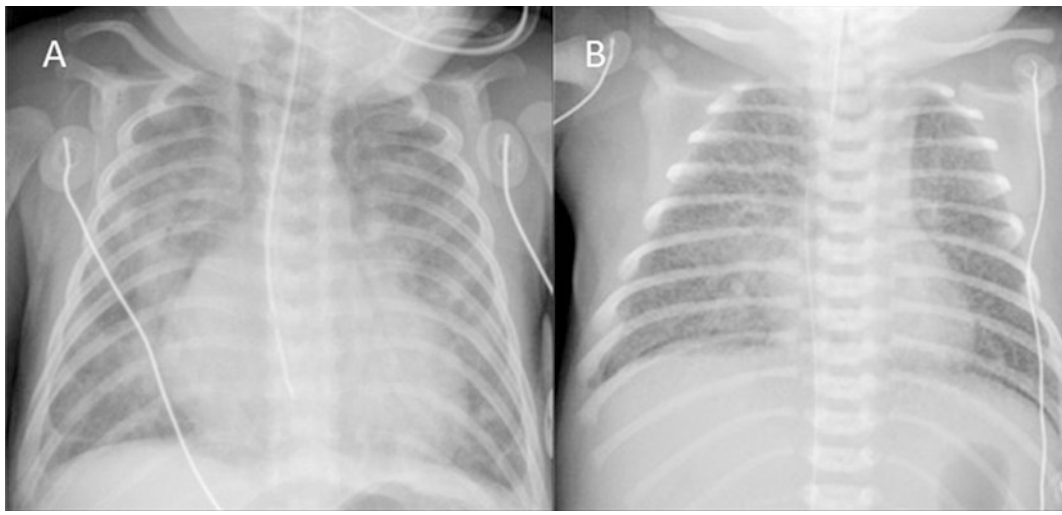

Fig. 23.30 Increased vascular flow. (**a**) Neonate with a ventricular septal defect. Chest radiograph shows cardiomegaly and increased vascular flow. Note that the tip of the nasogastric tube is malpositioned in the distal esophagus. (**b**) Chest radiograph in a neonate with total anomalous pulmonary venous return and interstitial edema. The heart is not enlarged. Bilateral pulmonary vessels are ill defined representing venous congestion. Prominent and bilateral interstitial markings are seen suggesting edema. Associated small right pleural effusion is noted

3. CT and MRI
   a. Echocardiography remains the primary imaging modality for cardiovascular anomalies in the neonate.
   b. MRI and CT are excellent imaging modalities which allow pre- and postoperative evaluation of vascular as well as complex cardiac anomalies. CT and MRI are especially useful in determining caliber and patency of small vessels or surgical shunts (Fig. 23.32). MRI also allows dynamic evaluation of cardiac function.

F. Developmental lung anomalies
   1. Congenital pulmonary airway malformation (CPAM)
      a. Previously referred to as congenital cyst adenomatoid malformation (CCAM).

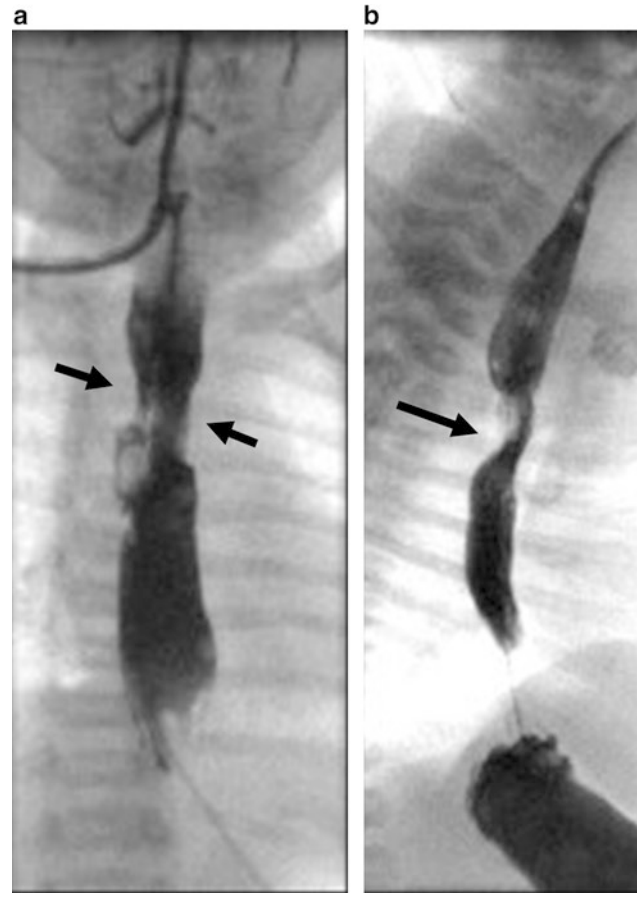

Fig. 23.31 Double-aortic arch. AP (**a**) and lateral (**b**) views from an esophagram show extrinsic compressions (*arrows*) posterior and to both sides of the esophagus caused by a double-aortic arch

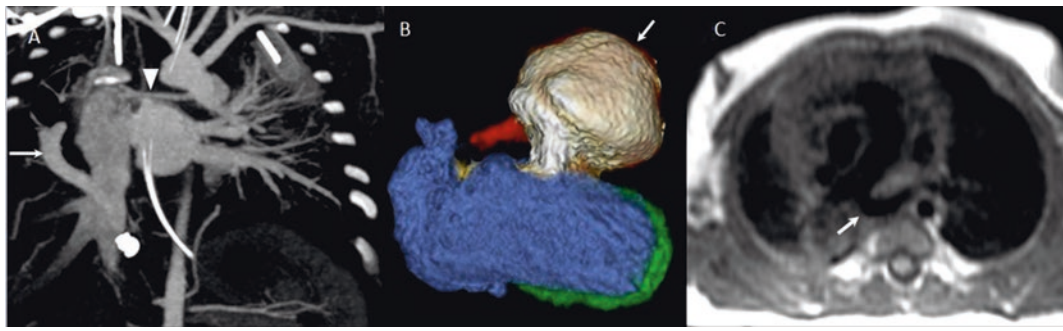

Fig. 23.32 Congenital cardiovascular anomalies. (**a**) Coronal CT angiogram in patient with Scimitar syndrome. Anomalous pulmonary vein draining into the infradiaphragmatic IVC (*arrow*) and hypoplastic right pulmonary artery (*arrowhead*). (**b**) Three-dimensional CT angiogram reformat in patient with a history of tetralogy of Fallot status post-repair shows a large postsurgical ventricular conduit aneurysm (*arrow*). (**c**) T1 axial MRI image in neonate with pulmonary sling shows an aberrant left pulmonary artery (*arrow*) arising from the right and encircling the trachea and esophagus

b. CPAM represents the most common lung malformation that results from hamartomatous proliferation of the terminal bronchioles. Imaging appearance is variable and depends on the size and composition of the lesion. Lesions are usually cystic but may be solid and/or mixed in composition (Fig. 23.33a). Most CPAMs are solitary with no lobar predilection and multiple lobes may be affected by one lesion.

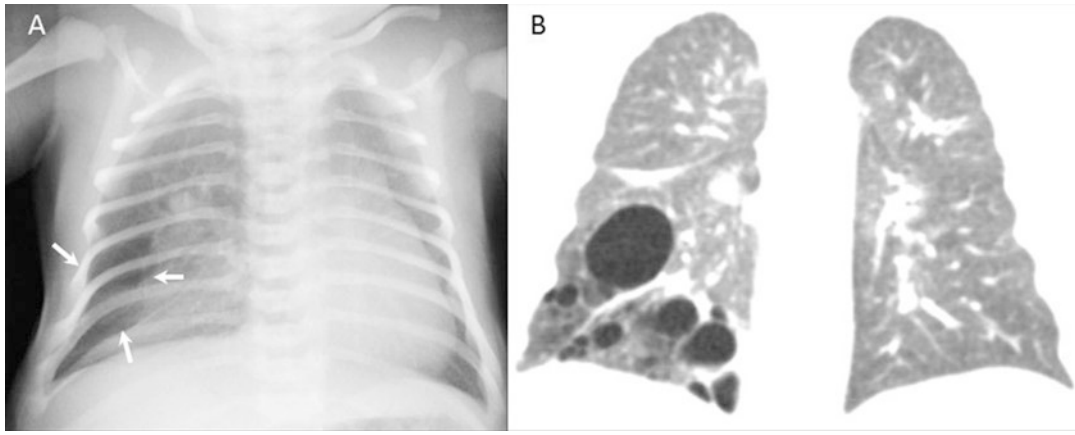

Fig. 23.33 CPAM. (**a**) Chest radiograph shows a large dense right lower lobe opacity with associated multi-cystic lesion (*arrows*). (**b**) Coronal CT image shows multiple well-defined air-filled cystic lesions (*arrows*) involving middle and lower lobes

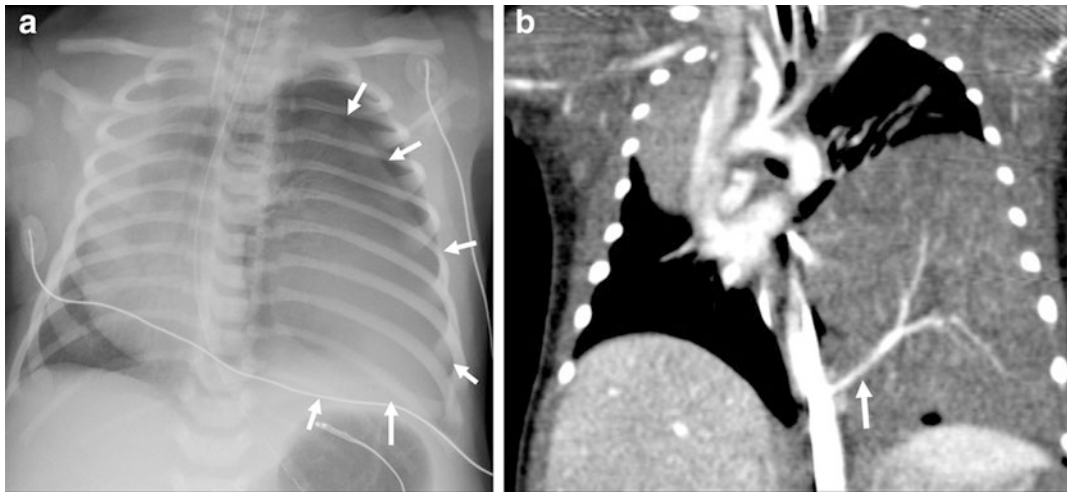

Fig. 23.34 Pulmonary sequestration. (**a**) Chest radiograph shows a well-defined left lung opacity (*arrows*) and significant mediastinal shift to the right. (**b**) Coronal CT image shows a large left lower lobe solid mass and a feeding vessel (*arrow*) arising from the aorta

c. CT is mainly used to evaluate size and location and is usually performed with intravenous contrast administration to evaluate the vascular anatomy (Fig. 23.33b).
d. It is often diagnosed on prenatal ultrasound. Pre- or post-natal MRI can also be performed to evaluate anatomy and extension.

2. Pulmonary sequestration
   a. Pulmonary sequestration represents an area of dysplastic, nonfunctional lung with a systemic arterial supply that typically arises from the aorta. The most common location is the left lower lobe, followed by the right lower lobe. Most neonatal sequestrations are extralobar and have their own pleura and systemic venous return. Intralobar sequestrations have pulmonary venous drainage and are invested within the pleura of the affected side. Associated gastrointestinal malformations are common with extra lobar sequestration.
   b. On conventional radiography, sequestrations are seen as dense and persistent focal masses (Fig. 23.34a).

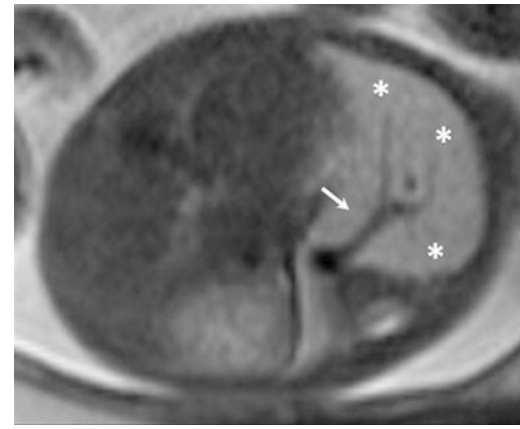

Fig. 23.35 Pulmonary sequestration. MRI performed prenatally in the same patients as in Fig. 23.34. Axial T2-weighted image shows a large left lower lobe mass (*arrowheads*) and a feeding vessel arising from the thoracic aorta (*arrow*)

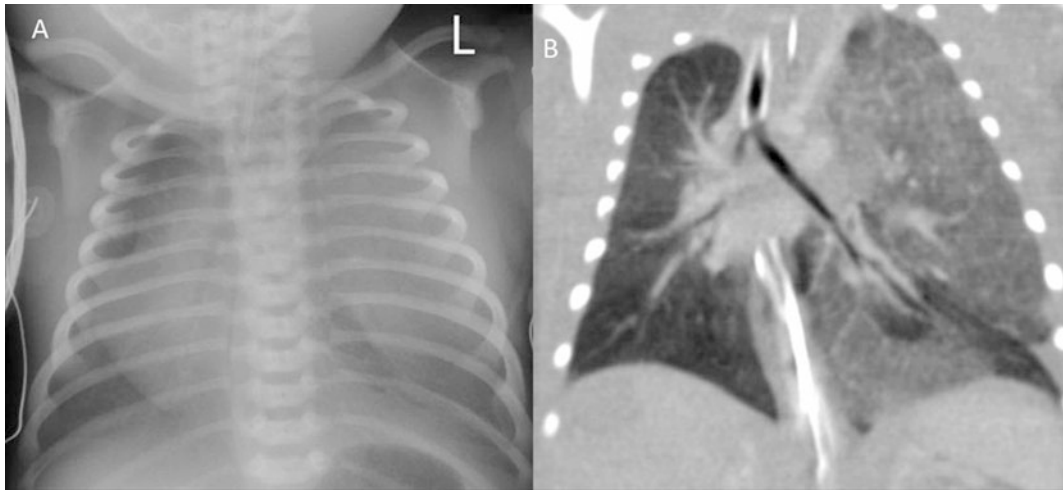

Fig. 23.36 Congenital lobar overinflation associated with bronchial atresia: (**a**) Chest radiograph shows an ill-defined left upper opacity and significant mediastinal shift to the right. (**b**) Coronal CT image shows left upper lobe ground-glass opacity density secondary to retained fluid

c. Pre-surgical evaluation with CT, MRI, and ultrasound is performed to evaluate the extent and identify the systemic vascular supply, which arises from below the diaphragm in 20 % of cases (Fig. 23.34b).
d. Pulmonary sequestration may occur in conjunction with CPAM ("hybrid lesions"), cardiac, diaphragmatic, skeletal, and other lung anomalies.
e. It is also often diagnosed on prenatal ultrasound. Fetal MRI also allows evaluation of anatomy and extension (Fig. 23.35).

3. Congenital lobar overinflation
   a. Formerly referred to as congenital lobar emphysema (CLE). It usually occurs secondary to bronchial obstruction with a valve mechanism that causes lobar hyperinflation.
   b. Initially, after birth, the overdistended lobe is filled with fluid and may be opaque (Fig. 23.36a). Subsequently, the typical appearance is that of an overdistended lung, which, depending on the size, may cause adjacent atelectasis and mediastinal shift to the contralateral side (Fig. 23.37a).
   c. CT may be performed for pre-surgical evaluation to better evaluate the anatomy (Figs. 23.36a and 23.37b).

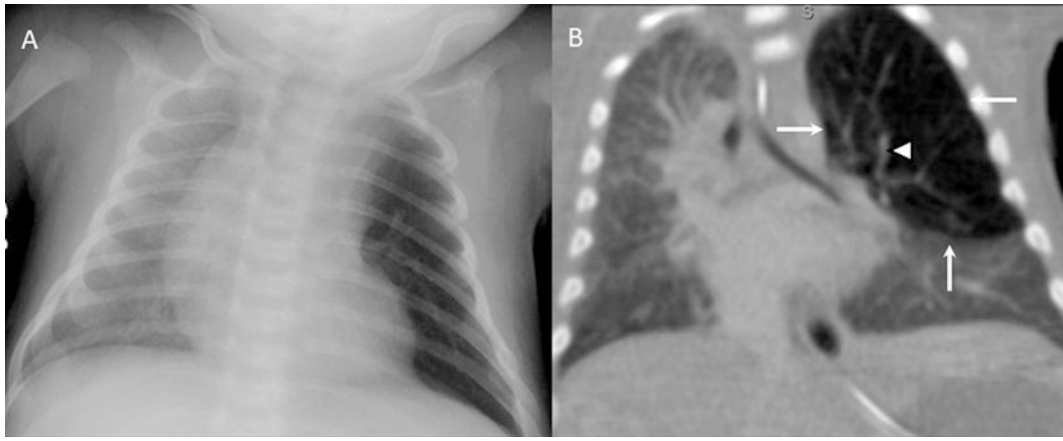

Fig. 23.37 Congenital lobar overinflation: (**a**) Chest radiograph shows left upper lobe lucency with mediastinal shift to the contralateral side and compressive right lung atelectasis. (**b**) Coronal CT image in the same patient. Marked hyperinflation of the left upper lobe (*arrows*) with significant mediastinal shift and right lung atelectasis. Note that the vascularity (*arrowhead*) in the affected lobe is attenuated

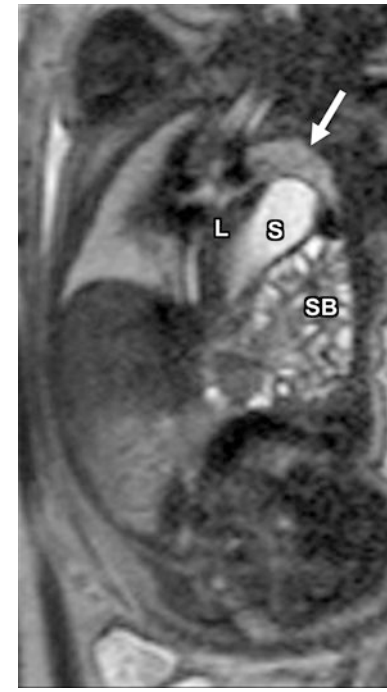

Fig. 23.38 Left-sided congenital diaphragmatic hernia coronal T2-weighted fetal MRI image shows herniation of part of the left hepatic lobe (L), stomach (S), and small and large bowel (SB) into the chest. Note the presence of a hypoplastic left lung (*arrow*))

G. Congenital diaphragmatic hernia (CDH)
   1. Congenital diaphragmatic hernias are frequently diagnosed on prenatal ultrasound.
   2. Fetal MRI now plays an important role in the pre-surgical and initial neonatal management. MRI characterizes the herniated structures, quantifies the degree of lung hypoplasia, and evaluates for the presence of associated anomalies (Fig. 23.38).
   3. On initial radiographs, herniated abdominal contents are seen as an opaque mass, more common on the left side, with ipsilateral lung hypoplasia and a contralateral mediastinal shift. During the hours following birth, air fills the herniated loops of bowel giving the typical appearance of multiple lucencies in the chest (Fig. 23.39).

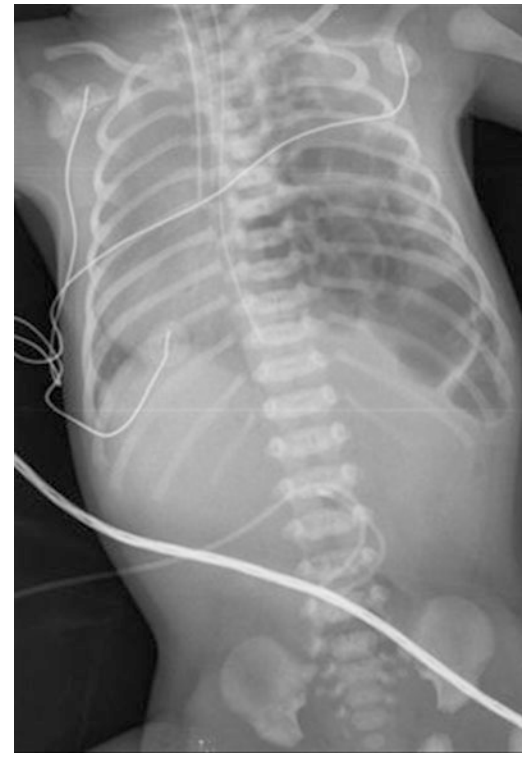

Fig. 23.39 Left-sided CHD. Radiograph of the chest and abdomen shows lack of abdominal gas and multiple gas-filled loops of bowel occupying the left hemithorax. The mediastinum is shifted to the right. Note the nasogastric tube tip in the distal esophagus and selective intubation of the right bronchus)

4. After surgical correction, "*ex vacuo*" pneumothorax is a frequent finding.

H. Esophageal atresia, tracheo-esophageal fistula, abnormal tracheal-bronchial tree anomalies
   1. A coiled gastric tube in the proximal esophagus suggests esophageal atresia in the adequate clinical setting. The presence of abdominal gas suggests the presence of an associated distal tracheo-esophageal fistula (Fig. 23.40). Cardiac, renal, vertebral, anal, and osseous limb anomalies are common associated findings.
   2. Contrast studies can be performed in equivocal cases, when pharyngeal perforation is in the differential diagnosis, when proximal trachea-esophageal fistula or trachea-esophageal fistula without atresia are suspected, and for post-surgical evaluation (Fig. 23.41).
   3. The presence of symmetrically hyperinflated lungs in a patient with acute, severe respiratory distress, no audible cry, and failed endotracheal intubation suggests the diagnosis of tracheal atresia (Fig. 23.42a, b).
   4. Rapid acquisition time, multi-planar, and volumetric capabilities make CT an excellent diagnostic tool when airway anomalies such as tracheal stenosis (Figs. 23.42c and 23.43), abnormal tracheal-bronchial tree development, or extrinsic compression are suspected.

I. Assessment of tubes and catheters (Fig. 23.44)
   1. Endotracheal tube (ETT)
      a. Endotracheal tube tip should be located in the mid to distal trachea above the carina.
      b. The position of the patient's head and neck may alter the ETT position: the tube tip moves caudally (towards the carina), with neck flexion and cephalic (towards the glottis) with neck extension and lateral rotation.

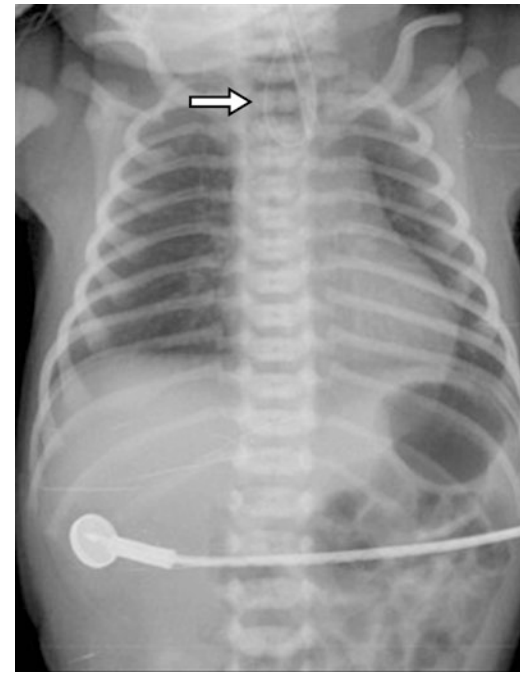

Fig. 23.40 Esophageal atresia and distal tracheaesophageal fistula. Radiograph of the chest and upper abdomen shows a coiled nasogastric tube (*arrow*) in the upper esophagus. The presence of abdominal gas determines the presence of a distal tracheo-esophageal fistula

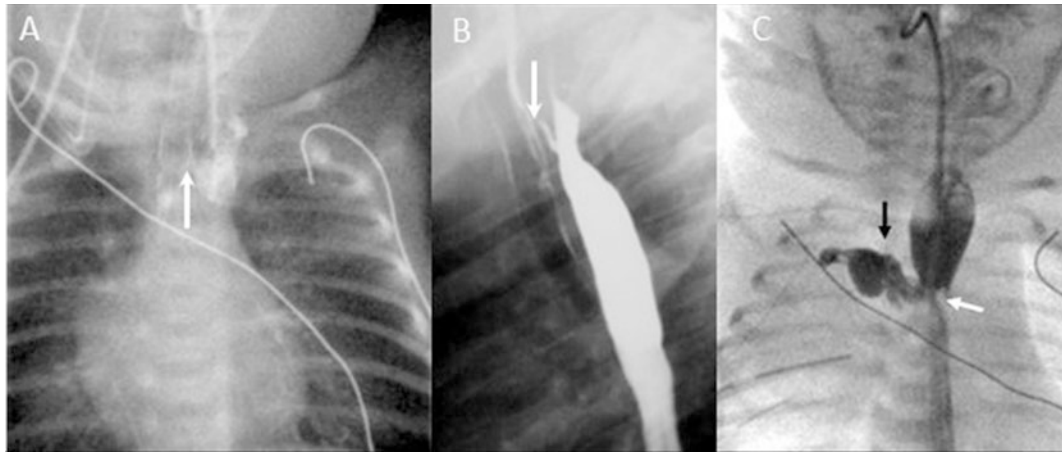

Fig. 23.41 Esophageal atresia and tracheo-esophageal fistula. (**a**) Esophagram performed through the pouch in a patient with esophageal atresia reveals the presence of a proximal tracheo-esophageal fistula (*arrow*). (**b**) Esophagram in neonate with aspiration pneumonias shows the presence of a tracheo-esophageal fistula without esophageal atresia. (**c**) Esophagram performed after surgical correction of esophageal atresia shows an area of narrowing (*white arrow*) at the level of the surgical anastomosis and leak of contrast (*black arrow*) into the right pleural space. Note the presence of three right chest tubes

c. Unintentional right main bronchus intubation is a common radiographic finding and usually associated with atelectasis of the contralateral lung.

2. Vascular catheters, gastric drainage tubes, and surgical drains
   a. Placement of vascular catheters, gastric drainage, and chest tubes may require additional imaging to assess correct position.

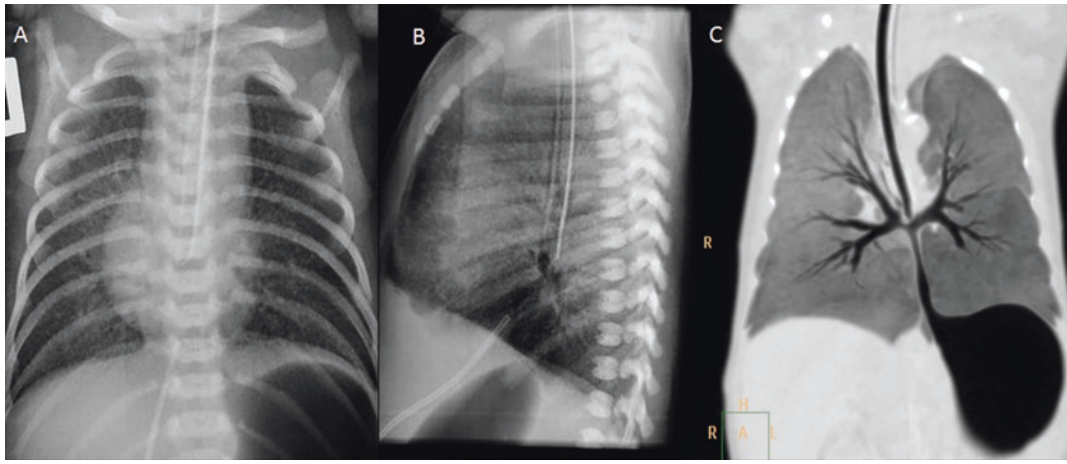

Fig. 23.42 Neonate with type II (Floyd classification) tracheal agenesis. Frontal (**a**) and lateral (**b**) views in a patient with severe respiratory distress reveal the presence of an endotracheal tube in the mid-distal esophagus with symmetrical hyperinflated lungs. (**c**) Coronal CT reconstruction shows the presence of total tracheal atresia with normal bronchi fusion in the midline at the level of the carina

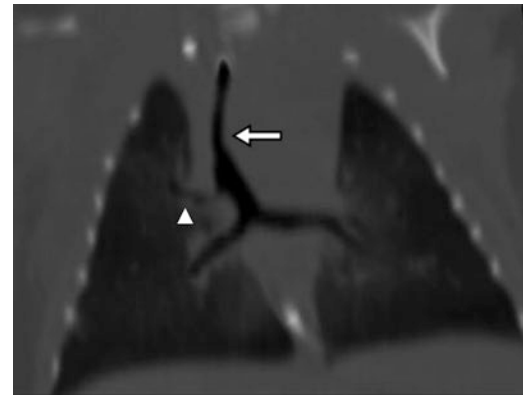

Fig. 23.43 Tracheal stenosis and accessory tracheal bronchus in a patient with a pulmonary sling. Reconstructed coronal CT image shows a long segment area of tracheal narrowing (*arrow*) and an accessory right bronchus (*arrowhead*) arising from the trachea

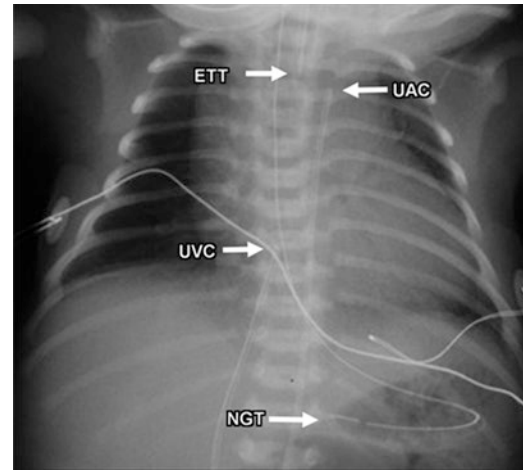

Fig. 23.44 Catheters and tubes. Neonate with RDS. Note the tip of the endotracheal tube (ETT), umbilical venous catheter (UVC), umbilical arterial catheter (UAC), and nasogastric tube (NGT)

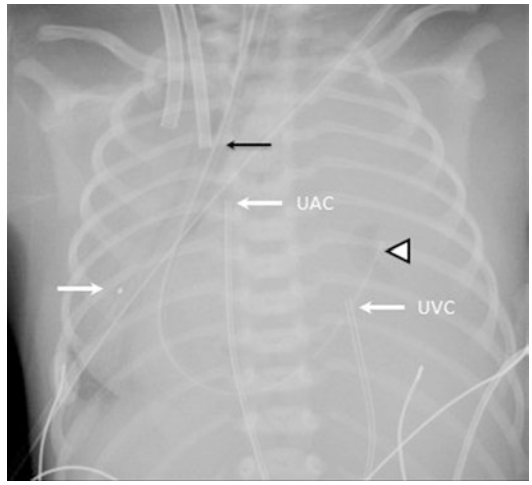

Fig. 23.45 ECMO cannulas. Chest radiograph in a neonate with left CHD on ECMO. The venous cannula tip (*white arrow*) is located at the expected location of the right atrium. The arterial cannula tip (*black arrow*) is located at the innominate artery/aorta junction. Note the tip of the NG tube (*arrowhead*) in the herniated stomach. Umbilical arterial catheter (UAC) is noted. Umbilical venous catheter (UVC) projects over the contralateral chest with tip likely in the left portal vein of the herniated liver

b. Umbilical venous catheter (UVC) tip is ideally located above the diaphragm and below the right atrium. The location of the UVC in patients with diaphragmatic hernia can be very challenging because of herniation of the liver (Fig. 23.45).
c. Umbilical arterial catheters (UAC): A high-line tip is usually located at the T7–T10 vertebral level. A low-line tip is ideally located at the L3–L4 vertebral body interspace.
d. Ultrasound can be used to guide peripherally inserted central catheter (PICC), umbilical catheter placement, and monitor possible complications.

3. Extracorporeal membrane oxygenation (ECMO) cannulas and liquid ventilation
   a. ECMO cannulas may be veno-arterial (V-A) or veno-venous (V-V).
   b. For V-A ECMO, the tip of the venous cannula should project within the right atrium, while the tip of the arterial cannula should be within the aortic arch at the expected location of the origin of the innominate artery (Fig. 23.45).
   c. After bypass, a whiteout of the lungs is a common radiological finding.
   d. A rapidly increasing pleural effusion is suggestive of anticoagulation-associated hemothorax.
   e. Conventional radiographs are used to evaluate distribution of perflubron when liquid ventilation is used (Fig. 23.46).

J. Chest wall deformities causing respiratory distress
1. Neuromuscular disease, skeletal dysplasia, and congenital osseous anomalies may be responsible for restrictive lung disease (Fig. 23.47). Lung hypoplasia, atelectasis, and aspiration may contribute to the development of respiratory distress.
2. CT and MRI can be performed to evaluate the extent of the deformity and lung volume (Fig. 23.48)

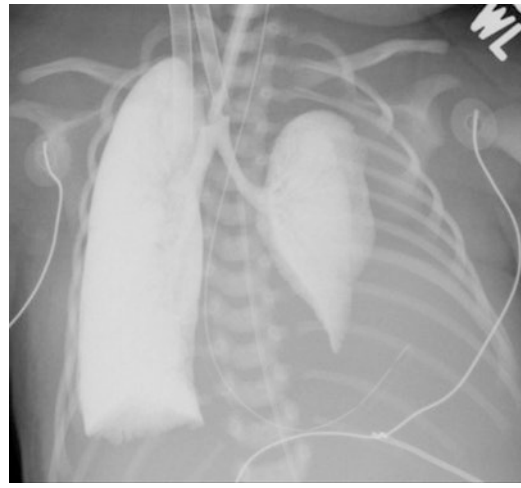

Fig. 23.46 Liquid ventilation. Chest radiograph performed in newborn with left CDH on ECMO and receiving liquid ventilation. Note the presence of ECMO cannulas, NG tube tip in stomach, located in the left hemithorax, ascending vascular catheter (UAC), and perflubron within tracheo-bronchial tree and the lungs. The left lung is hypoplastic secondary to the CDH

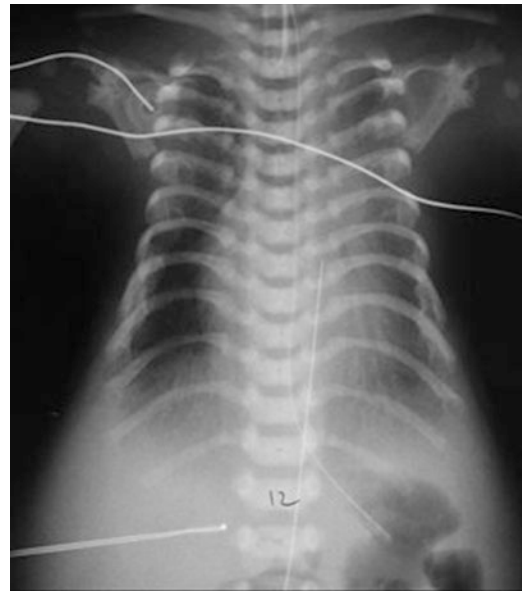

Fig. 23.47 Chest wall deformity. Chest radiograph of a patient with Jeune syndrome. Small chest with short, horizontally oriented ribs with irregular anterior ends. Note the NG tube tip in the stomach, a UAC with tip at the level of T6 vertebral body, and an ETT tip at the level of the cervicothoracic junction

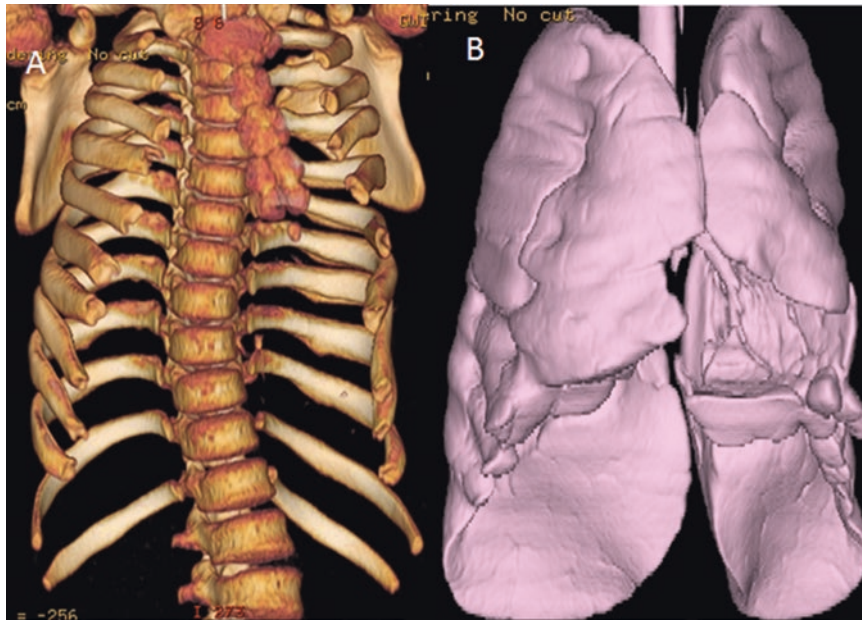

Fig. 23.48 Chest wall deformity. 3D volumetric reconstructed images with bone (**a**) and lung (**b**) algorithms in a patient with Jeune syndrome allow better delineation of chest wall deformity and lung volume assessment prior to and after thoracic expansion surgery

Suggested Reading

Agrons GA, Courtney SE, Stocker JT, Markowitz RI. From the archives of the AFIP: lung disease in premature neonates: radiologic-pathologic correlation. Radiographics. 2005;25:1047–73.

Donnelly L. Diagnostic imaging: pediatrics. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

Donoghue V. Radiological imaging of the neonatal chest. 2nd ed. Berlin: Springer; 2007.

Newman B. Imaging of medical disease of the newborn lung. Radiol Clin North Am. 1999;37:1049–65.

Strife JL, Crotty E. Neonatal chest imaging. In: Lucaya J, Strife JL, editors. Pediatric chest imaging: chest imaging in infants and children. Berlin: Springer; 2007. p. 417–39.

Taylor GA, Atalabi OM, Estroff JA. Imaging of congenital diaphragmatic hernias. Pediatr Radiol. 2009;39:1–16.

Transillumination

24

Steven M. Donn

I. Description: Use of a high-intensity light to help define normal from abnormal structure or function. Using transillumination, the density and composition of tissue are assessed by its diffusion of light.
II. Clinical Applications
  A. Diagnosis of air leaks
  B. Distinguishing cystic from solid masses
  C. Locating veins or arteries for blood sampling or catheter insertion
  D. Initial diagnosis of central nervous system abnormalities which involve formation of fluid collections
III. Technique
  A. Prepare light source
    1. Check power supply or batteries.
    2. Connect fiber-optic cable if necessary.
    3. Practice good infection control by disinfecting light probe with antiseptic solution.
  B. Darken room as much as possible. Allow some time for dark adaptation.
  C. Apply light probe to infant's skin surface in area to be examined; contralateral side can be used as control.
  D. Normally, extent of visible light corona around probe tip is 2–3 cm; presence of air (or fluid) in light path will substantially increase the degree of lucency. A significant collection of air will enable the entire hemithorax to "glow."
  E. Pneumomediastinum (Fig. 24.1)
    1. Suggested if cardiac pulsations are clearly evident in lucent area
    2. Best seen if light probe is placed next to costal margin
    3. High predictive value (94 %) if >20 mL air
  F. Pneumothorax (Fig. 24.2)
    1. Generally expand uniformly in anterior direction

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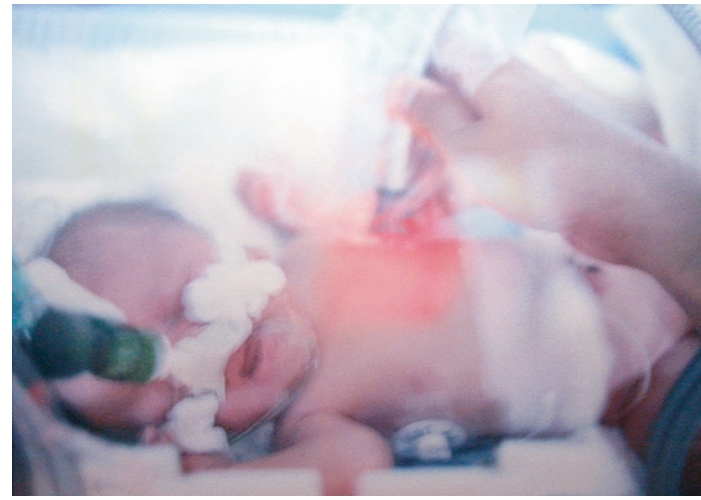

Fig. 24.1
Transillumination diagnosis of a pneumomediastinum

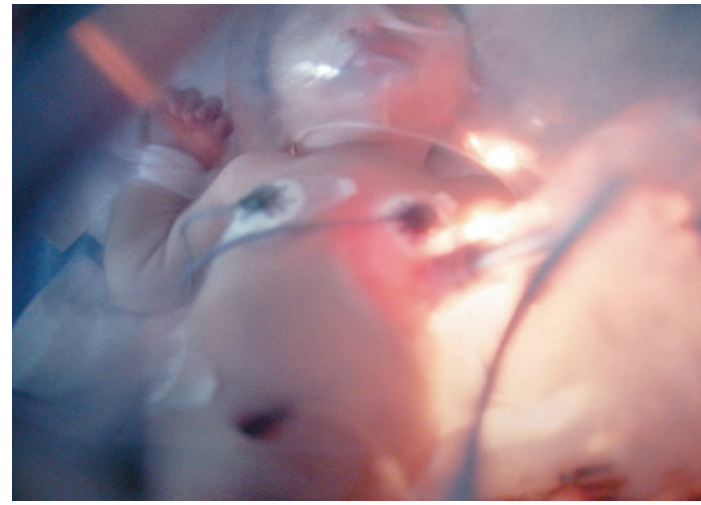

Fig. 24.2
Transillumination diagnosis of a pneumothorax

2. Best demonstrated if light probe is placed on anterior chest wall
3. Can be diagnosed with >95 % accuracy under favorable conditions.

G. Pneumopericardium
1. Place light probe in third or fourth intercostal space in left mid-clavicular line.
2. Angle light probe toward xiphoid process.
3. When probe is moved over thorax, corona will appear brightest over the pericardial sac, and silhouette of heartbeat may be seen.

H. All three collections may be aspirated under transillumination guidance.

IV. Special Considerations

A. Care must be taken to avoid burning the patient with the high-intensity light. This is accomplished by using a red filter inserted in front of the light source and limiting contact of the light probe with the skin.

B. Cross-contamination of patients is avoided by covering light with cellophane.

Suggested Reading

Cabatu EE, Brown EG. Thoracic transillumination: aid in the diagnosis and treatment of pneumopericardium. Pediatrics. 1979;64:958–60.

Donn SM. Transillumination. In: Donn SM, editor. The Michigan manual: a guide to neonatal intensive care. 2nd ed. Armonk, NY: Future Publishing Col; 1997. p. 27–8.

Donn SM. Historical perspective: neonatal transillumination. NeoReviews. 2005;6:e1–3.

Donn SM, Kuhns LR. Pediatric transillumination. Chicago: Chicago Year Book Medical Publishers; 1983.

Wyman ML, Kuhns LR. Accuracy of transillumination in the recognition of pneumothorax and pneumomediastinum in the neonate. Clin Pediatr. 1977;16:323–4.

Echocardiography

25

Jonathan P. Wyllie

I. Background
Until the advent of echocardiography, cardiac function in the ventilated baby was monitored by clinical assessment and invasive monitoring, which is limited by the size of the patient. Over the past 25 years, echocardiography in neonatal units has developed from an assessment of structural normality or identifying the presence or absence of a ductus arteriosus into a technique for the assessment of hemodynamic function in infants in an intensive care setting. Tissue perfusion is the most relevant parameter in assessing cardiovascular function. This depends upon peripheral vascular resistance and cardiac output. Previously, heart rate and blood pressure have been utilized as indicators of these parameters, but these have significant limitations. Echocardiography now offers a number of different modalities, which can be used to assess cardiac function in the ventilated infant and provide more information upon which to base clinical decisions.

II. Defining neonatal echocardiography
To distinguish echocardiography used by a pediatric cardiologist to delineate detailed cardiac structure from that used by a neonatologist to assess cardiac function and therapeutic intervention the following terms have been coined:
   A. Functional echocardiography
   B. Point-of-care echocardiography
   C. Point-of-care ultrasound
   D. Targeted neonatal echocardiography
   E. Clinician-performed cardiac ultrasound
   F. Neonatologist-performed cardiac ultrasound

III. Influences on Newborn Cardiovascular Adaptation
   A. Preterm delivery
   B. Surfactant deficiency
   C. Ventilation
   D. Hypoxia
   E. Acidosis

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IV. Effects of Prematurity and Respiratory Disease on Cardiovascular Adaptation
  A. Delayed fall in pulmonary vascular resistance
  B. Myocardial dysfunction
  C. Ductal patency
  D. Ventilation and diminished venous return
  E. Hypovolemia
V. Ideal Cardiac Assessment
  A. Right and left ventricular outputs
  B. Cardiac function
  C. Pulmonary resistance
  D. Tissue perfusion
  E. Systemic vascular resistance
VI. Echocardiographic Assessment
  A. Echocardiographic principles

Cross-sectional echocardiography is used to assess anatomy; allow accurate positioning of an M-mode, continuous wave Doppler, or pulsed-wave Doppler beam; and to give a subjective impression of function. Views used include:

1. Long-axis parasternal (Fig. 25.1)
2. Short-axis parasternal mitral (Fig. 25.2)
3. Short-axis parasternal pulmonary (Fig. 25.3)
4. Apical four chamber (Fig. 25.4)
5. Subcostal

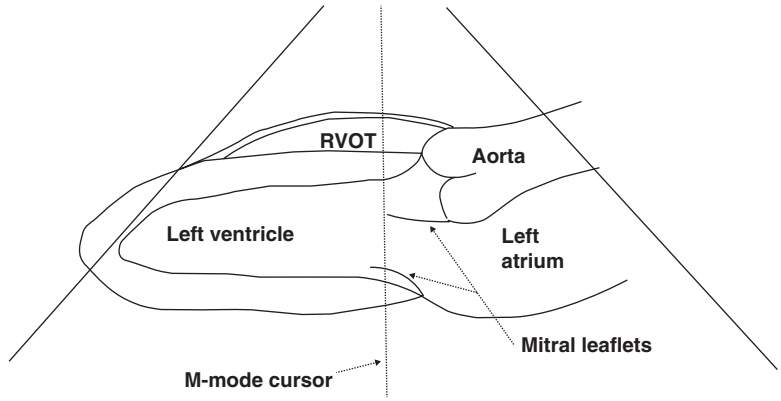

Fig. 25.1 Long-axis parasternal view. Positioning of M-mode cursor for left ventricular measurements is shown. *RVOT* right ventricular outflow tract

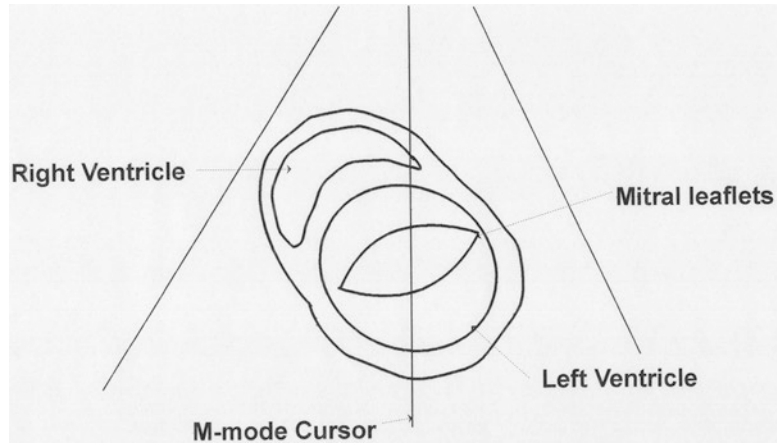

Fig. 25.2 Short-axis parasternal mitral view. Positioning of M-mode cursor for left ventricular measurements is shown

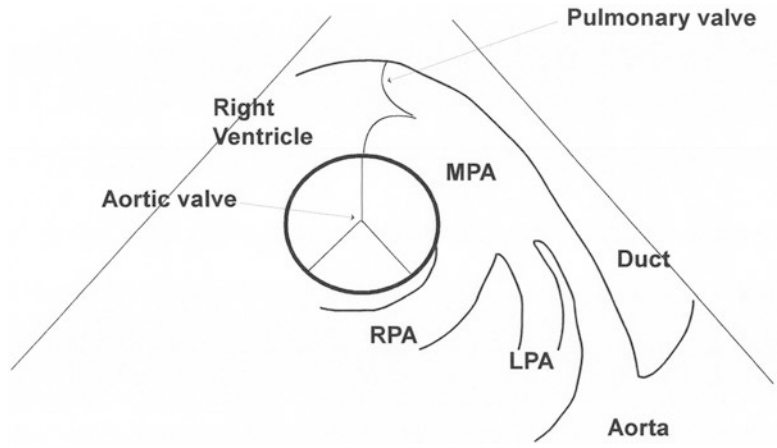

Fig. 25.3 Short-axis parasternal pulmonary view. *MPA* main pulmonary artery, *RPA* right pulmonary artery, *LPA* left pulmonary artery

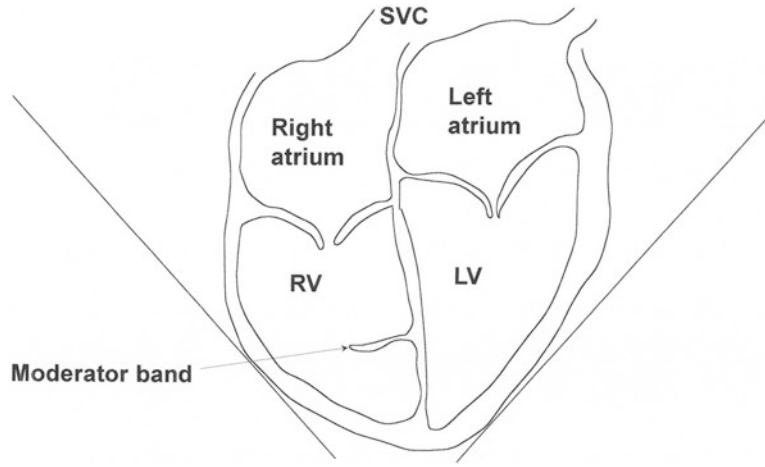

Fig. 25.4 Four-chamber apical view. Offset of tricuspid and mitral valves is seen. *SVC* superior vena cava, *RV* right ventricle, *LV* left ventricle

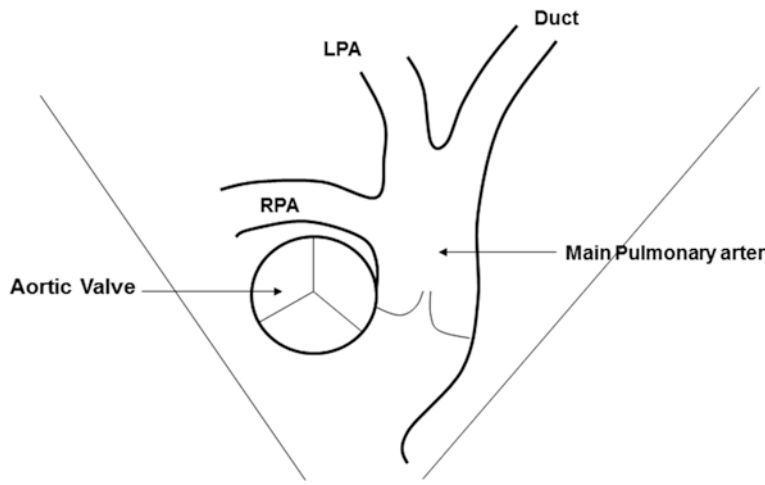

Fig. 25.5 Subcostal short-axis pulmonary view. *RPA* right pulmonary artery, *LPA* left pulmonary artery

6. Suprasternal view of aortic arch or ductal arch
7. Subcostal short axis (Fig. 25.5). Useful if lungs overdistended
8. Subcostal caudal view of mesenteric vessels and IVC

B. M-mode obtains detailed echocardiographic information along a thin beam. It is simplest to first position using a cross-sectional image (Fig. 25.1) and then switch to M-mode. It is used

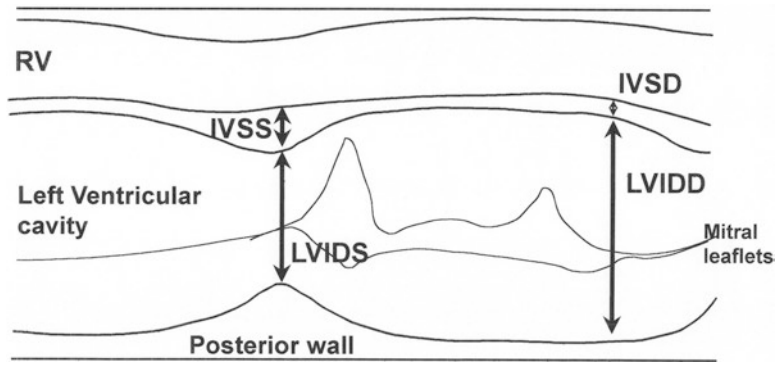

Fig. 25.6 M-mode view of left ventricle showing measurements. *RV* right ventricle, *IVSS* intraventricular septum systole, *LVIDS* left ventricular internal diameter systole, *IVSD* intraventricular septum diastole, *LVIDD* left ventricular internal diameter diastole

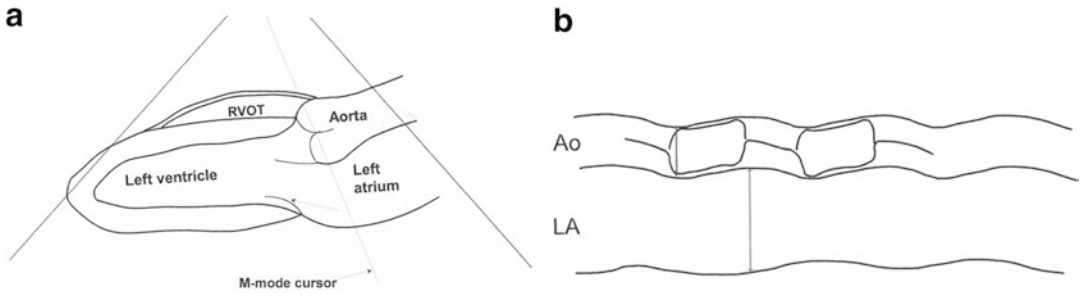

Fig. 25.7 (**a**) Long-axis parasternal view with M-mode cursor across aorta and left atrium (**b**) M-mode of aorta (Ao) and left atrium (LA) showing measurements of each

to obtain views of the left ventricle at the level of the mitral leaflets in assessment of left ventricular function and measurement of left ventricular dimensions (Fig. 25.6). It is also used in measurement of the left atrium and aorta (Fig. 25.7a, b).

C. Pulsed-wave Doppler uses Doppler shift of sound waves from moving red cells to assess flow velocity. It can sample the velocity at a point specified on a cross-sectional image (range gated), but is often only useful for relatively low velocities. It is useful for velocity measurement in the pulmonary artery, ductus arteriosus (Fig. 25.8), foramen ovale, superior vena cava, aortic arch celiac axis, and superior vena cava.

D. Continuous-wave Doppler also uses Doppler shift of sound waves from moving red cells to assess flow velocity but is not range gated and samples velocities along the cursor line (Fig. 25.8). It can be used in line with cross-sectional views or using a stand-alone "pencil" probe. Both continuous and pulsed-wave Doppler beams must be within 20° of the direction of flow to be accurate. Continuous-wave doppler is useful for measuring faster flow velocities. The various types of Doppler therefore allow estimation of both the direction and velocity of blood flow. With this information the pressure gradient can also be calculated using a modified Bernoulli equation (pressure gradient $= 4 \times \text{velocity}^2$) and by measuring the diameter of a vessel as well as the flow velocity, blood flow can be estimated.

E. Color Doppler simplifies accurate diagnosis and delineation of ductal patency. It also enables identification of tricuspid regurgitation and patency of the foramen ovale as well as the direction of flow. Flow velocity measurement is possible when used in conjunction with continuous- or pulsed-wave Doppler. It is used to measure ductal dimension.

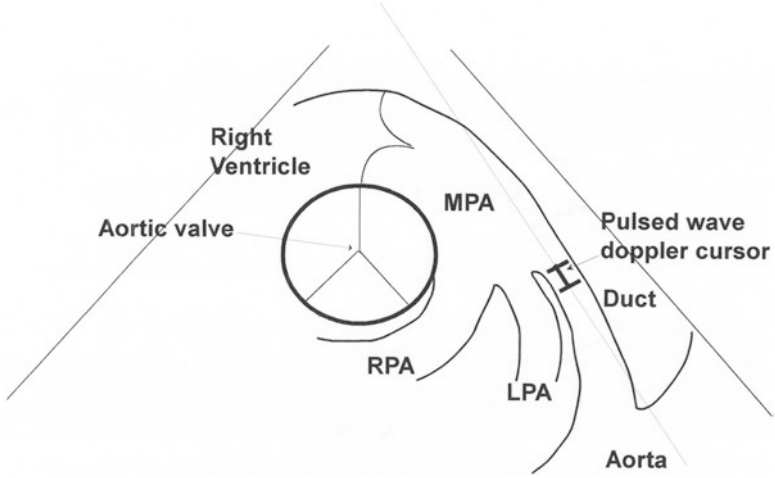

Fig. 25.8 Short-axis parasternal pulmonary view showing the position of the pulsed-wave Doppler cursor for sampling ductal flow velocity

VII. Indications for Echocardiographic Assessment
- A. Suspected congenital heart disease
- B. Suspected persistent pulmonary hypertension
- C. Suspected patent ductus arteriosus (60 % patency <28 weeks' gestation)
- D. Hypotension or shock
- E. Asphyxia
- F. Suspected cardiac dysfunction
- G. Use of high PEEP
- H. High-frequency oscillatory ventilation

VIII. Cardiac Function

Depressed ventricular function may occur in neonatal disease processes such as hypoxia, sepsis, hemolytic disease, hyaline membrane disease (RDS), persistent pulmonary hypertension, and transient tachypnea. Fifty percent of premature babies who develop hypotension have cardiac dysfunction in the first 24 h of life. A dysfunctional heart may be tachycardic and bradycardic, or have a normal rate. In hypotensive newborns cardiac function may be depressed, normal, or even hyperdynamic.

IX. Left Ventricular Assessment
- A. Cross-sectional and M-mode assessment
- B. Cross-sectional echocardiography permits accurate positioning of the M-mode beam just at the mitral leaflet tips in the long axis (parasternal, Fig. 25.1) or centered in the short-axis parasternal views (Fig. 25.2) of the left ventricle. Measurements must be taken from standard and reproducible positions; otherwise increased variability will obscure the results.
- C. On the M-mode picture (Fig. 25.6), the interventricular septal (IVS), left ventricular internal diameter (LVID), and posterior wall dimensions are measured at end-systole (S) and end-diastole (D). From these measurements several parameters of ventricular function can be calculated.
- D. The apical four-chamber view (Fig. 25.4) allows subjective assessment of both left and right ventricular function. This can be appreciated without taking the measurements above. It is useful in understanding clinical situations and taking a logical approach. However, it is much less helpful in monitoring the response to treatment.

1. Fractional shortening characterizes left ventricular contractility, although it is also affected by preload and afterload:

$$\text{Fractional shortening}(\%) = \frac{\text{LVIDD} - \text{LVIDS}}{\text{LVIDD}} \times 100\%$$

Normal ranges:	25–45 % adults
	25–41 % term babies
	23–40 % preterm babies

Errors in fractional shortening estimation may occur in early preterm life from distortion of the left ventricle and abnormal septal motion. Fractional shortening cannot be measured if there is paradoxical septal motion.

2. Circumferential Fiber Shortening

Mean velocity of circumferential fiber shortening (VCF) has been suggested as a simple alternative measurement of left ventricular contractility. It is less sensitive to minor dimensional discrepancies and involves no assumptions about ventricular shape, offering a reproducible measurement of neonatal ventricular contractility.

To calculate VCF, LVIDD, and LVIDS are measured as above, but ejection time is measured from the time of mitral valve closure to the onset of mitral valve opening:

$$\text{VCF} = \frac{\text{LVIDD} - \text{LVIDS}}{\text{LVIDD} \times \text{ejection time}}$$

The units are circumferences per second.

3. Stroke Volume
   a. Stroke volume measurement assumes an ellipsoidal ventricle. This is a reasonable assumption in adults but less so in neonates. Using measurements of left ventricular internal diameter in diastole (LVIDD) and systole (LVIDS), the stroke volume (SV) can be calculated:

$$\text{SV} = \text{LVIDD}^3 - \text{LVIDS}^3$$

   b. Similarly, a proportion of ventricular contents or ejection fraction (EF) can be calculated:

$$\begin{aligned}\text{EF} &= \text{Stroke volume} / \text{End diastolic volume} \\ &= \left(\text{LVIDD}^3 - \text{LVIDS}^3\right) / \text{LVIDD}^3\end{aligned}$$

4. Volume load assessment
   a. M-mode assessment of the left ventricle and atrial size provides information about changes in ventricular preload. The ratio of these chambers to the aorta is used to assess the effect of shunts upon the heart, especially the ductus arteriosus.
   b. Normal left atrial-to-aortic ratio is 0.84–1.39 in preterm infants and 0.95–1.38 in term infants.
   c. Left atrial:aortic ratio >1.5 suggests volume loading.
   d. Left ventricular internal diastolic diameter:aortic ratio >2:1 suggests ventricular volume loading.
   e. It is important to realize that apparent volume loading may also be due to poor contractility in a normovolemic neonate.

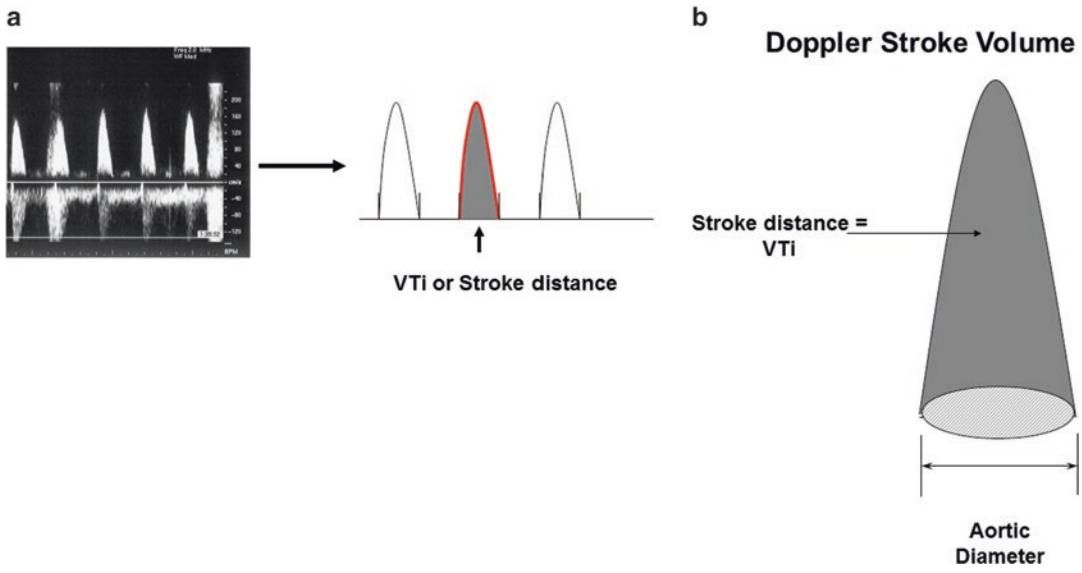

Fig. 25.9 (**a**) Aortic Doppler trace showing the measurement of the integral of the velocity time curve (VTi) or stroke distance. (**b**) Calculating stroke volume using the aortic diameter calculated from the diameter

X. Doppler Assessment of Systolic Function

A. Stroke volume

Calculated from the product of the integral of the Doppler velocity-time curve (VTI, also known as stroke distance) (Fig. 25.9a, b) and the cross-sectional area of the aorta derived from the M-mode diameter:

$$SV = VTI \times p(\text{Aortic diameter}/2)^2$$

B. Cardiac output

1. Left venticular output

Multiplying SV by the heart rate (HR) produces the left ventricular output (LVO):

$$LVO = VTI \times p(\text{Aortic diameter}/2)^2 \times HR$$

Note—Minute distance (MD = VTI × HR) is directly related to cardiac output but removes the aortic diameter from the calculation, which is the major source of error. This can be used to assess changes in therapy in an individual.

Normal ranges:	Preterm	221 ± 56 ml/kg/min
	Term	236 ± 47 ml/kg/min
	Range	158–325 ml/kg/min

2. Right ventricular output

In a similar way right ventricular output can be measured. Pulmonary artery diameter is measured in the short-axis pulmonary view (Fig. 25.3). RVO is less affected by ductal shunting; however, the pulmonary artery diameter varies more than the aorta during the cardiac cycle introducing more error into this measurement. The pulmonary VTI is obtained from the pulmonary Doppler velocity-time curve taken in the short-axis view (Fig. 25.3):

$$RVO = VTI \times p(\text{pulmonary diameter}/2)^2 \times HR$$

A useful screening measurement which can give an indication of RVO in the first 48 h is the maximum pulmonary velocity taken as above:

$$<0.35 \text{ mps} = \text{RVO likely to be less than 150 ml/kg/min}$$

3. Supra vena caval (SVC) flow measurements
   SVC flow has been used as representative of systemic flow unaffected by ductal shunting. SVC diameter is measured in a parasternal view; however, it is known that the SVC becomes crescent shaped during the cardiac cycle making accuracy of measurement an issue. SVC VTI is measured from the subcostal view:

$$\text{SVC (cardiac output)} = \text{VTI} \times p(\text{SVC diameter}/2)^2 \times \text{HR}$$

   A measurement of less than 40 ml/kg/min in the first 24 h of life has been associated with intraventricular hemorrhage and death or disability at 3 years of age.

XI. Right Ventricular Assessment
The normal shape of the right ventricle is more complex than the left. It consists of inflow, outflow, and apical segments and is wrapped around the left ventricle. This makes quantitative evaluation by M-mode difficult at any age and not useful in the newborn. However, qualitative information about right ventricular systolic function can be obtained by the experienced operator from cross-sectional views. Paradoxical movement of the intraventricular septum is seen in right ventricular dysfunction. Such movement prevents any assessment of left ventricular fractional shortening.

XII. Doppler Assessment of Systolic Function
One of the most important determinants of right ventricular systolic function in newborns is pulmonary arterial pressure. This can be estimated in several ways.

A. Tricuspid regurgitation. If present, the most accurate assessment of right ventricular (and therefore pulmonary) pressure is obtained by measuring the velocity of the regurgitant jet (V). Then, assuming right atrial pressure is low,

$$\text{Pulmonary pressure} = 4V^2$$

B. Pre-ejection period-to-right ventricular ejection time is related to pulmonary pressure and requires ECG monitoring while echoing the subject. It is useful for assessment of babies with chronic lung disease but difficult to interpret acutely.

C. Time to peak velocity (TPV)-to-right ventricular ejection time is inversely related to pulmonary pressure but does not require ECG monitoring to measure. A ratio of >0.3 indicates normal pulmonary pressures and <0.2 pulmonary hypertension. Between these two it is likely that the pulmonary pressure is mildly elevated.

D. Ductal flow. If the ductus arteriosus is patent, the direction of flow (as well as the pattern) gives an indication of pulmonary pressure (i.e., right-to-left = pulmonary > systemic) (Fig. 25.10a–d). However, the velocity of flow cannot accurately predict pulmonary pressure.

E. Foramen ovale. Right-to-left flow is suggestive of high right-sided pressures or dysfunction. It is seen best in the subcostal view.

F. Diastolic function
Few studies of diastolic function have been carried out in children or infants. Right ventricular filling is modified by positive pressure ventilation and especially by high positive end-expiratory pressure and oscillatory ventilation.

XIII. Assessment of the Patent Ductus Arteriosus (Chap. 83)

A. The ductus arteriosus is best seen in the parasternal short-axis view (Fig. 25.3), although the suprasternal and subcostal approaches may be needed in babies with overdistended lungs. Color Doppler simplifies identification and allows subjective assessment of flow and velocity. Doppler interrogation of the ductus arteriosus (Fig. 25.8) demonstrates the pattern of

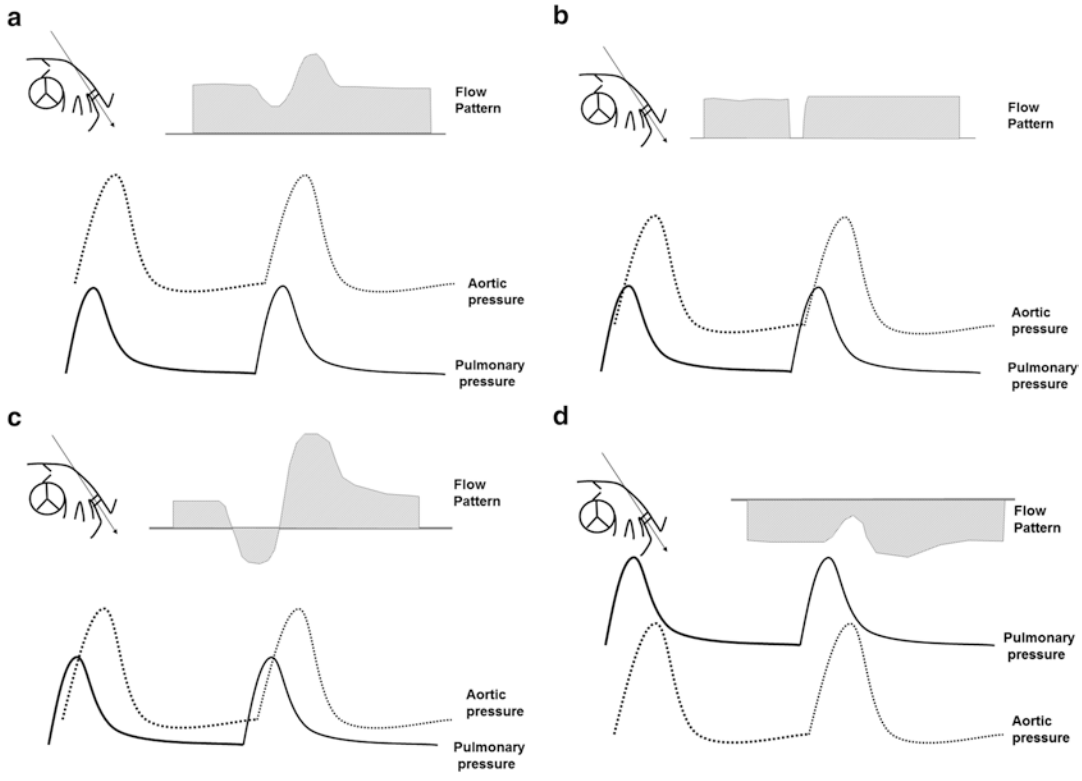

Fig. 25.10 Ductal flow patterns associated with differing systemic and pulmonary pressures: (**a**) Aortic > pulmonary pressure, (**b**) pulmonary = aortic pressure in early systole, (**c**) bidirectional flow with pulmonary > aortic pressure in early systole, (**d**) pulmonary > aortic pressure

flow and the velocity profile. Velocity depends upon both the size of the vessel and the pressure difference between aorta and pulmonary artery. The classical flow pattern associated with a large shunt is high in systole and low in diastole which is pulsatile and unrestrictive. Bidirectional, restrictive, and closing patterns can also be identified. The size can be estimated in cross-sectional view in relation to the branch pulmonary arteries or aorta.

B. Ductal diameter can be assessed by measuring the narrowest waist of the ductal color flow when the picture is frozen. Ensure maximal color Doppler scale, and optimize the color gain and measure. In some units this is used to predict which ducts are likely to be significant and require treatment. Diameter >1.5 mm in first 30 h has 83 % sensitivity and 90 % specificity for ductus needing treatment.
C. Measurement of the left atrium:aortic ratio (see above) gives some indication of flow but may not be accurate if the left atrium decompresses through the foramen ovale. Ratio >1.5 after the first day has sensitivity of 88 % and specificity of 95 % for ductus.
D. Sixty percent increase in left ventricular output predicts development of a significant duct.
E. Echocardiographic evidence of a significant ductus arteriosus precedes clinical evidence. On day 3 of life it can predict significance with 100 % sensitivity and 85 % specificity.
F. Assessment of descending aortic or celiac axis diastolic flow beyond ductal insertion.
   1. Normal: Continuous antegrade flow
   2. Abnormal: Absent or reversed diastolic flow

XIV. Preload/Volume Loading Assessment
   A. LA:Ao ratio
   B. LVEDD:Ao ratio
   C. Collapsibility of the inferior vena cava (IVC)
      1. The respiratory variations in IVC diameter in a mechanically ventilated patient are only observed when right atrial pressure is normal or low.
      2. Variation disappears in a volume-loaded heart with high RA pressure.

XV. Accuracy and Reproducibility
   A. M-mode measurements have been made using both leading and trailing edges. In measurements of the left ventricle both leading and trailing edges are used. Intraobserver variability for these measurements ranges from 5 % for distances to 10 % for calculated volumes. Interobserver variability is greater, ranging from 7 to 25 % for volume measurements.
   B. Measurement of the aorta and left atrium by M-mode is more reproducible in newborns if it is made from trailing-to-leading echo edge (i.e., the internal aortic diameter). Accuracy is vital, as a 1 mm error in the measurement of a 10 mm aorta will produce a 17 % error in cardiac output.
   C. The main sources of error in Doppler measurement are from the site of sampling and the angle of incidence of the Doppler wave. If the angle is less than 15°, the error will be <3 %. A further source of error in calculating cardiac output is coronary artery flow, which may cause a 10–15 % underestimate in flow.

Suggested Reading

Evans N, Girvan M. Practical echocardiography for the neonatologist. http://www.sswahs.nsw.gov.au/rpa/neonatal/cardiac.html

Evans N, Kluckow M. Early determinants of right and left ventricular output in ventilated preterm infants. Arch Dis Child. 1996;74:F88–94.

Gill AB, Weinding AM. Echocardiographic assessment of cardiac function in shocked very low birthweight infants. Arch Dis Child. 1993;68:17–21.

Hudson I, Houston A, Aitchison T, et al. Reproducibility of measurements of cardiac output in newborn infants by doppler ultrasound. Arch Dis Child. 1990;65:15–9.

Hunt R, Evans N, Reiger I, Kluckow M. Low superior vena cava flow and neurodevelopmental outcome at 3 years in very preterm infants. J Pediatr. 2004;145:588–92.

Kluckow M, Evans N. Early echocardiographic prediction of symptomatic patent ductus arteriosus in preterm infants undergoing mechanical ventilation. J Pediatr. 1995;127:774–9.

Kluckow M, Evans NJ. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. Arch Dis Child. 2000;82:F188–94.

Mertens L, Seri I, Marek J, et al. Targeted Neonatal Echocardiography in the Neonatal Intensive Care Unit: practice guidelines and recommendations for training. Writing Group of the American Society of Echocardiography (ASE) in collaboration with the European Association of Echocardiography (EAE) and the Association for European Pediatric Cardiologists (AEPC). J Am Soc Echocardiogr. 2011;24(10):1057–78.

Neonatal Echo Skills. www.neonatalechoskills.com

Skinner JR, Boys RJ, Hunter S, Hey EN. Pulmonary and systemic arterial pressure in hyaline membrane disease. Arch Dis Child. 1992;67:366–73.

Skinner J, Alverson D, Hunter S, editors. Echocardiography for the neonatologist. London: Churchill Livingstone; 2000.

TnEcho Targeted Neonatal Echocardiography. www.tnecho.com

Bronchoscopy

26

Neil N. Finer

I. While neonatal bronchoscopy remains an important and on occasion a life-saving tool in dealing with neonatal airway emergencies, over the past decade there has been little opportunity to teach this technique to neonatologists in training. While a few still practicing individuals have the requisite skill sets, even they are called upon less and less, and thus it seems prudent in 2016 to recommend that when a neonate has an indication for an acute or less urgent upper or lower airway endoscopy, each unit identifies an available skilled individual to perform this procedure. Such individuals may be pediatric pulmonologists, pediatric anesthetists, pediatric intensivists, pediatric otolaryngologists, or experienced adult endoscopists.

II. Equipment
   A. Flexible 2.2 or 2.7 mm bronchoscope
      1. This bronchoscope will pass through a 2.5 mm ETT or 3.0 mm ETT.
      2. A 2.2 mm scope does not have a suction channel.
   B. Appropriate light source (preferably xenon)
   C. Optional equipment includes video camera and recorder as well as a microphone (allows determination of phase of respiration).
   D. Consider use of videolaryngoscope to evaluate upper airway
      1. Useful for infants >1 kg
      2. Provides large clear image
      3. Easier to use for inexperienced operators

III. Patient Preparation
   A. Suction airway thoroughly.
   B. For intubated infants, utilize a bronchoscopic adapter on the ETT connector to maintain FiO_2, airway pressure, and support during procedure.
   C. Medications
      1. Atropine (0.01 mg/kg) can be used to decrease secretions and block vagal-mediated bradycardia.
      2. Morphine (0.05–0.1 mg/kg) or meperidine (0.5–1.5 mg/kg) may be given for analgesia at least 10–15 min prior to procedure.

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3. For non-intubated patients, apply topical xylocaine to one naris.
4. Inject xylocaine (4–7 mg/kg) at the tip of ETT, using a feeding catheter, 3 min prior to procedure. Suction again just prior to procedure.

D. Follow principles of conscious sedation; monitor continuously.
1. Pulse oximetry
2. Blood pressure, if available
3. Heart rate
4. Respiratory rate
5. Use $ETCO_2$ monitor or $TcPCO_2$ monitor if available

IV. Indications: Emergent (can be done in under 2 min by experienced operator)
A. Acute/subacute suspected airway obstruction or misplacement
1. Mucus
2. Blood
3. Dislodged ETT, tube in main bronchus, usually right sided, or esophageal. First check with $ETCO_2$ device!
4. Check ETT position after intubation if infant unstable.

B. Evaluation of airway obstruction in recently extubated baby
C. To perform fiber-optic nasotracheal intubation in conditions with associated airway anomalies
1. Pierre-Robin
2. Goldenhar, Treacher Collins syndromes
3. Other conditions where larynx cannot be visualized with laryngoscope

D. Procedure for fiber-optic intubation
1. Pre-medicate—use only topical xylocaine and smallest dose of narcotic for fiber-optic intubation; try initially awake following atropine.
2. Provide oxygen using a single nasal cannula, or use laryngeal mask.
3. Monitor as above.
4. Have equipment available to secure airway—oral airway, nasopharyngeal tube or endotracheal tube, and/or nasal trumpet to be used to maintain airway patency, and selection of appropriate masks.
5. Slide proper-size nasotracheal tube with proximal connector removed over bronchoscope and lodge at proximal end of scope.
6. Visualize larynx via nares.
7. Pass bronchoscope through vocal cords to carina during inspiration.
8. Have an assistant hold bronchoscope as straight as possible without pulling back.
9. Slide ETT over scope until in trachea, check position as bronchoscope is withdrawn, remove bronchoscope, and tape tube in place.
10. After taping, recheck ETT position to be approximately 1 cm above carina in 3 kg infant.

V. Indications: Intubated patient
A. Confirm ETT placement, rule out plug, tracheal narrowing, tracheomalacia
B. Persistent or recurrent atelectasis or wheezing in an intubated patient
C. Evaluation of known or suspected tracheoesophageal fistula pre-operatively
D. Assist placement of ETT for unilateral lung ventilation, or placement of Fogarty catheter for unilateral ventilation for pulmonary interstitial emphysema or to temporarily occlude tracheal fistula

VI. Indications: Non-intubated Patient
A. Evaluation of stridor, noisy breathing
B. Evaluation for evidence of reflux—inflammation around upper airway

Table 26.1 Common neonatal diagnoses amenable to bronchoscopy

Upper airway lesions	Lower airway lesions
Unilateral and bilateral choanal atresia	Tracheomalacia
Laryngomalacia	
Laryngeal dyskinesia	
Subglottic narrowing, secondary to edema, web, stenosis	Bronchomalacia
Vocal cord paralysis, unilateral or bilateral	Tracheal or bronchial granulations, mucus plugs, blood clots (especially in ECMO patients)
Laryngeal hemangioma, cystic hygroma	Obstructed, malpositioned, or dislodged ETT or tracheotomy tube
Laryngeal edema and/or inflammation	
Gastroesophageal reflux	Tracheoesophageal fistula
Laryngotracheoesophageal cleft	Tracheal stenosis or web abnormal tracheal anatomy, tracheal bronchus tracheal tear

VII. Practical Clinical Hints
   A. Take time out to properly identify patient and ensure that consent form is signed.
   B. Examine patient and review procedure with staff. It is essential in patients with a concern for a dysmorphic airway that one evaluates whether there is a cleft palate—best done by digitally palpating the palate.
   C. Always pre-oxygenate patient and provide continuous oxygen during procedure, using a single nasal cannula.
   D. Use either oximeter audible tone or heart rate monitor audible tone to be aware of patient status during procedure.
   E. Video-camera recording can decrease procedure time. In addition it can share findings with parents and consultants avoiding the need for re-examination.
   F. Consult with pediatric otolaryngologist when findings in doubt, and always for suspect vocal cord lesions or other laryngeal abnormalities.

VIII. Common Neonatal Diagnoses Amenable to Bronchoscopy (Table 26.1)

IX. Alternatives to Bronchoscopy
   A. CT scan—can diagnose tracheomalacia, bronchomalacia, tracheal tear—requires moving patient
   B. Videolaryngoscopy: Most useful as teaching tool
      1. Can use to show inexperienced operators larynx during intubation attempts and guide them during attempt—optimal with premedication
      2. Not as functional for infants <800 g
      3. Not recommended as an option to examine upper airway without adequate premedication—best done in operating theater

Suggested Reading

Berkowitz RG. Neonatal upper airway assessment by awake flexible laryngoscopy. Ann Otol Rhinol Laryngol. 1998;107:75–80.

Bloch ED, Filston HC. A thin fiberoptic bronchoscope as an aid to occlusion of the fistula in infants with tracheoesophageal fistula. Anesth Analg. 1988;67:791–3.

Ellis DS, Potluri PK, O'Flaherty JE, Baum VC. Difficult airway management in the neonate: a simple method of intubating through a laryngeal mask airway. Paediatr Anaesth. 1999;9:460–2.

Etches PC, Finer NN. Use of an ultrathin fiberoptic catheter for neonatal endotracheal tube problem diagnosis. Crit Care Med. 1989;17:202.
Finer NN, Etches PC. Fibreoptic bronchoscopy in the neonate. Pediatr Pulmonol. 1989;7:116–20.
Finer NN, Muzyka D. Flexible endoscopic intubation of the neonate. Pediatr Pulmonol. 1992;12:48–51.
Hawkins CM, Towbin AJ. Rupture of the left mainstem bronchus following endotracheal intubation in a neonate. Pediatr Radiol. 2011;41(5):668–70.
Hinton AE, O'Connell JM, van Besouw JP, Wyatt MEJ. Neonatal and paediatric fibre-optic laryngoscopy and bronchoscopy using the laryngeal mask airway. Laryngol Otol. 1997;111(4):349–53.
Lee YS, Soong WJ, Jeng MJ, et al. Endotracheal tube position in pediatrics and neonates: comparison between flexible fiberoptic bronchoscopy and chest radiograph. Zhonghua Yi Xue Za Zhi. 2002;65:341–4.
O'Shea JE, Thio M, Kamlin CO, McGrory L, Wong C, John J, Roberts C, Kuschel C, Davis PG. Videolaryngoscopy to teach neonatal intubation: a randomized trial. Pediatrics. 2015;136(5):912–9.
Reeves ST, Burt N, Smith CD. Is it time to reevaluate the airway management of tracheoesophageal fistula? Anesth Analg. 1995;81:866–9.
Rotschild A, Chitayat D, Puterman ML, et al. Optimal positioning of endotracheal tubes for ventilation of preterm infants. Am J Dis Child. 1991;145:1007–17.
Shinwell ES, Higgins RD, Auten RL, Shapiro DL. Fiberoptic bronchoscopy in the treatment of intubated neonates. Am J Dis Child. 1989;143:1064–5.
Vanderhal AL, Berci G, Simmons Jr CF, Hagiike MA. Videolaryngoscopy technique for the intubation of the newborn: preliminary report. Pediatrics. 2009;124(2):e339–46.
Vauthy PA, Reddy R. Acute upper airway obstruction in infants and children. Evaluation by the fiberoptic bronchoscope. Ann Otol Rhinol Laryngol. 1980;89:417–8.
Vijayasekaran D, Kalpana S, Ramachandran P, Nedunchelian K. Indications and outcome of flexible bronchoscopy in neonates. Indian J Pediatr. 2012;79(9):1181–4.

Section V

Noninvasive Ventilatory Techniques

Nasal Interfaces for Noninvasive Ventilation

27

Sherry Courtney

I. Overview
Since the last edition of this manual, the American Association for Respiratory Care has updated and revised its Clinical Practice Guideline on application of nasal continuous positive airway pressure (NCPAP). The reference is listed below.

II. Devices such as *head boxes and negative pressure boxes* are rarely used clinically and will not be discussed.

III. *Face mask NCPAP* is commonly given for brief periods in the delivery room or during resuscitation.
   A. The mask can be attached to a flow-inflating bag or T-piece resuscitator.
   B. No flow or NCPAP will be given if the mask is attached to a self-inflating bag.
   C. Face masks should not be used for prolonged NCPAP administration.

IV. *Endotracheal tubes* are sometimes used for noninvasive ventilation by shortening the tube and placing the tip in the hypopharynx. Evidence suggests that this is not as effective for NCPAP delivery as are nasal prongs.

V. *Nasal masks* can be used with some NCPAP devices, most often the variable-flow devices such as Infant Flow© or SiPAP©. Nasal masks are sometimes alternated with nasal prongs to decrease the chances of pressure sores of the columella, nose, and upper lip.

VI. *Nasal prongs* are the most common and most effective way of providing NCPAP.
   A. Babies are obligate nose breathers, so nasal prongs provide reliable NCPAP. However, if the mouth is open a large leak will occur and very little, if any, NCPAP will be given. A pacifier or chin strap can help reduce the leak.
   B. NCPAP prongs should be wide enough to fill the nares without blanching the surrounding tissue, in order to minimize leak as well as nasal injury.
   C. Long, thin nasal prongs have high resistance and can easily be blocked by secretions.
   D. It is essential to use a skin barrier, combined with excellent nursing care, to prevent nasal injury during the use of NCPAP. Some of these injuries are permanent, and can require plastic surgery. Commercial products such as Cannulaide© are available, or nurseries can fashion their own protective barriers.

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E. Some nasal prongs are specific to the NCPAP device.
   1. This is especially true for the Infant Flow©, SiPAP©, and Arabella© devices.
   2. The prongs are shaped in a fashion that entrains gas, thereby stabilizing the mean airway pressure, and the curvature of the prongs also decreases the work of breathing.
   3. No large randomized trials have demonstrated the superiority of one form of prong, or one form of NCPAP, over another.

F. For ventilator-generated NCPAP or free-standing devices such as bubble NCPAP, many different prongs can be used. Most commonly employed are Hudson© prongs, Inca© prongs, or the RAM© cannula.
   1. The RAM© cannula cannot be used with bubble NCPAP as it does not have an expiratory limb.
   2. Expiration occurs through the leaks at the nose and mouth.

G. In contrast to prongs used for NCPAP, prongs used for high-flow nasal cannula (HFNC) therapy must be small enough to provide a large leak at the nares.
   1. The mechanism of action of HFNC therapy is distinctly different from that of NCPAP and involves dead space washout with enhanced minute ventilation as opposed to a continuous, constant positive airway pressure.
   2. No leak or a small leak can potentially lead to high, uncontrolled, and unmeasured positive pressure.

Suggested Reading

AARC Clinical Practice Guideline. Application of continuous positive airway pressure to neonates via nasal prongs, nasopharyngeal tube, or nasal mask—2004 revision and update. Respir Care. 2004;49:1100–8.

Courtney SE, Pyon KH, Saslow JG, Arnold GK, Habib RH. Lung volume and breathing pattern changes during nasal continuous positive airway pressure in premature infants: a comparative study of three devices. Pediatrics. 2001;107:304–8.

De Paoli AG, Davis PG, Faber B, Morley CJ. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. Cochrane Database Syst Rev. 2002;4, CD002977.

Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med. 2009;103:1400–5.

Hogeling M, Fardin SR, Frieden IJ, Wargon O. Forehead pressure necrosis in neonates following continuous positive airway pressure. Pediatr Dermatol. 2012;29:45–8.

Li Y, Sepulveda A, Buchman EP. Late presenting nasal deformities after nasal continuous positive airway pressure injury: 33-year experience. J Plast Reconstr Aesthet Surg. 2015;68:339–43.

Newman KM, McGrath JM, Estes T, Jallo N, Salyer H, Bass WT. An integrative review of skin breakdown in the preterm infant associated with nasal continuous positive airway pressure. J Obstet Gynecol Neonatal Nurs. 2013;42:508–16.

Pandit PB, Courtney SE, Pyon KH, Habib RH. Work of breathing during constant- and demand-flow nasal continuous positive airway pressure in preterm neonates. Pediatrics. 2001;108:682–5.

Humidified High-Flow Nasal Cannula Therapy

28

Andrea Lampland and Mark C. Mammel

I. Humidified high-flow nasal cannula (HFNC) is a means to deliver non-invasive, positive pressure respiratory support
   A. Continuous positive airway pressure (CPAP) provides non-invasive positive pressure respiratory support in spontaneously breathing infants with a goal of preventing alveolar collapse and allowing sufficient gas exchange.
      1. Avoidance of intubation and use of nasal CPAP is an effective strategy for treating RDS.
      2. Early use of nasal CPAP has been associated with a decreased incidence of BPD in premature infants.
   B. Multiple devices are available through which CPAP can be delivered.
   C. Nasal cannulas are a common means of providing supplemental oxygen to neonates. However, recent investigations have shown the potential for delivering positive distending pressure via nasal cannulas with utilization of higher gas flow rates and larger diameter cannulas.
      1. Pressure = flow × resistance.
      2. The term "high-flow" nasal cannula relates to the use of >1 L/min of gas flow, most commonly 2–8 L/min in the neonatal population. Commercially available humidified HFNC systems are available and appear to deliver heated, humidified air as well as positive distending pressure (Chap. 33). HFNC systems are FDA approved to provide heated and humidified oxygen but not FDA approved to provide positive distending pressure to the airways. Typically these pre-packaged systems have an internal pressure-limiting mechanism as a safety measure to prevent excessive pressure delivery to the patient; however, the exact pressure limits vary and are different among systems.
      3. Closure of the infant's mouth allows more optimal delivery of positive distending pressure, but leak around the nares is still present.

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D. Proposed mechanisms of action of heated, humidified HFNC
   1. Flushing of dead space in the nasopharyngeal cavity leading to improved alveolar ventilation and carbon dioxide removal
   2. Adequate gas flow reduces inspiratory resistance in the nasopharynx and reduces work of breathing.
   3. Heated and humidified air improves pulmonary mechanics and prevents airway water loss and cooling.
   4. Delivery of positive distending pressure

II. Potential risks and benefits of heated, humidified HFNC
   A. Benefits
      1. Avoidance of nasal septal trauma, a drawback of the occlusive interface used with conventional nasal CPAP, by using a small nasal cannula interface that does not occlude the nares (Chap. 27)
      2. Avoidance of nasal mucosal irritation, decreased thickening of secretions, and decreased energy demand by providing heated and humidified air.
      3. Studies suggest no significant changes in lung mechanics or work of breathing compared to nasal CPAP.
      4. Easy to administer and well tolerated by patients
      5. Allows the care provider and patient families easier access to and interaction with the baby with minimal impediments related to the device
      6. Lower cost than nasal CPAP
   B. Limitations and risks
      1. Inability to consistently predict actual level of positive distending pressure delivered to the patient
         a. No direct measurement of pressure delivered by the HFNC circuit
         b. Improved delivery of continuous positive distending pressure if infant has mouth closed to minimize leak
         c. Significant intra-patient and inter-patient variability of amount of positive distending pressure delivered at same gas flow rates because of variable leaks around the nares and mouth, differences in patient physiology and anatomy, and differences in nasal cannula internal diameter
         d. Necessitates the calculation of effective F_iO_2 delivery to accurately predict oxygen delivery to the patient.
         e. Nasal cannula oxygen is a blend of the supplemental oxygen delivered by the nasal cannula and of room air inhaled through the mouth and nose.
      2. HFNC devices direct gas flow directly to the patient
         a. Nasal cannula requires proper fitting to have nasal cannula prongs occupy approximately 50 % of the naris diameter.
         b. Variable levels of positive distending pressure delivered with concern for lung overdistention, gastric distention, and air leak syndromes. Subcutaneous scalp emphysema, pneumo-orbitis, pneumocephalus, and pneumothorax have been reported with the use of humidified high-flow nasal cannulas.
         c. Commercially available HFNC systems typically have pressure-limiting controls; however, each system has a different pressure level limit. Some systems do not specifically quantify the upper pressure limit—the pressure above which the pressure-limiting valve will open and deflect direct pressure from the gas flow away from the patient.
         d. Hand-made high-flow systems (those not commercially produced) do not have pressure-limiting controls and, therefore, the only pressure-limiting "valves" are at the patient, most commonly at the nose and mouth.

3. Historical data with concern for increased rates of infection, in particular, Gram-negative bacteremia
4. Limited database with predominance of observational and retrospective studies
   a. Very few large randomized controlled trials (RCTs) with adequate power to assess safety and efficacy
   b. Few studies have directly compared nasal CPAP (standard of care) and varying levels of HFNC within the same population
   c. Difficult to compare and generalize current data to all neonatal populations secondary to variables related to the type of HFNC that was used, the presence or absence of a pressure-limiting valve within the HFNC system, and the diameter of the nasal cannula
   d. No studies to date with adequate power to assess long-term major clinical morbidities and neurodevelopmental outcomes

III. Potential clinical applications
   A. Humidified HFNC to provide positive distending pressure after extubation
      1. Currently insufficient evidence to conclude that HFNC is equivalent or superior to conventional nasal CPAP for preventing extubation failure. Data vary with regard to study design, use of different devices and equipment, and unknown severity of patient respiratory status.
      2. Randomized controlled trials
         a. Collins et al. (2013) compared rates of extubation failure within 7 days in 132 preterm infants <32 weeks' gestational age extubated to either nasal CPAP of 7–8 cm H_2O or Vapotherm® heated, humidified HFNC at 8 L/min.
            (1) Pre-defined extubation failure criteria of apnea (>20 s) with more than six episodes in 6 h or one requiring intermittent positive pressure ventilation, acidosis (pH < 7.25, PCO_2 > 66), and >15 % sustained increase in F_iO_2 from extubation. Decision to reintubate based on failure criteria left to discretion of treating physician.
            (2) No differences between groups in extubation failure criteria or reintubations within 7 days of extubation
            (3) Less nasal trauma in HFNC group compared to nasal CPAP group
         b. In their non-inferiority study, Manley et al. (2013) compared rates of extubation failure in 303 preterm infants born at <32 weeks' gestation who were randomized to either Fisher and Paykel® heated, humidified HFNC at 5–6 L/min or nasal CPAP at 7 cm H_2O.
            (1) Infants who failed HFNC could be transferred to "rescue" nasal CPAP. Nearly half of the infants who received "rescue" nasal CPAP did not require intubation.
            (2) HFNC was found to be non-inferior to nasal CPAP for preventing extubation failure. There was no difference in rates of reintubation between treatment groups.
            (3) Less nasal trauma in HFNC group compared to nasal CPAP group
         c. Yoder et al. (2013) compared early (<72 h) extubation failure in 432 infants of 28–42 weeks' gestation extubated to heated, humidified HFNC (3–5 L/min) versus nasal CPAP 5–6 cm H_2O.
            (1) A variety of CPAP and HFNC devices were used. Crossover between modes was not permitted.
            (2) No differences in early extubation failure between groups
            (3) Infants remained on HFNC longer than CPAP, but no significant differences in days on supplemental oxygen
         d. Campbell et al. (2006) compared rates of re-intubation in preterm infants with birth weight ≤1250 g who were extubated to nasal CPAP versus heated, humidified HFNC.

(1) Extubation failure rates within 7 days were 60 % with HFNC and 15 % with nasal CPAP.
(2) Increased oxygen use and more apnea and bradycardia in the babies extubated to HFNC

e. Woodhead et al. (2006) compared rates of extubation failure in infants exposed to HFNC versus Vapotherm 2000i® heated, humidified HFNC in the first 24 h after extubation. Extubation failure rates were 47 % in the HFNC group versus 0 % in the Vapotherm group.
f. Miller and Dowd (2010) compared rates of extubation failure in infants 26–29 weeks of age extubated to either Fisher and Paykel® or Vapotherm HFNC. There were no differences in extubation failure rates.

3. Retrospective studies
a. Shoemaker et al. (2007) compared a retrospective cohort of infants <30 weeks' gestation who received nasal CPAP or humidified HFNC within 96 h of birth. Extubation failure was higher in the nasal CPAP group.
b. Holleman-Duray et al. (2007) compared a retrospective cohort of infants 25–29 weeks' gestation before and after the introduction of an early extubation protocol to Vapotherm; there were no differences in extubation failure rates or oxygen use.

B. Humidified HFNC to prevent apnea of prematurity and increased work of breathing
1. Sreenan et al. (2011) compared stable premature infants in a crossover study of nasal CPAP and humidified HFNC.
a. There were no significant differences between the modes with respect to apnea, bradycardia, and desaturation events.
b. Infant oxygen requirements were no different between the two modes.
2. Saslow et al. (2006) evaluated the effects of nasal CPAP and Vapotherm HFNC on respiratory parameters and work of breathing indices in a crossover study of stable preterm infants requiring nasal CPAP or HFNC and weighing <2.0 kg at birth. There were no significant differences in work of breathing between the two groups.

C. HFNC as a weaning mode from nasal CPAP
1. Very little data evaluating utility of HFNC as a weaning mode from CPAP. Single-site studies with different HFNC systems and weaning methods make it difficult to extrapolate findings.
2. Abdel-Hady et al. (2011) evaluated two approaches to weaning 60 preterm infants >28 weeks' gestation from CPAP. All infants were stable on CPAP at $F_iO_2 \leq 30$ % at entry. At randomization, the first group was maintained on CPAP until in F_iO_2 21 % for 24 h and then weaned directly to room air. The second group weaned from initial CPAP to HFNC 2 L/min and maintained on HFNC until in F_iO_2 21 % for 24 h and then weaned off support to room air.
a. Infants in the CPAP-only group had shorter duration of exposure to oxygen and shorter duration of respiratory support.
b. The HFNC system used is unique to this site and not commercially available in the USA.
3. Fernandez-Alvarez et al. (2014) conducted a retrospective pair-matched cohort analysis of two approaches to weaning preterm infants ≤28 weeks' gestation and <1250 g from CPAP. All infants were stable on CPAP at $F_iO_2 < 40$ % at the time of transition off CPAP. The first cohort of 39 patients was managed on Vapotherm HFNC 8 L/min and weaned to 2 L/min before transitioning to a low-flow nasal cannula (LFNC). The second cohort of 40

patients was weaned from CPAP to a low-flow nasal cannula <0.3 L/min. All infants were taken off nasal cannula support once they had been in room air for over 24 h.

a. Total number of days on CPAP was significantly less in the group weaned from CPAP to HFNC versus CPAP to LFNC.
b. No difference in total days on respiratory support between the two groups
c. Nasal trauma only seen in babies while on CPAP

Suggested Reading

Abdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants in associated with prolonged oxygen requirement: a randomized controlled trial. Early Hum Dev. 2011;87:205–8.

Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for preterm infants. J Perinatol. 2006;26:546–9.

Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr. 2013;162:949–54.

Dani C, Pratesi S, Migliori C, Bertini G. High flow nasal cannula therapy as respiratory support in the preterm infant. Pediatr Pulmonol. 2009;44:629–34.

Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med. 2009;103:1400–5.

Fernandez-Alvarez JR, Gandhi RS, Amess P, Mahoney L, Watkins R, Rabe H. Heated humidified high-flow nasal cannula versus low-flow nasal cannula as weaning mode from nasal CPAP in infants ≤28 weeks of gestation. Eur J Pediatr. 2014;173:93–8.

Frizzola M, Miller TL, Rodriguez ME, Zhu Y, Rojas J, Hesek A, Stump A, Shaffer TH, Dysart K. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. Pediatr Pulmonol. 2011;46:67–74.

Haq I, Gopalakaje S, Fenton A, McKean M, O'Brien C, Brodlie M. The evidence for high flow nasal cannula devices in infants. Paediatr Respir Rev. 2014;15:124–34.

Holleman-Duray D, Kaupie D, Weiss MG. Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. J Perinatol. 2007;27:776–81.

Jasin LR, Kern S, Thompson S, Walter C, Rone JM, Yohannan MD. Subcutaneous scalp emphysema, pneumo-orbitis, and pneumocephalus in a neonate on high humidity high flow nasal cannula. J Perinatol. 2008;28:779–81.

Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? Pediatrics. 2008;121:82–8.

Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. J Pediatr. 2009;154:177–82.

Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, Donath SM, Davis PG. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013;369:1425–33.

Miller SM, Dowd SA. High-flow nasal cannula and extubation success in the premature infants: a comparison of two modalities. J Perinatol. 2010;30:805–8.

Saslow JG, Aghai ZH, Nakhla TA, Hart JJ, Lawrysh R, Stahl GE, Pyon KH. Work of breathing using high-flow nasal cannula in preterm infants. J Perinatol. 2006;26:476–80.

Shetty S, Greenough A. Review finds insufficient evidence to support the routine use of heated and humidified high-flow nasal cannula use in neonates. Acta Paediatr. 2014;103:898–903.

Shoemaker MT, Pierce MR, Yoder BA, DiGeronimo RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. J Perinatol. 2007;27:85–91.

Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. Pediatrics. 2011;107:1081–3.

Wilkinson D, Andersen C, O'Donnell CPF, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2011;(5):CD006405.

Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal intubation: a prospective, randomized, masked cross-over trial. J Perinatol. 2006;26:481–5.

Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics. 2013;131:e1482–90.

Continuous Distending Pressure

29

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I. Definitions
   A. Continuous distending pressure (CDP) is a pressure applied to the airways throughout the respiratory cycle. This chapter focuses on the use of CDP through continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP). Applying CDP through a continuous negative pressure box encircling the thorax to generate a negative intrathoracic pressure is now uncommon and will not be further discussed.
   B. High-flow nasal cannula (HFNC) use is increasingly common in premature infants. HFNC provides a CDP, with higher flows generating higher pressures. Thus, many of the concepts within this chapter are also seen with HFNC therapy. This chapter does not specifically discuss HFNC.
   C. Continuous positive airway pressure (CPAP) is a positive pressure applied to the airways of spontaneously breathing infants. We use the term to describe non-invasive CDP.
   D. Positive end-expiratory pressure (PEEP) is a pressure applied to the airways through an endotracheal tube (ETT) during invasive positive pressure mechanical ventilation.

II. The Pathophysiology Treated by Continuous Distending Pressure
   A. Overview
      1. The primary function of the lungs is gas exchange. An inability to establish and maintain lung volume decreases gas exchange and may result in respiratory failure.
      2. A low lung volume and atelectasis result in inadequate oxygenation through a reduction in the area available for alveolar ventilation and gas diffusion as well as increased ventilation/perfusion mismatch and intrapulmonary shunt. While carbon dioxide diffuses more readily, it can also be compromised by low lung volumes and atelectasis.

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B. Mechanisms Contributing to Disease

1. The alveolar epithelium secretes fluid into the fetal lungs. In a healthy term infant, labor-induced adrenergic hormones and fetal postural changes initiate the process of fluid absorption. This fluid absorption is predominantly driven by the transepithelial pressure gradient produced with the infant's first breaths, which generate negative pressures of up to 80 cm H_2O. Aeration of the lungs moves the fluid out of the airspaces and into the surrounding interstitium, where over time it is removed by lymphatics and blood vessels. Several mechanisms contribute to a slower clearance of fetal lung fluid after premature birth, most notably the infant's inability to generate large negative pressures during initial breaths. The premature lung may even continue to secrete fluid into the alveoli after birth. Elevated left atrial pressure and low plasma protein concentrations further slow the rate at which lung fluid is removed.
2. Functional residual capacity (FRC) is the volume of gas remaining in the lungs at the end of a normal expiration. It is established at the point of counterbalance between outward chest wall recoil and inward lung recoil. A newborn infant's chest wall has low elasticity and high compliance. As a result, the newborn lung has a low FRC close to airway closing volume and is prone to volume loss.
3. The chest wall of the premature infant is so soft and flexible that it distorts with the negative pressure generated by diaphragmatic contractions and is unable to hold the lungs open during excessive inspiratory efforts. The unstable chest wall results in "paradoxical" out-of-phase movements between the ribcage and abdomen, increasing work of breathing.
4. The horizontal ribs and round shape of the premature infant's chest wall reduce the potential for lung expansion. The diaphragm's flat shape and positional attachment to the rib cage contribute to inefficient mechanics. The premature diaphragm has fewer endurance fibers and its contractility may be impaired by reduced oxygen availability.
5. The upper airway in the term infant is supported by a fat-laden superficial fascia and is actively held open by pharyngeal muscles. The pharynx of a premature infant is less stable and prone to narrowing or collapsing with relatively small negative airway pressure changes or during periodic breathing.
6. The term infant maintains a small amount of positive end-expiratory pressure in the airways after birth by slight adduction of the larynx during expiration. The newborn with lung disease has two mechanisms to maintain FRC. The first is to breathe fast and shorten the expiratory time to prevent the lung from emptying. The second is to "grunt" during expiration. During these breaths the baby quickly inspires, and then closes the larynx to maintain any lung volume that has been achieved. Simultaneously, it contracts the abdominal muscles to increase intrathoracic pressure. It then opens the larynx slightly and rapidly exhales through a narrowed larynx to maintain pressure in the airways. This "work-intense" strategy becomes ineffective if the infant tires, and cannot maintain adequate laryngeal tone, or if the larynx is bypassed by an endotracheal tube.
7. The premature infant lacks the supportive internal lung architecture and collateral ventilation channels that help stabilize and maintain open air spaces.
8. Surfactant has two important functions in healthy newborn lungs. First, it lowers surface tension and facilitates lung aeration at birth. Second, during expiration it becomes compressed on the alveolar surface, thereby increasing the surface pressure and helping maintain the alveolus open. Both surfactant quantity and quality are decreased in premature infants. The resulting alveolar collapse results in further loss of surfactant from the alveolar surface by "squeeze out" as the surface area falls.

9. The epithelium of repeatedly collapsing lungs is easily damaged and plasma proteins exude onto the surface. This further inhibits surfactant function. These proteins form the hyaline membranes seen in the classic pathology of RDS.
10. The immature lung has thicker and fewer alveolar septa, further limiting diffusion and the surface area available for gas exchange.
11. Premature infants often have a patent ductus arteriosus. As the pulmonary artery pressure falls after birth, the ductus arteriosus shunts excess blood from the aorta to the pulmonary arteries and lungs. This may increase fluid in the lungs, predisposing to pulmonary edema, which in turn may impair gas exchange, surfactant function, and decrease compliance.

C. How Continuous Distending Pressure Helps
1. The primary benefit of CDP in infants with low lung volumes is to increase mean airway pressure, distending and supporting the airways to establish and maintain lung volumes and FRC. This increases the lung surface area available for alveolar ventilation and diffusion and reduces ventilation/perfusion mismatch, improving oxygenation and carbon dioxide elimination.
2. CPAP reduces upper airway occlusion, increasing the pharyngeal cross-sectional area and reducing upper airway resistance via mechanically splinting. In infants receiving PEEP, the endotracheal tube bypasses the upper airway.
3. CDP decreases the range of "opening" pressure gradients between different areas of the lung and reduces heterogeneity in delivered tidal ventilations within the lung.
4. CDP helps stabilize the compliant chest wall and decreases chest wall retractions and paradoxical breathing.
5. CDP alters the shape of the diaphragm and increases diaphragmatic activity.
6. CDP can improve lung mechanics and decrease work of breathing by reducing airway resistance and improving compliance. The distending pressure enables a greater tidal volume for a given driving pressure, whether a negative pressure generated by a spontaneously breathing infant on CPAP or an inflation with PEEP in a mechanically ventilated infant.
7. CDP increases the radius of curvature of the alveoli, thus decreasing the amount of pressure necessary to overcome surface tension, in accordance with LaPlace's law.
8. CDP conserves surfactant on the alveolar surface and prevents atelectasis; stabilization of alveoli reduces atelectasis-mediated inflammation.
9. CDP limits pulmonary edema by raising the transepithelial pressure. This applies to edema from residual lung fluid, transudates from ductus-mediated pulmonary blood flow, or inflammation-associated edema. This further protects surfactant function.

III. Potential Harms

A. Excessive CDP applied to a compliant lung may cause pulmonary over-distension and contribute to air leak syndromes, such as pneumothoraces and pulmonary interstitial emphysema.

B. Over-distention with excessive CDP can impair lung mechanics and decrease lung compliance. This can result in smaller tidal volumes for a given change in pressure and contribute to carbon dioxide retention.

C. Over-distension may increase intrathoracic pressures. This could diminish venous blood return and decrease cardiac output. The transmission of pressure to the thorax is proportional to the compliance of the lungs. Thus, the impact of CDP on intrathoracic pressures is less in those infants with the least compliant lungs.

D. Over-distension may increase pulmonary vascular resistance. Along with a decrease in cardiac output, this may increase *V*/*Q* mismatch. An elevated pulmonary vascular resistance may promote shunting of deoxygenated blood from the pulmonary artery to the aorta. Both *V*/*Q* mismatch and right-to-left shunt decrease systemic oxygenation.
E. Dislodgement of the nasal cannula, mask, or ETT can result in partial or complete loss of delivered airway pressure.
F. Direct pressure from a CPAP nasal mask or cannula can damage the columella, nasal septum, or nasal bridge. Similarly, fixation components can damage skin on the face and scalp. This can be minimized with careful application and vigilance of the CPAP interface.
G. CPAP can contribute to gastric distension or "CPAP belly." This is rarely of clinical importance and can be minimized with the placement of an orogastric tube for venting and intermittent aspiration.
H. Laryngeal breaking during expiration plays an important role in lung recruitment immediately after birth. Intubation with an ETT prevents this adaptive mechanism and may be harmful if the PEEP level is insufficient.

CPAP

Sections IV to VII apply specifically to the use of non-invasive CPAP in spontaneously breathing infants.

IV. Indications
A. Very premature infants should be started on prophylactic CPAP as soon as possible after birth to help establish lung volume, and formation of FRC, and improve gas exchange. Assessment for and implementation of initial resuscitative steps should be performed per existing guidelines. Early application of CPAP need not interfere with other aspects of resuscitation.
B. Very premature infants can be successfully started on nasal CPAP from birth and do not necessarily need to be intubated, ventilated, and treated with surfactant. Recent meta-analyses of randomized trials conclude that strategies favoring the use of non-invasive CPAP over invasive ventilation approximately halve the rate of intubation and surfactant use and result in a small but statistically significant reduction in death or bronchopulmonary dysplasia (BPD).
C. Although the success of CPAP without the need for invasive ventilation decreases with decreasing gestation, there is no gestational age cutoff at which CPAP should not be preferentially attempted immediately after birth.
D. Several studies have shown that very premature infants have improved gas exchange and are less likely to need re-intubation if treated with a nasal CPAP immediately post-extubation. Inadequate laryngeal function following extubation may explain some of this benefit.
E. Use of CPAP in late preterm or term infants should be based on observation of clinical signs and symptoms suggestive of respiratory distress. This may include tachypnea, retractions, grunting, supplemental oxygen need, low lung volumes on radiography, and frequent or severe episodes of apnea and/or bradycardia.
F. Infants with tracheomalacia or abnormalities of the upper airways predisposing to narrowing or collapse may benefit from CPAP treatment.
V. How to Administer
A. The following devices are used to deliver CPAP to newborns: face mask, short binasal prongs, single nasal prong, long nasopharyngeal prongs, and nasal mask. A head box with a neck seal is of historical interest, but is no longer used.

1. Face mask. It has the benefit of not losing pressure through the mouth. It is most commonly used for giving CPAP immediately after birth. Difficulty maintaining an adequate seal and need to remove the mask to access the nose or mouth limit its long-term use.
2. Short-binasal prongs. This commonly used device is inserted into the nostrils and attached to a pressure source for delivering CPAP.
3. A single nasal prong. The principal drawback is higher resistance compared to binasal prongs. A single prong can be short, inserted into the nostril about 1.5 cm, or inserted deep into the pharynx. An ETT cut down to about 5 cm can be used. We do not recommend this (see item C below).
4. Long nasopharyngeal prongs: Compared to short prongs, resistance is higher and the risk of obstruction with secretions is higher. We do not recommend this.
5. Nasal mask: This device surrounds the infant's nose. The pressure required to achieve a good seal can cause damage to the nasal bridge and columella.

B. More than one device (for example, short binasal prongs and nasal mask) can be alternated to reduce skin breakdown associated with sustained pressure to specific areas.
C. A systematic review of trials comparing devices concluded that binasal prongs are more effective than a short or long single prong in preventing re-intubation in premature infants.
D. A recent trial found that nasal mask is more effective than short binasal prongs in preventing primary intubation or re-intubation within 72 h of randomization; the difference attenuated over time.

VI. How to Determine CPAP Level
A. The CPAP level should be individualized to each infant's underlying pathophysiology and distending pressure need. Using one pressure for all infants is common but not appropriate.
B. An ideal CPAP level maximizes the benefits of achieving and maintaining appropriate lung volumes while minimizing potential harms associated with over-distension (sections II and III).
C. The same infant may require different CPAP levels as he or she progresses through their postnatal course.
D. Immediately after birth, CPAP levels between 4 and 8 cm H_2O are commonly used. Infants with poorly compliant lungs may benefit from levels in excess of these values.
E. There is limited evidence supporting specific CPAP levels or individualized approaches for selecting a CPAP level. Trials demonstrate that pressures between 4 and 8 cm H_2O do not typically affect hemodynamic performance in stable premature infants with lung disease.
F. Signs that an infant may require more distending pressure include poor oxygenation, low lung volumes or atelectasis on chest radiography and retractions, tachypnea, or grunting on physical exam.
G. Signs that an infant may require less distending pressure include over-inflated lungs, a flat diaphragm and reduced heart size on chest radiography, worsening gas exchange—in particular carbon dioxide retention, and hemodynamic changes such as tachycardia and decreased blood pressure.
H. Starting CPAP at 4–5 cm H_2O and gradually increasing pressures while monitoring for the signs described above is a reasonable empiric approach.

VII. Duration of CPAP Therapy
A. CPAP should be discontinued when its use no longer facilitates gas exchange, including prevention of apneic events, or when associated benefits no longer outweigh harms.
B. CPAP is typically reduced ("weaned") or discontinued when the infant requires little or no supplemental oxygen, and has little retraction of the chest wall and infrequent episodes of apnea, bradycardia, and desaturation.

C. Clinical research evidence to inform how long CPAP should be used, the preferred approach for determining treatment duration, and the best methods for weaning or discontinuing support is limited.
D. CPAP can be discontinued or reduced gradually. When discontinued, approaches include simple removal of CPAP to room air or transition to a different support strategy, such as nasal cannula. Gradual weaning methods include progressive pressure decrements or repeated transitions between periods on and off CPAP support, with a gradual increase in the amount of time off until CPAP support is fully discontinued—"time cycling." Several studies have shown that gradual weaning and transitions on and off CPAP do not confer advantages and increase the likelihood of CPAP wean failure and the total duration of CPAP treatment.
E. Trials of CPAP weaning strategies show that greater than 50 % of very premature infants trialed off CPAP directly to room air prior to 30 weeks' postmenstrual age require a return to distending pressure support for some period of time. However, this finding is inconsistent and the duration of CPAP therapy should be individualized to each infant.
F. Infants with greater oxygen need, increased work of breathing, or more frequent episodes of cardiorespiratory instability following a CPAP wean or discontinuation should be returned to their previous level of support and monitored closely.
G. Infants born at a lower gestational age typically require CPAP support to a later postmenstrual age.

PEEP

Sections VIII to XI apply specifically to the use of PEEP in mechanically ventilated infants.

VIII. Indications
A. Any use of mechanical ventilation
B. Placement of an ETT to establish and maintain an airway in infants with airway abnormalities
C. Failure of non-invasive support, for which definitions vary. The following ranges include commonly applied threshold parameters:
1. FiO_2 0.40–0.60 to maintain oxygen saturation targets
2. $PaCO_2 > 60$–70 mmHg (8.0–9.3 kPa) and pH < 7.20–7.25
3. Repeated episodes of apnea, bradycardia, and desaturations requiring stimulation or more than one requiring bag mask ventilation within a one hour period
4. Severe work of breathing with notable tachypnea, retractions, and asynchronous breathing
5. Cardiovascular instability, with mean blood pressure (in mmHg) below the infant's gestational age, poor perfusion on physical exam, or progressive metabolic acidosis

IX. How to Administer
A. The ventilator delivers PEEP by closing an exhalation valve on the ventilator at the pre-set pressure. This is placed on the expiratory limb of the ventilator circuit.
B. Ventilators measure PEEP in two phases; the start value of the measurement corresponds to the set PEEP on the ventilator and the end value is intrinsic PEEP.
C. Intrinsic PEEP is the actual end-expiratory pressure in the lung. Ideally, this should be the same as the set PEEP. However, there can exist an interaction between the set ventilator parameters and the time required for expiration. This depends on ventilator parameters such as the inspiratory:expiratory time ratio and respiratory rate, as well as properties of the lung, such as thoracic compliance, as well as airway and ETT resistance, the product of which is called the "time constant." When time for expiration is insufficient, gas trapping and intrinsic (or "inadvertent") PEEP can occur. Infants at risk for air trapping (i.e., meconium aspiration)

or with heterogeneous lung disease (severe bronchopulmonary dysplasia) are at risk for intrinsic PEEP. It can be appreciated by curves displayed on the ventilator monitoring when the fall in inflation pressure during expiration does not reach zero before the next inflation starts (Fig. 22.5).

X. How to Determine PEEP Level
   A. At zero end-expiratory pressure (ZEEP) in a mechanically ventilated infant, the lung is repeatedly closing and re-expanding with each inflation. This is injurious and should be avoided.
   B. The PEEP level should be individualized to each infant's underlying pathophysiology and distending pressure need. Using one pressure for all infants is common but not appropriate.
   C. An ideal PEEP level maximizes the benefits of achieving and maintaining appropriate lung volumes while minimizing potential harms associated with over-distension (sections II and III).
   D. The same infant may require different PEEP levels as he or she progresses through his or her postnatal course.
   E. Immediately after birth, PEEP levels between 4 and 6 cm H_2O are commonly used. A broader range (2–8 cm H_2O) is described in the limited and older clinical research literature. Older premature infants with evolving or established BPD may require PEEP levels above these values.
   F. There is limited randomized evidence supporting specific PEEP levels or individualized approaches for selecting PEEP levels. A Cochrane review identified a single randomized trial meeting inclusion criteria.
   G. The few prospective studies comparing PEEP levels in premature infants are limited to short-term physiologic measures such as gas exchange, hemodynamics, and pulmonary compliance. They confirm the expected pattern of better oxygenation and decreased ventilation with increasing PEEP; implications for clinical practice are equivocal.
   H. Two recent, small randomized trials using oxygenation parameters during a lung recruitment maneuver (LRM) to select an individualized PEEP showed a reduction in the duration of mechanical ventilation and oxygen support compared to routine care. These strategies will require further study.
   I. Signs that an infant may require more PEEP include poor gas exchange, in particular oxygenation; low lung volumes or atelectasis on chest radiography; and chest wall retraction or tachypnea.
   J. Signs that an infant may require less PEEP include over-inflated lungs; a flat diaphragm and a small cardiac shadow on chest radiography; worsening gas exchange, in particular increased carbon dioxide; and hemodynamic changes such as increased heart rate and decreased blood pressure.
   K. The availability of pressure-volume (*PV*) information on modern ventilators theoretically provides additional information in intubated infants. It is sometimes taught that setting the PEEP just above the lower inflexion point of the *PV* curve, just below the upper inflexion point of the *PV* curve, or maximizing dynamic compliance is a suitable approach for PEEP individualization. However, the construction of *PV* curves to accurately describe the relationship between pressure and volume requires apneic or muscle-relaxed infants. Constructing static *PV* curves is technically difficult and may pose unacceptable clinical risks (requirement of sedation/paralysis, assessment at low lung volumes) in this population. It is also uncertain how many infants with lung disease show definable inflection points. Automated ventilator *PV* curves and compliance measurements may have limited accuracy, in particular with large leaks, when using variable flow or with a spontaneously breathing infant. All are common to neonatal ventilation.

L. Starting PEEP at 4–6 cm H_2O and gradually increasing pressures as needed while monitoring for the signs described above is a reasonable empirical approach.

XI. Duration of PEEP Therapy
   A. Invasive mechanical ventilation should be discontinued as soon as it is no longer needed. Continuous distending pressure can be continued with CPAP.
   B. Most clinicians decrease PEEP as part of weaning ventilator settings, and consider extubation at levels of 5–6 cm H_2O; a less conservative range may be acceptable.

Suggested Reading

Alegria X, Claure N, Wada Y, Esquer C, D'Ugard C, Bancalari E. Acute effects of PEEP on tidal volume and respiratory center output during synchronized ventilation in preterm infants. Pediatr Pulmonol. 2006;41:759–64.

Ammari A, Suri M, Milisavljevic V, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. J Pediatr. 2005;147:341–7.

Bamat N, Millar D, Suh S, Kirpalani H. Positive end expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia. Cochrane Database Syst Rev. 2012;1, CD004500.

Bancalari E. Inadvertent positive end-expiratory pressure during mechanical ventilation. J Pediatr. 1986;108: 567–9.

Beker F, Rogerson SR, Hooper SB, Wong C, Davis PG. The effects of nasal continuous positive airway pressure on cardiac function in premature infants with minimal lung disease: a crossover randomized trial. J Pediatr. 2014;164:726–9.

Buckmaster AG, Arnolda G, Wright IM, Foster JP, Henderson-Smart DJ. Continuous positive airway pressure therapy for infants with respiratory distress in non-tertiary care centers: a randomized, controlled trial. Pediatrics. 2007;120:509–18.

Castoldi F, Daniele I, Fontana P, Cavigiolo F, Lupo E, Lista G. Lung recruitment maneuver during volume guarantee ventilation of preterm infants with acute respiratory distress syndrome. Am J Perinatol. 2011;28:521–8.

Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. Cochrane Database Syst Rev. 2003;2, CD000143.

Davis P, Davies M, Faber B. A randomised controlled trial of two methods of delivering nasal continuous positive airway pressure after extubation to infants weighing less than 1000 g: binasal (Hudson) versus single nasal prongs. Arch Dis Child Fetal Neonatal Ed. 2001;85:F82–5.

De Klerk AM, De Klerk RK. Nasal continuous positive airway pressure and outcomes of preterm infants. J Paediatr Child Health. 2001;37(2):161–7.

De Paoli AG, Morley CJ, Davis PG, Lau R, Hingley E. In vitro comparison of nasal continuous positive airway pressure devices for neonates. Arch Dis Child Fetal Neonatal Ed. 2002;87:F42–5.

De Paoli A, Davis P, Faber B, Morley C. Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. Cochrane Database Syst Rev. 2008;1, CD002977.

DiBlasi RM. Nasal continuous positive airway pressure (CPAP) for the respiratory care of the newborn infant. Respir Care. 2009;54:1209–35.

Dunn MS, Kaempf J, de Klerk A, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128:e1069.

Elgellab A, Riou Y, Abbazine A, et al. Effects of nasal continuous positive airway pressure (NCPAP) on breathing pattern in spontaneously breathing premature newborn infants. Intensive Care Med. 2001;27(11):1782–7.

Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362(21):1970–9.

Fischer HS, Buhrer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. Pediatrics. 2013;132:e13351–e1360.

Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure. Am Rev Respir Dis. 1987;136:730–6.

Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. Eur J Pediatr. 1997;156(5):384–8.

Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med. 1971;284(24):1333–40.

Gupta S, Sinha SK, Tin W, Donn SM. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus Infant Flow Driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. J Pediatr. 2009;154:645–50.
Hooper SB, te Pas AB, Kitchen MJ. Respiratory transition in the newborn: a three-phase process. Arch Dis Child Fetal Neonatal Ed. 2005;0:F1–6.
Jardine LA, Inglis GD, Davies MW. Strategies for the withdrawal of nasal continuous positive airway pressure (NCPAP) in preterm infants. Cochrane Database Syst Rev. 2011;2, CD006979.
Kamlin CO, Davis PG, Morley CJ. Predicting successful extubation of very low birthweight infants. Arch Dis Child Fetal Neonatal Ed. 2006;91:F180–3.
Karlberg P, Cherry RB, Escardo FE, Koch G. Pulmonary ventilation and mechanics of breathing in the first minutes of life, including the onset of respiration. Acta Paediatr Scand. 1962;51:121–36.
Kieran EA, Twomey AR, Molloy EJ, Murphy JFA, O'Donnell CPF. Randomized trial of prongs or mask for nasal continuous positive airway pressure in preterm infants. Pediatrics. 2012;130:E1170–6.
Lachmann B. Open up the lung and keep it open. Intensive Care Med. 1992;18:319–21.
Levy P. A method for studying the static volume-pressure curves of the respiratory system during mechanical ventilation. J Crit Care. 1989;4:83–9.
Monkman S, Andersen CC, Nahmias C, et al. Positive end-expiratory pressure above the lower inflection point minimized influx of activated neutrophils into lung. Crit Care Med. 2004;32:2471–5.
Morley CJ, Davis PG. Continuous positive airway pressure: scientific and clinical rationale. Curr Opin Pediatr. 2008;20:119–24.
Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358(7):700–8.
Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med. 1994;149:1327–34.
Nair V, Swarnam K, Rabi Y, et al. Effect of nasal continuous positive airway pressure (NCPAP) cycling and continuous NCPAP on successful weaning: a randomized controlled trial. Indian J Pediatr. 2015;82:787–93.
O'Donnell SM, Curry SJ, Buggy NA, et al. The NOFLO trial: low-flow nasal prongs therapy in weaning nasal continuous positive airway pressure in preterm infants. J Pediatr. 2013;163:79–83.
Polin RA, Sahni R. Newer experience with CPAP. Semin Neonatol. 2002;7(5):379–89.
Robertson NJ, McCarthy LS, Hamilton PA, Moss AL. Nasal deformities resulting from flow driver continuous positive airway pressure. Arch Dis Child Fetal Neonatal Ed. 1996;75:F209–12.
Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics. 2009;123:137–42.
Sandri F, Ancora G, Lanzoni A, et al. Prophylactic nasal continuous positive airways pressure in newborns of 28–31 weeks gestation: multicentre randomised controlled clinical trial. Arch Dis Child Fetal Neonatal Ed. 2004;89:F394–8.
Sandri F, Plavka R, Ancora G, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics. 2010;125(6):e1402–9.
Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. BMJ. 2013;347:f5980.
Siew ML, Te Pas AB, Wallace MJ, et al. Positive end-expiratory pressure enhances development of a functional residual capacity in preterm rabbits ventilated from birth. J Appl Physiol. 2009;106:1487–93.
Simbruner G. Inadvertent positive end-expiratory pressure in mechanically ventilated newborn infants: detection and effect on lung mechanics and gas exchange. J Pediatr. 1986;108:589–95.
Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. Pediatrics. 2001;107:1081–3.
te Pas AB, Spaans VM, Rijken M, Morley CJ, Walther FJ. Early nasal continuous positive airway pressure and low threshold for intubation in very preterm infants. Acta Paediatr. 2008;97:1049–54.
Todd DA, Wright A, Broom M, et al. Methods of weaning preterm babies <30 weeks gestation off CPAP: a multicenter randomized controlled trial. Arch Dis Child Fetal Neonatal Ed. 2012;97:F236–40.
Verder H. Nasal CPAP has become an indispensable part of the primary treatment of newborns with respiratory distress syndrome. Acta Paediatr. 2007;96:482–4.
Vyas H, Milder AD, Hopkin IE. Intra-thoracic pressures and volume changes during the spontaneous onset of respiration in babies born by cesarean-section and by vaginal delivery. J Pediatr. 1981;99:787–91.
Wu R, Li SB, Tian ZF, et al. Lung recruitment maneuver during proportional assist ventilation of preterm infants with acute respiratory distress syndrome. J Perinatol. 2014;7:524–7.
Wyszogrodski I, Kyei-Aboagyye K, Taeusch HW, Avery ME. Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. J Appl Physiol. 1975;38(3):461–6.

Sustained Inflations

30

Helmut D. Hummler

I. Introduction
   A. Aeration of the lung after birth
      1. Normal respiratory transition of the fetus: The fetus has fluid-filled lungs which need to be aerated immediately after birth for the newborn to survive. The term infant usually takes a few deep breaths to aerate its lungs, resulting in transport of fluid to the alveoli and from the alveoli to the surrounding interstitial tissue, where it is cleared within minutes/hours by lymphatic drainage and via resorption by the pulmonary vasculature. Aeration of the lungs reduces pulmonary vascular resistance to increase pulmonary blood flow and is essential for respiratory and cardiovascular transition after birth. Thus, healthy full-term infants may clear lung fluids with a few breaths within minutes after birth.
      2. Preterm infants have very compliant chest walls and weak respiratory muscles, structural immaturity of the lung, immature alveolar Na^+ resorption, and less surfactant. Depending on the degree of immaturity, a large proportion of preterm infants may require immediate respiratory support to aerate the lungs in order to survive.
      3. Respiratory support of the newborn: Current standards for respiratory support to aerate the lungs after birth include continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) with positive end-expiratory pressure (PEEP). European guidelines suggest the use of a slightly longer inspiratory time with the first breaths (up to a few seconds).
   B. Physiologic rationale for sustained inflations
      1. The pressure gradient produced by term infants provides the driving force to move lung fluid distally and allows gas to enter the alveolar system. This hydrostatic pressure gradient may be extremely large (>100 cm H_2O) in normal newborn infants to overcome the high resistive forces imposed by the high viscosity of fluid present in the airways resulting in a long time constant.
      2. To avoid large transpulmonary pressures, longer inflation times may help to move the lung fluid distally. Therefore, the use of a prolonged inflation time of up to 15–20 s, called

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"sustained inflation" (SI), to maintain the peak inflation pressure may allow clearance of lung fluid from the airways without the need for large transpulmonary peak pressures.

II. History

Boon et al. (1979a, b) studied the formation of the tidal volume and of a functional residual capacity (FRC) with gas in 20 asphyxiated neonates intubated immediately after birth. They noted that a so-called opening pressure of 13–32 cm H_2O was needed to move air from the trachea to the distal airways. Vyas et al. (1981a, b) showed in spontaneously breathing newborn infants immediately after birth that most infants were able to move air with rather small pressure gradients across the lungs. They studied the physiologic responses to prolonged and slow-rise inflation (5 s duration) in the resuscitation of a cohort of nine term newborn infants with asphyxia. They were able to show that *time*, rather than *pressure*, was needed to move air from the airways to the alveoli and create an FRC filled with gas. This approach, however, has never been tested clinically in a significant number of term infants with more important clinical outcomes beyond physiologic variables. Research is ongoing.

III. Experimental Studies

A. te Pas et al. (2009a, b) showed that PEEP is important to form FRC in newborn rabbits, that sustained inflations were particularly useful to aerate the lungs within seconds, and that the combination of PEEP and SIs was most effective. In another experiment they found that longer inspiration times (up to 20 s) were needed to fully aerate the lungs and that this approach resulted in a more uniform aeration of the lungs.

B. Sobotka et al. (2011) demonstrated that a single SI improved lung function without adverse circulatory effects. In asphyxiated lambs however, the same group found evidence for a disruption of the blood–brain barrier, which may exacerbate brain injury (2016).

C. Hillman et al. (2013) studied the effects of SI on the pro-inflammatory response in lungs of preterm lambs and were not able to document lung protection compared to conventional respiratory support.

D. In summary, SIs seem to work in carefully controlled animal experiments to clear the lung fluid, form FRC, and stabilize gas exchange immediately after birth, and the use of SIs in human newborn infants clearly reflects a physiologic approach to support preterm infants during transition.

IV. Clinical Studies

A. Cohort studies

1. Lindner et al. (1999) reported the use of SIs in 67 preterm infants compared to a historical cohort of 56 infants supported with conventional respiratory support. Using up to 2 SIs (20/25 cm H_2O for 15 s) compared to an approach based on conventional IPPV, the rate of intubation and mechanical ventilation in the delivery room and the rates of BPD and IVH grade 3–4 were reduced.
2. Lista et al. (2011) studied 89 preterm infants given up to 2 SIs (25 cm H_2O for 15 s). Compared to a historical control group supported with conventional IPPV, they found a decreased need for mechanical ventilation and a significantly lower rate of BPD.
3. Grasso et al. (2015) exposed 78 preterm infants to SIs. Compared to a matched cohort of infants exposed to conventional respiratory support, they found a decreased rate of intubation and mechanical ventilation and a reduced exposure to mechanical ventilation. Infants in the SI group received less surfactant, but there were no differences in mortality and morbidity. The authors report a trend towards a higher rate of IVH (23 % vs. 14 %, $P=0.15$).
4. Van Vonderen et al. (2014) studied airway pressure and airflow/tidal volume immediately after birth in preterm infants exposed to SIs and recognized that FRC was recruited more effectively if the infants had their own respiratory activity during exposure to SIs. This observation may be extremely important, as inflations given to support newborn infants

with apnea have been reported to be obstructed in clinical circumstances, whereas in most animal experiments, the upper airway is bypassed, suggesting that extrapolation to human neonates is difficult (Finer et al. 2014).

5. Fuchs et al. (2012) studied pre-ductal arterial oxygen saturation and cerebral tissue oxygenation (using near-infrared spectroscopy) immediately after birth in 51 preterm infants exposed to SIs. Cerebral tissue saturation increased almost as rapidly when compared to ten vigorous preterm infants requiring CPAP only, suggesting that gas exchange and brain perfusion are not impaired by the increased intrathoracic pressure imposed by SI.

B. Randomized trials

1. Lindner et al. (2005) randomized 61 preterm infants in need of some respiratory support immediately after birth to SIs vs. conventional IPPV using a nasopharyngeal tube interface. Up to 3 SIs (PIP, increased stepwise at 20, 25, and 30 cm H_2O) were given in the experimental group according to the infants' responses. Primary outcome was treatment failure (need for intubation and mechanical ventilation according to predefined criteria), which occurred in 61 % of the infants in the SI group vs. 70 % in the IPPV group (P = NS). There were no differences in mortality, BPD, IVH, and other morbidities, although the study lacked power because of early closure from slow recruitment.
2. Harling et al. (2005) randomized 51 preterm infants to SIs (25–30 cm H_2O for 5 s duration) vs. conventional IPPV. Primary outcome measures were cytokine concentrations in bronchoalveolar lavage fluid collected immediately after intubation and again at 12 h of age. There were no differences in cytokine levels as well as for mortality and other clinically relevant variables between groups.
3. te Pas et al. (2007) randomized 207 preterm infants to SIs (20 cm H_2O for 10 s, with 25 cm H_2O/10 s for the second SI depending on response) and conventional IPPV using nasopharyngeal tubes vs. face mask (SI vs. conventional groups). Primary outcome was the need for intubation and mechanical ventilation (<72 h), which was lower in the SI group (37 % vs. 65 %, $P < 0.05$). Surfactant was used less frequently in the SI group and the rate of moderate/severe BPD was lower, favoring the SI group. However, the use of SIs was part of an intervention package that included CPAP (5–6 cm H_2O) and/or nasal IPPV, which was not used in the control group. Therefore, it is unclear which part of the package made the difference in outcomes.
4. In the largest study (291 randomized infants) so far, infants received SIs (25 cm H_2O for 15 s up to two times with a face mask interface) in a prophylactic approach regardless of their own respiratory effort (Lista et al. 2015). They found a lower rate of intubation and mechanical ventilation in the first 72 h of life but no differences in mortality, and in the rates of BPD or IVH, and a trend for more air leaks in the SI group.
5. Two systematic reviews have been published on the use of SIs in preterm infants (Schmölzer et al. 2015; O'Donnell et al. 2015). Both found that the rate of intubation and mechanical ventilation within 3 days of life was reduced [RR 0.87 (0.77–0.97) and 0.85 (0.72–1.02)] and the rate of patent ductus arteriosus was increased with the use of SIs compared to conventional respiratory support in the delivery room. There were no differences in mortality and the rates for BPD or IVH. Both reports suggested that the general use of SIs should be restricted to randomized clinical trials at this time.

V. Recommendations

A. Currently there is some limited evidence for the clinical use of SIs for preterm infants, and very little for its use in term neonates.

B. Recommendations based on ILCOR guidelines published in 2015 discourage the routine use of initial SI (>5 s duration) for preterm infants without spontaneous respirations immediately

after birth, but an SI "may be considered in individual clinical circumstances or research settings" (weak recommendation, low-quality evidence, Perlman et al. 2015).

C. If, on an individual basis, SIs are used in the delivery room in preterm infants, the settings used should be based upon methods in clinical studies:
   1. Peak pressure: 20–25 cm H_2O should be used initially.
   2. Duration of SIs: within the range used in the published clinical studies (5–15 s). According to animal experiments, SIs of 5 s duration may be too short to be effective to clear the airways of lung fluid.
   3. Time between sustained inflations: There should be enough observation time between SIs (if multiple SIs are used) to observe the infant's response to the SI. On the other hand, the observation time needs to be limited, as the SI may be ineffective secondary to airway obstruction. A backup strategy based on current guidelines should be available.
   4. PEEP/CPAP: 5–8 cm H_2O. Observe for efficacy of the SI per general guidelines for neonatal resuscitation.
   5. Is the SI is effective? Compared to the use of short inflations, the chest expansion during SIs may be very slow and be difficult to judge. If it is not clear if the chest is moving in response to SIs, the response has to be judged on its effect on heart rate and pulse oximetry. As this approach takes time, there may be considerable delay until the treatment is recognized as ineffective. Routine measurement of airway pressure and airflow/tidal volume in the delivery room may help to recognize whether gas is/was delivered during SIs.
   6. Number of sustained inflations: Unknown. Most clinical studies have used 1–3 SIs, some starting with 25 cm H_2O pressure, whereas others used escalating pressures starting at 20 cm H_2O for the first SI, increasing to 25 cm H_2O for the second if there was no response.
   7. SI algorithm: We use SIs as a routine for preterm infants needing respiratory support immediately after birth. We have developed an algorithm, which was primarily based on the ILCOR 2010 guidelines (Fig. 30.1). A very similar approach is currently being utilized in the Sustained Aeration of Infant Lungs (SAIL) international clinical trial comparing SIs to conventional IPPV in 600 extremely preterm infants (Foglia et al. 2015).

VI. Controversies

A. Air leaks: Some clinical studies suggested that there may be an increased risk for air leaks using SIs in preterm infants (Lista et al. 2015; Hummler et al. 2015). However, the data from meta-analyses currently do not show a difference compared to conventional support.

B. Sustained inflations in infants with asphyxia: Recent experimental evidence suggests that the rapid improvement in gas exchange and hemodynamics secondary to the use of SIs for resuscitation may have detrimental effects on the brain. Therefore, it may be advisable to avoid SIs for asphyxiated infants until further data become available (Sobotka et al. 2016).

C. Unresolved issues:
   1. What is the ideal and safe peak inflation pressure during SIs?
   2. Should SIs be pressure or volume targeted?
   3. What is the ideal duration of SI in newborn infants with different gestational ages, especially for extremely low-birth-weight infants?
   4. How should the response in aeration be monitored (by observing chest movement, by measuring flow and tidal volume, or just by looking at the heart rate response)?
   5. Should the maneuver be individualized based on feedback monitoring?
   6. Which interface should be used to deliver the SI?
   7. Should exogenous surfactant be administered prior to or after SIs?
   8. Experimental and clinical studies need to answer these important questions before SIs can be recommended as a clinical routine in newborn infants.

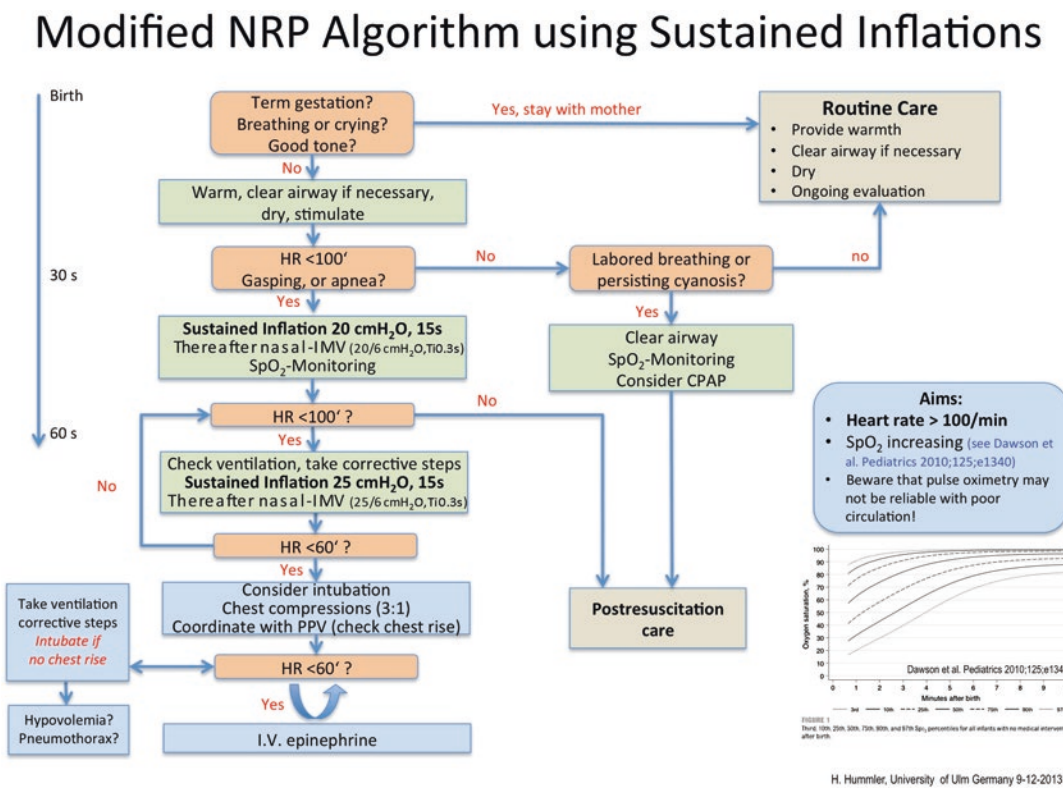

Fig. 30.1 Algorithm for resuscitation of neonates

Suggested Reading

Boon AW, Milner AD, Hopkin IE. Lung expansion, tidal exchange, and formation of the functional residual capacity during resuscitation of asphyxiated neonates. J Pediatr. 1979a;95(6):1031–6.

Boon AW, Milner AD, Hopkin IE. Physiological responses of the newborn infant to resuscitation. Arch Dis Child. 1979b;54(7):492–8.

Finer NN, Katheria AC. Sustained inflations as the initiating positive pressure support for preterm infants—not yet ready for prime time. J Pediatr. 2014;165(5):886–9.

Foglia EE, Owen LS, Thio M, Ratcliffe SJ, Lista G, Te Pas A, et al. Sustained Aeration of Infant Lungs (SAIL) trial: study protocol for a randomized controlled trial. Trials. 2015;16:95.

Fuchs H, Lindner W, Buschko A, Almazam M, Hummler HD, Schmid MB. Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants. J Perinatol. 2012;32(5):356–62.

Grasso C, Sciacca P, Giacchi V, Carpinato C, Mattia C, Palano GM, Betta P. Effects of Sustained Lung Inflation, a lung recruitment maneuver in primary acute respiratory distress syndrome, in respiratory and cerebral outcomes in preterm infants. Early Hum Dev. 2015;91(1):71–5.

Harling AE, Beresford MW, Vince GS, Bates M, Yoxall CW. Does sustained lung inflation at resuscitation reduce lung injury in the preterm infant? Arch Dis Child Fetal Neonatal Ed. 2005;90(5):F406–10.

Hillman NH, Kemp MW, Noble PB, Kallapur SG, Jobe AH. Sustained inflation at birth did not protect preterm fetal sheep from lung injury. Am J Physiol Lung Cell Mol Physiol. 2013;305(6):L446–53.

Hummler HD, Parys E, Mayer B, Essers J, Fuchs H, Schmid M. Risk indicators for air leaks in preterm infants exposed to restrictive use of endotracheal intubation. Neonatology. 2015;108(1):1–7.

Lindner W, Högel J, Pohlandt F. Sustained pressure-controlled inflation or intermittent mandatory ventilation in preterm infants in the delivery room? A randomized, controlled trial on initial respiratory support via nasopharyngeal tube. Acta Paediatr. 2005;94(3):303–9.

Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? Pediatrics. 1999;103(5 Pt 1):961–7.

Lista G, Fontana P, Castoldi F, Cavigioli F, Dani C. Does sustained lung inflation at birth improve outcome of preterm infants at risk for respiratory distress syndrome? Neonatology. 2011;99(1):45–50.

Lista G, Boni L, Scopesi F, Mosca F, Trevisanuto D, Messner H, et al. Sustained lung inflation at birth for preterm infants: a randomized clinical trial. Pediatrics. 2015;135(2):e457–64.

McCall KE, Davis PG, Owen LS, Tingay DG. Sustained lung inflation at birth: what do we know, and what do we need to know? Arch Dis Child Fetal Neonatal Ed. 2016;101:F175–80.

O'Donnell CPF, Bruschettini M, Davis PG, Morley CJ, Moja L, Calevo MG, et al. Sustained versus standard inflations during neonatal resuscitation to prevent mortality and improve respiratory outcomes. Cochrane Database Syst Rev. 2015;7, CD004953.

Perlman JM, Wyllie J, Kattwinkel J, Wyckoff MH, Aziz K, Guinsburg R, et al. Part 7: Neonatal Resuscitation: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2015;2015:S204–41.

Schmölzer GM, Kumar M, Aziz K, Pichler G, O'Reilly M, Lista G, et al. Sustained inflation versus positive pressure ventilation at birth: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2015;100(4):F361–8.

Sobotka KS, Hooper SB, Allison BJ, te Pas AB, Davis PG, Morley CJ, et al. An initial sustained inflation improves the respiratory and cardiovascular transition at birth in preterm lambs. Pediatr Res. 2011;70(1):56–60.

Sobotka KS, Hooper SB, Crossley KJ, Ong T, Schmölzer GM, Barton SK, et al. Single sustained inflation followed by ventilation leads to rapid cardiorespiratory recovery but causes cerebral vascular leakage in asphyxiated near-term lambs. PLoS One. 2016;11(1):e0146574.

te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. Pediatrics. 2007;120(2):322–9.

te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, et al. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. Pediatr Res. 2009a;65(5):537–41.

te Pas AB, Siew M, Wallace MJ, Kitchen MJ, Fouras A, Lewis RA, et al. Effect of sustained inflation length on establishing functional residual capacity at birth in ventilated premature rabbits. Pediatr Res. 2009b;66(3):295–300.

van Vonderen JJ, Hooper SB, Hummler HD, Lopriore E, te Pas AB. Effects of a sustained inflation in preterm infants at birth. J Pediatr. 2014;165(5):903–8.e1.

Vyas H, Milner AD, Hopkin IE, Boon AW. Physiologic responses to prolonged and slow-rise inflation in the resuscitation of the asphyxiated newborn infant. J Pediatr. 1981a;99(4):635–9.

Vyas H, Milner AD, Hopkins IE. Intrathoracic pressure and volume changes during the spontaneous onset of respiration in babies born by cesarean section and by vaginal delivery. J Pediatr. 1981b;99(5):787–91.

Non-invasive Ventilation: An Overview

31

Brigitte Lemyre and Haresh Kirpalani

I. Definition
   A. This chapter covers methods of assisted ventilation without an endotracheal tube in the trachea, and using interfaces either just at the nares or sealing the entire nose with a mask. These methods can deliver positive pressure throughout the respiratory cycle with additional intermittent increases in the airway pressure. This additional intermittent airway pressure can be either synchronized to the patient's own breaths or non-synchronized, depending on the delivery system used.
   B. The terminology used for non-invasive ventilation can be confusing. When non-invasive ventilation is provided via a conventional ventilator, it usually delivers short (0.3–0.5 s) but high (20–25 cm H_2O) peak pressure, similar to a ventilator breath. This mode is to be distinguished from "bi-level"—discussed below.
   C. The following abbreviations denote commonly used synonyms:
      1. NV (nasal ventilation)
      2. NIMV (nasal intermittent mandatory ventilation)
      3. NIPPV (nasal intermittent positive pressure ventilation)
   D. The term NIPPV will be used here.
   E. The mode can be synchronized or not. When synchronized it is prefaced with an "s," as sNIPPV (synchronized nasal intermittent positive pressure ventilation).
   F. Some specific devices (Infant Flow, SiPAP) are designed to provide positive pressure throughout the respiratory cycle by alternating between a higher pressure and a lower pressure. In these systems, the duration of the higher pressure is longer (0.5–1.0 s) and the peak pressures are lower (9–11 cm H_2O) than with modalities described above, which are provided via a ventilator. Patients can breathe at both levels of pressure.

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1. Bi-level will be used here to refer to non-invasive ventilation delivered via such a device
2. BiPAP (bi-level positive airway pressure)
3. These biphasic devices are usually operated in a synchronized mode (although they have not yet been approved for use in the USA with the synchronizing device).

G. In experimental animals, nasal high-frequency oscillation decreases alveolar damage, showing improved histologic appearance compared to intubated and ventilated animals. Nasal high-frequency oscillation (HFO) at the nares was first reported in the 1980s and more recently in small series. Its use is reported in several countries. All reports show efficacy in CO_2 removal but have not yet been adequately tested in randomized trials. One small pilot study showed short-term efficacy with nasal percussive high-frequency ventilation. Nasal HFOV modes have potential but will not be discussed further for lack of data.

II. Likely Physiologic Mechanism Underlying Putative Benefits of NIPPV

A. Both CPAP (continuous positive airway pressure) and NIPPV or bi-level likely exert any benefits to infants through similar physiologic mechanisms. The final common result is to reduce the fatigue from the floppy chest wall and poor diaphragmatic function of preterm infants. All three also splint open the upper airway and reduce obstruction. In summary, they expand the lung, increase functional residual capacity, prevent alveolar collapse, and improve ventilation-perfusion mismatch.

B. sNIPPV may result in a higher tidal volume over nCPAP breaths, and non-synchronized NIPPV. Increases in tidal volume possibly result from stimulation of the upper airway.

C. All forms of nasal ventilation also provide additional positive pressure breaths. These provide slightly higher mean airway pressure and possibly higher tidal volumes. Whether synchronized or not, they reduce thoraco-abdominal asynchrony and improve chest wall stabilization, resulting in decreased work of breathing. These effects have been shown particularly with synchronized nasal ventilation.

III. Current State of Evidence

A. NIPPV was first tested in an RCT in 1970; however, its use was limited by poor interfaces leading to unacceptable rates of complications, including facial edema and gastrointestinal perforation.

B. Modern usage with new silastic interfaces has resulted in a much easier application, with a far less adverse event rate.

C. The present randomized data are summarized in the 2014 Cochrane review. Although those data suggest benefit in prevention of extubation failure, there are insufficient data to support its use in apnea of prematurity or prevention of BPD.

D. In considering the new trials to date, they also do not unequivocally answer several outstanding questions:

1. Is synchronization superior, for post-extubation, primary treatment of respiratory failure, or treatment of apnea of prematurity?
2. Are bi-level devices comparable to NIPPV delivered via a ventilator for important short-term outcomes (failure of extubation, prevention of intubation)? Inferences can be made from systematic reviews that ventilator-delivered NIPPV improves short-term outcomes compared to bi-level. Only one trial compared both devices (unsynchronized bilevel and synchronized NIPPV); no difference was observed in short-term outcomes (see below)

E. In addition, one large retrospective study appears to show clinically important reductions in BPD and neurodevelopmental impairment at age 18 months from the use of sNIPPV; however, these positives were puzzlingly only present in one subgroup of infants (BW 500–750 g). The methodologic limitations of this study prevent firm conclusions.

F. The largest pragmatic randomized controlled trial enrolled 1009 infants <1000 g and randomized them to nasal ventilation (via a ventilator or bi-level) or nCPAP, either as a primary

mode or as a post-extubation. There was no difference in death or moderate/severe BPD at 36 weeks' corrected gestational age between the treatment groups. The major limitation of this trial is the inability to assess whether synchronization might improve these effects, since the majority of infants were on non-synchronized NIPPV.

IV. How Can Non-invasive Ventilation be Delivered?
   A. Nasal interface (Chap. 27): Airflow may be delivered by nasal prongs, which can be short (tip in the nose) or long (tip in the nasopharynx), single or bi-nasal, or can be delivered via a nasal mask. If using prongs, short prongs are advocated. Effectiveness and safety critically depend upon methods of fixation. Nursing care and minimization of loose fittings with infant head movements is critical. It is imperative to avoid movement of the tubing, which can be minimized by anchoring it to the cheek. It is also key to make sure that there is appropriate fit to the nares.
   B. A recent RCT comparing synchronized CMV-NIPPV with non-synchronized BiPAP-NIPPV as the primary mode (124 infants with GA <32 weeks, birth weight <1500 g) did not show a difference in the primary outcomes (failure of or duration of non-invasive respiratory support) between the two groups.
   C. Synchronized nasal ventilation can be delivered by some ventilators with specific triggering devices. The devices are pneumatic capsules that are used to detect abdominal movement at the start of inspiration. These, however, have trigger delays and can be unreliable. The availability of sNIPPV has decreased in North America. Newer devices, available in some European countries, are able to trigger using airway-derived flow signals, but are not available in North America as of now.
   D. Finally, the use of NAVA (neutrally adjusted ventilatory assist) (Chap. 50) is beginning to be assessed in the newborn population. This method relies on placing a catheter (similar to a nasogastric tube) with two electrodes (above and below the diaphragm) that sense the trans-diaphragmatic potential. This enables triggering of a ventilator breath with a tidal volume proportional to the magnitude of the trans-diaphragmatic potential. Since only case series are available to date, and no trials are available, it should be considered experimental at this time.

V. Indications for Use
   A. Post-extubation. As of 2015, ten randomized controlled trials have compared nasal ventilation to CPAP after extubation in premature infants, with eight included in a meta-analysis. Five used synchronized devices. A meta-analysis of these trials demonstrated a reduction in extubation failure (NNT = 4). However, the time up to which this was assessed varied and the longest was 1 week post-extubation. Two trials used a non-synchronized device (one CMV-NIPPV and one bi-level NIPPV); neither could demonstrate a reduction in extubation failure. One last trial used a mix of devices.
   B. Apnea of prematurity. Three studies compared CPAP with nasal ventilation (non-synchronized) for the treatment of apnea of prematurity. Trials were of short term (hours) and results were conflicting. One other short-term, crossover trial compared sNIPPV to non-synchronized NIPPV to CPAP and reported a decrease in apneic episodes per hour.
   C. Primary mode of ventilation for respiratory distress syndrome. Eight randomized controlled trials, with 850 patients, examined this question. Five used non-synchronized nasal ventilation delivered via a ventilator, while one used synchronized NIPPV. Two further studies used synchronized bi-level. The baseline population was mixed, with some studies allowing for surfactant via the INSURE technique to be provided prior to randomization. The primary outcome was failure of non-invasive respiratory support with need for intubation (4 h to 1 week). Six trials found no difference between treatment approaches, while the other two found less treatment failure with NIPPV.

VI. Device Settings
   A. The settings depend on the device used and the clinical indication.
      1. In post-extubation trials, settings similar to those on the ventilator just prior to extubation were used. These included rates of 20–30/min, PEEP 5–6 cm H_2O, inspiratory times of 0.3–0.5 s, and peak inspiratory pressures of 16–18 cm H_2O.
      2. Settings for infants with RDS included PIP up to 22 cm H_2O and rates up to 50/min. Inspiratory times varied between 0.3 and 0.5 s.
      3. For apnea of prematurity, settings are generally lower, as lungs are healthier: PIP 10–14 cm H_2O, PEEP of 4–6 cm H_2O, and rates of 20/min.
   B. Bi-level devices cannot achieve such levels of PIP and also require longer inspiratory times. Usually, a Ti of 0.5–1.0 s is required, and PIP is set at 3–4 cm H_2O above PEEP. Rates can start at 10–40/min.

VII. Putative Benefits
   A. Avoidance of re-intubation, when used immediately after extubation: This was found consistently in devices providing synchronized nasal ventilation and ventilator-generated NIPPV.
   B. Reduction in post-extubation apnea has not been convincingly shown.
   C. Prevention of intubation in RDS
   D. Possible reduction in BPD (post-extubation and primary mode trials)

VIII. Potential Complications
   A. Abdominal distention from flow delivered preferentially to the stomach (mainly seen in earlier studies)
   B. Gastric perforation. There was an association between the use of NIPPV and gastric perforation in a case-control study. NIPPV was being used as a primary mode of ventilation for RDS and delivered via a face mask in older interfaces. None of the subsequent randomized controlled trials with newer interfaces has reported this complication.
   C. Pneumothorax or other air leaks (no increased incidence has been reported in randomized trials to date)
   D. Nasal erosion and injuries may result from the prongs or nasal mask, but this is equally true for nCPAP. Again, nursing care and minimization of movement of the interface are crucial.

Suggested Reading

Armanian AM, Badiee Z, Heidari G, Feizi A, Salehimehr N. Initial treatment of respiratory distress syndrome with nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure: a randomized controlled trial. Int J Prev Med. 2014;5(12):1543–51.

Barrington KJ, Bull D, Finer NN. Randomized trial of nasal synchronized intermittent mandatory ventilation compared with continuous positive airway pressure after extubation of very low birth weight infants. Pediatrics. 2001;107:638.

Bhandari V. Nasal intermittent positive pressure ventilation in the newborn: review of literature and evidence-based guidelines. J Perinatol. 2010;30(8):505.

Bhandari V, Finer NN, Ehrenkranz RA, Saha S, Das A, Walsh MC, Engle WA, VanMeurs KP, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Synchronized nasal intermittent positive-pressure ventilation and neonatal outcomes. Pediatrics. 2009;124(2):517–26.

Bisceglia M, Belcastro V, Poerio F, Raimondi I, Mesurace C, Crugliano C, Pio Corapi U. A comparison of nasal intermittent versus continuous pressure delivery for the treatment of moderate respiratory syndrome in preterm infants. Minerva Pediatr. 2007;59(2):91.

Chang HY, Claure N, D'urgard C, Torres J, Nwajei P, Bancalari E. Effects of synchronization during nasal ventilation in clinically stable preterm infants. Pediatr Res. 2011;69(1):84–9.

Colaizy TT, Younis UM, Bell EF, Klein JM. Nasal high-frequency ventilation for premature infants. Acta Paediatr. 2008;97(11):1518–22.
Davis PG, Lemyre B, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (nCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2001;3, CD003212.
Davis PG, Morley CJ, Owen LS. Non-invasive respiratory support of preterm neonates with respiratory distress: continuous positive airway pressure and nasal intermittent positive pressure ventilation. Semin Fetal Neonatal Med. 2009;14:14.
De Paoli AG, Davis PG, Lemyre B. Nasal continuous positive airway pressure versus nasal intermittent positive pressure ventilation for preterm neonates: a systematic review and meta-analysis. Acta Paediatr. 2003;92:70.
Dumas De La Roque E, Bertrand C, Tandonnet O, Rebola M, Roquand E, Renesme L, Elleau C. Nasal high frequency percussive ventilation versus nasal continuous positive airway pressure in transient tachypnea of the newborn: a pilot randomized controlled trial (NCT00556738). Pediatr Pulmonol. 2011;46:218–23.
Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I, Czernik C. Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries. Eur J Pediatr. 2015;174(4):465–71.
Friedlich P, Lecart C, Posen R, et al. A randomized trial of nasopharyngeal synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. J Perinatol. 1999;19:413.
Gao WW, Tan SZ, Chen YB, Zhang Y, Wang Y. Randomized trail of nasal synchronized intermittent mandatory ventilation compared with nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome. Zhongguo Dang Dai Er Ke Za Zhi. 2010;12(7):524–6.
Garland JS, Nelson DB, Rice T, Neu J. Increased risk of gastrointestinal perforations in neonates mechanically ventilated with either face mask or nasal prongs. Pediatrics. 1985;76:406.
Gizzi C, Montecchia F, Panetta V, Castellano C, Mariani C, Campelli M, Papoff P, Moretti C, Agostino R. Is synchronised NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A randomised crossover trial. Arch Dis Child Fetal Neonatal Ed. 2015;100(1):F17–23.
Jasani B, Nanavati R, Kabra N, Rajdeo S, Bhandari V. Comparison of non-synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as post-extubation respiratory support in preterm infants with respiratory distress syndrome: a randomized controlled trial. J Matern Fetal Neonatal Med. 2015;10:1–6.
Kahramaner Z, Erdemir A, Turkoglu E, Cosar H, Sutcuoglu S, Ozer EA. Unsynchronized nasal intermittent positive pressure versus nasal continuous positive airway pressure in preterm infants after extubation. J Matern Fetal Neonatal Med. 2014;27(9):926–9.
Khalaf MN, Brodsky N, Hurley J, Bhandari V. A prospective randomized controlled trial comparing synchronized nasal intermittent positive pressure ventilation versus nasal continuous positive airway pressure as modes of extubation. Pediatrics. 2001;108:13.
Khorana M, Paradeevisut H, Sangtawesin V, Kanjanapatanakul W, Chotigeat U, Ayutthaya JKN. A randomized trial of non-synchronized nasopharyngeal intermittent mandatory ventilation (nsNIMV) vs nasal continuous positive airway pressure (NCPAP) in the prevention of extubation failure in preterm <1500 grams. J Med Assoc Thai. 2008;91 Suppl 3:S136.
Kiciman NM, Andreasson B, Bernstein G, et al. Thoracoabdominal motion in newborns during ventilation delivered by endotracheal tube or nasal prongs. Pediatr Pulmonol. 1998;25:175.
Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS, NIPPV Study Group. A trial comparing noninvasive ventilation strategies in preterm infants. N Engl J Med. 2013;369(7):611–20.
Kishore MSS, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. Acta Paediatr. 2009;98:1412.
Kugelman A, Fefferkorn I, Riskin A, Chistyakov I, Kaufman B, Bader D. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized controlled prospective study. J Pediatr. 2007;150:521–6.
Kugelman A, Bar A, Riskin A, Chistyakov I, Mor F, Bader D. Nasal respiratory support in premature infants: short-term physiological effects and comfort assessment. Acta Paediatr. 2008;97(5):557–61.
Lemyre B, Davis PG, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. Cochrane Database Syst Rev. 2014;9, CD003212.
Lin CH, Want ST, Lin YJ, Yeh TF. Efficacy of nasal intermittent positive pressure ventilation in treating apnea of prematurity. Pediatr Pulmonol. 1998;26:349.
Lista G, Castoldi F, Fontana P, Daniele I, Cavigioli F, Rossi S, Mancuso D, Reali R. Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a randomised control trial. Arch Dis Child Fetal Neonatal Ed. 2010;95(2):F85–9.
Llewellyn MA, Tilak KS, Swyer PR. A controlled trial of ventilation using an oro-nasal mask. Arch Dis Child. 1970;45:453–9.

Meneses J, Bhandari V, Alves JG, Herrmann D. Noninvasive ventilation for respiratory distress syndrome: a randomized controlled trial. Pediatrics. 2011;127(2):300.

Moretti C, Giannini L, Fassi C, Gizzi C, Papoff P, Colarizi P. Nasal flow-synchronized intermittent positive pressure ventilation to facilitate weaning in very low-birthweight infants: unmasked randomized controlled trial. Pediatr Int. 2008;50(1):85–91.

O'Brien K, Campbell C, Brown L, Wenger L, Shah V. Infant flow biphasic nasal continuous positive airway pressure (BP-NCPAP) vs. infant flow NCPAP for the facilitation of extubation in infants' ≤1,250 grams: a randomized controlled trial. BMC Pediatr. 2012;12:43.

Owen LS, Morley CJ, Davis PG. Pressure variation during ventilator generated nasal intermittent positive pressure ventilation in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2010;95(5):F359–64.

Pantalitschka T, Sievers J, Urschitz MS, Herberts T, Reher C, Poets CF. Randomised crossover trial of four nasal respiratory support systems for apnoea of prematurity in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed. 2009;94:F245.

Reyburn B, Li M, Metcalfe DB, Kroll NJ, et al. Nasal ventilation alters mesenchymal cell turnover and improves alveolarization in preterm lambs. Am J Respir Crit Care Med. 2008;178(4):407–18.

Ryan CA, Finer NN, Peters KL. Nasal intermittent positive pressure ventilation offers no advantages over nasal continuous positive airway pressure in apnea of prematurity. Am J Dis Child. 1989;143:1196.

Salama GSA, Ayyash FF, Al-Rabadi AJ, Alquran ML, Shakkoury AG. Nasal IMV vs nasal CPAP as an initial mode of respiratory support for premature infants with RDS: a prospective randomized clinical trial. Rawal Med J. 2015;40(2):197–202.

Salvo V, Lista G, Lupo E, Ricotti A, Zimmermann LJ, Gavilanes AW, Barberi I, Colivicchi M, Temporini F, Gazzolo D. Noninvasive ventilation strategies for early treatment of RDS in preterm infants: an RCT. Pediatrics. 2015;135(3):444–51.

Squires AJ, Hyndman M. Prevention of nasal injuries secondary to NCPAP application in the ELBW infant. Neonatal Netw. 2009;28(1):13–27.

van der Hoeven M, Brouwer E, Blanco CE. Nasal high frequency ventilation in neonates with moderate respiratory insufficiency. Arch Dis Child Fetal Neonatal Ed. 1998;79(1):F61–3.

Nasal Intermittent Positive Pressure Ventilation

32

Vineet Bhandari

I. Introduction
   A. Nomenclature
      1. Nasal intermittent positive pressure ventilation (NIPPV) provides nasal continuous positive airway pressure (NCPAP) in the intermittent mandatory ventilation (IMV) mode.
      2. When synchronized with the infant's respiratory effort, it is known as SNIPPV.
      3. Primary mode refers to its use soon after birth. This may or may not include a short period (≤2 h) of endotracheal intubation or less invasive means for surfactant administration, prior to extubation to NIPPV.
      4. Secondary mode refers to its use after a longer period (>2 h to days to weeks) of endotracheal intubation to provide IPPV, prior to extubation.
   B. Technique
      1. Nasal interface: short bi-nasal prongs (preferred). Nasopharyngeal prongs or nasal mask may also be used.
      2. NIPPV: any ventilator that can provide NCPAP and IMV
      3. SNIPPV: Infant Star with Star Sync® (used a Graseby capsule for synchronization; discontinued in the USA); Giulia ventilator (uses flow synchronization; Ginevri, Italy); Servo-i® (uses neutrally adjusted ventilator assist or NAVA; Maquet, Getinge group, Germany).
      4. Not considered SNIPPV: Infant Flow®Si-PAP™ (CareFusion, Becton Dickinson group, USA)—this is a bi-level NCPAP device. The peak inspiratory pressures (PIP) generally range from 9 to 11 cm H_2O and the inspiratory times (Ti) are typically prolonged, even up to 1.0 s.
   C. Mechanism of action (mostly in reference to SNIPPV)
      1. Decreased thoraco-abdominal asynchrony and flow resistance, improved stability of the chest wall, and pulmonary mechanics

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2. Addition of PIP above positive end-expiratory pressure (PEEP) leads to intermittent increased distending pressure above PEEP, with increased flow delivery to the upper airway
3. Increased tidal and minute volumes
4. Recruitment of collapsed alveoli and increased functional residual capacity
5. Decreased work of breathing

II. Contraindications
   A. Upper airway abnormalities
      1. Choanal atresia
      2. Cleft palate
      3. Esophageal atresia with/without a tracheo-esophageal fistula
   B. Severe cardiovascular instability

III. Equipment and Supplies
   A. Ventilator
   B. Nasal prongs (or mask)
      1. Small
      2. X-small
   C. Tape
   D. DuoDERM®
   E. Oro-gastric tube (8 or 9 F)
   F. Suction catheter

IV. Procedure
   A. Estimate appropriate size prongs for the infant.
      1. >1000 g—small
      2. ≤1000 g—x-small
   B. Place DuoDERM® strips in front of the nostrils, after making holes in the strips that will fit the nasal prongs snugly. Also, place a DuoDERM® strip over the upper lip, if the prongs are going to be resting there.
   C. Position the prongs in the infant's nose. The short bi-nasal prongs should fit fully inside the nostrils.
   D. Place the head cap over the infant's head and secure the nasal interface with Velcro® straps, if appropriate.
   E. Insert an oro-gastric tube; connect the other end of the tube to a 10 mL syringe, remove plunger, and place it higher than the infant, and open to the atmosphere.
   F. Connect the nasal interface setup to the ventilator (Fig. 32.1).

V. Primary mode—initial settings
   A. Frequency (rate): ~40 breaths/min
   B. PIP: 4 cm H_2O > than the PIP required for manual ventilation; adjust PIP based on chest rise and aeration on auscultation
   C. PEEP: 4–6 cm H_2O
   D. Ti: ~0.45 s
   E. Fraction of inspired oxygen (FiO_2): adjusted to keep SpO_2 in desired range
   F. Flow: 8–10 LPM
   G. Caffeine: recommend a loading dose prior to placing on NIPPV
   H. Hematocrit: ≥35 %

VI. Primary mode—monitoring and maximal support
   A. Monitor: SpO_2, heart rate (HR), and respiratory rate (RR)
   B. Obtain blood gas in 15–30 min

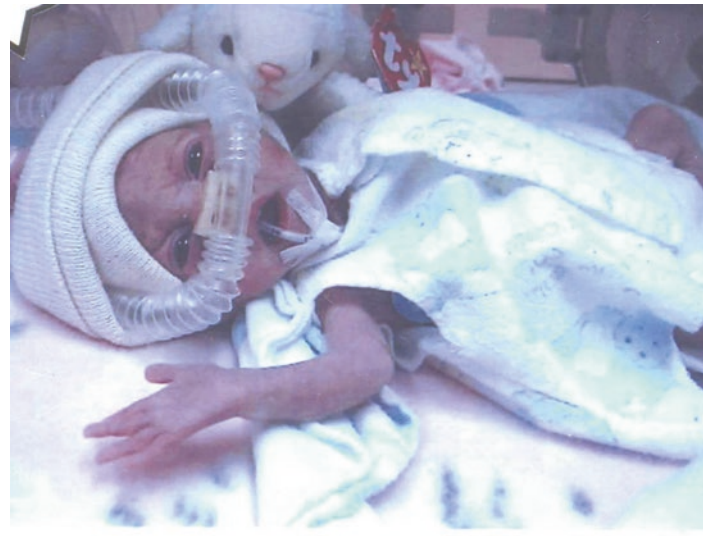

Fig. 32.1 Preterm infant managed with NIPPV. The "nasal protective barrier" uses DuoDERM. Note the "fixation" of the prongs using the cap. A large-bore orogastric tube shown in the picture is connected to the end of a 10 mL syringe, minus the plunger, and is kept open and above the level of the baby (not in the picture) to decompress the stomach. This is also used for feeding via gravity drip, as evidenced by a little bit of milk in the tube

C. Adjust ventilator settings to maintain blood gases
D. Suction mouth and pharynx, as necessary
E. Maximal support recommendations
   1. >1000 g—mean airway pressure (Pāw) 16 cm H_2O
   2. ≤1000 g—Pāw 14 cm H_2O

VII. Extubation criteria—while on conventional ventilation, prior to placing on secondary mode NIPPV
   A. Frequency (rate): 15–25 breaths/min
   B. PIP: ≤16 cm H_2O
   C. PEEP: ≤5 cm H_2O
   D. Ti: ~0.45 s
   E. FiO_2: ≤0.35
   F. Caffeine
   G. ≥35 %

VIII. Secondary mode—initial settings
   A. Frequency (rate): 15–25 breaths/min
   B. PIP: 2–4 cm H_2O > than the PIP on conventional ventilation; adjust PIP based on chest rise and aeration on auscultation
   C. PEEP: ≤5 cm H_2O
   D. Ti: ~0.45 s
   E. FiO_2: adjusted to keep saturation in desired range
   F. Flow: 8–10 LPM
   G. Caffeine: suggest a loading dose at least 1 h prior to placing on NIPPV
   H. Hematocrit: ≥35 %

IX. Secondary mode—monitoring and maximal support
   A. Monitor: SpO_2, HR, and RR
   B. Obtain blood gas in 60 min
   C. Adjust ventilator settings to maintain blood gases

D. Suction mouth and pharynx, as necessary
E. Maximal support recommendations
   1. >1000 g—Pāw 16 cm H_2O
   2. ≤1000 g—Pāw 14 cm H_2O

X. NIPPV—maintenance
   A. Attempt to minimize air leak from the mouth
      1. Use a pacifier.
      2. Use a chin strap.
   B. Attempt to keep PIP/Pāw within 4/2 cm H_2O of the targeted value.
   C. The orogastric (large bore) decompression tube
      1. Connect to an empty 10 mL syringe, with the plunger removed, open to the atmosphere.
      2. Keep at a higher level than the infant to decrease abdominal distension.
      3. Can be used for feeding via gravity drip
   D. If requiring continuous feeds, a 6 F orogastric tube can be placed (passed along the large-bore decompression tube and can be taped to it) and connected to a syringe pump.

XI. NIPPV—consideration for re-intubation, despite maximal support settings
   A. Blood gas: pH < 7.25 and $PaCO_2 \geq 60$ mmHg
   B. Severe apnea: any episode requiring bag and mask resuscitation
   C. Frequent (>2–3 episodes/h) apnea/bradycardia (cessation of respiration for >20 s associated with an HR <100/min) not responding to methylxanthines
   D. Frequent desaturation ($SpO_2 \leq 85\%$): ≥3 episodes/h, not responding to increased ventilator settings

XII. NIPPV failures
   A. Group 1
      1. Usually intubated within a few hours of extubation
      2. Infants tend to be <750 g weight.
      3. Chest radiograph shows significant areas of collapse.
      4. After re-intubation, minimize ventilation settings.
      5. Attempt re-intubation usually after 7 days and/or when infants have gained another ~100 g weight.
   B. Group 2
      1. Usually intubated after 3 days of NIPPV
      2. Over the 3 days the infant starts developing micro-atelectasis and when a significant portion of the lung is involved, fail NIPPV. To prevent this:
         a. Keep caffeine at higher end of the therapeutic range.
         b. Transfuse if hematocrit is <35 % with $FiO_2 > 0.35$.
         c. Increase NIPPV settings to keep $FiO_2 < 0.6$.
      3. Proper anticipation and preemptive management as outlined above may avoid the endotracheal tube in such predisposed infants.
   C. Group 3
      1. Infants who get systemic infections may fail NIPPV fairly quickly.
      2. Cardiorespiratory compromise secondary to sepsis is the inciting event.
      3. Do not attempt extubation of such infants to NIPPV until clinical manifestations of the sepsis syndrome have resolved.

XIII. Weaning NIPPV settings—consider weaning to nasal cannula (preferred) or oxyhood when:
   A. Frequency (rate) <20 breaths/min
   B. PIP ≤14 cm H_2O
   C. PEEP ≤4 cm H_2O

D. FiO_2 ≤0.3
E. Flow 8–10 LPM
F. Blood gases within normal limits

XIV. Post-NIPPV
A. Nasal cannula: adjust flow to 1–2 LPM and FiO_2 to maintain saturation
B. Oxyhood: adjust FiO_2 to maintain saturation

XV. Potential hazards/complications
A. Obstruction of prongs from mucus plugging
B. Feeding intolerance
C. Abdominal distension
D. Abdominal perforation
E. Ventilator-induced lung injury
F. Hypoventilation
G. Infection
H. Epistaxis/nasal irritation
I. Skin irritation and pressure necrosis

Suggested Reading

Bhandari V. Nasal intermittent positive pressure ventilation in the newborn: review of literature and evidence-based guidelines. J Perinatol. 2009;30:505–12.

Bhandari V. Non-invasive respiratory support. Clin Perinatol. 2012;39:497–511.

Bhandari V. The potential of non-invasive ventilation to decrease BPD. Semin Perinatol. 2013;37:108–14.

Dumpa V, Katz K, Northrup V, Bhandari V. SNIPPV vs. NIPPV: does synchronization matter? J Perinatol. 2012;32:438–42.

Mehta P, Berger J, Bucholz E, Bhandari V. Factors affecting nasal intermittent positive pressure ventilation failure and impact on bronchopulmonary dysplasia in neonates. J Perinatol. 2014;30:754–60.

Precision Flow Vapotherm

33

N. Kevin Ives

I. Introduction.
   A. The Precision Flow® (Vapotherm®, Exeter, New Hampshire, USA) is the manufacturer's second-generation purpose-built device for delivering non-invasive respiratory support in the form of warmed humidified blended gas via high-flow nasal cannula (HFNC). Its predecessor was the Vapotherm 2000i®. The Precision Flow has neonatal, pediatric, and adult applications, but the characteristics and uses described below are only relevant to neonatology where flow rates are restricted to between 1 and 8 L/min.
   B. The use of HFNC, or nasal high-flow therapy (HFT), has been widely adopted over the last decade as a stepdown from other forms of non-invasive respiratory support requiring a nasal seal, or as an alternative to such devices in either primary or post-extubation treatment modalities. Recent trials show that nasal HFT is a safe and effective alternative to nasal continuous positive airway pressure (CPAP) in preterm infants after extubation, and there is a growing experience of its role as a primary treatment and its use in more mature infants.
   C. References to the mode of action, clinical trials, and recent meta-analyses of nasal HFT are provided below. A key message is that nasal HFT is associated with significantly less nasal trauma than CPAP.
   D. The technical information which follows is from the manufacturer's online device information. The guidance on the use of nasal HFT is based on the author's personal experience over 11 years, and may be seen in the context of an evolving international consensus. A wide range of practice exists and this will be further refined by the next phase of clinical research into this still relatively novel therapy.

II. Precision Flow® Specifications I
   A. Device design and use
      1. Sterile water is used to prime the disposable patient circuit, which incorporates a vapor transfer cartridge and a triple lumen-heated patient delivery tube. It is recommended that both these can be used on a single patient for up to 30 days.

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2. After the system has reached the set temperature, an appropriately sized Vapotherm cannula is placed on the patient before connection to the patient delivery tube. It is recommended that the cannula can be used on a single patient for up to 1 week.
3. There is no direct contact between the water and gas streams, which are separated by the multiple polymer fibers of the vapor transfer cartridge. The saturated gas stream leaves the cartridge at the set temperature and is kept warm in a central lumen surrounded by an outer jacket of circulating warmed water. The system is designed to minimize rainout.
4. A single setting control knob allows for adjustment of the three variables: oxygen percentage, temperature, and flow rate of the delivered gas.

III. Precision Flow® Specifications II
   A. Power: 100–240 V AC, 50–60 Hz
   B. Backup power:
      An internal battery (4.8 V) maintains the set flow and oxygen blend for 15 min during a temporary loss of AC power, but the water-circulating pump and heater will stop. It should be appreciated that this is NOT a transport device.
   C. Gas supply:
      Medical air and oxygen at inlet pressures between 4 and 85 psi (28–586 kPa). Note that only if both gases are at inlet pressures of at least 40 psi (276 kPa) will the full range of flow and oxygen percentage be available.
   D. Performance:
      Temperature range: 33–43 °C at exit from the delivery tube. Accuracy ±2 °C. Warm-up time <5 min.
   E. Oxygen percentage:
      Range 21–100 %. Accuracy ±2 %. It should be noted that at the 22 and 23 % oxygen blend setting the delivered oxygen is still 21 %.
   F. Flow rate:
      Neonatology "Low Flow" cartridge 1–8 L/min in 0.5 L/min increments.
      Pediatric/adult "High Flow" cartridge 5–40 L/min in 1.0 L/min increments.
      HI (High) or LO (Low) Cartridge selection is displayed on the front panel of the Precision Flow® device. The "High Flow" cartridge should not be used in neonatal patients.

IV. Precision Flow® Indicators and Alarms
   A. "Battery charging"
      The internal battery backup is not fully charged.
   B. "Unit in battery mode."
      Gas flow continues without heat or water circulation.
   C. "Water out"
      No water in disposable water path.
   D. "Blocked tube"
      High gas pressure at inlet to delivery tube. Obstructed or kinked cannula or too small a cannula for selected flow rate.
   E. "O_2 sensor fault"
      Depleted or defective O_2 sensor.
   F. "Gas supply"
      Gas supply pressure outside operating range
   G. "Cartridge fault"
      Cartridge not detected or excessive gas/water diffusion through cartridge fibers
   H. "Temperature"
      Temperature out of range. Unit will not operate.

V. Patient selection
   A. Any patient considered suitable for non-invasive respiratory support using a nasal seal system (i.e., nasal CPAP, or dual-level CPAP) may be suitable.
   B. A patient with nasal trauma from nasal seal CPAP should be considered a candidate for "rescue" with nasal HFT.
   C. Parental and nursing preferences are likely to dictate patient selection.

VI. Nasal cannula selection
   A. Only Vapotherm® cannulas should be used with the Precision Flow, and Vapotherm cannulas should not be used with other humidification devices that deliver nasal HFT. The Precision Flow device is designed to deliver safely with high upstream pressure to drive flows of up to 8 L/min through the smallest of cannulas, thus creating a higher velocity flow stream in the nasal cavity to facilitate purging of expired gas. If narrow-diameter prongs in a cannula that incorporates a pressure pop-off valve are used in conjunction with a Precision Flow device, flow is likely to be restricted. Equally, if the small Vapotherm cannulas are used with devices that incorporate an upstream pressure release valve of 40 cm H_2O, there will be restriction of flow at the cannula tip.
   B. The cannula tips should not occlude more than 50 % of the area of the nares in order to allow optimal washout of the dead space. In effect, this equates to a cannula prong tip width of no more than 70 % of the internal diameter of the nares. The manufacturer recommends a safety margin of using cannula prong tips that are not more than 50 % of the internal diam-

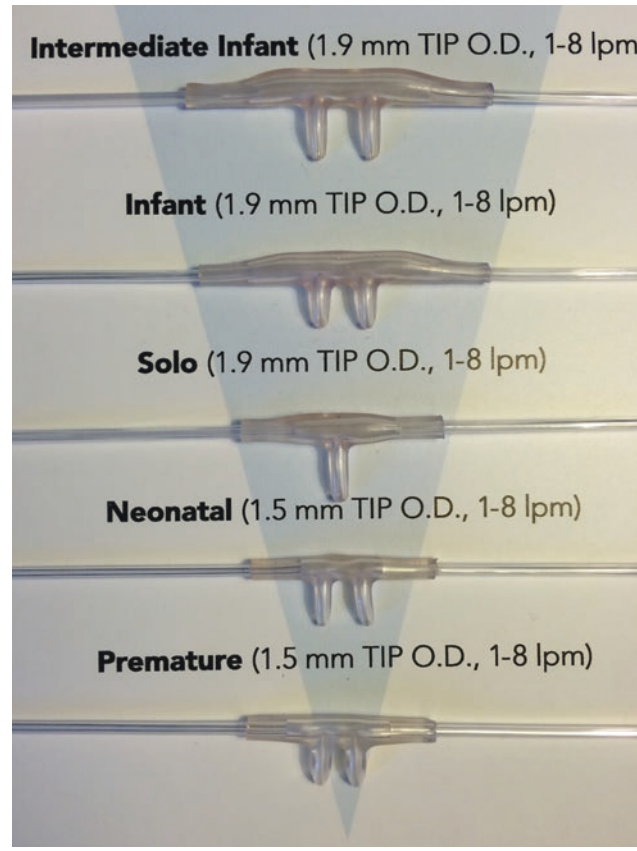

Fig. 33.1 The Vapotherm® cannula range for use in neonatal patients

eter of the nares. The inter-prong distance is also taken into account when choosing a Vapotherm cannula for an individual patient.

C. The Vapotherm cannula range is shown in Fig. 33.1. The *Premature* and the *Neonatal* cannula prongs have an outer diameter measurement at the tip of 1.5 mm and differ only in the spacing of the prongs. The same applies to the *Infant* and *Intermediate Infant* cannulas, which both have an outer diameter measurement at the tip of 1.9 mm. A single-pronged cannula, the "Solo," can be alternated in babies with very small nares, where the *Premature* or *Neonatal* cannulas are judged to be encroaching on dead space washout.

VII. Implementation and Adjustment of Settings

A. In the absence of comparative trial evidence, experience has placed the starting flow rate at between 3 and 8 L/min. The author uses 4–6 L/min. There are clinicians who prefer to start lower and work up, or to start at 8 L/min and work down. In the neonatology setting, body weight and gestation are infrequently taken into account in choice of flow. When transitioning from mechanical ventilation, some clinicians use the mean airway pressure to offer guidance on likely flow requirement.

B. Oxygen delivery is adjusted to maintain the baby in the targeted oxygen saturation range.

C. Increments in flow rate by 0.5 to 1.0 L/min up to a maximum of 8 L/min are made in response to increased work of breathing, elevated respiratory rate, increased oxygen requirement, and respiratory acidosis.

D. The temperature of the warmed gas mixture is set optimally at 37 °C. If there is rainout in the delivery tubing and cannula, it may be necessary to reduce this to as low as 34–35 °C at flow rates of <4 L/min. This is rarely necessary if the distal delivery system is in the infant's warm incubator or the ambient nursery temperature is well maintained.

VIII. Patient Monitoring and Assessment for Escalation of Respiratory Support

A. The same level of monitoring and nursing observations should be adopted as those used for a baby receiving nasal CPAP.

B. Escalation of respiratory support is based on the same criteria of blood gases, oxygen requirement, apnea, or clinical work of breathing as would be used for a baby receiving nasal CPAP. For such babies, clinical trials using Vapotherm devices have not adopted the "rescue" approach with nasal CPAP or NIPPV preferred by some clinicians.

IX. Weaning

A. Oxygen delivery is weaned first as tolerated according to the targeted oxygen saturation range.

B. Until oxygen delivery is 30 % or less it may not be possible to wean the flow rate.

C. In a clinically stable infant receiving ≤30 % oxygen, attempts should be made to wean the flow rate by 0.5 to 1.0 L/min every 12–24 h. Weaning on Precision Flow can continue to flow rates of 2.5–3.0 L/min or lower. From these rates, treatment can be stopped if in air or transferred to a low flow oxygen delivery system.

D. Some infants will require re-escalation of the flow rate if the weaning process has over-shot or if there is a clinical deterioration. In such cases, the approach outlined in VII C above should be adopted. To a large extent, the infant guides the nurse and clinician as to the flow rate that is most suitable, and may remain on static settings for some days despite attempts to wean support.

X. Interfacing with Additional Therapies and Patient Monitoring

A. An inline adaptor is available for the Precision Flow to utilize nebulized medications. It is designed for use with the Aerogen® Aeroneb® Solo.

B. There are licensed technology adaptations of the Precision Flow circuit for delivery of both nitric oxide and heliox.
C. As with other ventilatory and non-ventilatory respiratory support modalities, the prospect of servo-controlled oxygen delivery is being explored.

Suggested Reading

Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airways pressure postextubation in premature infants. J Pediatr. 2012;162(5):949–54.

Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. Respir Med. 2009;103:1400e5.

Frizzola M, Miller TL, Rodriguez ME, et al. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. Pediatr Pulmonol. 2011;46:67–74.

Kotecha SJ, Adappa R, Gupta N, Watkins WJ, Kotecha S, Chakraborty M. Safety and efficacy of high-flow nasal cannula therapy in preterm infants: a meta-analysis. Pediatrics. 2015;136(3):542–53.

Manley BJ, Owen LS. High-flow nasal cannula: mechanisms, evidence and recommendations. Semin Fetal Neonatal Med. 2016. doi:10.1016/j.siny.2016.01.002.

Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. Neonatology. 2012;102(4):300–8.

Manley BJ, Owen LS, Doyle LW, Anderson CC, Cartwright DW, Pritchard MA, Donath SM, Davis PG. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013;369:1423–33.

McQueen M, Rojas J, Sun SC, Tero R, Ives K, et al. Safety and long term outcomes with high flow nasal cannula therapy in neonatology: a large retrospective cohort study. J Pulm Respir Med. 2014;4:216.

Reynolds P, Leontiadi S, Lawson T, Otunla T, Ejiwumi O, Holland N. Stabilisation of premature infants in the delivery room with nasal high flow. Arch Dis Child Fetal Neonatal Ed. 2016;0:F1–4.

Wilkinson D, Andersen C, O'Donnell CPF, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev 2016;(2):CD006405. doi:10.1002/14651858.CD006405.pub3. (IF 5.9).

Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics. 2013;131(5):e1482–90.

Section VI

Ventilatory Modes and Modalities

Intermittent Mandatory Ventilation

34

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I. Description
   A. Definition
      1. Intermittent mandatory ventilation (IMV) provides a fixed rate of mechanical ventilation, determined by the clinician, and allows spontaneous breathing between mechanical breaths.
      2. This mode may be utilized in the acute care phase (high rates) or the weaning phase (low rates), and can be either pressure or volume targeted.
   B. Characteristics
      1. Mandatory breaths occur at fixed intervals determined by the preset breath rate (BR). Total cycle time is the BR (bpm) divided by 60 s/min.
      2. With pressure targeting, the mandatory tidal volume (V_T) is determined by the preset pressure limit (PL), flow, and inspiratory time (T_I), as well as the patient's compliance (C_L) and airway resistance (R_{AW}).
      3. V_T may not be stable breath to breath, particularly if the patient is breathing asynchronously with the ventilator.
      4. The patient may breathe spontaneously between mandatory breaths from a flow of gas, with a preset oxygen fraction (F_iO_2), provided from the ventilator (continuous and/or demand flow). Spontaneous breaths are supported only by the provided level of positive end-expiratory pressure (PEEP, also known as baseline pressure).
      5. The spontaneous BR, V_T, peak flow, and T_I are determined by the patient.
      6. PEEP may be increased to a preset level to enhance the patient's oxygenation.

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C. Indications
   1. Hypoxemic respiratory failure—$PaO_2 < 50$ Torr (6.7 kPa) while receiving $F_iO_2 \geq 0.5$
   2. Hypercapnic respiratory failure—$PaCO_2 > 60$ Torr (8 kPa)
   3. Unstable cardiovascular status (bradycardia, hypotension)
   4. Impaired respiratory drive (apnea, neurologic impairment)
   5. Excessive work of breathing (impaired pulmonary function, airway obstruction)

D. Management of Potential Complications
   1. Overdistension/barotrauma/volutrauma
      a. If possible, avoid inspiratory pressure (IP) settings above 35 cm H_2O. Wean pressure aggressively.
      b. The risk of lung injury, as well as intraventricular hemorrhage, in preterm infants increases when the patient is breathing asynchronously with the ventilator. Consider use of sedation and/or paralytics if synchronized ventilation is not available.
   2. Cardiovascular compromise
      a. The risk increases at mean airway pressures >15 cm H_2O. Avoid excessive ventilator settings whenever possible.
      b. Additional medical management of hypotension and/or hypovolemia may be required.
   3. Airway complications including upper airway trauma, endotracheal tube malposition, and tube obstruction from plugging or kinking.
      a. Endotracheal tubes and ventilator circuits should be firmly secured to avoid excessive movement.
      b. Lavage and suction should be performed when the physical assessment indicates the need to do so and is most safely accomplished by two people.
   4. Oxygen toxicity
      a. Utilize optimum mean airway pressure and PEEP to improve oxygenation.
      b. Wean oxygen as quickly as possible.
   5. Ventilator-acquired infection
      a. Infection control policies and procedures should be strictly followed.
      b. Prophylactic use of antibiotics is a common practice, although of unproven efficacy and potential toxicity.

E. Advantages
   1. The clinician-selected rate will deliver mechanical breaths at fixed intervals, even if the baby is completely apneic.
   2. Useful mode when skeletal muscle relaxants or heavy sedation is required.
   3. Easier to avoid inversion of inspiratory:expiratory ratio and gas trapping.

F. Disadvantages
   1. May result in significant dyssynchrony between baby and ventilator resulting in wide variability in delivered tidal volumes depending upon whether the baby is breathing *with* the ventilator (large tidal breath), *against* the ventilator (small tidal volume), or somewhere in between.
   2. Consequences of dyssynchrony
      a. Inefficient gas exchange
      b. Gas trapping
      c. Air leak
      d. Association with intraventricular hemorrhage

II. Controls, Monitors, and Alarms
   A. Breath rate (BR)
      1. BR adjusts the number of mandatory (i.e., ventilator-controlled breaths) delivered each minute.
      2. Conventional ventilators typically have a range of 0 (CPAP) to 150 breaths per minute (BPM).
      3. Initial BR will generally be between 30 and 60 BPM; however, rates ≥60 BPM may be necessary.
   B. Inspiratory pressure
      1. IP adjusts the peak inspiratory pressure applied to the airway during the inspiratory phase. It is the primary determinant of the delivered V_T (i.e., the depth of inspiration).
      2. Typically the adjustable range will be 3–80 cm H_2O.
      3. The IP is usually started at the lowest level (e.g., 15–20 cm H_2O) necessary to produce adequate breath sounds and chest excursions and adjusted upward in 1–2 cm H_2O increments.
      4. If the ventilator system in use has a V_T monitor, IP may be set to achieve a desired V_T based on weight. General rules are 4–6 mL/kg for very-low-birth-weight (VLBW), 5–7 mL/kg for low-birth-weight (LBW), and 5–8 mL/kg for term infants.
   C. Inspiratory time (T_I)
      1. T_I adjusts the length of time pressure is applied to the airway during inspiration (i.e., the length of the inspiratory phase).
      2. The adjustable range is typically 0.1–3.0 s.
      3. Initial T_I generally ranges from 0.3 to 0.5 s. A shorter T_I may be required if BR > 60 BPM.
   D. Flow rate
      1. This control generally has a dual purpose. First, it adjusts the magnitude of flow directed to the airway during the inspiratory phase of each breath. It also determines the flow available for spontaneous breathing between mandatory breaths. Some ventilators automatically adjust the flow available for spontaneous breathing to a value lower than the preset inspiratory flow to reduce expiratory resistance.
      2. The range of flow varies among ventilators. The low end is usually 2–3 L/min (LPM) with the high end 20–30 LPM, and in some cases up to 40 LPM.
      3. To avoid excessive expiratory resistance the flow rate should be set to the lowest value that will generate the desired IP and produce satisfactory pressure and/or flow waveforms and loops. They will typically be 5–8 LPM in preterm infants and up 10–12 LPM for term infants.

III. Positive End-Expiratory Pressure (PEEP) (Chap. 29)
   A. PEEP enhances lung volume (FRC) by preventing the collapse of alveoli at end expiration. Increases in PEEP increase mean airway pressure, which correlates with improvement in oxygenation.
   B. The range of PEEP available on most ventilators is 1.0 to 20–25 cm H_2O.
   C. PEEP should be started at moderate levels (4–8 cm H_2O) and increased in 1 cm H_2O increments until the desired effect is achieved. In newborns, PEEP levels higher than 10 cm H_2O are only utilized occasionally.
   D. Monitors and Alarms
      1. The peak inspiratory pressure (PIP) monitor reflects the highest pressure recorded during the inspiratory phase of mandatory breaths. It reflects the IP control setting and, therefore, it usually does not vary breath to breath. Some ventilators also have an airway pressure gauge which reflects the dynamic increase and decrease in pressure between the IP and PEEP (ΔP or amplitude).

a. The High Pressure alarm, usually set at 5–10 cm H_2O above the IP setting, audibly and visually alarms for an increase in airway pressure.
b. The Low Pressure alarm is generally set at 5–10 cm H_2O below the IP. It audibly alarms for a patient circuit leak or disconnection.
c. The Low PEEP alarm is set at 2–3 cm H_2O below the PEEP setting. It also alarms for a patient circuit leak or disconnect.

2. The mean airway pressure monitor reflects the average pressure applied over time (i.e., a moving average). This monitor responds to changes in the IP, BR, T_I, flow, and PEEP settings.
3. In IMV, the BR and T_I monitors reflect the control settings for these parameters. The expiratory time (T_E) and *I*:*E* ratio monitors reflect calculated values based on the T_I and BR settings. *I*:*E* ratio and T_E are valuable in assessing the risks of gas trapping and inadvertent or auto-PEEP.
4. The Apnea alarm reflects decreases in respiratory rate. Often, it is factory preset at 20 s but may be adjustable from 10 s to 2 min on some ventilators.
5. Neonatal ventilators do not always include an oxygen analyzer. However, a stand-alone monitor may be added externally. Most monitors include high and low F_iO_2 alarms which are usually set at 0.05 above and below the preset level.
6. Most present-generation ventilators include V_T and minute volume monitors, either built-in or as external options. Inspiratory/expiratory V_T is the volume (mL) inspired or expired per breath. When both are provided, the degree of airway leak can be assessed. Minute volume is the volume exhaled during a 1 min time frame.
   a. The V_T monitor is a valuable tool for titrating the IP setting to achieve an optimal V_T (see above).
   b. The Low Minute Volume alarm can alert a significant drop in V_T, BR, or a leak/disconnection in the patient circuit. It may be set 20–25 % below the prevailing minute volume.
7. An early sign of failure to wean from mechanical ventilation may be tachypnea. Some ventilator monitoring systems may include a High Breath Rate alarm or a High Minute Volume alarm to alert the clinician to this situation.
8. Most ventilators include alarms for loss of air and/or oxygen gas pressure, loss of electrical power, and ventilator-inoperative conditions. These alarm conditions should be addressed immediately as patient compromise may be highly likely.

IV. Patient Management
   A. Ventilation
      1. The primary controls which adjust the level of ventilation are the amplitude ($\Delta P = \text{IP} - \text{PEEP}$) and BR.
      2. IP should be adjusted to achieve adequate lung inflation and discourage atelectasis. Assessment of bilateral breath sounds, chest excursion, exhaled V_T, and chest radiography can guide subsequent adjustments.
      3. Once adequate lung inflation has been achieved, BR should be adjusted to maintain $PaCO_2$ and pH within target ranges. Minute ventilation can be very useful to assess this trend.
   B. Oxygenation
      1. The primary parameters that affect oxygenation are F_iO_2 and mean P_{AW}.
      2. F_iO_2 should be maintained below 0.6, if possible, to avoid an increased risk of oxygen toxicity.
      3. Excessive PEEP levels should be avoided to reduce the risk of cardiovascular compromise. However, do not be reluctant to use whatever PEEP is necessary, as long as the patient is adequately monitored.

4. Mean airway pressure correlates with oxygenation. Increases in T_I may improve oxygenation, without changes in F_iO_2 or PEEP, but care should be taken to avoid using an inadequate expiratory time.

C. Weaning (Chap. 78)
1. As the patient's compliance increases, delivered V_T will increase. To avoid overinflation, the IP should be decreased in 1–2 cm H_2O decrements for minor adjustments, and 3–5 cm H_2O decrements for moderate adjustments, to a minimum of 10–15 cm H_2O.
2. BR should be decreased in 3–5 BPM decrements for slight adjustments in $PaCO_2$, and 5–10 BPM decrements for moderate adjustments, to a minimum of 5–10 BPM.
3. PEEP should be weaned in 1–2 cm H_2O decrements to a minimum of 3–4 cm H_2O.
4. F_iO_2 should be weaned aggressively to <0.4.
5. Once ventilator parameters have been weaned to minimum values, readiness for extubation may be assessed. Evaluation of respiratory parameters, chest radiography, airway clearance, and hemodynamics can aid the decision process.

V. Commentary

A. With the evolution of mechanical ventilators, there should be very limited use of IMV, given the superiority of virtually every other mode of ventilation.
1. SIMV
2. Assist/control
3. Pressure support

B. About the only situations where IMV should be used are in babies requiring skeletal muscle relaxants or those without any respiratory drive whatsoever.

Suggested Reading

Aloan CA, Hill TV. Respiratory care of the newborn. 2nd ed. Philadelphia: Lippincott; 1997.

Chatburn RL. Fundamentals of mechanical ventilation. A short course in the theory and application of mechanical ventilators. Cleveland Heights, OH: Mandu Press Ltd.; 2003.

Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co, Inc.; 1998.

Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal-perinatal medicine: diseases of the fetus and infant. 9th ed. St. Louis: Elsevier/Mosby; 2015. p. 1116–40.

Goldsmith JP, Karatokin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: W.B. Saunders Co.; 2009.

Koff PB, Eitzman D, Neu J. Neonatal and pediatric respiratory care. St. Louis: Mosby; 1993.

Whitaker KB. Comprehensive perinatal and pediatric respiratory care. 3rd ed. Albany, NY: Delmar Publishers, Inc; 2001.

Synchronized Intermittent Mandatory Ventilation

35

Steven M. Donn and Sunil K. Sinha

I. Description
   A. Ventilatory mode in which mechanical breaths are synchronized to the onset of a spontaneous patient breath (if trigger threshold is met), or delivered at a fixed rate if patient effort is inadequate or absent. Spontaneous patient breaths between mechanically assisted breaths are supported only by baseline pressure (PEEP).
   B. A form of patient-triggered ventilation (PTV)
II. Cycling mechanisms
   A. Time. Inspiration ends after a pre-set time.
   B. Flow. Inspiration ends when flow decreases to a chosen percentage of the peak inspiratory flow rate.
   C. Volume
III. Trigger mechanisms
   A. Airway flow change
      1. Heated wire anemometer
      2. Differential pressure transducer
   B. Airway pressure change
   C. Diaphragmatic EMG signal
IV. Synchronized Intermittent Mandatory Ventilation (SIMV) Breath
   A. In SIMV, the breathing time is divided into "breath periods" or "assist windows" based on the selected ventilator rate.
   B. The first time a patient attempts to initiate a breath during an assist window (which begins immediately after a mechanically delivered breath), the ventilator delivers an assisted breath, provided that patient effort exceeds the trigger threshold.
   C. Further attempts to breathe during the same assist window result only in spontaneous breaths, supported only by the baseline pressure.

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D. Mechanical breaths are only delivered if there is insufficient patient effort or apnea during the preceding assist window.
E. Patient-controlled variables
1. Spontaneous respiratory rate
2. Inspiratory time (if flow cycled)
F. Clinician-controlled variables
1. Peak inspiratory pressure (if pressure targeted)
2. Tidal volume delivery (if volume targeted)
3. Inspiratory time (if time cycled)
4. Flow
5. SIMV rate
G. Flow cycling
1. Inspiration is terminated at a percentage of peak flow rather than time
2. Synchronizes expiratory as well as inspiratory phase, and thus total patient/ventilator synchrony can be achieved for assisted breaths

V. Spontaneous Breath
A. Supported by baseline pressure (PEEP) only
B. Work of breathing is higher than for assist/control or with pressure support ventilation
C. Observation of spontaneous tidal volume is a useful indicator of suitability to wean

VI. Patient Management
A. Indications
1. Works best as a weaning mode, although many clinicians prefer it to assist/control as a primary management mode
2. Flow triggering especially useful in extremely low-birth-weight infants
3. Provides partial ventilatory support, as patient can breathe between mechanical breaths
4. Synchrony can decrease the need for sedatives/paralytics.
B. Initiation
1. Use minimal assist sensitivity.
2. Set SIMV rate at reasonable level to maintain adequate minute ventilation.
3. For flow cycling, termination at 5–10 % of peak flow generally works best but must check to see that patient is receiving adequate tidal volume and inspiratory time
4. Other parameters set as for IMV
C. Weaning
1. Primary weaning parameters include SIMV rate, peak inspiratory pressure (for time or flow cycling), and tidal volume (for volume targeting)
2. If P_aCO_2 is too low, it is most likely the result of overventilation. Lower the rate, pressure, or volume depending on lung mechanics.
3. As patient status improves, spontaneous tidal volumes will increase, enabling lowering of SIMV rate.
4. Can extubate directly from SIMV, or add or switch to pressure support ventilation (PSV)
5. Can also wean by increasing assist sensitivity, thus increasing patient work and therefore tolerance

VII. Problems
A. Auto-cycling and false triggering
1. Leaks anywhere in the system (around ETT, in circuit, etc.) can cause flow- and pressure-triggered devices to misread this as patient effort resulting in delivery of a mechanical breath.
2. Auto-cycled breaths all look identical on graphic monitor and can be distinguished from rapid breathing.

B. Failure to trigger
   1. Assist sensitivity set too high
   2. Patient unable to reach trigger threshold
   3. Patient fatigue. Spontaneous breaths may be inadequately supported by PEEP, increasing the work of breathing

C. Inadequate inspiratory time (flow cycling) results in inadequate tidal volume delivery. Patient may compensate by breathing rapidly.

Suggested Reading

Donn SM, Sinha SK. Controversies in patient-triggered ventilation. Clin Perinatol. 1998;25:49–62.

Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. J Perinatol. 1994;14:90–4.

Donn SM, Becker MA, Nicks JJ. Special ventilatory techniques I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St. Louis: Elsevier Saunders; 2011. p. 220–34.

Sinha SK, Donn SM. Advances in neonatal conventional ventilation. Arch Dis Child. 1996;75:F135–40.

Assist/Control Ventilation

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Steven M. Donn and Sunil K. Sinha

I. Description
   A. Ventilatory mode in which mechanical breaths are either patient (assist) or ventilator (control) initiated
   B. Another form of patient-triggered ventilation
II. Cycling Mechanisms
   A. Time
   B. Flow
III. Trigger Mechanisms
   A. Airway flow
      1. Heated wire anemometer
      2. Differential pressure transducer
   B. Airway pressure
   C. Thoracic impedance
   D. Diaphragmatic EMG signal
IV. Assist Breath
   A. If patient effort exceeds trigger threshold, a mechanical breath is initiated.
      1. Trigger delay (response time) is the time from signal detection to rise in proximal airway pressure.
      2. Long trigger delay increases work of breathing as patient may complete own inspiratory cycle before receiving ventilatory assistance from the mechanical breath.
   B. Patient-controlled variables
      1. Respiratory rate
      2. Inspiratory time (if flow-cycled)
   C. Clinician-controlled variables
      1. Peak inspiratory pressure (if pressure-targeted)

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2. Tidal volume delivery (if volume-targeted)
3. Inspiratory time (if time-cycled)
4. Flow (if time-cycled, pressure-limited; if volume-targeted)
5. Control rate

D. Flow-Cycling
1. Inspiration is terminated at a percentage of peak flow rather than time.
2. Fully synchronizes patient and ventilator (during both inspiratory and expiratory phase)
3. Prevents inversion of inspiratory:expiratory ratio and minimizes gas trapping
4. May occasionally result in insufficient inspiratory time and tidal volume delivery

V. Control Breath
A. Essentially a safety net, providing back-up IMV in case of insufficient patient effort or apnea
B. Provides a minimal minute ventilation if baby is unable to trigger the ventilator or fails to breathe
C. However, if rate is set too high, patient may "ride" the ventilator and not breathe spontaneously.
D. If patient is consistently breathing above the control rate, lowering it has no effect on the mechanical ventilatory rate.

VI. Patient Management
A. Indications
1. Works well for virtually all patients
2. Flow-triggering especially useful in extremely low birth weight infants
3. Provides full ventilatory support
4. Synchrony can decrease need for sedatives/paralytics.

B. Initiation
1. Use minimal assist sensitivity.
2. Set control rate at reasonable level until patient demonstrates reliable respiratory drive, usually 20–40 breaths/min.
3. For flow-cycling, termination at 5–10 % of peak flow generally works best, but check to see that patient is receiving adequate tidal volume.
4. Other parameters set as for IMV

C. Weaning
1. Since reduction in ventilator rate will have no impact on minute ventilation if patient breathes above control rate, primary weaning parameter is peak inspiratory pressure in pressure-targeted ventilation or delivered volume in volume-targeted ventilation.
2. If P_aCO_2 is too low, it is most likely the result of overventilation (too high a peak inspiratory pressure), as infant is unlikely to spontaneously hyperventilate. Lower the pressure or volume.
3. As soon as patient demonstrates reliable respiratory drive, lower the control rate (20–30 bpm).
4. Can extubate directly from assist-control or switch to SIMV or SIMV/PS (Chap. 37)
5. Can also wean by increasing assist sensitivity, thus increasing patient work and therefore developing tolerance.

VII. Problems
A. Auto-cycling and false triggering
1. Leaks anywhere in the system (around ETT, in circuit, etc.) can cause flow and pressure-triggered devices to misread this as patient effort resulting in delivery of a mechanical breath. Setting the assist sensitivity at a level above the measured leak can avoid this.
2. Excessive "rainout" in the ventilator circuit may also cause flow changes sufficient to initiate auto-cycling. Make sure to remove condensation.

B. Failure to trigger
   1. Assist sensitivity too high
   2. Patient unable to reach trigger threshold
   3. Faulty sensor
   4. Patient fatigue
   5. Sedative drugs

C. Inadequate inspiratory time (flow-cycling) may result in inadequate tidal volume delivery. Patient may compensate by breathing rapidly, which further decreases inspiratory time. May need to switch mode.

D. Metabolic acidosis. Baby may attempt to achieve respiratory compensation (alkalosis) by breathing rapidly.

Suggested Reading

Donn SM, Sinha SK. Controversies in patient-triggered ventilation. Clin Perinatol. 1998;25:49–62.

Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. J Perinatol. 1994;14:90–4.

Donn SM, Becker M, Nicks JJ. Special ventilator techniques and modalities I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St Louis: Saunders Elsevier; 2011. p. 220–34.

Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD000456. doi:10.1002/14651858.CD000456.pub3.

Sinha SK, Donn SM. Advances in neonatal conventional ventilation. Arch Dis Child. 1996;75:F135–40.

Sinha SK, Donn SM. Newer forms of conventional ventilation for preterm newborns. Acta Paediatr. 2008;97:1338–43.

Pressure Support Ventilation

37

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I. Description
   A. Ventilatory mode in which spontaneous breaths are partially or fully supported by an inspiratory pressure assist above baseline pressure to decrease the imposed work of breathing created by the narrow lumen endotracheal tube, ventilator circuit, and demand valve, if one is used.
   B. A form of patient-triggered ventilation providing synchrony both during initiation and termination of inspiratory effort.
   C. May be used either alone in babies showing reliable respiratory drive, or in conjunction with SIMV.

II. Cycling Mechanisms
   A. Time: inspiratory time limit, chosen by clinician, which cannot be exceeded.
   B. Flow: termination of inspiratory cycle is based on a percentage of peak flow. This varies according to both delivered tidal volume and specific algorithm of the ventilator in use. For most neonatal ventilators, this occurs at 5–10 % of peak inspiratory flow.
   C. Inflation will be terminated by the first condition met (flow or time).

III. Trigger Mechanisms
   A. Airway pressure change (minimum 1.0 cm H_2O)
   B. Airway flow change (minimum 0.1 LPM)

IV. Pressure Support Breath
   A. A spontaneous inspiratory effort which exceeds the trigger threshold will initiate delivery of a mechanically generated pressure support breath.
   B. There is a rapid delivery of flow to the patient, which peaks, then decelerates.
   C. The airway pressure will rise to the pressure support level, set by the clinician as a value above baseline (PEEP).

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D. When flow-cycling criterion is met (decline to the termination level), the breath will end and flow will cease. If this has not occurred by the end of the set inspiratory time limit, the inspiratory phase of the mechanical breath will be stopped.
E. Unlike the fixed flow used in traditional neonatal ventilation, in PSV the amount of flow delivered to the patient during inspiration is variable and depends to a certain extent on the underlying respiratory mechanics, and will be proportional to patient effort.
F. Patient-controlled variables
   1. Respiratory rate
   2. Inspiratory time
   3. Peak inspiratory flow
G. Clinician-controlled variables
   1. Pressure support level
   2. Inspiratory time limit
   3. Baseline flow
   4. Baseline pressure (PEEP)
   5. SIMV rate, flow (except with pressure control), inspiratory time, and tidal volume or pressure limit (if SIMV is used)
   6. Rise time. This is a semi-quantitative variable, which allows alteration in the inspiratory flow rate and modulates the slope of the inspiratory pressure waveform.

V. Patient Management
A. Indications
   1. Designed primarily as a weaning mode to enable full or partial unloading of respiratory musculature during mechanical ventilation
   2. Pressure support is fully synchronized with spontaneous breathing and can decrease the need for sedatives/paralytics.
B. Initiation
   1. Use minimal assist sensitivity.
   2. The pressure support level can be adjusted to provide either full support (PS_{max}), delivering a full tidal volume breath, or at a lower level to provide partial support. Remember that the pressure support level is the pressure applied above baseline (i.e., a patient receiving 4 cm H_2O PEEP and 16 cm H_2O pressure support actually gets 20 cm H_2O peak inspiratory pressure).
   3. Set the inspiratory time limit for the pressure support breath.
   4. Set parameters for the SIMV breaths if they are to be used.
      a. These can be used analogously to control breaths during assist/control ventilation, providing a "safety net" of background ventilation in the event of inadequate effort (triggering) or apnea.
      b. If the SIMV rate is set too high, and the majority of minute ventilation is provided by SIMV, the patient may have no impetus to breathe, thus defeating the purpose of pressure support.
C. Weaning
   1. Weaning may be accomplished in a variety of ways.
      a. Decrease the SIMV rate to as low a level as possible, thus increasing the need for spontaneous effort.
      b. Decrease the pressure support level, thus increasing the percentage of the work of breathing assumed by the patient.
      c. Consider the use of pressure support alone in patients with reliable respiratory drive who have no difficulty triggering.

2. Consider extubation when the pressure support level has been reduced to the point where it delivers about 3–4 mL/kg tidal volume if the patient appears comfortable and is not tachypneic at this level.

VI. Problems
   A. Failure to trigger (may occur with small endotracheal tubes and inadequate patient effort)
   B. Pressure overshoot
   C. Premature termination
   D. A common error is using a high SIMV rate with PSV. This interrupts the synchrony of PSV and subjects the patient to possibly unnecessary mandatory breaths. If a high SIMV rate is needed, the baby may not be ready for PSV and might do better in assist/control.

VII. Clinical Applications
   A. Weaning mode
   B. Bronchopulmonary dysplasia (BPD)
      1. Infants with BPD exhibit reactive airways with elevated inspiratory resistance.
      2. Pulmonary mechanics in most modes display flattened inspiratory flow-volume loop.
      3. Variable inspiratory flow during pressure support ventilation enables patient to overcome increased inspiratory resistance and lowers ventilatory work.

VIII. Advantages of Pressure Support Ventilation
   A. Complete patient-ventilator synchrony
   B. Decreased work of breathing compared to other modes
      1. Same tidal volume delivered at lower work of breathing
      2. Larger tidal volume delivered at same work of breathing
      3. Stabilization of spontaneous breathing pattern/rate
   C. Adults treated with pressure support ventilation have described increased comfort and endurance compared to other weaning modes.
   D. Short term clinical studies in the neonatal population have also confirmed advantages in terms of reduced work of breathing and improved synchrony associated with reduced need for mechanical respiratory support.

IX. Additional Applications and Variations
   A. Volume assured pressure support
      1. Used primarily in adults, but now available for infant use on some devices.
      2. Combines features of volume-controlled ventilation and pressure support ventilation.
      3. Clinician determines minimum tidal volume.
      4. As long as spontaneous patient effort results in delivery of desired tidal volume, breath "behaves" like a pressure support breath.
      5. If breath delivers a tidal volume below the desired minimum, it is transitioned to a volume-controlled breath by prolonging inspiration at the minimal set flow and slightly ramping up the pressure, assuring delivery of desired tidal volume.
   B. Mandatory minute ventilation
      1. This mode combines pressure support ventilation with SIMV.
      2. Clinician chooses a minute ventilation rate which the patient is to receive by selecting a desired tidal volume and frequency.
      3. As long as spontaneous breathing results in minute ventilation which exceeds the minimum, all breaths are pressure support breaths.
      4. If minute ventilation falls below the set minimum, the ventilator will provide sufficient SIMV breaths to allow the patient to "catch up" to the desired level of minute ventilation. This is based on a moving average.

Suggested Reading

Donn SM, Becker MA. Baby in control: neonatal pressure support ventilation. Neonatal Intensive Care. 1998a; 11:16–20.

Donn SM, Becker MA. Mandatory minute ventilation: a neonatal mode of the future. Neonatal Intensive Care. 1998b;11:20–2.

Donn SM, Sinha SK. Pressure support ventilation of the newborn. Acta Neonatologica Japonica. 1997;33:472–8.

Donn SM, Sinha SK. Controversies in patient-triggered ventilation. Clin Perinatol. 1998;25:49–62.

Donn SM, Becker MA, Nicks JJ. Special ventilator techniques and modalities I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St Louis: Saunders Elsevier; 2011. p. 220–34.

Gupta S, Sinha SK, Donn SM. The effect of two levels of pressure support ventilation on tidal volume delivery and minute ventilation in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2009;94:F80–3.

Guthrie SO, Lynn C, LaFleur BJ, et al. A crossover analysis of mandatory minute ventilation compared to synchronized intermittent mandatory ventilation in neonates. J Perinatol. 2005;25:643–6.

Nicks JJ, Becker MA, Donn SM. Bronchopulmonary dysplasia: response to pressure support ventilation. J Perinatol. 1994;11:374–6.

Patel D-S, Rafferty GF, Lee S, Hannam S, Greenough A. Work of breathing during SIMV with or without pressure support. Arch Dis Child. 2009;94:434–6.

Sarkar S, Donn SM. In support of pressure support. Clin perinatol. 2007;34:117–28.

Sinha SK, Donn SM. Advances in neonatal conventional ventilation. Arch Dis Child. 1996;75:F135–40.

Sinha SK, Donn SM. Pressure support ventilation. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk: Futura Publishing Co.; 1998. p. 301–12.

Volume-Targeted Ventilation

38

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I. Description
   A. A form of mechanical ventilation where tidal volume is the primary target variable and pressure is permitted to fluctuate to deliver this volume
   B. Although tidal volume may be monitored at the ventilator, measurement at the proximal airway is more accurate and safer for the neonatal patient.
   C. Because uncuffed endotracheal tubes are used in newborns, there may be a variable loss of delivered gas volume from leaks. It is thus more appropriate to describe this form of ventilation as volume-controlled, volume-limited, or volume-targeted, rather than volume-cycled ventilation.

II. Modes which Can be Utilized with Volume-Targeted Ventilation (VTV)
   A. Intermittent mandatory ventilation (IMV)
   B. Synchronized intermittent mandatory ventilation (SIMV)
      1. Alone
      2. With pressure support (PSV)
   C. Assist/control (A/C)
   D. Pressure regulated volume control
   E. Volume assured pressure support (VAPS)
   F. Mandatory minute ventilation (MMV)
   G. Volume guarantee (VG)

III. Characteristics of Volume-Controlled Breaths
   A. Continuous inspiratory flow produces the characteristic "square wave" on the flow waveform
      1. This results in ramping of pressure, with peak pressure and volume delivery occurring at the end of inspiration.

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2. This differs from pressure-targeted breaths, which utilize an accelerating–decelerating flow waveform, producing a breath in which peak pressure and peak volume delivery occur early in inspiration. Thus, there is a fundamental difference.
3. Theoretically, pressure-targeted breaths are advantageous in treating homogeneous lung disease in which there is a need for a high opening pressure, such as early in RDS.
4. Volume-targeted breaths are advantageous in treating heterogeneous lung disease, where slower inflation of the lung should lead to better distribution of gas flow.

B. May be patient-triggered or machine-initiated
   1. Flow or pressure trigger
   2. May be at proximal airway or within ventilator (see above)
C. Flow-limited (fixed flow rate)
   1. Determines inspiratory time
   2. Square flow waveform; some ventilators allow choice of decelerating flow.
   3. Some newer ventilators offer variable flow, but data regarding use in newborns are unavailable.
D. Dependent variable is pressure.
   1. Low compliance will result in higher pressure delivery.
   2. As compliance improves, pressure will be auto-weaned.
   3. May be influenced by inspiratory flow setting. Flow determines inspiratory time. The higher the flow, the shorter the inspiratory time.
E. Tidal volume is "assured."
F. Maximum alveolar distension depends on end alveolar pressure.

IV. Advantages of Volume-Controlled Ventilation
A. Consistent tidal volume delivery even in the face of changing compliance
B. Volume-limited breaths; avoidance of volutrauma
C. Combination with other modes to facilitate weaning
   1. PSV
   2. VAPS
   3. MMV
D. Auto-weaning of pressure as compliance improves and conversely, increasing pressure to provide same volume if compliance decreases

V. Clinical Limitations
A. Minimal tidal volume delivery
   1. Must know smallest tidal volume machine is capable of delivering
   2. Should not exceed patient's physiologic tidal volume
      a. <1000 g: 4–7 mL/kg
      b. >1000 g: 5–8 mL/kg
   3. Ventilator circuit should be of reasonable rigidity (compliance) so as not to cause excessive compressible volume loss in circuit if pulmonary compliance is low.
   4. Smaller patients with smaller ETT (2.5–3.0 mm) may have difficulty triggering (especially if pressure-triggered).
   5. High flow may result in inadequate inspiratory time in smaller patients.
   6. Leaks
      a. May cause loss in baseline pressure
      b. May result in auto-cycling
      c. Remember that because uncuffed endotracheal tubes are used, leaks are also present during pressure-targeted ventilation but less obvious because they generally are not monitored.

VI. Clinical Indications
  A. Respiratory failure. Virtually all forms of neonatal respiratory failure have been shown to be amenable to VTV.
  B. Ventilator-dependent cardiac disease with normal lungs
  C. Weaning infants recovering from respiratory illness
  D. Bronchopulmonary dysplasia, particularly if lung parenchyma is involved

VII. Initiating Volume Ventilation
  A. Select desired mode.
    1. A/C or SIMV recommended for acute illness
    2. SIMV and/or PSV recommended for weaning
  B. Select desired delivered tidal volume. This is done by adjusting the delivered volume (Vdel).
    1. <1000 g: 4–7 mL/kg
    2. >1000 g: 5–8 mL/kg
    3. Confirm that patient is receiving appropriate tidal volume.
      a. Volume monitoring
      b. Pulmonary graphics
        (1) Tidal volume waveform
        (2) Pressure–volume loop
  C. Set flow rate to achieve desired inspiratory time. This can be modified by adding an inspiratory hold to avoid using an inspiratory time that is inadequate (too short) at higher flow rates. Make sure there is sufficient hysteresis on the pressure–volume loop.
  D. Set mechanical ventilatory rate
  E. Set trigger sensitivity if using patient-triggered mode
    1. Generally use minimal setting unless auto-cycling
    2. Assure patient is able to trigger ventilator.
  F. Some clinicians prefer to set a pressure limit; do not set this too close to peak pressure, or desired tidal volume may not be delivered if compliance decreases.
  G. Some ventilators have a leak compensation system. While beneficial in maintaining a stable baseline in the presence of a leak, it may increase the work of breathing and possibly expiratory resistance.
  H. Assessment of patient
    1. Adequacy of breath sounds
    2. Adequacy of chest excursions
    3. Patient-ventilator synchrony
    4. Patient comfort
    5. Blood gases
    6. Pulmonary mechanics

VIII. Weaning Infants from Volume-Controlled Ventilation
  A. As pulmonary compliance improves, inspiratory pressure will be automatically decreased to maintain desired tidal volume delivery.
  B. Adjustments in delivered tidal volume should be made to maintain desired tidal volume delivery within the physiologic range.
  C. Adjustments in flow rate may need to be made to maintain the same inspiratory time or I:E ratio.
  D. If using A/C:
    1. Decrease control rate (allow patient to assume greater percentage of work of breathing)
    2. May also increase assist sensitivity (trigger)

E. If using SIMV:
   1. Decrease SIMV rate, but remember that patient receives no support for spontaneous breaths other than positive end-expiratory pressure.
   2. Consider adding pressure support (Chap. 37), or even switching to it completely if the baby has consistently reliable respiratory drive.

F. Newer modes (VAPS, MMV) may prove even more beneficial for weaning but have limited clinical experience in the newborn at present.

IX. Clinical Implications

A. Recent meta-analysis has demonstrated that compared to pressure-targeted ventilation, volume-targeting results in
   1. A lower incidence of air leak
   2. Fewer ventilation days
   3. Less BPD
   4. Fewer severe neuroimaging abnormalities

B. May be especially beneficial immediately post-surfactant administration, when compliance may change rapidly.

Suggested Reading

Bandy KP, Nicks JJ, Donn SM. Volume-controlled ventilation for severe neonatal respiratory failure. Neonatal Intensive Care. 1992;5:70–3.

Donn SM. Alternatives to ECMO. Arch Dis Child. 1994;70:F81–4.

Donn SM, Becker MA. Baby in control: neonatal pressure support ventilation. Neonatal Intensive Care. 1998a; 11:16–20.

Donn SM, Becker MA. Mandatory minute ventilation: a neonatal mode of the future. Neonatal Intensive Care. 1998b;11:22–4.

Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal-perinatal medicine: diseases of the fetus and infant. 9th ed. St. Louis: Elsevier/Mosby; 2015. p. 1116–40.

Nicks JJ, Becker MA, Donn SM. Neonatal respiratory failure: response to volume ventilation. J Perinatol. 1993; 13:72–5.

Peng W, Zhu H, Shi H, Liu E. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2014;99:F158–65.

Singh J, Sinha SK, Clark P, et al. Mechanical ventilation of very low birthweight infant: is volume or pressure a better target variable? J Pediatr. 2006;149:308.

Singh J, Sinha SK, Donn SM. Volume-targeted ventilation of newborn. Clin Perinatol. 2007;34:93–105.

Sinha SK, Donn SM. Volume controlled ventilatory modes for the newborn: variations on a theme. Clin Perinatol. 2001;8:547–60.

Sinha SK, Donn SM. Volume-targeted ventilation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St Louis: Saunders Elsevier; 2011. p. 186–99.

Sinha SK, Donn SM, Gavey J, McCarty M. Randomized trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. Arch Dis Child. 1997;77: F202–5.

Tsai WC, Bandy KP, Donn SM. Volume controlled ventilation of the newborn. In: Donn SM, editor. Neonatal and pediatric pulmonary graphic analysis: principles and clinical applications. Armonk: Futura Publishing Co.; 1998. p. 279–300.

Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. Cochrane Database Syst Rev. 2010;(11): CD003666. doi:10.1002/14651858.CD003666.pub3.

Volume Guarantee Ventilation

39

Martin Keszler

I. Description:
   A. Volume guarantee (VG) is one of the several microprocessor-based modalities of volume-targeted ventilation (VTV) that combines advantages of pressure-controlled (PC) ventilation with the ability to deliver a more consistent tidal volume (V_T).
   B. VG is a pressure-limited, volume-targeted, time- or flow-cycled form of ventilation that automatically adjusts peak inflation pressure to target a user selected V_T, based on the exhaled V_T of the previous inflation. In contrast, volume-controlled (VC) ventilation directly controls volume delivered into the ventilator circuit and generates whatever pressure is needed to deliver that volume, up to a pressure pop-off. Inflation is more gradual and is completed when the set V_T is delivered. Because of loss of volume to compression of gas in the ventilator circuit and leak around uncuffed endotracheal tubes (ETT), the V_T that reaches the lungs of small infants bears only an indirect relationship to the set volume.
   C. VG in its original form is a specific modality available on the Draeger Babylog 8000+, the newer VN 500 (Draeger Medical, Telford, PA), and the Leoni Plus (Heinen + Löwenstein GmbH, Bad Ems, Germany-not available in the USA). Recently, CareFusion, San Diego, CA, implemented a version of this modality on its AVEA ventilator, and certain other devices (e.g., Hamilton Medical, Reno, Nevada) utilize their own proprietary volume-targeting modalities that appear to functionally mimic VG. Thus, the name VG is now increasingly used as a generic term, rather than referring only to the specific modality that originally bore that name.
   D. Optimal use of VG requires knowledge of appropriate V_T targets, understanding of the complexities of patient–ventilator interactions and the use of the open lungs strategy to assure even distribution of the tidal volume into a well-recruited lung.

II. Benefits
   A. Avoidance of excessive tidal volume. There is sound evidence that volume, not pressure, is the primary agent responsible for ventilator-induced lung injury. High inflation pressure by itself, without generating correspondingly high lung volume or regional overexpansion,

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does not lead to lung injury. VTV has been shown to reduce the number of excessively large tidal volume inflations, rate of airleak, and the incidence of bronchopulmonary dysplasia.

B. Avoidance of hypocapnia. Extensive evidence indicates that hyperventilation is associated with increased risk of periventricular leukomalacia (PVL) and severe intraventricular hemorrhage (IVH). VTV reduces the incidence of hypocapnia, IVH, and PVL, compared to PC ventilation.

C. Faster weaning from mechanical ventilation. When lung compliance and patient respiratory effort improve, VG lowers inflation pressure in real time, rather than intermittently in response to blood gases. Weaning occurs throughout the day, not just during rounds or when a blood gas is obtained, thus resulting in a shorter duration of ventilation.

D. Compensation for highly variable respiratory drive of an extremely low gestational age newborn with immature respiratory control. With synchronized mechanical ventilation the V_T is determined by the combination of the ventilator-generated inflation pressure and the spontaneous inspiratory effort of the infant. VG generates a higher inflation pressure when the infant hypoventilates or becomes apneic and less to no additional inflation pressure when the infant generates an excessive V_T, thus maintaining a relatively stable V_T even in immature infants with extreme periodic breathing.

E. Fewer blood gas measurements. With stable minute ventilation ensured by VG, along with non-invasive pulse oximetry monitoring, only 1–2 invasive blood gas measurements/day are needed once the appropriate settings are confirmed.

F. Real time notification of significant change in lung mechanics. When set correctly, VG provides real time feedback about deteriorating lung mechanics or ETT migration, allowing for prompt diagnosis and correction.

III. Controls/displays/alarms

A. Controls

1. Basic ventilator mode. VG is an option that can be combined with any of the standard synchronized modes. It functions best when combined with modes that support each spontaneous breath: Assist/control (AC) or Pressure support (PSV). When used with SIMV + PS, only the SIMV inflations are subject to VG. Control variables specific to each mode must be selected first.
2. Target tidal volume. One size does not fit all. See Sect. IV D.
3. Pressure limit. The microprocessor will adjust inflation pressure up to the limit set by the operator. Set the PIP 3–5 cm H_2O above current inflation pressure for optimal safety.
4. With the VN500 ventilator the operator must choose whether or not to use the V_T corrected for ETT leak. This is set as a default in the ventilator setup. I strongly recommend using the compensated V_T, because it allows accurate V_T measurement and control even with a leak up to 70–75 %.

B. Displays

Most ventilator screens are configurable to user preference. Key variables are

1. Measured exhaled tidal volume
2. Tidal volume target
3. Working pressure
4. PIP limit
5. % ETT leak
6. Scalar waveforms for pressure, flow, and volume (N.B., when using the leak compensated V_T, you will not be able to appreciate visually the ETT leak, as the curves are generated using the compensated value.)

C. Alarms
   1. Standard ventilator alarms (high or low minute ventilation, obstruction, disconnect, etc.) remain in place.
   2. Additional alarm is the low tidal volume alarm. This is activated when the tidal volume cannot be reached with the set pressure limit. This may result from a variety of conditions discussed under Sect. VII Troubleshooting.

IV. Initiating VG
   A. Use VG soon after initiation of mechanical ventilation, because this is when lung compliance changes most rapidly.
   B. Choose basic mode of synchronized ventilation: AC or PSV is preferred.
   C. Select PEEP, Ti, and ventilator rate/back-up (control) rate appropriate for patient size and underlying disease process.
   D. Select target V_T based on disease process, patient size, and age.
      1. 4.5 mL/kg for typical preterm infant with RDS
      2. 4 mL/kg for large preterm infant with RDS/pneumonia
      3. 4 mL/kg for infant with congenital diaphragmatic hernia
      4. 5–6 mL/kg if <700 g
      5. 5–6 mL/kg if MAS, air trapping
      6. 6 mL/kg if >1–2 weeks of age, BPD
   E. Alternately, if changing from pressure-controlled mode to VG and PCO_2 is acceptable, observe the average V_T over a minute while on PC and then set the V_T target at that level.
   F. Set PIP limit 3–5 cm H_2O above current PIP or anticipated PIP need.
   G. If unable to reach target V_T, verify ETT position, ETT leak, reassess target V_T.
   H. Attempt to optimize lung recruitment to improve compliance and oxygenation and to ensure that the V_T will be evenly distributed into an open lung.

V. Reassessing Settings
   A. Suggested V_T settings are appropriate starting points based on typical/average values and will work for most infants, but there is range for all biologic variables.
   B. It is essential to re-evaluate how the infant is responding to your initial settings.
   C. Confirm adequacy of support by observing chest rise, auscultating breath sounds, and monitoring FiO_2/SpO_2 and blood gas analyses.
   D. Tachypnea, retractions, low working pressure, and high FiO_2 all indicate inadequate support (V_T is too low for baby's needs). This may be secondary to:
      1. Very small baby where the dead space of flow sensor is relatively large
      2. Increased alveolar dead space—overexpansion, air trapping
      3. Metabolic acidosis, for which the baby is trying to compensate
   E. Cessation of spontaneous respiratory effort may indicate that V_T is set too high, resulting in respiratory alkalosis that has turned off the infant's respiratory drive.
   F. When PCO_2 is out of target range, V_T should be adjusted by about 0.5 mL/kg to achieve a change of ~5 mmHg.
   G. Remember that pH drives the respiratory effort; lowering V_T when the PCO_2 is low but pH is also low from a base deficit will result in inadequate support.
   H. Periodic reassessment of the appropriateness of V_T target is needed on a regular basis (at least daily).
   I. Do not forget to increase V_T target as baby grows.
   J. Anticipate need to increase V_T with advancing age because of increasing alveolar dead space and stretching of upper airway.

K. Anticipate increasing ETT leak as larynx stretches over time. Except with the VN500 where large leaks can be compensated effectively, a leak >40 % affects accuracy. When the measured value underestimates true V_T, the ventilator will increase PIP, potentially leading to overventilation.

VI. Weaning from VG
- A. VG is a self-weaning mode. As long as pH is low enough to stimulate the infant's respiratory drive (<7.35), the infant will breathe actively and the microprocessor will lower working pressure as the lung compliance and the spontaneous effort improve. No action is needed.
- B. It is unnecessary and inappropriate to continue to decrease V_T during weaning. The physiologic V_T needed to satisfy the infant's needs does not decrease, instead the pressure needed to generate that V_T decreases automatically.
- C. Under normal circumstances, V_T should not be decreased to <3.5–4 mL/kg and in infants who needed a larger V_T even 4 mL/kg may be too low.
- D. When working pressure is sufficiently low (<12–16 cm H_2O), the infant is breathing comfortably without tachypnea, and the FiO_2 is <0.30–0.35, extubation should be attempted.

VII. Troubleshooting
- A. Low V_T alarm
  1. VG modes generate alarms not encountered with simple PC; these can become annoying when they are excessive. However, they are there to provide feedback regarding adequacy of ventilator support and should not be ignored.
  2. Low V_T alarm is activated when the V_T cannot be reached with the set pressure limit. This may result from a variety of conditions.
     a. PIP limit is set too close to working PIP
     b. Worsening lung compliance (atelectasis, pneumothorax, and abdominal distention)
     c. Decreased patient effort (sepsis, narcotic suppression of respiratory effort, etc.)
     d. ETT in the right main bronchus or against tracheal wall/carina
     e. Excessive leak around the ETT/inadvertent extubation
     f. Episodic breath-holding spells/forced exhalation episodes that temporarily oppose the ventilator inflation
  3. Persistent low V_T alarm suggests an important change in patient status, lung mechanics, or ETT position. The possible cause must be promptly investigated and corrected.
  4. Note that the relationship between lung compliance, PIP, and V_T is the same, regardless of manual vs. automatic adjustment of PIP (i.e., PC vs. VG). If more than expected PIP is needed, target V_T might be too high or the lungs are very stiff—surfactant and/or a lung volume recruitment maneuver may be needed. Simply changing back to PC ventilation will not change the underlying pathophysiology nor adequacy of support.
- B. PCO_2 is too high. This means that the alveolar minute ventilation/V_T is too low to meet patient's need. After evaluation, correct by increasing V_T and/or rate. Possible causes include
  1. V_T is set too low because of failure to tailor settings to unique patient characteristics.
  2. Increased alveolar dead space (air trapping, BPD)
  3. Relatively increased instrumental dead space (tiny baby)
  4. Inadequate respiratory rate (narcotic respiratory depression, sepsis)
  5. Increased CO_2 production (fever, sepsis, and cold stress)
- C. PCO_2 is too low.
  1. V_T target may be too high.
  2. Infant may be compensating for metabolic acidosis and the PCO_2 may be appropriate.
  3. Infant is agitated.

4. PEEP is too low, resulting in tachypnea.
5. The ventilator is auto-cycling with excessively rapid rate from condensation in ventilator circuit.

D. V_T target is reached but the baby is tachypneic/retracting.
1. The V_T may be set too low, forcing the infant to breathe above the set V_T with little or no PIP generated by the ventilator
2. Agitation
3. Inadequate PEEP

VIII. Risks/Potential Complications

VTV represents a significant paradigm shift. A thorough understanding of key operating principles is essential for safe and effective operation. As with all devices, unfamiliarity with the modality is perhaps the greatest risk.

A. Greatest risk is inadvertent main bronchus intubation with the entire V_T delivered into one lung. This risk can be minimized by setting PIP limit sufficiently close to current/expected PIP.

B. Inadvertent hyperventilation may occur if there is a very large leak around the ETT, which is not adequately compensated. Exhaled V_T is underestimated with excessive leak and the microprocessor will increase PIP to attempt to reach the target. This problem is virtually eliminated by using the leak compensated V_T in the VN500.

C. If VG is utilized during surfactant administration, a drop in PIP to roughly half of the previous value may occur if the ventilator senses complete ETT obstruction. This is a safety feature to avoid overshoot when obstruction is relieved, but it could result in transiently inadequate support.

D. With some forms of VG, the ventilator will default to the PIP limit if the flow sensor is removed or malfunctions, or when manual inflations are delivered via the ventilator, resulting in excessive V_T. This risk can be mitigated by maintaining PIP limit reasonably close to working pressure. The VN500 eliminates this risk because it uses the last PIP generated before the disconnection or manual inflation.

E. When the target V_T too low the infant may be able to generate sufficient V_T and maintain adequate gas exchange on her own but PIP will be very low (essentially ET CPAP). This may lead to increased oxygen consumption, fatigue, and atelectasis, thereby prolonging ventilator dependence. This problem is easily avoided by appropriate V_T settings.

F. Worsening respiratory status may develop if the operator fails to appropriately increase target V_T with growth and advancing postnatal age.

Suggested Reading

Abubakar K, Keszler M. Effect of volume guarantee combined with assist/control vs synchronized intermittent mandatory ventilation. J Perinatol. 2005;25:638–42.

Dreyfuss D, Saumon G. Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis. 1993;148:1194–203.

Keszler M. State of the art in conventional mechanical ventilation. J Perinatol. 2009;29:262–75.

Keszler M. Update on mechanical ventilatory strategies. NeoReviews. 2013;14:e237–51. http://neoreviews.aappublications.org/content/14/5/e237.

Keszler M. The long road to acceptance. Commentary on O. Chowdhury et al.: Randomised trial of volume-targeted ventilation versus pressure-limited ventilation in acute respiratory failure in prematurely born infants. Neonatology. 2013;104:290–294, 295–297.

Keszler M, Nassabeh-Montazami S, Abubakar K. Evolution of tidal volume requirement during the first 3 weeks of life in infants <800 g ventilated with volume guarantee. Arch Dis Child Fetal Neonatal Ed. 2009;94:F279–82.

Klingenberg C, Wheeler KI, Davis PG, Morley CJ. A practical guide to neonatal volume guarantee ventilation. J Perinatol. 2011;31:575–85.

Nassabeh-Montazami S, Abubakar K, Keszler M. The impact of instrumental dead-space in volume targeted ventilation of the extremely low birth weight infant. Pediatr Pulmonol. 2009;44:128–33.

Peng W, Zhu H, Shi H, Liu E. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2014;99:F158–65.

Sharma S, Abubakar KM, Keszler M. Tidal volume in infants with congenital diaphragmatic hernia supported with conventional mechanical ventilation. Am J Perinatol. 2015a;32:577–82.

Sharma S, Clark S, Abubakar K, Keszler M. Tidal volume requirement in mechanically ventilated infants with meconium aspiration syndrome. Am J Perinatol. 2015b;32:916–9.

Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. Cochrane Database Syst Rev. 2010:CD003666.

Pressure Control Ventilation

40

Steven M. Donn

I. Description
   A. Pressure control (PC) was developed in the 1980s for the treatment of ARDS. It is now included in many neonatal ventilators.
   B. Mechanical breaths are delivered at a pre-set peak inspiratory pressure, with a fixed or variable inspiratory time and variable inspiratory flow, which distinguishes PC from traditional time-cycled, pressure-limited (TCPL) ventilation in which inspiratory flow is fixed.
   C. It may be applied as IMV, SIMV (with or without pressure support), or A/C.

II. Features
   A. Constant peak inspiratory pressure
   B. Variable tidal volume depending on patient lung mechanics
   C. Square or plateau pressure waveform
   D. Decelerating flow waveform
   E. Variable pressure rise time
      1. Rise time refers to the slope of the inspiratory pressure waveform.
      2. It is a qualitative number, and it differs from one ventilator to another.
      3. If slope is excessive, pressure overshoot may occur. This may be observed as a notch on the inspiratory limb of the pressure–volume loop or a notch at the top of the pressure waveform.
      4. If slope is inadequate, there may be inadequate hysteresis on the pressure–volume loop. Severe flow starvation results in a "figure 8" appearance of the loop.
   F. High flow rapidly pressurizes ventilator circuit resulting in rapid gas delivery and alveolar filling.

III. Clinical Applications
   A. Patients at risk for barotrauma but in need of high peak pressure
      1. RDS
      2. BPD
      3. MAS (but be observant for gas trapping)

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Table 40.1 Comparison of pressure-targeted modalities

Parameter	Pressure-limited	Pressure control	Pressure support
Limit	Pressure	Pressure	Pressure
Flow	Continuous, fixed	Variable	Variable
Cycle	Time or flow	Time or flow	Flow (time-limited)
Breath type	Mechanical	Mechanical	Spontaneous

   B. Patients with airway obstruction or high airway resistance
   C. Best applied when lung disease is homogeneous
IV. Clinician-set Parameters
   A. Peak inspiratory pressure
   B. PEEP
   C. Inspiratory time (or cycle termination, if flow-cycled)
   D. Mode
   E. Rate
   F. F_iO_2
   G. Trigger sensitivity
   H. Rise time
   I. Alarm limits
V. Advantages
   A. Variable flow capability to meet patient demand
   B. Reduced inspiratory muscle workload
   C. Lower peak inspiratory pressures than TCPL
   D. Adjustable inspiratory time or flow-cycling on some ventilators
   E. Rapid filling of the alveoli
   F. Improved gas distribution, V/Q matching, and oxygenation
VI. Disadvantages
   A. Delivered tidal volume is variable and depends upon the patient's lung mechanics, including changes in airway resistance and lung compliance.
   B. May have adverse effects on tidal volume delivery
   C. Pressure overshoot
   D. Limited data on use in newborns
   E. May aggravate V/Q mismatch in heterogeneous lung disease
VII. Comparison to other Pressure-Targeted Modalities (Table 40.1)

Suggested Reading

Donn SM, Sinha SK. Newer techniques of mechanical ventilation: an overview. Semin Neonatol. 2002;7:401–8.
Donn SM, Sinha SK. Invasive and noninvasive neonatal mechanical ventilation. Respir Care. 2003;48:426–41.
Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal-perinatal medicine: diseases of the fetus and infant. 9th ed. St. Louis: Elsevier/Mosby; 2015. p. 1116–40.

Section VII

High-Frequency Ventilation

High-Frequency Ventilation: General Concepts

41

J. Bert Bunnell

I. High-Frequency Ventilation (HFV)
   A. How Conventional Mechanical Ventilation (CMV) Causes Lung Injury and HFV Either Prevents or Reduces It
      1. Barotrauma. HFV uses lower transpulmonary pressure than any other modality of assisted ventilation, including the iron lung.
         a. HFV pressure waveforms quickly attenuate as they advance towards the alveoli.
         b. Pressure amplitude at terminal airways and alveoli is very small.
      2. Volutrauma. HFV uses tidal volumes that are smaller than any other modality of assisted ventilation (1/2 to 1/10 of those used during CMV).
      3. Atelectrauma. the only type of lung injury that is not inherently lessened by HFV.
         a. Caused by using too little positive end-expiratory pressure (PEEP) or mean airway pressure (Pāw), which are nearly equivalent in their physiologic effect (allowing alveoli to collapse, remain collapsed, or open and collapse with every breath).
         b. One has to properly manage PEEP/Pāw during HFV to achieve and maintain optimal lung volume.
         c. It is safer to use higher PEEP/Pāw with HFV compared to CMV. (It is the large tidal volumes and pressure amplitudes on top of PEEP that cause lung injury when PEEP/Pāw is raised during CMV.)
         d. Raising PEEP/Pāw too high may interfere with pulmonary blood flow and cardiac output.
         e. Optimizing PEEP/Pāw improves pulmonary blood flow and maximizes potential gas exchange.
      4. Rheotrauma (airway injury caused by the shear forces of high gas flow rates)
         a. High frequency jet ventilation (HFJV) uses highly accelerated inspirations that were suspected of causing tracheal injury in the past, but no evidence such injury arose in numerous randomized controlled trials with either HFJV or high frequency oscillatory ventilation (HFOV).

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b. HFJV uses very low overall gas flow rates (<1 LPM when ventilating preterm infants).
c. HFOV uses much higher overall gas flow rates, but most of the gas bypasses the patient.

5. Biotrauma. All forms of mechanical ventilation trigger biochemical and biophysical injury caused by release of inflammatory mediators and cells.
   a. Animal studies have demonstrated less biotrauma with more gentle forms of assisted breathing such as continuous positive airway pressure (CPAP), and HFV is as close to CPAP as possible with assisted ventilation.
   b. Parameters and mechanisms for this type of lung injury have yet to be fully explored.

B. If HFV is so inherently lung protective, why aren't all patients treated with HFV?
   1. No ventilator is totally safe.
      a. The primary risk of HFV is hyperventilation and potential cerebral injury.
      b. A secondary risk is atelectrauma from improper management of lung volume via PEEP and Pāw.
      c. A third risk is lung hyperinflation from gas trapping.
   2. HFV is a "disruptive" technology.

II. Why is HFV disruptive?
   A. Disruptive technologies are not "normal;" they change the way people normally do things, and people are resistant to change.
   B. HFV, unlike CMV, does not try to mimic normal ventilation.
      1. HFV rates are many times greater than normal breathing rates, although comparable rates and examples of enhanced pulmonary gas exchange in nature occur in running and panting animals.
      2. HFV tidal volumes can be smaller than anatomic dead space volume.
      3. Intrapulmonary distribution of fresh gas during HFV is not as affected by lung compliance as normal breathing and conventional ventilation.
   C. It takes education. Disruptive technologies require experience to understand and realize the full benefits of HFV.

III. How Does HFV Work?
   A. Increased Convection (Bulk Flow) and Enhanced Diffusion
      1. Abundant fresh gas of high frequency inspirations washes expired gas from upper airways.
      2. Increased washout of expired gases increases O_2 and decreases CO_2 partial pressures at the intra-airway/alveolar gas exchange boundary, thereby increasing diffusion.
   B. Resonant frequency phenomenon enables use of minimal airway pressures.
      1. Experiments with forced oscillations revealed that lungs have a natural or "resonant" frequency of 4–8 Hz (1 Hz = 60 cycles per minute) in adult humans.
      2. Impedance to gas moving in and out of the lungs includes compliance, airway resistance, and inertance, which is related to momentum.
      3. At resonance:
         a. Timing and energies are matched, minimizing energy needed to move gas in and out of the lungs.
         b. Gas momentum supplies energy sufficient to overcome lung compliance, and lung elastic recoil supplies the energy necessary to reverse gas momentum and send gas out of the lungs.
         c. Only airway resistance is left to impede gas flow, so only enough pressure to overcome airway resistance is needed for ventilation.
   C. Oscillatory Flow-Streaming (HFOV)
      1. In HFOV, inspirations are considered to be laminar, which creates a parabolic (i.e., bullet-shaped) velocity profile of gas entering the airways.

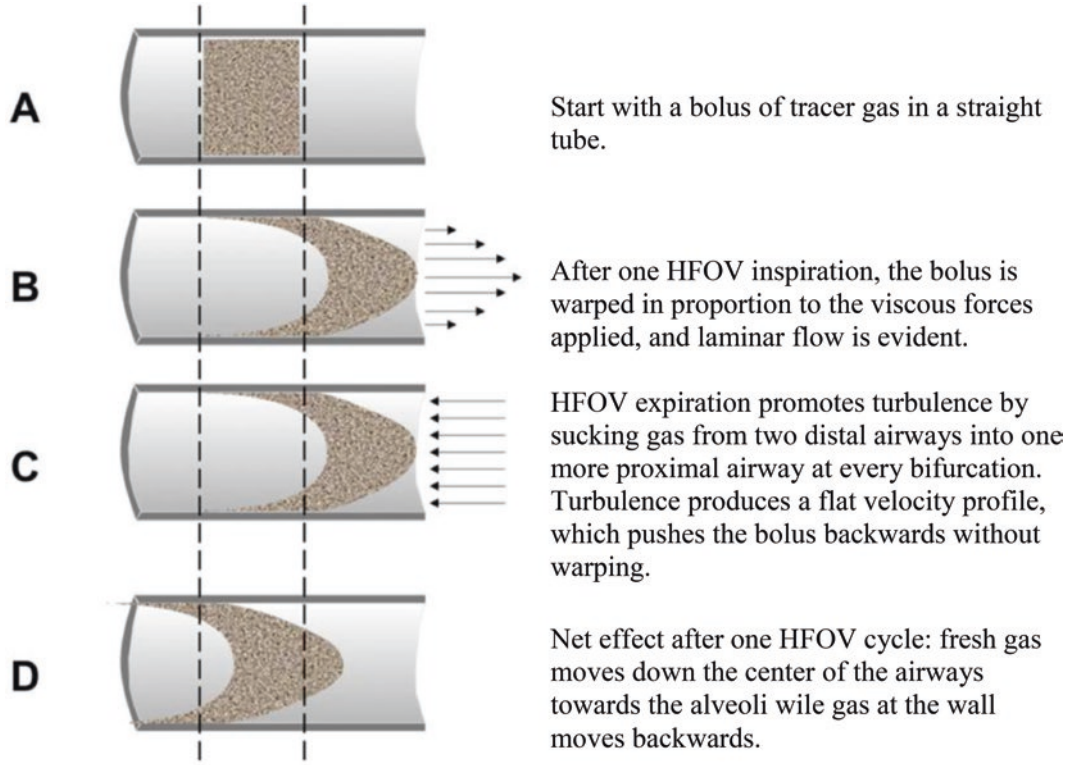

Fig. 41.1 Viscous shear and airway velocity profiles associated with HFOV. Modified with permission from Haselton FR, Scherer PW: Bronchial bifurcations and respiratory mass transport. Science 208: 69, 1980. Reprinted with permission from AAAS

2. "Active" HFOV expirations are considered to be turbulent as gas accelerates at every bifurcation when gas from two airways is sucked into one, more proximal airway, causing acceleration and a turbulent, flat expiratory wave front (velocity profile).
3. The net effect of several HFOV cycles: fresh gas advances down the core of airways while exhaled gas moves out along airway walls (Fig. 41.1).

D. HFJV Flow-Streaming, Dead Space Reduction
1. High velocity HFV inspiratory gas spirals into the lungs down the central core of airways, dissecting through the anatomic dead space, rather than pushing gas expired from the last breath back into alveoli ahead of the fresh gas in the new breath.
   a. Although the inspired HFJV gas pulses embody enough energy for the creation of turbulence, there is insufficient time for turbulence to develop, because inspiration is so brief.
   b. Thus, "transitional" flow (transitional between laminar and turbulent flow) may be created, which is characterized by an exaggerated laminar-type velocity profile, where gas in the center of the airways swirls into the lungs much faster than gas near the airway walls, dramatically reducing physiologic or effective pulmonary dead space volume.
2. The higher the velocity, the sharper the point on the parabolic velocity profile of the inrushing gas (Fig. 41.2). (If inspiration lasts too long, turbulence develops and gas flows in with a flat velocity profile.)

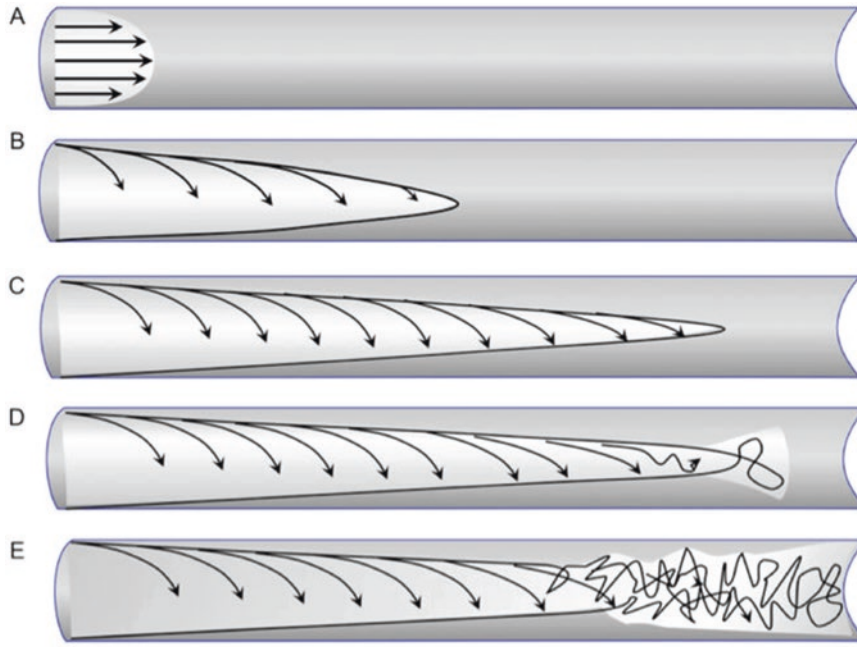

Fig. 41.2 When fluid (liquid or gas) flows into a tube, the velocity profile of the flow is determined by energy and time. Used with permission. © 2011, Bunnell Inc. (**A**). When energy is low, overall flow is relatively slow and laminar with molecules in the center of the tube moving faster than those at the wall, creating a parabolic velocity profile. (**B**). As the fluid moves faster with more energy, the flow begins to spiral with greater velocity in the center of the tube. (**C**). The degree to which flow in the center of the tube outpaces that at its wall is determined by the combination of energy and time or distance. A short, energetic flow pulse (e.g., an HFJV inspiration) will produce a spiral with an exaggerated parabolic velocity profile. (**D**). With either sufficient (i.e., excessive) energy or time, the tip of the moving fluid transitions into turbulence. (**E**). Once turbulence is established, molecular motion is chaotic and the velocity profile of the fluid is flat across the diameter of the tube

3. Since only portions of the anatomic dead space are used, HFJV tidal volumes reduce effective (i.e., physiologic) dead space.

E. Tidal volume must be greater than physiologic (i.e., effective) dead space volume for gas exchange to take place.
   1. Brief, high velocity HFV inspirations are smaller than anatomic dead space volume when physiologic dead space volume is reduced to the point that VT < VD, anatomic.
   2. Typical anatomic dead space of mammalian lungs is 2 mL/kg body mass.
   3. Tidal volumes < 1 mL/kg have been measured in animal studies with HFJV.

IV. HFV in the NICU
   A. Every HFV device offers the promise of using a smaller V_T within the limits of its design.
   B. Clinicians must learn individual device controls that enable management of ventilation and oxygenation, when it is appropriate to increase or decrease Pāw, and how to effectively use concomitant CMV breaths, if available, for alveolar recruitment.
   C. Available Modalities
      1. High Frequency Jet Ventilation (HFJV) (Chaps. 42 and 54)
         a. HFJV in the USA is provided by the Life Pulse® Ventilator (Bunnell Inc., Salt Lake City, UT) as time-cycled, pressure-limited servo-controlled ventilation.
         b. Inspired gas is pulsed into a patient's endotracheal tube (ETT) through a jet nozzle, which is built into a special 15-mm ET tube adapter ("LifePort®" ETT adapter, Bunnell Inc.) with two side ports.

c. Expiration during HFJV is passive, as it is with CMV.
d. A conventional ventilator is attached to the proximal end of the LifePort adapter via a standard 15-mm connector, which is used for:
(1) providing gas flow for the patient's spontaneous breathing through the main lumen of the adapter
(2) delivery (HFJV of normal size tidal volumes for recruitment of atelectatic alveoli
(3) producing PEEP, which generates most of the Pāw during HFJV (as all exhaled gas exits via the CMV PEEP valve).

2. High Frequency Oscillatory Ventilation (HFOV) (Chaps. 43 and 55)
a. HFOV is provided in the USA by the 3100A® (CareFusion, San Diego, CA) as sinusoidal, push–pull, pneumatic piston ventilation (typical frequency from ~3 to 15 Hz or 180 to 900 bpm).
b. % I-time is adjustable from 30 to 50 %, producing I:E from 1:2.3 to 1:1.
c. Mean airway pressure and pressure amplitude are adjustable, along with "bias flow," which is adjustable from 0 to 40 LPM. (These settings control ventilation and mean lung volume, which are fine tuned with a piston-centering) adjustment.)

3. Combined CMV + HFOV Devices
a. CMV + HFOV in the USA is provided by VDR® and Bronchotron® Ventilators (Percussionaire®, Sagle, ID) as time-cycled, pressure-limited, fluidic-controlled ventilators that superimpose HFOV upon CMV breaths.
b. Outside the USA, ventilators that can switch from various modes of CMV to HFOV with "sigh" (alveolar recruitment) breaths and "volume guarantee" (VG) regulation of HFOV tidal volumes are available (e.g., the Babylog® VN500 Ventilator, Dräger Medical GmbH, Lübeck, Germany) (Chap. 49).

D. Device Similarities
1. All HFV devices produce a train of fresh gas pulses that penetrate through the dead space of the airways without pushing all the resident dead space gas ahead of the fresh gas as happens when we breathe normally or are ventilated conventionally.
2. Airway pressures that HFV generates attenuate as inspired gases approach the alveoli.
3. Each device provides the means to manage PEEP/Pāw for optimal lung volume.

E. Pressure Waveforms and Intrapulmonary Gas Distribution
1. HFJV inspiratory airway pressure rises sharply from PEEP and ends abruptly at the end of its T_i, which is usually 0.020 s. (Fig. 41.3)
2. HFJV expiration is passive, so the expiratory pressure waveform is in the form of a classic natural exponential decay.
3. HFOV produces a sinusoidal waveform, with inspiratory airway pressure rising and returning to its Pāw within the inspiratory portion of the breath cycle, so it is rounded at its peaks. (HFOV T_i is only as brief as that of HFJV at 15 Hz where $T_i = 0.022$ s.)
4. HFOV expiratory airway pressure falls and returns to its Pāw within the expiratory portion of the breath cycle, which typically lasts twice as long as inspiration (when % Inspiration Time = 33 and inspiratory to expiratory time ratio, I:E = 1:2).
a. The greater the HFOV pressure amplitude, the lower the minimum pressure excursion, which can go low enough to cause airway collapse and gas trapping.
b. Raising Pāw, which increases intra-airway pressure, usually alleviates gas trapping with HFOV.
5. Airway resistance determines intrapulmonary distribution of HFV because of the high velocity of its inspirations.

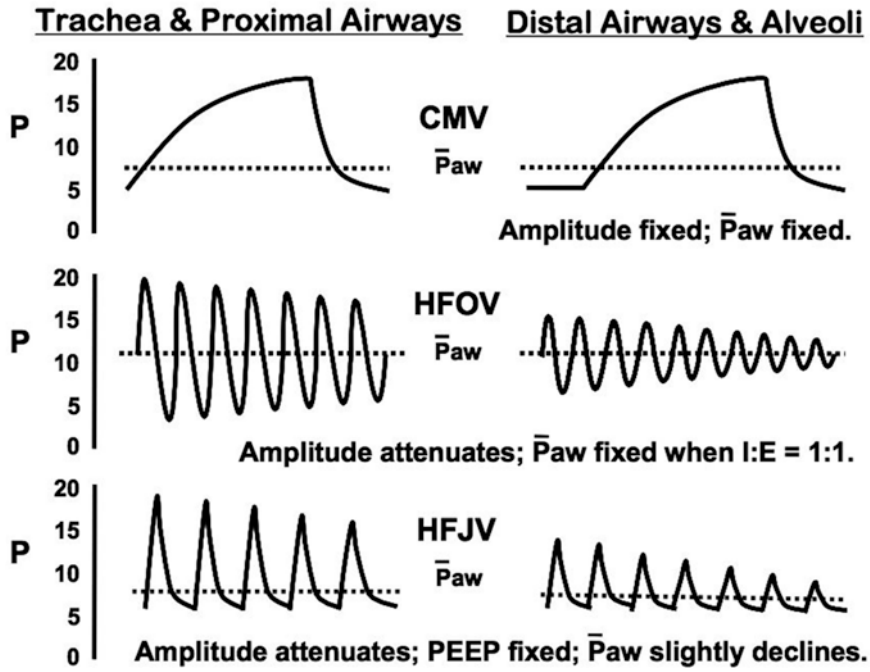

Fig. 41.3 CMV and HFV airway pressure waveforms, showing how HFV pressure amplitude is dampened as inspired gas approaches the alveoli, whereas airway pressure from CMV has enough time and volume to equilibrate throughout the lungs, producing pressure in the alveoli that is close to that introduced in the trachea. Used with permission. © 2003, Bunnell Inc

a. The faster the inspiration, the less gas will penetrate inflamed and restricted peripheral airways like those found in pulmonary interstitial emphysema (PIE).
b. This concept may explain why HFJV works well for treating PIE; it automatically reduces ventilation of injured areas in favor of healthier areas of the lungs.
c. Ventilation of injured parts of the lungs is counterproductive; it only increases injury in areas that do not participate in gas exchange.

F. Other Device Differences
1. HFOV can be used at higher frequencies (e.g., 15 Hz) compared to HFJV because whatever is pushed into the lungs is also sucked out, although higher frequencies may not be optimal. (See "corner frequency," below.)
   a. Tidal volume decreases with increasing HFOV frequency with a set I:E, because of the concomitant decrease in the time allotted for inspiration.
   b. Ventilation (CO_2 elimination) is proportional to the square of tidal volume (V_T^2) during HFV, so ventilation paradoxically decreases with increasing HFOV frequency.
   c. Raising HFOV frequency may therefore require an increase in pressure amplitude to maintain appropriate ventilation.
   d. Lowering HFOV frequency increases delivered tidal volume, which may improve gas exchange, enable reduction in pressure amplitude, and alleviation of gas trapping, as long as frequency does not go too far below the corner frequency.

2. HFJV rates are generally lower than HFOV frequencies in order to accommodate passive exhalation.
   a. Tidal volume is independent of frequency as long as T_i is constant and there is sufficient exhalation time to avoid gas trapping.
   b. With T_i typically set, rate determines I:E and exhalation time (T_e).
   c. With T_i set at its minimum of 0.020 s, for example, I:E changes from 1:4 at 600 bpm to 1:9 at 300 bpm).
   d. HFJV is therefore similar to CMV: the faster you go, the more CO_2 you eliminate, as long as rate is not too high to cause gas trapping.
   e. Lowering HFJV frequency decreases minute volume, but it may improve gas exchange if it alleviates gas trapping; otherwise, it may require an increase in pressure amplitude to provide adequate ventilation.
3. HFJV inspirations are typically smaller and faster than those of HFOV.
   a. HFJV inspirations are generated in a component located close to the patient, which minimizes compressible dead space volume and enhances inspiratory penetration. (Percussionaire® combined CMV + HFOV ventilators similarly generate inspirations close to the ETT with their pneumatic clutch assembly, the Phasitron®).
   b. Overall gas flow during HFJV is most conservative, requiring 1–8 L/min for infants and small children vs. up to 20 L/min with HFOV.
4. HFOV inspirations at 10–15 Hz are comparable to those of HFJV but slower at lower frequencies, producing laminar to transitional flow, where gas in the center of the airways travels towards the alveoli faster than gas near the airway walls.
5. Combined CMV + HFOV performance is positively and negatively affected by inherent design features.
   a. Ease of use of CMV + HFOV ventilators that provide CMV alveolar recruitment techniques is superior compared to stand-alone HFOV or to HFJV, which must be used in tandem with CMV devices.
   b. HFOV inspirations of combined CMV/HFOV ventilators are dampened by the compressible volume in the tubing and humidifier between where HFOV is created and where it is delivered to the ETT.
6. Expiration
   a. In HFJV, exhaled gas exits passively with lung recoil by spiraling out around the incoming gas, seeking the path of least resistance in the annular or "unused" spaces around the highly accelerated inspired gas as illustrated in Fig. 41.4.
   b. In HFOV, exhaled gas is pulled from the patient's lungs during exhalation ("active exhalation") in typically twice the time of inspiration (i.e., when % I-time is set at 33 % and I:E = 1:2), which helps reduces the threat of creating choke points. (See Potential for Gas Trapping, below.)
   c. Net effects of passive vs. active expiration
      (1) HFJV is usually operated at frequencies lower than those used with HFOV, which lengthens exhalation time and enables complete exhalation.
      (2) HFOV is usually operated at higher Pāw compared to HFJV in order to counteract the active low-pressure excursion of airway pressure during exhalation (see below).
7. Potential for Gas Trapping
   a. Gas trapping is a primary concern with HFV, and it becomes apparent when $PaCO_2$ rises and cannot be reduced by increasing airway pressure amplitude.

Fig. 41.4 Exhaled gas exits passively with lung recoil during HFJV, spiraling out around the high velocity inspired gas that spirals down the central core of the airways. Used with permission.

b. Gas trapping occurs during all forms of ventilation, including HFV, but may occur by different mechanisms.
c. The primary mechanism causing gas trapping is not allowing enough time for exhaled gas to fully exit before a subsequent inspiration.
(1) This mechanism causes gas trapping during CMV and HFJV where exhalation is passive, relying on the elastic recoil of the lungs.
(2) This mechanism can also occur during HFOV where gas is pulled from the lungs during exhalation, but it is secondary to another mechanism called "choking."
d. Choking occurs when pressure outside an airway exceeds the pressure inside that airway, overcomes its structural strength, and causes airway collapse.
(1) This mechanism can cause gas trapping during HFOV.
(2) As gas is pulled from the lungs during HFOV, pressure in the airways drops below what would be PEEP if exhalation were to occur passively.
(3) If the pressure drop is sufficient, the airway collapses.

8. Spontaneous Breathing
a. Gas flow used during HFJV is quite low (1–8 LPM in infants), so gas for spontaneous breathing is supplied by tandem CMV. (Hybrids supply gas for spontaneous breathing in a similar manner.)
b. Information concerning spontaneous breathing by infants during HFOV is lacking.

G. Who HFV May Help, How, and Why
1. According to theories related to resonant frequency, HFV is ideally suited to treatment of restrictive lung disorders that are characterized by poor lung compliance.
a. Gas can flow in and out of such lungs very quickly in either direction.
b. The diffuse, homogeneous nature of RDS is well suited to HFOV's sinusoidal waveform.
2. Used properly, HFV is the epitome of "lung protective ventilation"
a. Get the lungs open,
b. Keep them open.

c. Ventilate as gently as possible.

3. Although prevention of lung injury is the primary goal of HFV, many if not most applications of HFV occur after lung injury has already occurred.
4. HFJV has proven effective in treating non-homogenous lung injury and air leaks such as PIE.
   a. High velocity inspirations avoid injured areas of the lungs (secondary to inflammation and/or high resistance), which improves ventilation/perfusion matching.
   b. Deflation of injured areas of the lungs can be achieved by lowering HFJV rate while keeping T_i at its shortest setting (0.020 s), producing I:E as long as 1:12.
   c. HFJV can be used with lower Pāw, but it is usually better to use enough PEEP to maintain adequate lung volume without any CMV breaths. (Cardiac patients are an exception since raising PEEP increases right ventricle afterload.)
   d. Although HFOV studies have focused on preventing rather than treating lung injury, inherent lung protective ventilation features of HFOV support its use in preference to CMV.
5. HFV devices can ventilate patients that are impossible to ventilate effectively any other way, such as:
   a. Severe congenital diaphragmatic hernia, where small V_T and high Pāw can preserve what little lung is available for ventilation
   b. Upper airway leaks and fistulas where HFJV "pulses" inspired gas right past disruptions, enabling downstream ventilation and airway injuries to heal
   c. Cardiac surgery patients
      (1) HFJV can facilitate better pulmonary perfusion and cardiac output by mildly hyperventilating at relatively low Pāw.
      (2) Surgical repair can be accomplished while on HFJV, providing improved access to the heart and major vessels.
      (3) Chest may be closed post-surgery without adverse effects on cardiac output.
   d. Obstructive lung disorders, such as meconium aspiration syndrome (MAS), where HFV may facilitate removal of excess secretions and improve V/Q matching
   e. Patients with conditions where HFV may facilitate delivery or improve the benefits of using specialty gases such as nitric oxide or helium (e.g., PPHN or status asthmaticus)
   f. Bronchopulmonary dysplasia (BPD) where small V_t and lower rates with longer exhalation times may facilitate healing and decompression of hyperinflated lungs

V. How to Maximize the Benefits and Minimize the Risks of HFV

A. Ideally, HFV should begin as soon as exogenous surfactant is administered and/or nasal CPAP/CMV appear to be inadequate, although early use is controversial because of a higher incidence of cerebral injury (IVH, PVL) in earlier studies, where ill-advised management strategies were used.
   1. Strategy is key to avoiding such injuries.
      a. Most important: avoid hyperventilation by careful monitoring of $PaCO_2$ ($TcPCO_2$ is recommended).
      b. Full lung recruitment and maintenance of appropriate lung volume
   2. HFV is more like CPAP than CMV.

B. Match ventilator strategy to pathophysiology and the availability of an appropriate ventilator.
   1. Using appropriate ventilator strategies for specific lung disorders is more important than which ventilator you use, but learn the limitations of the devices you use.
   2. HFJV Limitations

a. Passive Exhalation
(1) May require use of lower rates compared to HFOV to avoid gas trapping
(2) More compliant lungs may also require lower rates and longer T_i.
b. Use of tandem CMV may be overdone.
(1) CMV breaths should be used to aid alveolar recruitment, not to assist ventilation.
(2) Follow instructions for finding optimal PEEP (see below), and do not leave CMV settings at anything other than minimum settings unless you are actively recruiting lung volume.
(3) If oxygenation suffers when you reduce the size or frequency of CMV breaths, increase PEEP until CMV breaths are no longer needed. (Cardiac patients are an exception. Increasing PEEP may be contraindicated for some cardiac patients, and a CMV rate of 5–10 bpm can help maintain oxygenation.)
c. HFJV may unexpectedly mobilize secretions.
(1) Be ready to suction right after initiation of HFJV.
(2) Only suction when indicated to avoid collapse of alveoli.

3. HFOV Limitations
a. Active Exhalation
(1) May require increased Pāw to avoid gas trapping
(2) Select patients for HFOV who will tolerate or even benefit from higher Pāw (e.g., RDS).
b. May not work well with non-homogeneous lung disorders because of limited I:E.
c. Watch out for mucus impaction.

4. Limitations of Conventional Ventilators with built-in HFV
a. Compressible volume of conventional-style patient circuits and humidifier limits HFV effectiveness.
b. Manage concomitant CMV appropriately.
(1) Increase CMV rate to actively recruit collapsed alveoli (~5 bpm).
(2) Decrease CMV (to CPAP if possible) when atelectasis resolves.
(3) Cease CMV (i.e., use CPAP) when air leaks are present.

C. Choose an HFV rate/frequency to provide adequate ventilation with the lowest ΔP (pressure amplitude), smallest V_t, and no gas trapping.

1. Set rate and duty cycle (I:E) that are compatible with the patient's pulmonary time constants.
a. Preterm infants have small, stiff lungs with uniformly short time constants, so higher rates and I:E settings with relatively short inspiratory and expiratory times are appropriate.
b. Rates as low as 240 bpm (4 Hz) where I:E = 1:12 work best with lung disease characterized by long exhalation time constants such as PIE, BPD, and MAS.

2. Venegas and Fredberg developed a formula for calculating optimal frequency using time constants, which they called the "corner frequency:" $fc = 1/(2\pi CR)$, where fc = corner frequency, C = compliance, R = resistance.
a. Plotting peak pressure or pressure amplitude measured at the carina versus frequency for lungs being ventilated with constant tidal volume for infants in various conditions illustrates this equation (Fig. 41.5).
(1) Peak pressure falls rapidly with increasing frequency until it reaches a "corner," where pressure either flattens or begins to rise.

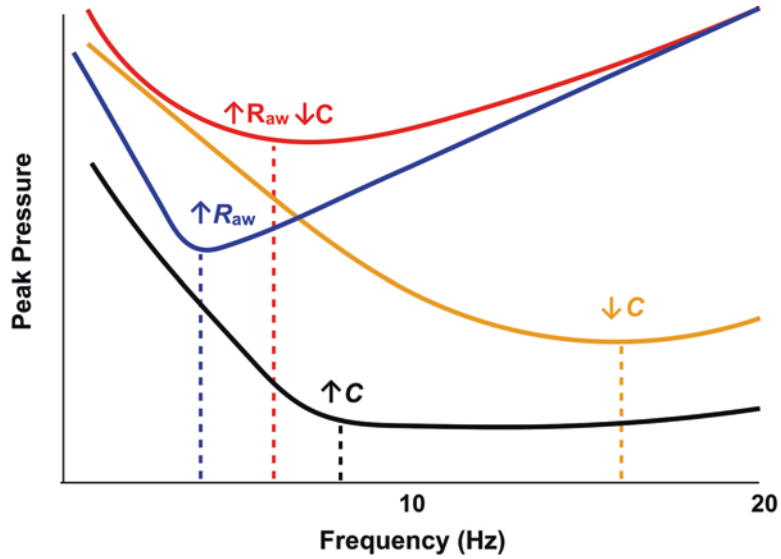

Fig. 41.5 Optimal HFV rates enable adequate ventilation with the lowest airway pressure, and pulmonary time constants (compliance and airway resistance) determine them. Decreased compliance increases the optimal frequency, and increased airway resistance decreases it. Lungs with poor airway resistance and hyperinflated by trapped gas, as happens in infants with BPD, have a sharply lower optimal frequency. Note how infants with RDS may be well ventilated at a frequency 10–15 Hz, but if their condition deteriorates into PIE or BPD, they may be better ventilated at lower frequencies. These concepts were developed from the theories and numerical analyses of Jose Venegas and Jeff Fredberg. See: Venegas JG, Fredberg JJ, Understanding the pressure cost of high frequency ventilation: why does high-frequency ventilation work? Crit. Care Med. 1994; 22: S49-57. Used with permission. © 2015, Bunnell Inc

(2) At this frequency, the lowest pressure is required for ventilation without gas trapping.
(3) Using a frequency too far below or above the corner frequency of the lung may result in unnecessarily large pressure amplitudes in the proximal airways.

b. In general, when lung compliance worsens, the corner frequency increases, and when airway resistance worsens, the corner frequency decreases.
c. Using this equation with typical values of compliance (0.2 mL/cm H_2O) and airway resistance (50 cm H_2O/L/s) for an extremely preterm baby produces a recommended frequency of 16 Hz or 960 bpm although the curve for such patients (Fig. 41.5) is not terribly clear where that "corner" is.
d. As compliance improves, optimal frequency decreases. (Thus, a larger baby with a lung compliance of 0.4 mL/cm H_2O would do better at a frequency of 8 Hz or 480 bpm.)
e. Since mechanical ventilation triggers inflammation, airway resistance usually worsens the longer an infant is ventilated; thus, it is wise to use lower frequencies for sicker babies as well as bigger babies with aspiration pneumonia or bronchiolitis.
(1) A large baby with MAS might have a compliance of 0.4 mL/cm H2O and airway resistance of 100 cm H_2O/L/s.
(2) Corner frequency for such a baby, $fc = 1/(2\pi CR) = 4$ Hz or 240 bpm.
f. As airway resistance improves, optimal frequency increases because it is easier for inspired gas to egress quickly.

(1) A baby recovering from MAS might have a lung compliance of 0.5 mL/cm H_2O and airway resistance = 50 cm H_2O/L/s.
(2) Corner frequency for this baby, fc = 1/(2πCR) = 6 Hz or 360 bpm.

g. As illustrated in Fig. 41.5, using lower frequencies when airway resistance is problematic is essential, whereas the difference in the peak pressure necessary to ventilate at higher frequencies flattens when lung compliance is the primary issue.

D. Stabilize infant with appropriate Pāw.
1. HFOV: Pāw will typically be at least 2 cm H_2O higher than that required by CMV or HFJV to maintain the same oxygenation.
   a. Use chest radiographs in conjunction with pulse oximetry to assess atelectasis, lung volume, and need for more Pāw.
   b. Maintain a balance between adequate lung volume and cardiac output.
2. HFJV: maintain Pāw currently in use when starting HFJV unless it is very high (>15 cm H_2O) or switching from HFOV to HFJV.
   a. If starting from CMV, raise PEEP by ~2 cm H_2O to maintain Pāw.
   b. If starting from HFOV, either maintain Pāw or reduce it by 1–2 cm H_2O.

E. Set pressure amplitude/tidal volume to provide adequate ventilation.
1. As soon as infant is stabilized, check $PaCO_2$.
2. Do not use rate to manage $PaCO_2$ if you are confident that you set and adjusted rate appropriately at the outset of HFV.
   a. Adjust ΔP and Power on HFOV.
   b. Adjust PIP on HFJV, which alters ΔP = PIP − PEEP.
   c. Adjust settings that create tidal volume on other devices.
3. Avoid hyperinflation.
   a. HFOV: if you cannot adequately ventilate without changing rate, delivered T_i may be too large to be exhaled in the time allotted.
      (1) Lowering rate will extend exhalation time and increase tidal volume.
      (2) If lowering rate does not bring ventilation under adequate control, you may need to switch to a different device to achieve longer exhalation times.
   b. HFJV: if monitored PEEP > set PEEP, it may indicate inadvertent PEEP caused by gas trapping.
      (1) Lowering rate will increase exhalation time but decrease minute volume.
      (2) May need to increase PIP to maintain adequate ventilation.
      (3) If increasing PIP does not reduce $PaCO_2$, increasing T_i will increase V_T. (Start by increasing T_i from 0.020 to 0.026, and use the maximum of 0.034 s if necessary.)
4. Avoid hyperventilation by vigilant PCO_2 monitoring.

F. Optimize PEEP/Pāw and maintain appropriate lung volume for good oxygenation (the most important and challenging goal of lung protective ventilation with HFV).
1. HFOV: find and maintain optimal Pāw using pulse oximetry and chest radiography to assess lung inflation.
   a. Recommendations for achieving optimal lung inflation during HFOV based on position of the diaphragm:
      (1) Below the 11th rib, decrease frequency first in 2 Hz decrements until 10 Hz is reached, then decrease Pāw by 20 %.
      (2) Between the 10th and 11th rib, decrease frequency first in 2 Hz decrements until 10 Hz is reached, then decrease Pāw by 10 %.
      (3) Between 8 and 9.5 ribs, no change.

(4) Above the 8th rib, increase Pāw by 10 %.
(5) Above the 7th rib, increase Pāw by 20 %.

b. Assuming acceptable lung inflation during HFOV:
(1) F_iO_2 >0.40, increase Pāw in 1 cm H_2O increments until F_iO_2 no longer decreases.
(2) F_iO_2 0.30–0.40, may increase Pāw or make no change, depending on lung inflation.
(3) F_iO_2 <0.30, decrease Pāw in 1 cm H_2O decrements until F_iO_2 begins to increase.
(4) If F_iO_2 changes by 0.2, evaluate lung inflation.

2. HFJV: use CMV to help recruit collapsed alveoli and PEEP to stabilize the lungs.
a. Set CMV at 5 bpm with PIP set high enough to cause adequate chest rise to determine if PEEP is adequate once SpO_2 is stable and F_iO_2 is adjusted so that SpO_2 is close to 90 %.
(1) Switch from 5 bpm CMV to CPAP or as close to 0 bpm as you can get without causing apnea alarms on the CMV (i.e., use minimal CMV rate, PIP, and T_i).
(2) If SpO_2 remains stable, PEEP is adequate and CMV breaths are not needed. (Continue with CMV in CPAP mode or at minimal rate, PIP, and T_i.)
(3) If SpO_2 falls, increase PEEP by 1–2 cm H_2O and reinstitute CMV at 5 bpm for a few minutes until SpO_2 increases to where it was before (~90 %).
b. Repeat switch to CPAP or minimal CMV with higher PEEP until HFJV can continue with CPAP or minimized CMV with SpO_2 stabilized near 90 % with reduced F_iO_2.
c. If F_iO_2 <0.50, weigh risks vs. benefits of further alveolar recruitment.

3. HFOV + CMV: use an approach similar to that for HFJV above.

G. Adjust HFV settings rationally as patient's condition changes.
1. In general, do not drop PEEP or Pāw when F_iO_2 is still >0.30.
2. Do not switch back to CMV; it may cause further lung injury and prolong overall mechanical ventilation.
a. If unacceptable blood gas, reassess and adjust strategy.
b. If normal or better blood gas, wean appropriately.
3. Strategy for Treating Hyperinflation with HFJV
a. No CMV breaths.
b. PEEP sufficient to maintain airway patency (typically ≥8 cm H_2O).
c. Lower HFJV rate to prolong T_e and enable diffusion of gas from affected areas (e.g., 240 bpm with I:E = 1:12).
d. Success with this strategy requires patience (average time to extubation was 7 days in a small retrospective study of ten patients treated with HFJV).
e. In extreme cases, where patients with diffuse lung injury are suffering extraordinary hypercarbia in spite of optimizing rate and raising PIP:
(1) Increase T_i from 0.020 s in 0.004–0.006 s increments to a maximum of 0.034 s.
(2) This change can increase V_T delivery by as much as 70 % while decreasing T_e by <10 %.

H. Wean to nasal CPAP or other non-invasive modes of support.

VI. Conclusions
A. HFV can be extraordinarily beneficial if the appropriate device is used on the appropriate patient in the appropriate strategy at the appropriate time.
1. Initiate HFV sooner rather later (prevention of lung injury is better, albeit less dramatic than rescuing infants in dire straights).

2. Know the capabilities and limitations of the HFV devices you have available.
3. Develop application strategies based upon lung time constants and pathophysiology.

B. Be prepared to change strategy as conditions dictate.
C. Wean to nasal CPAP or other non-invasive mode of ventilation.
D. Let common sense and solid knowledge of pulmonary pathophysiology, lung mechanics, and HFV device characteristics be your guides.

Suggested Reading

Bandy DP, Donn SM, Nicks JJ, Naglie RA. A comparison of proximal and distal high-frequency jet ventilation in an animal model. Pediatr Pulmonol. 1986;2:225–9.

Boros SJ, Mammel MC, Coleman JM, et al. A comparison of high-frequency oscillatory ventilation and high-frequency jet ventilation in cats with normal lungs. Pediatr Pulmonol. 1989;7:35–41.

Boynton BR, Villanueva D, Hammond MD, et al. Effect of mean airway pressure on gas exchange during high-frequency oscillatory ventilation. J Appl Physiol. 1991;70:701–7.

Clark RH. High-frequency ventilation. J Pediatr. 1994;124:661–70.

Donn SM, Zak LK, Bozynski MEA, et al. Use of high-frequency jet ventilation in the management of congenital tracheo-esophageal fistula associated with respiratory distress syndrome. J Pediatr Surg. 1990;25:1219–21.

Dubois AB, et al. Oscillation mechanics of lungs and chest in man. J Appl Physiol. 1956;8:587.

Froese AB, Bryan AC. High frequency ventilation. Am Rev Resp Dis. 1987;135:1363–74.

Harris TR, Bunnell JB. High-frequency jet ventilation in clinical neonatology. In: Pomerance JJ, Richardson CJ, editors. Neonatology for the clinician. Norwalk: Appleton & Lange; 1993. p. 311–24.

Haselton FR, Scherer PW. Bronchial bifurcations and respiratory mass transport. Science. 1980;208:69–71.

Henderson Y, Chillingworth FP, Whitney JL. The respiratory dead space. Am J Physiol. 1915;38:1–19.

Keszler M, Durand DJ. Neonatal high-frequency ventilation. Past, present, and future. Clin Perinatol. 2001;28:579–607.

Kocis KC, Meliones JN, Dekeon MK, Callow LB, et al. High-frequency jet ventilation for respiratory failure after congenital heart surgery. Circulation. 1992;86(suppl II): II-127–II-132.

Musk GC, Polglase GR, Bunnell JB, McLean CJ, Nitsos I, Song Y, Pillow JJ. High positive end-expiratory pressure during high frequency jet ventilation improves oxygenation and ventilation in preterm lambs. Pediatr Res. 2011;69:319–24.

Perez Fontan JJ, Heldt GP, Gregory GA. Mean airway pressure and mean alveolar pressure during high-frequency jet ventilation in rabbits. J Appl Physiol. 1986;61:456–63.

Slutsky AS. Mechanisms affecting gas transport during high-frequency oscillation. Crit Care Med. 1984;12:713–7.

Slutsky AS. Lung injury caused by mechanical ventilation. Chest. 1999;116(1 Suppl):9S–15.

Venegas JG, Fredberg JJ. Understanding the pressure cost of high frequency ventilation: why does high-frequency ventilation work? Crit Care Med. 1994;22:S49–57.

High-Frequency Jet Ventilation

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Martin Keszler

I. Indications
   A. Late rescue treatment. High-frequency jet ventilation (HFJV) has been used extensively for the treatment of refractory respiratory failure unresponsive to conventional ventilation (CMV). Air leak syndrome has been the most commonly treated underlying disorder, but infants with pulmonary hypoplasia secondary to congenital diaphragmatic hernia (CDH), respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), and pneumonia are also treated using HFJV with considerable success in the rescue mode.
   B. Early rescue treatment. HFJV has documented efficacy and is used extensively in the treatment of moderate to severe RDS, pulmonary interstitial emphysema (PIE), large leaks through a broncho-pleural fistula (intractable pneumothorax) or tracheo-esophageal fistula, abdominal distention with poor chest wall compliance, CDH, and MAS with or without pulmonary hypertension.
   C. Prophylactic use. Despite evidence of effectiveness of HFJV in lowering the incidence of bronchopulmonary dysplasia (BPD) in one large multicenter study, first-line treatment of infants with RDS at high risk for developing BPD is not widely practiced.

II. Benefits of HFJV
   A. Lower pressure amplitude (ΔPressure = peak inspiratory pressure (PIP) − positive end-expiratory pressure, PEEP), compared to CMV
   B. Very effective CO_2 elimination
   C. Flexibility to use both low and high mean airway pressure (MAP, Pāw) as indicated
   D. More rapid resolution of air leaks
   E. Decrease in airflow through points of airway disruption
   F. Ability to use high PEEP safely
   G. Effective recruitment and maintenance of lung volume with background sigh
   H. Improved hemodynamics because of less interference with venous return
   I. Mobilization of secretions and aspirated material
   J. Decreased risk of BPD

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III. Possible Complications of HFJV
  A. Mucosal damage to the trachea and large bronchi was reported in some early studies when inadequate humidification was used. This is no longer a problem.
  B. Increased incidence of periventricular leukomalacia and intraventricular hemorrhage (IVH) reported in one study, likely related to inadvertent hyperventilation and hypocapnia. Similar findings were seen in some oscillatory ventilation studies and with conventional hyperventilation. Risk of inadvertent hyperventilation can be minimized by using $TcPCO_2$ monitoring, especially when initiating HFJV.
  C. Air trapping is possible if inappropriately high ventilator rate is used. This is a phenomenon that can occur with all ventilators.

IV. Clinical Use
  A. Patient selection
    1. Risks and benefits should be carefully considered before initiating HFJV.
    2. Early, rather than late, initiation is preferable in most situations.
    3. Patient selection should be based on clinical experience and published evidence of efficacy.
    4. Like any other ventilator, the LifePulse Jet ventilator is a tool that works only as well as the user's clinical skill, attention to detail, and knowledge of the underlying pathophysiology allow it to.
  B. Basic control of gas exchange
    1. Basic principles of gas exchange with HFJV are no different from conventional or oscillatory ventilation.
    2. Similar to other types of ventilation, oxygenation is determined by FiO_2 and Pāw: Increased Pāw = improved oxygenation.
    3. Pāw is determined by PIP, PEEP, and inspiratory time with PEEP being by far the most important factor. Because of the extremely short Ti, the Pāw is only slightly above PEEP. For this reason, PEEP values higher than those commonly used with CMV are often required. It is not unusual to need PEEP of 10–12 cm H_2O in sick infants.
    4. Ventilation (CO_2 elimination) is primarily controlled by pressure amplitude ($\Delta P = PIP - PEEP$), which determines the delivered tidal volume (V_T). In HFJV, CO_2 elimination is proportional to $(V_T)^2$; therefore, even small changes in V_T can result in large swings in $PaCO_2$. Under normal circumstances, PIP should be increased by 1–2 cm H_2O to lower $PaCO_2$ and lowered by 1–2 cm H_2O to increase $PaCO_2$. Smaller changes, repeated if necessary, are preferred to a single large decrease, which could have unanticipated effects.
    5. When lung volume is optimized, compliance may improve dramatically and this can lead to a large increase in V_T and a corresponding drop in $PaCO_2$. Close observation of the chest wall movement and aggressive lowering of PIP may be needed to avoid dangerously low $PaCO_2$,. $TcPCO_2$ monitoring is recommended to minimize this risk.
    6. Rate has a relatively minor effect on ventilation. Usual range is 300–450 cycles/min, depending on size of baby and time constants. A rate that is too fast may increase $PaCO_2$ because of gas trapping.
    7. Unlike with HFOV, a change in ventilator rate does not change the V_T, unless the rate change eliminates or causes gas trapping.
    8. With HFJV, exhalation is passive. T_i should almost always remain at the lowest possible value of 0.02 s to maximize T_e.
    9. Background IMV rate of 2–5 inflations/min may be superimposed on the HFJV pulses to recruit/maintain lung volume (periodic sigh). The PIP should be slightly lower than the

HFJV PIP or so as not to interrupt the jet ventilator. T_i of the sighs should be about 0.5 s. Background IMV should be omitted in the presence of overexpansion or airleak.

10. Sighs recruit lung volume but adequate Pāw (PEEP) is needed to maintain it. Some authorities recommend omitting sighs once lung volume recruitment is achieved. This author prefers to continue a very low rate of 2 sighs/min to maintain lung volume with lower Pāw.
11. Weaning from HFJV is accomplished primarily by weaning PIP, and leaving the rate unchanged, except when there is a suspicion of gas trapping from increased airway resistance.
12. Decreasing Δ P by lowering PIP also lowers Pāw and thus affects oxygenation. This problem can be avoided by increasing PEEP.

C. Important principles of clinical application
   1. The standard 15 mm endotracheal tube (ETT) adapter needs to be replaced with the Bunnell LifePort® adapter prior to initiating HFJV. The jet and pressure monitoring lines should initially be capped, then connected to the jet circuit with the ventilator in STANDBY MODE.
   2. The tip of the ETT should not be too close to the carina—optimally at least 1 cm above—to avoid inadvertently directing the jet stream preferentially down one or the other main bronchus.
   3. The ETT should be cut to the shortest practical length to avoid bending and kinking, the patient circuit should be supported so as to keep the tube straight.
   4. The baby's head must be kept midline and slightly extended with a shoulder roll, to keep the ETT as straight as possible and optimize penetration of the jet stream down the airways. Allowing the head to be turned to the side results in the jet stream hitting the wall of the trachea, because the ETT enters the trachea at an angle. This may result in mucosal damage and is certain to reduce the efficiency of gas exchange.

D. Matching ventilator strategy to disease pathophysiology
   1. Choosing an appropriate ventilator strategy is critical—a wrong strategy may lead to lack of response and/or complications.
   2. Ventilator settings should be selected according to each patient's specific needs.
   3. The underlying disease, postnatal age, and patient size must all be considered in choosing an appropriate strategy and settings.

E. Low Pressure strategy
   1. This was the traditional approach to treating airleak in the early days of HFJV, but has largely been abandoned. It may still occasionally be necessary when refractory air leak is a major problem (e.g., severe PIE with gross overexpansion, large broncho-pleural fistula) and the imperative is to reduce peak and mean airway pressures in an effort to resolve the air leak. This situation is now uncommon.
   2. Widespread use of the low pressure strategy in the early days of HFJV is the reason for the misconception that HFJV is not good for oxygenation. When used with an optimal volume strategy, HFJV results in equally good oxygenation as HFOV.
   3. PIP should be set 10–15 % below current level on CMV.
   4. PEEP should be 5–6 cm H_2O, depending on severity of air leak and co-existing lung disease (may need to be higher if atelectasis co-exists with PIE).
   5. Remember that oxygenation is related to Pāw and that it may deteriorate with the drop in PIP and short Ti. Marginal PaO_2 may have to be accepted and higher FiO_2 is often needed.
   6. Permissive hypercapnia is generally considered appropriate in this setting.

7. Use of the low pressure strategy should be limited to infants with severe diffuse PIE and persistent lung overexpansion; less severe or more localized PIE is best treated with an optimal lung volume strategy to avoid atelectasis.
8. T_i should be kept at the minimum value of 0.02 s to promote exhalation.
9. Background IMV should be omitted. Optimal HFJV rate depends on an estimation of the patient's time constants, which are generally increased with PIE. Usual range 360–420 breaths/min to allow adequate expiratory time.
10. If marginal oxygenation prevents further decrease in PIP but $PaCO_2$ is low, decrease the pressure amplitude by increasing PEEP to avoid hypocapnia and to maintain oxygenation.
11. If diffuse atelectasis develops and oxygenation is inadequate, an increase in Pāw (i.e., higher PEEP) is indicated, provided ventilation is adequate. Some sighs may be needed at this time to re-recruit lung volume.
12. If ventilation is also inadequate, PIP should be increased as well.
13. As air leak resolves and atelectasis becomes the dominant problem transition to the optimal volume strategy (see below).

F. Optimal volume strategy
1. This strategy is appropriate in most situations, especially in RDS.
2. The goal is to optimize lung volume, thereby improving V/Q matching, ensure even distribution of V_T into an open lung and avoid the recruitment/de-recruitment cycle typical of conventional large V_T ventilation.
3. When switching from CMV, a slight increase in MAP should be achieved by increasing PEEP.
4. The following rule of thumb can be used for initial PEEP settings:
   a. Set PEEP at 6–7 cm H_2O if FiO_2 is <0.30
   b. Set PEEP at 7–8 cm H_2O if FiO_2 is 0.30–0.50
   c. Set PEEP at 9–12 cm H_2O if FiO_2 is >0.50
5. PIP should initially remain the same as on CMV, which results in lower pressure amplitude. If starting HFJV without prior CMV, choose a pressure that results in adequate but not excessive chest wall movement.
6. Background sigh rate is set at 5/min with T_i of 0.3–0.5 s and PIP set 1–2 cm H_2O below the jet PIP.
7. The default rate of 420 cycles/min with T_i of 0.02 s is appropriate early in the course of RDS, because time constants are short. Later, as compliance improves, and airway resistance increases, the rate may need be lowered to avoid gas trapping.
8. Optimization of lung volume is reflected by marked improvement in oxygenation. If the initial settings do not allow weaning of FiO_2 to <0.35, PEEP should be increased further.
9. When adequate lung volume recruitment has been achieved, as evidenced by improved oxygenation, discontinue the background IMV and observe for possible deterioration of oxygenation in the next few minutes. If oxygenation remains good, the PEEP is adequate. If oxygenation deteriorates, return to a rate of 5 signs/min to re-recruit lung volume and increase PEEP by 1–2 cm H_2O. Repeat the process, if necessary. When oxygenation remains stable for 10–15 min with the background IMV off, the PEEP is adequate. You may keep the IMV off or restart a background rate of 2 sighs/min.
10. It is uncertain if background IMV is beneficial once stable lung volume is reached. However, please note that the published randomized clinical trials were done using background sighs.

11. The background sigh rate or pressure should *not* be increased as a primary means of increasing Pāw. Higher Pāw is more safely accomplished by raising PEEP. Remember that the large V_T of conventional ventilation is the very thing you are trying to avoid.
12. Once lung volume is optimized, compliance may improve rapidly. This will be reflected in improved chest wall movement and CO_2 elimination. *PIP must be lowered promptly to avoid hypocapnia*. Follow $PaCO_2$ closely and use $TcPCO_2$ monitoring, if available.
13. The decreased PIP will lower Pāw as well, which is appropriate, because the recruited lungs are now more compliant and require less distending pressure to maintain recruitment (LaPlace's Law).
14. If the FiO_2 is ≤0.30–0.35, the Pāw (PEEP) may need to be lowered further to avoid overexpansion.
15. Periodic chest radiographs are helpful in verifying adequate lung expansion or detecting overexpansion. The goal is 8½ to 9 rib expansion.

G. Treatment of MAS and persistent pulmonary hypertension of the newborn (PPHN)
1. MAS (Chap. 71) is a heterogeneous disorder and evolves rapidly over time. The effectiveness of HFJV in this syndrome is variable, ranging from poor to dramatic.
2. Very early on, when large airways are obstructed with particulate meconium, HFJV may be ineffective as the jet stream is broken up by the obstructing debris. This can usually be corrected by effective suctioning of the airway.
3. HFJV provides a sort of internal vibration that helps to mobilize secretions/aspirated material. The expiratory flow along the periphery of the large airways brings the secretions proximally. Be ready to suction when initiating HFJV, as large amounts of meconium may be reflux.
4. When the surfactant inactivation or inflammatory effect of MAS predominates, HFJV is usually quite effective and the optimal volume strategy is appropriate. However, beware of overexpansion and gas trapping secondary to inadequate expiratory time. Remember: larger infants with airway obstruction have long time constants and need slower rates. Typical range is 240–360 cycles/min (4–6 Hz).
5. If there is evidence of overexpansion and/or CO_2 retention, the correct intervention is to lower the rate and allow more expiratory time, thus eliminating dynamic PEEP, rather than lowering the set PEEP. Adequate PEEP is needed to maintain airway patency and lung volume; PEEP values ≥10 cm H_2O are often needed in infants with severe lung disease.
6. Although HFJV is an effective and relatively gentle means of hyperventilation, it is no longer recommended to treat PPHN with respiratory alkalosis. Avoid extremes of $PaCO_2$ and pH, which are easily achieved with HFJV, but are associated with increased risk of intracranial hemorrhage and periventricular leukomalacia.

H. Miscellaneous conditions responsive to HFJV
1. When diaphragmatic excursion is impaired by increased intra-abdominal pressure, the small V_T of HFJV with sufficiently high PEEP to apply counter-pressure on the diaphragm and maintain lung volume is advantageous. Babies with acute abdominal distention from necrotizing enterocolitis or similar conditions, and those post-repair of gastroschisis, CDH, or omphalocele often respond dramatically with improved gas exchange and hemodynamics. Inadvertent hypocapnia may occur unless great care is taken to monitor chest wall movement, $TcPCO_2$, and blood gases.
2. Infants with airway disruption such as intractable pneumothorax with constant large flow through chest tubes, tracheo-esophageal fistula, or tracheal tear respond with improved gas exchange and decreased flow through the point of airway disruption. This is because the jet stream moves down the center of the airway with virtually no lateral pressure on the

airway wall. The gas that does escape is probably expiratory gas. A strategy intermediate between the optimal volume and low pressure strategy is probably best in these situations. Each patient must be individually assessed regarding the appropriate strategy.

3. Infants with lung hypoplasia appear to benefit from the gentler ventilation and smaller V_T made possible by HFJV. Because of the decreased number of alveoli in hypoplastic lungs, each lung unit must accept a larger than normal V_T with CMV, thus leading to volutrauma. Mild permissive hypercapnia is usually tolerated, but occasionally infants with PPHN need to have their $PaCO_2$ lowered into the high 30s before PPHN will respond to iNO. An intermediate approach between the optimal volume and low pressure strategy works best. Beware of overexpansion of the lungs, which will exacerbate pulmonary hypertension. A trial of a lower ventilator rate is appropriate when lung volume is too high or CO_2 elimination is suboptimal, suggesting gas trapping.
4. Limited clinical experience and small studies suggest that HFJV may be useful in extremely immature preterm infants with evolving or established chronic lung disease. These infants have distended, "floppy" airways and are very prone to gas trapping as the airways collapse during expiration. HFJV may benefit these infants by splinting these airways open with fairly high PEEP (7–10 cm H_2O), and allowing more efficient gas exchange and more even aeration of the lungs, in part because HFJV breaths are less affected by variation in regional impedance. Several small studies suggest that HFJV may be more effective than HFOV in these infants.

I. Weaning from HFJV
   1. Weaning is accomplished by lowering FiO_2 first and PEEP second, once the FiO_2 is $\leq$0.30.
   2. PIP is lowered in response to low/normal $PaCO_2$ or excessive chest wall movement. Remember to compensate for decreasing PIP by increasing the PEEP, if necessary, to maintain Pāw.
   3. Ventilator rate is not decreased as a means of weaning. However, it may need to be lowered to accommodate lengthening time constants because of increasing compliance and/or increasing airway resistance as RDS evolves into early BPD.
   4. Infants can be weaned from HFJV directly to CPAP. This is usually possible, once PIP is $\leq$12–15 cm H_2O and PEEP $\leq$7 cm H_2O.
   5. Alternately, once the pressure is $\leq$16–20 cm H_2O and PEEP $\leq$7 cm H_2O, the infant can be switched to CMV. Usually a 10 % higher ΔP is needed after the change to maintain ventilation. PEEP may be lowered by 1 cm H_2O to maintain constant Pāw.

Suggested Reading

Donn SM, Zak LK, Bozynski MEA, et al. Use of high-frequency jet ventilation in the management of congenital tracheo-esophageal fistula associated with respiratory distress syndrome. J Pediatric Surg. 1990;25:1219–22.

Engle WA, Yoder MC, et al. Controlled prospective randomized comparison of HFJV and CV in neonates with respiratory failure and persistent pulmonary hypertension. J Perinatol. 1997;17:3–9.

Gonzalez F, Harris T, Black P, et al. Decreased gas flow through pneumothoraces in neonates receiving high-frequency jet versus conventional ventilation. J Pediatr. 1987;110:464–6.

Harris TR, Bunnell JB. High-frequency jet ventilation in clinical neonatology. In: Pomerance JJ, Richardson CJ, editors. Neonatology for the clinician. Norwalk: Appleton & Lange; 1993. p. 311–24.

Keszler M. High-frequency ventilation: evidence-based practice and specific clinical indications. NeoReviews. 2006;7(5):e234–49.

Keszler M, Durand D. High-frequency ventilation: past, present, and future. Clin Perinatol. 2001;28:579–607.

Keszler M, Donn S, Bucciarelli R, et al. Multi-center controlled trial of high-frequency jet ventilation and conventional ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr. 1991;119:85–93.

Keszler M, Modanlou HD, Brudno DS, et al. Multi-center controlled clinical trial of high frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics. 1997;100:593–9.
Sugiura M, Nakabayashi H, Vaclavik S, Froese AB. Lung volume maintenance during high frequency jet ventilation improves physiological and biochemical outcome of lavaged rabbit lung. Physiologist. 1990;33:A123.
Wiswell TE, Graziani LJ, Kornhauser MS, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. Pediatrics. 1996a;98:1035–43.
Wiswell TE, Graziani LJ, Kornhauser MS, et al. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. Pediatrics. 1996b;98:918–24.

High-Frequency Oscillatory Ventilation

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I. Introduction
   A. Definition—High-frequency oscillatory ventilation (HFOV) is rapid-rate, low-tidal-volume form of mechanical ventilation. HFOV uses a constant distending pressure (mean airway pressure) with pressure oscillations around the mean pressure. The ventilatory rates range from 300 to 900 cycles per minute. Tidal volumes are often less than the dead space so HFOV relies on alternative mechanisms of gas exchange to promote carbon dioxide removal from the lung.
   B. Reasons for development of HFOV
      1. To improve gas exchange in patients with severe respiratory failure
      2. To reduce ventilator-induced lung injury (VILI)
         a. Prevention of volutrauma. HFOV dramatically reduces the tidal volume needed to maintain ventilation (normocapnia). During HFOV, the lung can be held close to mean lung volume. There is minimal change in lung volume with each delivered breath. Visually, this translates to chest wall vibration that is barely perceptible. In contrast, during conventional mechanical ventilation (CMV), the lung is cycled from low to high volume with each breath, such that chest rise and fall is easily visible.
         b. Reduced exposure to inspired oxygen. HFOV improves the uniformity of lung inflation, reduces intrapulmonary shunt, and improves oxygenation. The need for supplemental oxygen is reduced and exposure to oxygen-free radicals is decreased.
         c. Prevention of atelectrauma (open-lung approach). In healthy infants and children, lung volumes, both end-inspiratory and end-expiratory, change rapidly. At the end of a normal exhalation, the chest wall interacts with the lung to define functional residual capacity (FRC, lung volume at the end of expiration of a normal tidal volume breath). In neonates with retained lung fluid, lung disease, or lung injury, FRC is decreased, and portions of the lung, generally the dependent areas, are collapsed. Alveolar units are prone to collapse in patients with lung disease in which there is inadequate or dysfunctional surfactant. The breath-to-breath cycle of recruitment and subsequent "de-recruitment" of these units causes lung injury. This mechanism of injury explains the observation that

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recruitment of lung volume and normalization of FRC protects the lung against VILI and also reduces the need for high levels of inspired oxygen. A goal of respiratory support is to open these areas and to normalize end-expiratory lung volume (i.e., FRC). HFOV does this by reducing changes in lung volume and promoting lung recruitment. Strategies that promote lung recruitment and reduce tidal volume act synergistically to reduce VILI.

3. To decrease pulmonary morbidity in patients who require assisted ventilation
4. To provide a method of assisted ventilation that allows severe pulmonary air leaks to heal

II. Differences between HFOV and CMV

A. Parameter	CMV	HFOV
1. Rate (breaths per minute)	0–150	180–1500
2. Tidal volume (mL/kg)	4–20	0.1–5
3. Alveolar pressure (cm H_2O)	5–50	0.1–20
4. End-expiratory lung volume	low	high

B. Advantages of HFOV
   1. Improves ventilation at lower pressure and volume swings in the lung.
   2. Safer way of using "super" positive end-expiratory pressure (PEEP). The lung can be inflated to higher mean volumes without having to use high peak airway pressures to maintain ventilation (carbon dioxide removal).
   3. Produces more uniform lung inflation.

C. Disadvantages of HFOV
   1. As with CMV, there is the potential for gas trapping and the development of inadvertent PEEP. The time for exhalation during HFOV is very short. Gas delivered to the lung during the inspiratory cycle may become trapped in the lung. This "trapped" gas can cause overinflation of the lung and lung injury (stretch injury or air leak). The propensity for gas trapping is dependent on the high-frequency device being used. Devices that facilitate exhalation are less likely to cause gas trapping than devices that depend on the passive recoil of the chest and lung.
   2. Defining optimal mean lung volume is difficult, yet crucial, to the safe use of HFOV.
      a. Increasing lung volume results in decreasing venous return, which can be severe enough to compromise cardiac output. Lung overinflation can also cause acute lung injury, especially if cardiac output is compromised.
      b. Underinflation of the lung is equally dangerous. Collapsed lungs are difficult to recruit, and recruitment of collapsed lungs can be associated with significant lung injury. Atelectasis is associated with increased pulmonary vascular resistance, increased intra- and extrapulmonary shunts, and life threatening hypoxemia.

III. Types of HFOV

A. Diaphragm HFOV with variable fractional inspiratory time. The SensorMedics 3100A oscillatory ventilator (Chap. 55) is the only HFOV device approved for use in newborns in the USA. It has an electronically controlled diaphragm that produces pressure oscillation in the patient circuit. Adjusting the power, frequency, or fractional inspiratory time to the diaphragm driver controls the airway pressure amplitude. The mean airway pressure is set independently from the pressure oscillations. Adjusting the bias flow or the outlet resistance in the patient circuit controls mean airway pressure.

B. Piston HFOV with a fixed fractional inspiratory time. These types of HFOV devices have used a 1:1 inspiratory-to-expiratory (I:E) ratio. In healthy adult rabbits the use of a 1:1 I:E ratio has been shown to be associated with gas trapping and inadvertent PEEP. Newer devices allow for 1:2 and 1:1 I:E ratios. The Hummingbird is the best example of this type of HFOV.

C. Hybrid devices employ a Venturi to generate negative pressure during the expiratory cycle.

IV. Calculations of Minute Ventilation
   A. For conventional ventilation and normal breathing: Rate × V_T
   B. For HFOV: $\text{Rate}^{(0.5-1)} \times V_T^{(1.5-2)}$
      1. This equation predicts that factors effecting tidal volume delivery have a much larger impact on ventilation during HFOV than they do for CMV. Changes in endotracheal tube size, lung compliance, airway resistance, and chest wall rigidity all impact delivery of "tidal volume."
      2. It is also important to remember that the impedance of the respiratory system increases with frequency. During HFOV, as frequency is increased, tidal volume delivery and minute ventilation may decrease.
      3. Some devices, such as the SensorMedics 3100A, have lower V_T output at higher frequencies. This can be compensated by increasing the power setting.
   C. Theory for improved ventilation during HFOV
      1. Enhanced molecular diffusion
      2. Enhanced convection (Pendelluft effect)—regional differences in time constants for inflation and deflation cause gas to recirculate among lung units and improve gas exchange
      3. Taylor dispersion—augmented diffusion occurs because of turbulent air currents that result from interaction between axial velocity and the radial concentration gradient in the airways; and molecular diffusion
      4. Asymmetric velocity profiles—convective gas transport is enhanced by asymmetry between inspiratory and expiratory velocity profiles that occur at branch points in the airways
      5. Reduced dependence on bulk convection
      6. Kaczka et al. have suggested that oscillation with simultaneous multiple frequencies may be a more efficient ventilator modality compared with traditional single-frequency HFOV.
   D. Oxygenation
      1. Directly related to the degree of lung inflation (lung surface area)
      2. Directly related to amount of inspired oxygen (FiO_2)
      3. Both over- and underinflation of the lung can lead to decreased venous return, increased pulmonary vascular resistance, and compromised cardiac output.
   E. Physiologically targeted strategies of HFOV
      1. Poor lung inflation. HFOV has its most dramatic effects in infants whose primary pathophysiology is decreased lung inflation. When used with continuous distending pressure (CDP) directed at recruiting lung volume, and followed by careful weaning of the CDP once lung inflation is improved and FiO_2 is decreased, HFOV reduces lung injury and improves oxygenation. This approach exploits the concept of pressure–volume hysteresis, assuming the lung is not too badly injured and still has some recruitable volume. By using a CDP that is higher than the lung opening pressure (and usually greater than that which is generally accepted during CMV), HFOV recruits collapsed lung units. Once open, these lung units can be maintained open at a mean airway pressure lower than that used for lung recruitment.
      2. Pulmonary hypertension. HFOV can be effective in patients with pulmonary hypertension, if the process leading to pulmonary hypertension is poor lung inflation and regional hypoxia and hypercarbia. Improving lung inflation improves V/O matching and gas exchange, thereby relaxing the pulmonary vascular bed and decreasing pulmonary arterial pressure. HFOV is not as effective in patients with airway obstruction or in patients with poor cardiac output, especially from myocardial dysfunction. Airway obstruction attenuates the pressure signal as it is propagated across the airways to the alveoli. This attenuation

decreases the alveolar ventilation and reduces ventilator efficiency. In patients with poor cardiac output, the constant high end expiratory pressure decreases venous return and adds to further impair cardiac output.

3. Reported indications for HFOV. Numerous clinical reports of uncontrolled trials of the use of HFOV as a rescue technique have been published. The absolute indications and contraindications remain to be established by carefully controlled clinical trials. The following list represents reported indications for rescue HFOV:
   a. Persistent air leak (e.g., bronchopleural fistula, pulmonary interstitial emphysema)
   b. Persistent neonatal respiratory failure associated with:
      (1) Respiratory distress syndrome (RDS)
      (2) Pneumonia
      (3) Adult respiratory distress syndrome (ARDS)
      (4) Meconium aspiration syndrome (MAS)
      (5) Lung hypoplasia syndromes
      (6) Congenital diaphragmatic hernia (CDH)
      (7) Hydrops fetalis
      (8) Potter's variant
   c. Tracheoesophageal fistula in patients who are unable to undergo surgical correction quickly (e.g., premature infants)
   d. Primary pulmonary hypertension, which is responsive to reversal of atelectasis.
4. Reported contraindications
   a. Airway disease associated with gas trapping. Most authors agree that HFOV is not effective in patients with airway obstruction. The use of HFOV in patients with airway disease can accentuate problems with gas trapping.
   b. Uncorrected shock. Appropriate use of HFOV increases mean lung volume. As lung volume increases, right atrial volume will decrease. These changes impede venous return. Reduced venous return may amplify problems with hypotension unless preload is increased through aggressive treatment of shock and its causes. These problems are identical to the problems seen with increasing levels of positive end-expiratory pressure during CMV.

F. Specific reports and summary of clinical trials
1. Respiratory distress syndrome (RDS)
   a. The largest prospective study involving HFOV was reported by the HIFI Study Group. Of 673 preterm infants weighing between 750 and 2000 g, 346 were assigned to receive CMV and 327 to receive HFOV. No infant received surfactant. The incidence of bronchopulmonary dysplasia (BPD) was nearly identical in the two groups. HFOV did not reduce mortality or the level of ventilatory support during the first 28 days. HFOV was associated with an increased incidence of pneumoperitoneum, grades 3 and 4 intracranial hemorrhage, and periventricular leukomalacia. These results suggested that fixed ratio HFOV, as used in this trial, did not offer any advantage over CMV), and it might be associated with undesirable side effects.
   b. In a much smaller study ($n=98$), also in non-surfactant-treated infants, Clark et al. showed that HFOV could be used to reduce the incidence of chronic lung disease in premature infants with RDS without increasing the incidence of intraventricular hemorrhage (IVH). The HFOV strategy used in this study was designed to recruit lung volume. The average CDP used during HFOV was 2–3 cm H_2O higher than the mean P_{AW} used during CMV.

c. In a multicenter trial ($n = 176$), the HIFO study group showed that rescue HFOV could be used to reduce the incidence of air leak syndromes in infants with established severe lung disease. There was a slight increase in incidence of grades 3 and 4 IVH in those infants treated with HFOV.
d. Gerstmann et al. did the first study in which all infants received surfactant. The purpose of this study was to compare the hospital course and clinical outcome of preterm infants with RDS treated with surfactant and managed with HFOV or CMV as their primary ventilatory support. A total of 125 infants ≤35 weeks' gestation with a/A <0.5 were studied. HFOV was used in a strategy to promote lung recruitment and maintain lung volume. Patients randomized to HFOV demonstrated the following significant findings compared with CMV-treated patients: less vasopressor support; less surfactant re-dosing; improved oxygenation, sustained during the first 7 days; less prolonged supplemental oxygen or ventilator support; reduced treatment failures; more survivors without BPD at 30 days; less need for continuous supplemental oxygen at discharge; lower frequency of necrotizing enterocolitis; fewer abnormal hearing tests; and decreased hospital costs. In pulmonary follow-up at 6 years of age, infants randomized to HFOV had normal lung volume measurements, whereas those randomized to CMV had larger than normal residual volume and decreased vital capacity.
e. The two largest clinical studies show conflicting results.
   (1) Courtney et al. studied 500 infants. Those randomly assigned to HFOV were successfully extubated earlier than infants assigned to synchronized intermittent mandatory ventilation (SIMV). Of infants assigned to HFOV, 56 % were alive without need for supplemental oxygen at 36 weeks of postmenstrual age, compared to 47 % of those receiving SIMV. There was no difference between the groups in the risk of IVH, cystic PVL, or other complications.
   (2) Johnson et al. studied 400 infants who were assigned to HFOV and 397 who were assigned to CV. The composite primary outcome (death or CLD diagnosed at 36 weeks of postmenstrual age) occurred in 66 % of the infants assigned to receive HFOV and 68 % of those in the CV group. There were also no significant differences between the groups in a range of other secondary outcome measures, including serious brain injury and air leak.
f. Meta-analysis by Cools et al. assessed the effectiveness of elective HFOV versus CMV in premature patients with RDS. Nineteen eligible clinical studies involving 4096 infants were included. Meta-analysis comparing HFOV with CV showed survival was similar for both groups and these results were consistent across studies and in subgroup analyses. The risk of BPD in survivors was significantly reduced with the use of HFOV but this effect was inconsistent across studies. Subgroup analysis by HFOV strategy showed a similar effect in trials using a lung volume recruitment strategy and trials with a less strict lung volume recruitment strategy. Pulmonary air leaks, defined as gross air leaks or pulmonary interstitial emphysema, occurred more frequently in the HFOV group, whereas the risk of severe retinopathy of prematurity was significantly reduced. The overall meta-analysis revealed no significant differences in effect between HFOV and CMV on intracranial hemorrhage and/or periventricular leukomalacia. Most trials did not find a significant difference in long-term neurodevelopmental outcome, although one recent trial showed a significant reduction in the risk of cerebral palsy and poor mental development.

g. Current status
   (1) Animal studies show that HFOV reduces lung injury, promotes more uniform lung inflation, improves gas exchange, and prolongs the effectiveness of exogenous surfactant in experimental models of acute lung injury.
   (2) Clinical studies show that the results are strategy-specific. When used with a strategy designed to optimize and maintain lung inflation, HFOV can be used safely to reduce the occurrence of BPD. However, technology is ever-changing and the debate over the best surfactant and the gentlest mode of ventilation continues.

2. Air leak syndromes
   a. Pulmonary interstitial emphysema (PIE). Clark et al. showed that HFOV improved gas exchange in premature infants with severe respiratory failure and PIE. Compared to previously reported data involving CMV, HFOV also appeared to improve survival. Similar results have been reported with HFJV.
   b. Current status: PIE remains a serious complication of assisted ventilation. The introduction of surfactant has reduced the incidence of PIE, but has not eliminated the disease process. HFOV improves gas exchange and appears to improve the outcome of patients with PIE. However, affected infants are at high risk for long-term pulmonary and neurologic morbidity.
3. Pneumothorax
   a. Blum-Hoffman et al. showed that HFOV was effective in improving oxygenation and ventilation in patients with air leak syndromes. Carter et al. reported similar results.
   b. Current status: Both HFJV and HFOV appear to improve gas exchange and allow for more rapid resolution of pneumothoraces.
4. Congenital diaphragmatic hernia—Al-Jazaeri et al. and Migliazza et al. have suggest that HFOV can be used to support infants with congenital diaphragmatic hernia and reduce lung injury but there are no RCTs that evaluate this hypothesis.
5. Extracorporeal Membrane Oxygenation (ECMO) candidates
   a. Paranka et al. demonstrated that 50 % of the ECMO-eligible patients could be rescued with HFOV alone. The outcome of patients rescued with HFOV was as good as for those who went on ECMO. Patients with CDH (30 %) and MAS (50 %) were not as likely to respond to HFOV as were patients with pneumonia (85 %) and/or RDS (90 %).
   b. Vaucher et al., using a different type of HFOV and a different clinical strategy, did not demonstrate results as encouraging. Patients who met criteria and were treated with ECMO had less BPD than infants who were "rescued" with alternative therapies. Walsh-Sukys presented similar findings. Both these studies show that prolonged use of HFOV or CMV to avoid ECMO may increase the risk of BPD.
   c. Kinsella et al. reported that treatment with HFOV and inhaled nitric oxide was more effective than either therapy alone in the management of babies with lung disease and PPHN. This finding was particularly true for infants with RDS or MAS.
   d. Chen et al. investigated the clinical efficiency of HFOV combined with pulmonary surfactant (PS) for the treatment of neonatal meconium aspiration syndrome (MAS). Clinical data of 53 MAS patients admitted for neonatal intensive care unit were collected. Early use of HFOV combined with pulmonary surfactant to treat MAS had a significant therapeutic effect, especially for the treatment of severe MAS.
   e. Current status: Results achieved with HFOV are likely to be device- and strategy-specific. The relative roles surfactant, inhaled nitric oxide, liquid ventilation, HFOV, and ECMO. play in the management of term infants with severe respiratory failure have not yet been determined.

G. Reported complications of HFOV
   1. Adverse cardiopulmonary interactions. It is essential to maintain the balance between adequate lung volume and cardiac preload. During HFOV, lung volume is nearly constant. Failure to maintain adequate preload and/or optimal lung volume can result in progressive hypotension and hypoxemia.
   2. Mucostasis
      a. The HFOV I:E setting effects mucus clearance from the lung. Mucus can build up in the airways during HFOV. When weaned from HFOV and returned to CMV, some patients will rapidly mobilize these secretions. Airways can become occluded and frequent suctioning may be required during the 24- to 48-hour period following HFOV. Airway trauma associated with suctioning should be avoided by passing the suction catheter only 1 cm below the endotracheal tube. While mucostasis is an uncommon complication of HFOV, it can be life threatening.
      b. Premature patients with RDS who were treated with HFOV may actually require less suctioning.
      c. Management of airway secretions must be individualized. Try to avoid suctioning unless clinically indicated (increasing $PaCO_2$, visible airway secretions, or decreasing oxygen saturation).
   3. Gas trapping—see above.
   4. IVH and PVL. Some studies have suggested that the association between HFOV and poor neurologic outcome is more related to how HFOV is used than whether it is used. HFOV can cause rapid reduction in $PaCO_2$, which can cause sudden changes in cerebral blood flow. To use HFOV safely, acute changes in ventilation, especially overventilation (i.e., hypocapnia and alkalosis), must be avoided. A $TcPCO_2$ monitor may help.
   5. Long-term follow work of infants at 11–14 years of age has been reported by Greenough et al. who concluded extremely prematurely born infants entered into a randomized trial of HFOV versus CV demonstrated significant differences in lung function in favor of HFOV. In addition, HFOV children did better in some school subjects. Similarly, Truffert et al. suggest "that early use of high-frequency ventilation, compared with conventional ventilation, may be associated with a better neuromotor outcome." The small number of patients studied by Truffert et al. limits the power of this observation, but it is reasonable to suggest that HFOV is not associated with a poorer neuromotor outcome.

J. General- and disease-specific recommendations
   1. Atelectasis with diffuse radio-opacification of the lung (RDS or pneumonia)
      a. The CDP required to optimize lung inflation is higher than that which is usually achieved on CMV. Mean airway pressure can be increased in 1–2 cm H_2O increments until PaO_2 improves or the chest radiograph shows normal inflation. Evidence of overinflation or signs of cardiac compromise should be avoided. Radiographic signs of overinflation include "extra clear" lung fields, a small heart, flattened diaphragms, and more than nine posterior ribs of lung inflation. Signs of cardiac compromise include increased heart rate, decreased blood pressure, poor peripheral perfusion, and metabolic acidosis.
      b. Mean airway pressures used in the management of uncomplicated RDS in premature infants are generally lower than those used to treat term newborns. The severity of the lung disease, the age at the start of HFOV, the use of surfactant, and the presence of infection will all influence the amount of pressure that is required. CDPs commonly reported are
         (1) For infants <1 kg, 5–18 cm H_2O
         (2) For infants 1–2 kg, 6–20 cm H_2O
         (3) For infants >2 kg 10–25 cm H_2O

   c. Frequency is generally held constant at 8–15 Hz. Most clinical data report the use of 10 Hz. In infants who are <1 kg, extreme caution must be taken to avoid hyperventilation and alkalosis. If $PaCO_2$ is low and the pressure amplitude is less than 20 cm H_2O, the frequency may need to be increased in order to decrease minute ventilation and allow the $PaCO_2$ to rise to a normal range. Also, if small changes in power settings result in large changes in $PaCO_2$, ventilation control will be improved by increasing the frequency to 15 Hz.

2. Meconium aspiration syndrome
   a. Some of these patients present with diffuse lung injury with limited pulmonary hypertension and minimal airway obstruction. These patients respond as described above.
   b. In contrast, some newborns with MAS have severe airway obstruction and PPHN and these infants are not as responsive to HFOV as infants whose primary problem is poor lung inflation.
   c. During the initiation of HFOV in patients with MAS, a chest radiograph should be obtained to assess lung inflation and to rule out evidence of gas trapping. Lowering the frequency and increasing CDP may reduce gas trapping.
   d. Patients who have poor lung inflation, minimal improvement in gas exchange during HFOV, and clinical evidence of pulmonary hypertension are more likely to respond to a combination of HFOV and inhaled nitric oxide than to either therapy alone.
3. Lung hypoplasia syndromes
   a. Similar to patients with MAS, the patients most likely to respond to HFOV are those in whom the primary pathophysiologic process is poor lung inflation.
   b. Patients whose lung volumes have been optimized on HFOV, as evidenced by clear lung fields but who still have severe pulmonary hypertension, are less likely to respond to HFOV alone.
   c. Patients with both poor lung inflation and pulmonary hypertension may be best treated with a combination of HFOV and inhaled nitric oxide.
4. Air leak syndrome
   a. Patients who have severe persistent air leak (like PIE or recurrent pneumothoraces) require a different approach. The goal of assisted ventilatory support must be to allow the air leak to resolve. If the air leak is unilateral, placing the involved lung in the dependent position will increase the resistance to gas flow to this lung and promote atelectasis. Both lung collapse and decreased ventilation of the dependent lung will promote air leak resolution.
   b. In addition to dependent positioning, using a strategy of HFOV that emphasizes decreasing mean airway pressure over decreasing FiO_2 will help allow air leak resolution.
5. Idiopathic PPHN with normal lung inflation. These patients are easy to ventilate on low levels of conventional support. HFOV is not as effective in these patients and can be associated with the development of life threatening hypoxemia if the balance between preload and lung volume is not carefully addressed.

Suggested Reading

Al-Jazaeri A. Repair of congenital diaphragmatic hernia under high-frequency oscillatory ventilation in high-risk patients: an opportunity for earlier repair while minimizing lung injury. Ann Saudi Med. 2014;34:499–502.

Chen DM, Wu LQ, Wang RQ. Efficiency of high-frequency oscillatory ventilation combined with pulmonary surfactant in the treatment of neonatal meconium aspiration syndrome. Int J Clin Exp Med. 2015;8:14490–6.

Clark RH, Gerstmann DR, Null DM, et al. Pulmonary interstitial emphysema treated by high-frequency oscillatory ventilation. Crit Care Med. 1986;14(11):926–30.
Clark RH, Gerstmann DR, Null Jr DM, Delemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics. 1992;89(1):5–12.
Clark RH, Gerstmann DR, Jobe AH, Moffitt ST, Slutsky AS, Yoder BA. Lung injury in neonates: causes, strategies for prevention, and long-term consequences. J Pediatr. 2001;139(4):478–86.
Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev. 2015;3, CD000104.
Courtney SE, Durand DJ, Asselin JM, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med. 2002;347(9):643–52.
Gerstmann DR, Wood K, Miller A, et al. Childhood outcome after early high-frequency oscillatory ventilation for neonatal respiratory distress syndrome. Pediatrics. 2001;108(3):617–23.
Greenough A, Peacock J, Zivanovic S, Alcazar-Paris M, Lo J, Marlow N, et al. United Kingdom Oscillation Study: long-term outcomes of a randomised trial of two modes of neonatal ventilation. Health Technol Assess. 2014;18:v-95.
HiFO Study Group. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. HiFO Study Group. J Pediatr. 1993;122(4):609–19.
Johnson AH, Peacock JL, Greenough A, et al. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med. 2002;347(9):633–42.
Kaczka DW, Herrmann J, Zonneveld CE, Tingay DG, Lavizzari A, Noble PB, et al. Multifrequency oscillatory ventilation in the premature lung: effects on gas exchange, mechanics, and ventilation distribution. Anesthesiology. 2015; 123:1394–1403.
Keszler M, Donn SM, Bucciarelli RL, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr. 1991;119(1 Pt 1):85–93.
Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr. 1997;131(1 Pt 1):55–62.
Migliazza L, Bellan C, Alberti D, Auriemma A, Burgio G, Locatelli G, et al. Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and presurgical stabilization. J Pediatr Surg. 2007;42:1526–32.
Paranka MS, Clark RH, Yoder BA, Null Jr DM. Predictors of failure of high-frequency oscillatory ventilation in term infants with severe respiratory failure. Pediatrics. 1995;95(3):400–4.
The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med. 1989;320(2):88–93.
Thome U, Kossel H, Lipowsky G, et al. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. J Pediatr. 1999;135(1):39–46.
Truffert P, Paris-Llado J, Escande B, Magny JF, Cambonie G, Saliba E, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. Pediatrics. 2007;119:e860–5.

Section VIII

Commonly Used Neonatal Ventilators

Ventilator Mode Classification

44

Robert L. Chatburn

I. Introduction

In the last 30 years, the complexity of ventilator design has increased alarmingly. Early ventilators used for neonates had at most 4 modes of ventilation (CPAP, Assist, Control, and Assist/Control). The most recent infant ventilator (the Dräger VN500 Babylog) has 25 modes! To manage this level of complexity, this text has adopted the mode taxonomy (classification system) developed by Chatburn et al. Using this taxonomy, any mode can be specified using a three level hierarchy (1) the control variable, (2) the breath sequence, and (3) the targeting scheme.

II. Control variable

A. Equation of motion

The concept of a control variable is based on the equation of motion for the respiratory system:

$$P\text{vent}(t) = E \times V + R \times \dot{V}$$

where $P\text{vent}(t)$ is the pressure driving inspiration (i.e., airway pressure relative to end expiratory pressure) delivered by the ventilator as a function of time (t); E is respiratory system elastance ($\Delta P/\Delta V$), the reciprocal of compliance; V is volume change above end expiratory volume; R is respiratory system resistance ($\Delta P/\dot{V}$); and $\dot{V}$ is flow (relative to end expiratory flow).

B. Pressure control

Pressure control means that the left side of the equation of motion is preset, either as a constant value with respect to inspiratory time, or it is adjusted automatically by the ventilator to be proportional to the patient's inspiratory effort (measured, for example, using the electrical signal from the diaphragm as in the mode called neurally adjusted ventilatory assist, NAVA). Thus, pressure is the independent variable in the equation, whereas volume and flow are dependent on respiratory system mechanics.

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C. Volume control

Volume control means that the right-hand side of the equation of motion is preset. The operator determines both the tidal volume (V_T, the change in lung volume during the inspiratory time) and the inspiratory flow (sometimes just the peak value, sometimes also the waveform, depending on the ventilator). Thus, volume and flow are the independent variables in the equation whereas pressure is dependent on respiratory system mechanics.

D. Time control

For some modes (e.g., high frequency oscillatory ventilation and intrapulmonary percussive ventilation), pressure, volume, and flow are not preset. Rather, the operator sets the inspiratory and expiratory times and the other variables become functions of the respiratory system mechanics. In this case, the control variable is time.

III. Breath Sequence

Ventilators deliver two kinds of breaths: spontaneous and mandatory. The words spontaneous and mandatory have specific meanings in the context of mechanical ventilation. They are defined in terms of how inspiration is started (triggered) and stopped (cycled).

A. Spontaneous breaths

Spontaneous breaths are those for which inspiration is **both** triggered **and** cycled by the patient, independent of any ventilator setting for breath frequency.

B. Mandatory breaths

Mandatory breaths are those for which inspiration is **either** machine-triggered **or** machine-cycled, independent of the patient.

C. Sequences

Given the above definitions, there are only three possible breath sequences:

1. All breaths are spontaneous, called continuous spontaneous ventilation, CSV.
2. All breaths are mandatory (or more precisely, spontaneous breaths are not allowed between mandatory breaths, as every inspiratory effort results in mandatory breath delivery), called continuous mandatory ventilation, CMV (or Assist/Control).
3. Spontaneous breaths are possible between mandatory breaths, called intermittent mandatory ventilation, IMV. Whether or not the timing of the mandatory breaths is synchronized with the patient's inspiratory efforts, as in SIMV, is ignored in this taxonomy.

IV. Targeting scheme

The targeting scheme for a mode of mechanical ventilation is essentially the relation between the operator input and the ventilator output, typically some form of feedback control algorithm. Targeting schemes are what give modes their great variety and complexity on current ventilators. There are seven basic targeting schemes in current use across all brands of ventilators, but only three are important for neonatal ventilation.

A. Set-point

A targeting scheme for which the operator sets all the parameters of the pressure waveform (pressure control modes) or volume and flow waveforms (volume control modes). The ventilator does not adjust any targets automatically. This is the targeting scheme used in the mode historically called "time-cycled, pressure-limited" used for neonates.

B. Servo

A targeting scheme for which the output of the ventilator (e.g., inspiratory pressure) automatically follows a varying input (e.g., inspiratory effort). Simply put, inspiratory pressure is proportional to inspiratory effort. To date, the only examples for neonatal ventilation are NAVA and proportional assist ventilation (not currently available in the USA).

C. Adaptive

A targeting scheme allows the ventilator to automatically set one target (e.g., pressure within a breath) to achieve another target (e.g., average tidal volume over several breaths). Modes

that use pressure control with adaptive targeting are often referred to in the pediatric literature as "volume targeted" or "volume guaranteed" forms of pressure control. Specific mode names include "Pressure Regulated Volume Control," "Volume Assured Pressure Support," "AutoFlow," and "Volume Control Plus." The problem is that some authors use the word "volume targeted" to mean actual volume control instead of pressure control with adaptive targeting.

D. Primary vs. secondary
For modes with the IMV breath sequence, we specify a primary targeting sequence for the mandatory breaths and a secondary targeting scheme for the spontaneous breaths.

V. Mode classification

A. Overview
As mentioned above, any mode can be classified in terms of a *control variable*, a *breath sequence*, and a *targeting scheme*.

B. Abbreviations
The mode classification may be abbreviated using letters: **P** (pressure), **V** (volume), **T** (time), **CMV** (continuous mandatory ventilation), **IMV** (intermittent mandatory ventilation), **CSV** (continuous spontaneous ventilation), **s** (set-point targeting), **r** (servo targeting), and **a** (adaptive targeting). For modes that are classified as IMV, we specify the targeting scheme(s) for both mandatory and spontaneous breaths (i.e., lower case letters separated by a comma; the first lower case letter represents the mandatory breaths and the second one represents the spontaneous breaths).

C. Examples
The mode called "Time-Cycled, Pressure-Limited" is classified as **PC-IMVs,s** because inspiratory pressure is preset (pressure control), spontaneous breaths may occur between mandatory breaths (IMV), and no targets are automatically adjusted by the ventilator (set-point targeting, s) for either mandatory or spontaneous breaths. The mode called "Pressure Support" is classified as **PC-CSVs** because inspiratory pressure is preset, all breaths are spontaneous (patient-triggered) and patient-cycled, and again, set-point targeting is used. The mode called NAVA is classified as **PC-CSVr**, differing from pressure support in that the inspiratory pressure is proportional to inspiratory effort (servo targeting, **r**). The mode called "Pressure Regulated Volume Control" is classified as **PC-CMVa**. Inspiratory pressure is preset automatically by the ventilator (implying both pressure control and adaptive targeting, **a**). In addition, every breath is machine-cycled (preset inspiratory time), hence every breath is mandatory, resulting in the CMV breath sequence.

Suggested Reading

Chatburn RL, Mireles-Cabodevila E. Closed-loop control of mechanical ventilation: description and classification of targeting schemes. Respir Care. 2011;56(1):85–102.

Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

Mireles-Cabodevila E, Hatipoglu U, Chatburn RL. A rational framework for selecting modes of ventilation. Respir Care. 2013;58(2):348–66.

VIP BIRD Gold Ventilator

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Steven M. Donn

I. Introduction. Although the BIRD VIP Gold ventilator (CareFusion, San Diego, CA) is no longer manufactured, it is still in wide enough use around the world to be included. It provides both neonatal and pediatric ventilation. The ventilator breaths are synchronized in all modes. Continuous tidal volume, graphic monitoring of waveforms and mechanics are also available.

II. Monitoring
   A. Internal
      1. AC Power
      2. External DC Power
      3. Patient Effort
      4. Demand Flow (pressure limited modality only)
      5. Peak Inspiratory Pressure (PIP)
      6. Mean Airway Pressure (Pāw)
      7. Positive End Expiratory Pressure (PEEP)
      8. Rate (total breath rate)
      9. Inspiratory Time
      10. I:E Ratio
      11. Tidal Volume (I = inspiratory or E = expiratory)
      12. Expiratory Minute Volume
      13. Airway Pressure monometer (aneroid gauge)
   B. Bird Graphic Monitor
      1. Waveforms (2 of the 3 displayed at the same time)
         a. Flow
         b. Volume
         c. Pressure
      2. Mechanics
         a. Pressure–Volume Loop

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b. Flow–Volume Loop
3. Trends (24 h trend monitoring)
4. Pulmonary mechanics calculations
   a. Compliance and C_{20}/C ratio
   b. Resistance

III. Alarms
A. Alarms/Limits
1. Blender input gas alarm
2. High breath rate alarm
3. High pressure alarm
4. High/prolonged pressure alarm
5. High tidal volume
6. Low inlet gas pressure alarm
7. Low minute volume alarm
8. Low PEEP/continuous positive airway pressure (CPAP) pressure alarm
9. Low peak pressure alarm
10. Pressure Support/VAPS time limit

IV. Nomenclature
A. Pressure vs. Volume ventilation
1. Pressure Ventilation
   a. Inspiratory pressure is pre-set.
   b. The volume delivery varies with changes in compliance.
   c. There are three pressure modalities: time-cycled, pressure-limited (TCPL), pressure control (PC), and pressure support (PS).
2. Volume Ventilation
   a. Both delivered volume and inspiratory flow are pre-set.
   b. The pressure varies with changes in compliance.

B. Assist/Control vs. SIMV/PS
1. Assist/Control (A/C)
   a. A pre-set number of mandatory breaths (time- or volume controlled inspiration) are delivered in the event of apnea or failure to trigger.
   b. Every inspiratory effort triggers a mandatory breath (assuming sensitivity is set appropriately and met).
2. SIMV/PS
   a. A pre-set number of mandatory breaths are delivered.
   b. Spontaneous breaths (patient triggered and cycled inspirations) are possible between mandatory breaths and may be supported by using pressure support (PS).

C. Flow-Cycling (Fig. 45.1)
1. Use of "termination sensitivity" (cycle threshold) enables the baby to end mechanical inspiration nearly synchronously with his/her own spontaneous breathing.
2. Inspiration ends at a percentage (almost always 5 %) of the peak inspiratory flow rate rather than the set inspiratory time, and if properly set, this occurs before the set T_I.
3. Flow-cycling prevents inversion of the I:E ratio during rapid breathing and greatly reduces gas trapping which could occur in A/C at a fixed T_I, because T_E is shortened the faster the baby breathes.
4. In rare instances, the baby may "choose" a T_I that is too short to provide an adequate V_T. Switch to TCPL or PC.

V. Modalities of Ventilation

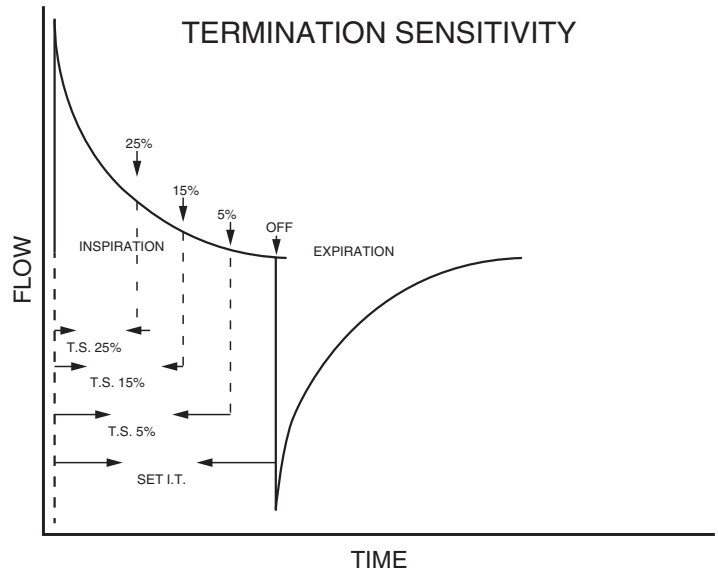

Fig. 45.1 Termination sensitivity® or expiratory trigger. Inspiration is initiated by a change of flow at the airway. When the lungs have inflated, flow decreases at the proximal airway, which results in the breath being terminated. The point of termination is clinician-adjustable, and represents a percentage of peak inspiratory flow. Thus, a 5% termination sensitivity setting means that the breath will be terminated when airway flow has decreased to 5% of peak flow (i.e., there has been a 95% decay of the curve). *IT* inspiratory time

A. Time-Cycled, Pressure-Limited
   1. Continuous flow
   2. Mechanical breaths are pressure-limited and may either be time-cycled or synchronized to the patients own respiratory effort by flow-cycling, changes that are detected by a proximal flow sensor (pneumotachograph).
   3. The pressure is controlled and the volume varies with lung compliance.

B. Pressure Control
   1. A pressure limited breath is delivered at a variable flow rate.
   2. It accelerates to peak flow and then decelerates.
   3. The endotracheal tube resistance and the patient compliance determine the flow rate, which can also be modulated with "Rise Time" (see below).

C. Pressure Support
   1. A pressure-limited breath that is patient-triggered. The patient has primary control of the inspiratory time and flow.
   2. The inspiratory flow may be adjusted with Rise Time, an adjustment that affects the flow and pressure waveforms. The setting of 1 is the steepest rise. The breath will be given quickly. The setting of 7 will give the breath more slowly and may be very helpful in the management of infants with high resistance disease or small endotracheal tubes.

D. Volume-Controlled (Targeted) Ventilation
   1. A pre-set volume is delivered with each breath.
      a. The volume is constant and pressure varies depending upon the patient's lung compliance.
      b. The breaths are triggered by a flow change at the flow sensor, indicating the patient is making a respiratory effort.
      c. The minimum tidal volume leaving the ventilator is 10 mL.
   2. Because cuffed endotracheal tubes are not used in newborns, there is usually some leakage of delivered volume. It is more appropriate to refer to this as volume-controlled or volume-limited ventilation, and not volume-cycled ventilation.

E. Volume-Assured Pressure Support (VAPS)
   1. VAPS begins in pressure control at the pre-set inspiratory pressure.
   2. A minimal volume target and inspiratory flow are set.
   3. Flow decays exponentially (for a passive patient).
   4. If the volume target is met before the flow decays to the pre-set value, inspiration is terminated.
   5. If the volume is not met by the time flow has decreased to the pre-set value, inspiration switches to volume control at a constant flow equal to the pre-set value. The inspiratory time extends and the pressure increases until the minimal target volume is achieved or the maximum inspiratory time limit ends the breath. This mode will deliver either patient-triggered breaths or a control rate if the patient has no effort.

F. Continuous Positive Airway Pressure
   1. Continuous gas flow through the circuit with expiratory resistance to provide the desired pressure.
   2. May be oxygen-enriched.
   3. No additional volume or pressure boost is provided.

G. Mode Map (Table 45.1)

VI. Management

A. Ventilator management
   1. Ventilation (P_aCO_2). Carbon dioxide removal is related to the minute ventilation (MV). MV = tidal volume (V_T) *X* respiratory rate. Measured inspiratory tidal volumes should be 4–8 mL/kg to avoid overinflation. Normal MV = 240–360 mL/kg/min
      a. Pressure-Targeted
         (1) V_T is adjusted by the change in pressure or ΔP (PIP—PEEP).
         (2) Compliance and resistance will affect the delivered tidal volume.
      b. Volume-Targeted

Table 45.1 Mode Map

	Mode classification				
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	Tag
Assist control TCPL[a]	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Assist control volume	Volume	CMV	Set-point	N/A	VC-CMVs
Assist control pressure control	Pressure	CMV	Set-point	N/A	PC-CMVs
Assist control assured volume[b]	Pressure	CMV	Dual	N/A	PC-CMVd
(S)IMV/CPAP/PS TCPL	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
(S)IMV/CPAP/PS volume	Volume	IMV	Set-point	Set-point	VC-IMVs,s
(S)IMV/CPAP/PS pressure control	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
(S)IMV/CPAP/PS assured volume[b]	Pressure	IMV	Dual	Set-point	PC-IMVd,s

[a]This mode is a form of IMV because spontaneous breaths (patient-triggered and patient-cycled inspiration) may occur between mandatory breaths (machine-triggered or machine-cycled); all breaths are patient (flow) cycled
[b]For mandatory breaths, inspiration starts in pressure control and switches to pressure control if the tidal volume is not met when flow decays to set flow

(1) The inspiratory tidal volume delivered to the patient is determined by the set tidal volume minus the volume that is compressed in the ventilator circuit (and any leak).
(2) The compressed volume varies with the pressure that is generated within the circuit and patient compliance.
(3) Always monitor the measured inspiratory and expiratory volumes to determine the leak volume.

2. Oxygenation (P_aO_2). Correlated directly to Pāw (mean airway pressure) and F_iO_2
   a. Increases in PIP, inspiratory time, PEEP, and rate all contribute to higher Pāw and an increase oxygenation.
   b. F_iO_2

VII. Weaning and Extubation (Chap. 78)
A. Weaning the ventilator. Our weaning strategies encourage the patient to breathe above the set respiratory rate. This is done by decreasing the rate to the point where the patient breaths spontaneously.
1. Pressure modes
   a. Weaning in A/C
      (1) It is possible to wean in either A/C or SIMV/PS.
      (2) As compliance improves the patient requires less pressure to deliver the appropriate desired inspiratory tidal volume.
   b. Weaning in SIMV/PS
      (1) Set the mandatory (SIMV) breath ΔP (PIP-PEEP) to deliver an inspiratory tidal volume of 4–8 mL/kg.
      (2) The pressure support (PS) level should be set at the same (PS_{max}) or slightly lower pressure, delivering approximately an inspiratory tidal volume of 4–8 mL/Kg.
      (3) Decrease the rate of the control breaths until all the breaths are PS breaths. (A low SIMV rate of 6–10/min may be used as a safeguard.)
      (4) Extubate from a rate of zero and a minimal PS level (PS_{min} = 3–4 mL/kg V_T).
2. Volume modes
   a. Weaning in A/C
      (1) Weaning in volume A/C is difficult.
      (2) Decrease the rate until the patient begins spontaneous respirations.
      (3) At rates of ≤20–40, change to SIMV/PS to continue weaning.
   b. Weaning in SIMV/PS
      (1) Set the volume parameter to deliver a measured inspiratory tidal volume of 5–6 mL/kg.
      (2) The pressure support (PS) should be set at the same (PS_{max}) or slightly lower pressure that is being generated by the volume breath, delivering an inspiratory tidal volume of approximately 4–6 mL/kg.
      (3) Decrease the rate of the control breaths until all the breaths are PS breaths. (A low SIMV rate of 6–10/min may be used as a safeguard.)
      (4) Extubate from a rate of zero and a minimal PS level (PS_{min} = 3–4 mL/kg V_T).
3. VAPS
   a. Weaning in A/C
      (1) VAPS A/C is generally not considered a weaning mode.
      (2) As compliance improves, the PIP may be decreased. Review waveforms for the occurrence of transitional breaths (a switch to volume-targeted breaths).
   b. Weaning in SIMV/PS

(1) Decrease the rate of the control breaths until all the breaths are PS breaths.
(2) Extubate from a rate of zero and a minimal PS level.

B. Extubation. When to extubate has always been a subjective decision. We have attempted to make it more objective with the initiation of a minute ventilation trial.
   1. Record the total minute ventilation (MV) measured by the proximal flow sensor. Do not change the respiratory support.
   2. Change the ventilator mode to SIMV (CPAP), rate of zero, and no pressure support. Use the TCPL mode because in this mode the patient can breathe spontaneously from the continuous flow provided by the ventilator.
   3. After ten minutes, record the spontaneously generated MV.
   4. If spontaneous MV is ≥50 % of the mechanically delivered MV, extubate the baby.

Suggested Reading

Chatburn RL, Khatib ME, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.
Donn SM, editors. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co.; 1998.
Donn SM, Sinha SK. Controversies in patient-triggered ventilation. Clin Perinatol. 1998;25:49–61.
Donn SM, Sinha SK. Neonatal ventilation - aspects of weaning and extubation: Physiological considerations. Perinatology. 1999;1:317–24.
Donn SM, Sinha SK. Newer modes of mechanical ventilation for the neonate. Curr Opin Pediatr. 2001;13: 99–103.
Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. J Perinatol. 1994;14:90–4.
Gillespie LM, White SD, Sinha SK, Donn SM. Usefulness of the minute ventilation test in predicting successful extubation in newborn infants: a randomized controlled trial. J Perinatol. 2003;23:205–7.
Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate, 54th ed. St. Louis: Elsevier Saunders; 2011.
Nicks JJ, Becker MA, Donn SM. Bronchopulmonary dysplasia: response to pressure support ventilation. J Perinatol. 1994;14:495–7.
Sinha SK, Donn SM. Advances in neonatal conventional ventilation. Arch Dis Child. 1996;75:F135–40.
Sinha SK, Donn SM. Neonatal ventilation - aspects of weaning and extubation: clinical aspects. Perinatology. 2000a;2:1–10.
Sinha SK, Donn SM. Weaning infants from mechanical ventilation: art or science? Arch Dis Child. 2000b;83:F64–70.
Sinha SK, Donn SM. Newer modes of neonatal ventilation. Int J Intensive Care. 2000c;7:109–15.
Sinha SK, Donn SM. Volume controlled ventilatory modes for the newborn: variations on a theme. Clin Perinatol. 2001;8:547–60.
Sinha SK, Nicks JJ, Donn SM. Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. Arch Dis Child. 1996;75:F213–8.
Sinha SK, Donn SM, Gavey J, McCarty M. Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. Arch Dis Child. 1997;77:F202–5.
Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co.; 2000.
Wilson Jr BJ, Becker MA, Linton ME, Donn SM. Spontaneous minute ventilation predicts readiness for extubation in mechanically ventilated preterm infants. J Perinatol. 1998;18:436–9.
Wiswell TE, Donn SM, editors. Surfactant and mechanical ventilation. Clin Perinatol. 2007;34:1–217.

AVEA Ventilator

46

Steven M. Donn and Anthony Iannetta

I. Introduction. The AVEA ventilator (CareFusion, San Diego CA), a single platform device, is designed to meet the needs for ventilator support in the neonatal, pediatric, and adult patient populations. Each population has unique options of available modes and modalities of ventilation. This review will focus only upon the neonatal applications.

II. Description. Both volume- and pressure-targeted ventilation are available for the neonatal population. A proximal flow sensor is used to provide flow-triggered synchronization of all ventilator breaths as well as proximal volume measurements.

III. Additional Features

A. Artificial airway compensation

1. When activated the ventilator automatically calculates the drop in pressure through the endotracheal tube and adds that amount of pressure to the system.
2. It takes into consideration flow, gas composition, tube diameter and length, as well as the pharyngeal curve.

B. Leak compensation: the flow control valve and the exhalation valve work together to compensate for baseline leaks.

C. Circuit compliance compensation: not active for neonatal patients.

D. Heliox delivery: by connecting an 80/20 mixture of heliox via the smart connector technology, the ventilator is not only able to deliver an accurate heliox concentration but also to measure accurate tidal volume delivery.

E. An adjustable FiO_2 concentration when either the increase oxygen or suction button is activated. In the infant mode, the default is an increase in FiO_2 of 20 % (from the set FiO_2). It may be adjusted from 0 to 79 %.

F. Internal battery and compressor: automatically activated backup for the loss of electricity or air gas source.

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IV. Monitoring
  A. Internal
  B. Graphic monitoring
    1. Waveforms
      a. Flow
      b. Volume
      c. Pressure
    2. Mechanics
      a. Pressure–volume loop
      b. Flow–volume loop
    3. Trends: 24 h trending of over 50 monitored respiratory parameters
    4. Pulmonary mechanics calculations: at present, only dynamic compliance can be calculated for neonatal patients.

V. Alarms/Limits
  A. High rate (bpm)
  B. Low Vte (mL)
  C. High Vte (mL)
  D. Low Ve (L)
  E. High Ve (L)
  F. Low speak (cm H_2O)
  G. High speak (cm H_2O)
  H. Low PEEP (cm H_2O)
  I. Apnea interval (sec)

VI. Nomenclature
  A. Pressure versus volume control ventilation
    1. Pressure control ventilation
      a. The pressure is preset, flow is variable.
      b. Volume varies with changes in pulmonary compliance and airway resistance and the patient's ventilatory efforts.
    2. Volume control ventilation
      a. The tidal volume and inspiratory flow are both pre-set.
      b. The pressure varies with changes in pulmonary compliance and airway resistance and the patient's ventilatory efforts.
  B. Modes
    1. Assist/Control (A/C)
      a. A pre-set number of mandatory (machine triggered and machine cycled) breaths are delivered.
      b. If the patient triggers the ventilator with a spontaneous effort another mandatory breath of the same type is delivered.
    2. SIMV/PS
      a. Generally considered to be a weaning mode of ventilation
      b. A pre-set number of mandatory breaths are delivered and spontaneous breaths are allowed between mandatory breaths.
      c. If the patient's spontaneous effort triggers the ventilator above the set mandatory rate, the additional breaths with be supported by a pressure-limited breath called pressure support (PS).

C. Flow-Cycling
1. Use of flow-cycling (ending inspiration when flow decays to a pre-set threshold value) enables the baby to end mechanical inspiration nearly synchronously with spontaneous breathing.
2. Inspiration ends at a percentage (adjustable from 5 to 45 %) of the peak inspiratory flow rate rather than a set inspiratory time.
3. Flow-cycling helps to prevent inversion of the I:E ratio during rapid breathing and greatly reduces the risk of gas trapping. In time-cycled A/C, rapid breathing results in shortening of the expiratory phase because the inspiratory phase is fixed.
4. Flow-cycling enables better synchronization between the baby and ventilator.
   a. The baby initiates the inspiratory flow (inspiratory trigger).
   b. The baby terminates the inspiratory flow (expiratory trigger).
5. In rare instances, the baby may "choose" a Ti that is too short to provide an adequate V_T. In this case it may be appropriate switch to a mode using time-cycling.

VII. Modalities of Ventilation
A. Pressure modalities
1. There are three pressure modalities available for the neonatal population.
   a. Time-cycled pressure-limited (TCPL)
   b. Pressure control (PC)
   c. Pressure support (PS)
2. Time-cycled, pressure-limited
   a. Flow through the patient circuit is operator preset and continuous. However, this pre-set flow determines only the peak inspiratory flow. Subsequent inspiratory flow (as a function of time) is determined by the pressure settings and the respiratory system mechanics (including patient effort).
   b. Mandatory breaths are pressure-limited and synchronized to the patient's own respiratory effort by flow changes, detected by a proximal flow sensor (hot wire anemometer).
   c. The pressure is controlled and the volume varies with lung mechanics.
3. Pressure control (PC)
   a. Peak inspiratory pressure is pre-set to a constant value.
   b. The flow wave form shows rapid acceleration followed by rapid deceleration.
   c. The endotracheal tube resistance and the patient compliance determine the inspiratory flow rate, which may also be modulated by the "Rise Time" setting (see below). Inspiratory flow is modified by any ventilator efforts made by the patient.
4. Pressure support (PS)
   a. A pressure controlled spontaneous breath that is patient triggered and patient (flow) cycled. The patient has primary control of the inspiratory flow and inspiratory time (which may be limited to a maximum value in the event that flow-cycling does not work, e.g., from leak).
   b. The inspiratory flow can be modified by adjusting the Rise Time parameter. The Rise Time settings are qualitative, ranging from 1 to 9. The setting of 1 is the steepest acceleration of flow; the breath will be delivered quickly and peak flow will be higher. The Rise Time setting of 9 will deliver the breath with a slower acceleration of flow and peak flow will be lower. The proper Rise Time may help to avoid pressure overshoot, premature cycling, or inadequate hysteresis on the pressure–volume loop.

5. Continuous positive airway pressure (CPAP) is also available and is achieved by continuous gas flow through the circuit with expiratory resistance to provide the desired pressure.
   a. May be oxygen-enriched.
   b. No additional volume or pressure boost is provided.

B. Volume control (volume-targeted)
1. A pre-set volume and inspiratory flow are delivered to the airway opening with each breath (although flow delivered to the lungs may be less in the case of leak around the endotracheal tube). May be very useful in attempting to control ventilation in the treatment of patients with changing lung mechanics.
2. The volume is measured proximally at the patient's endotracheal tube. In the monitoring area, this value is referred to as machine volume.
3. The volume leaving the machine is constant and the pressure will vary dependent upon the patient's lung compliance and airway resistance (and patient ventilator efforts). However, there may be compression (loss) of volume within the ventilator circuit when lung compliance is poor. This is referred to as compressible volume loss. This volume is approximated by the ventilator and added to the volume that is pre-set to get the desired target delivered volume.
4. The set volume, flow rate, and inspiratory pause parameters determine the inspiratory time.

C. Volume guarantee (pressure control with adaptive targeting)
1. Overview
   a. In pressure controlled ventilation with set-point targeting, V_T varies based on compliance and resistance (and patient ventilator effort).
   b. Rapidly changing lung mechanics can cause variable tidal volumes resulting in the risk of lung injury, progressive atelectasis, and sub-optimal ventilation.
   c. Volume guarantee automatically adjusts inspiratory pressure to deliver consistent average expiratory tidal volume.
   d. Incorporates the benefit of pressure breaths (flow synchrony) with a targeted tidal volume
   e. In AVEA, the volume guarantee function is available in the neonatal patient size setting only.
   f. PRESSURE and TCPL ventilation modes in both the SIMV and assist/control breath patterns.
   g. This function provides an additional operator setting for target tidal volume.
   h. The control pressure for mandatory breaths will then be adjusted by the ventilator to maintain the expired tidal volume close to the pre-set target volume.
2. Settings
   a. Volume target (expired tidal volume)
      (1) 2–300 mL (pressure + VG)
      (2) 2–100 mL (TCPL + VG)
   b. Flow cycle
      (1) Available for TCPL only (in VG).
      (2) Flow-cycling will suspend the VG algorithm until a time-cycled breath is delivered.
   c. Machine Vol—not available when VG is enabled.
   d. Inspiratory pressure—in VG, inspiratory pressure is no longer a primary control. The operator-set inspiratory pressure is an advanced control of volume, and is used for test breaths and acts as a backup pressure setting during certain alarm conditions.

e. The inspiratory pressure setting in the advanced controls window should be set at an appropriate level for the patient to avoid under or over delivery of tidal volume during test breaths and certain alarm conditions.
   (1) Range: 0–80 cm H_2O.
   (2) Default: The pressure setting of the pressure or TCPL mode used prior to enabling VG.

3. Pressure delivery
   a. In volume guarantee ventilation the delivered pressure is not an operator setting, it is the pressure provided by the ventilator to maintain the set expiratory tidal volume.
      (1) Default: Inspiratory pressure plus PEEP
      (2) Minimum: PEEP + 2 cm H_2O
      (3) Maximum: High Peak Pressure −3 cm H_2O
   b. Delivered pressure will be limited when it reaches the high pressure limit setting of −3 cm H_2O. When this occurs, the message "Volume Guarantee Pressure is Limited" is displayed. The Low Vte or Low Ve alarms may occur.
4. Limit Volume
   a. All VG breaths will be cycled by volume if inspired volume exceeds a threshold based on the set volume target and the leak averaged over the previous 30 s.
      Mean Leak <63 %
   b. Volume limit = (Volume Target × 1.3) × ([1.1 × Leak] + 1)
      Mean Leak ≥63 %:
   c. Volume limit = Volume Target × 2.2

D. Mode map (Table 46.1)
   Note: the AVEA offers an unusually large number of modes, but they are all not applicable to neonates.

VIII. Management

With the newer generation ventilators, combine three assessments to enable determination of the best strategy: physical patient assessment, monitoring of measured values, and graphic assessment to enable individual strategies based upon pathophysiology and the interaction of the baby and the ventilator.

A. Ventilation ($PaCO_2$). Carbon dioxide removal is related to the minute ventilation (MV). MV = (V_T) X respiratory rate. Measured inspiratory tidal volumes should be 4–7 mL/Kg to avoid over inflation. The normal MV = 240–360 mL/Kg/min. This calculation is based on expiratory tidal volume (V_{Te}) and will be affected by endotracheal tube leaks.
   1. Pressure modalities
      (a) The V_T is adjusted by setting the inspiratory pressure (IP) in TCPL/PC and pressure support ventilation. This pressure is above the level of PEEP; the difference between peak pressure and PEEP is also be referred to as ΔP or amplitude.
      (b) Compliance and resistance will affect the delivered tidal volume.
   2. Volume-Targeted
      (a) The inspiratory tidal volume (V_{Ti}) delivered to the patient is determined by the set tidal volume minus the volume that is compressed in the ventilator circuit.
      (b) The compressible volume loss varies with the pressure that is generated within the circuit, which in turn is a reflection of compliance.
      (c) Always monitor both the inspiratory and expiratory tidal volumes (or % Leak) to determine the volume of leak. This is important because of the use of uncuffed endotracheal tubes in neonates.

Table 46.1 Mode Map

		Mode classification			
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
Volume A/C	Volume	CMV	Set-point	N/A	VC-CMVs
Volume SIMV	Volume	IMV	Set-point	Set-point	VC-IMVs,s
Volume SIMV with artificial airway compensation	Volume	IMV	Set-point	Set-point/servo	VC-IMVs,sr
Volume A/C with demand flow	Volume	IMV	Dual	Dual	VC-IMVd,d
Volume SIMV with demand flow	Volume	IMV	Dual	Set-point	VC-IMVd,s
Volume SIMV with demand flow and artificial airway compensation	Volume	IMV	Dual	Set-point/servo	VC-IMVd,sr
Pressure A/C	Pressure	CMV	Set-point	N/A	PC-CMVs
Time-cycled pressure-limited A/C	Pressure	CMV	Dual	N/A	PC-CMVs
Pressure A/C with machine volume	Pressure	CMV	Dual	N/A	PC-CMVd
Pressure A/C with volume guarantee	Pressure	CMV	Adaptive	N/A	PC-CMVa
Time-cycled pressure-limited A/C with volume guarantee	Pressure	CMV	Adaptive	N/A	PC-CMVa
Volume A/C with Vsync	Pressure	CMV	Adaptive	N/A	PC-CMVa
Pressure regulated volume control A/C	Pressure	CMV	Adaptive	N/A	PC-CMVa
Pressure A/C with flow cycle	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure A/C with flow cycle and artificial airway compensation	Pressure	IMV	Set-point	Set-point/servo	PC-IMVs,sr
Pressure SIMV	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure SIMV with artificial airway compensation	Pressure	IMV	Set-point	Set-point/servo	PC-IMVs,sr
CPAP/pressure support ventilation with volume limit	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
CPAP/pressure support ventilation with volume limit and artificial airway compensation	Pressure	IMV	Set-point	Set-point/servo	PC-IMVs,sr
Infant nasal IMV	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Infant nasal IMV with artificial airway compensation	Pressure	IMV	Set-point	Set-point/servo	PC-IMVs,sr
Airway pressure release ventilation/biphasic	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Time-cycled pressure-limited A/C with flow cycle	Pressure	IMV	Set-point	Set-point	PC-IMVs,s

(continued)

Table 46.1 (continued)

		Mode classification			
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
Time-cycled pressure-limited SIMV with artificial airway compensation	Pressure	IMV	Set-point	Set-point/servo	PC-IMVs,sr
Time-cycled pressure-limited SIMV	Pressure	IMV	Dual	Set-point	PC-IMVs,s
Pressure SIMV with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure SIMV with volume guarantee and artificial airway compensation	Pressure	IMV	Adaptive	Set-point/servo	PC-IMVa,sr
Time-cycled pressure-limited A/C with flow cycle and volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Time-cycled pressure-limited SIMV with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Time-cycled pressure-limited SIMV with volume guarantee and artificial airway compensation	Pressure	IMV	Adaptive	Set-point/servo	PC-IMVa,sr
Volume A/C with Vsync and flow cycle	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Volume SIMV with Vsync	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Volume SIMV with Vsync and artificial airway compensation	Pressure	IMV	Adaptive	Set-point/servo	PC-IMVa,sr
Pressure regulated volume control A/C with flow cycle	Pressure	IMV	Adaptive	adaptive	PC-IMVa,a
Pressure regulated volume control SIMV with flow cycle	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure regulated volume control SIMV	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure regulated volume control SIMV with artificial airway compensation	Pressure	IMV	Adaptive	Set-point/servo	PC-IMVa,sr
Time-cycled pressure-limited A/C with flow cycle and volume guarantee	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVas,sr
Volume A/C with Vsync and flow cycle and artificial airway compensation	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVar,sr
Pressure regulated volume control A/C with flow cycle and artificial airway compensation	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVar,ar

(continued)

Table 46.1 (continued)

		Mode classification			
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
Pressure regulated volume control SIMV with flow cycle and artificial airway compensation	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVar,sr
Time-cycled pressure-limited A/C with flow cycle and artificial airway compensation	Pressure	IMV	Set-point/servo	Set-point/servo	PC-IMVsr,sr
CPAP/pressure support ventilation	Pressure	CSV	Set-point	N/A	PC-CSVs
CPAP/pressure support ventilation and artificial airway compensation	Pressure	CSV	Set-point/servo	N/A	PC-CSVsr

B. Oxygenation (PaO_2) correlates directly with mean airway pressure (Pāw) and FiO_2.
   1. Increases in peak inspiratory pressure (PIP), inspiratory time, positive end expiratory pressure (PEEP), and rate all contribute to increases in Pāw. Increased Pāw increases oxygenation by increasing pulmonary surface area.
   2. FiO_2 increases will also increase oxygenation unless there is a diffusion barrier or ventilation:perfusion mismatch.

IX. Weaning and Extubation (Chap. 78)
   A. Weaning the ventilator. Typical weaning strategies encourage the patient to breath above the set (control or mandatory) respiratory rate. This is done by decreasing the rate to the point where the patient breaths spontaneously and triggers most, if not all, of the breaths.
      1. Pressure
         a. Weaning in assist control (A/C)
            (1) Adjust in IP to maintain the measured inspiratory tidal volumes between 4 and 7 mL/Kg.
            (2) As the patient's compliance improves, the required IP will decrease.
         b. Weaning in SIMV/PS
            (1) Adjust IP of the mandatory TCPL or PC breaths to keep the measured inspiratory tidal volumes between 4 and 7 mL/Kg.
            (2) The IP of the PS breath can be adjusted to deliver either a full tidal volume breath (called PSmax) or at a lower level to provide a partially supported breath. At the lowest level, PSmin, the delivered V_T matches the imposed work of breathing created by the endotracheal tube and ventilator circuit.
            (3) If the SIMV rate is set too high, it may interfere with spontaneous breathing and offset the advantages of PS.
      2. Volume
         a. Weaning in A/C
            (1) Weaning directly to extubation is difficult to accomplish in the volume assist control mode
            (2) Changing to SIMV/PS is recommended

b. Weaning in SIMV/PS
   (1) Decrease the rate of volume control breaths and supplement the minute ventilation by additional PS breaths.
   (2) Wean the control rate and adjust the PS IP to provide a reasonable V_T.
   (3) Once the PS IP has been weaned to a level which provides a 3–4 mL/kg V_T, the baby is usually able to be extubated.

Suggested Reading

Chatburn RL, Khatib ME, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

Donn SM, Becker MA, Nicks JJ. Special ventilatory techniques I: patient-triggered ventilation. In: Goldsmith JP, Karotkin EH editors. Assisted ventilation of the neonate. 5th ed. St. Louis: Elsevier Saunders; 2011. pp. 220–34. http://www.carefusion.com/pdf/Respiratory/Ventilation/AVEA_brochur.

Twinstream Ventilator

47

Gerfried Zobel

I. Introduction
   A. The Twinstream® ventilator (Carl Reiner GMBH, Vienna, Austria) (Fig. 47.1) is an electric-driven microprocessor-controlled jet ventilator, which allows simultaneous application of two different jet streams (low frequency and high frequency) resulting in a pulsatile BiLevel ventilation (p-BLV) mode.
   B. The basic module with classical high frequency jet ventilation is used in laryngeal and tracheal surgery. The addition of the p-BLV® module enables pulsatile BiLevel ventilation (p-BLV®) which can be used in critically ill infants and children with acute respiratory insufficiency. The p-BLV-Module® (Fig. 47.2) *c*onsists of a double venturi chamber containing two entrainment ports (low and high frequency entrainment), one expiration port, two inlet ports for the low and high frequency jet streams and the outlet port connected to the expiratory limb of the breathing tube system.

II. Basic principle
   A. A variable bias flow, warmed and humidified in the inspiratory limb of breathing circuit, reaches the y-piece connected to the endotracheal tube. The expiratory limb of the breathing circuit is connected with the p-BLV module® and the inspiratory bias flow will now be modified by two jet streams resulting in an oscillating gas column to the patient's airway. In addition, the p-BLV module® acts as a pneumatic driven PEEP generator.
   B. Breathing circuit and humidification system
      1. During p-BLV® optimal gas conditioning (warming, humidification) is extremely important. The very effective Humicare 200 TS® humidifier has a large surface and works well at low gas flow rates.
      2. The inspiratory and expiratory limbs of the breathing circuit are heated, resulting in a correctly conditioned inspiratory gas.
      3. The combination of warmed, humidified gas with effective oscillations in the airways allows efficient mobilization of airway secretions and improved gas exchange. Special adapters between the inspiratory limb of the breathing circuit and the y-piece enable the administration of inhalational medications.

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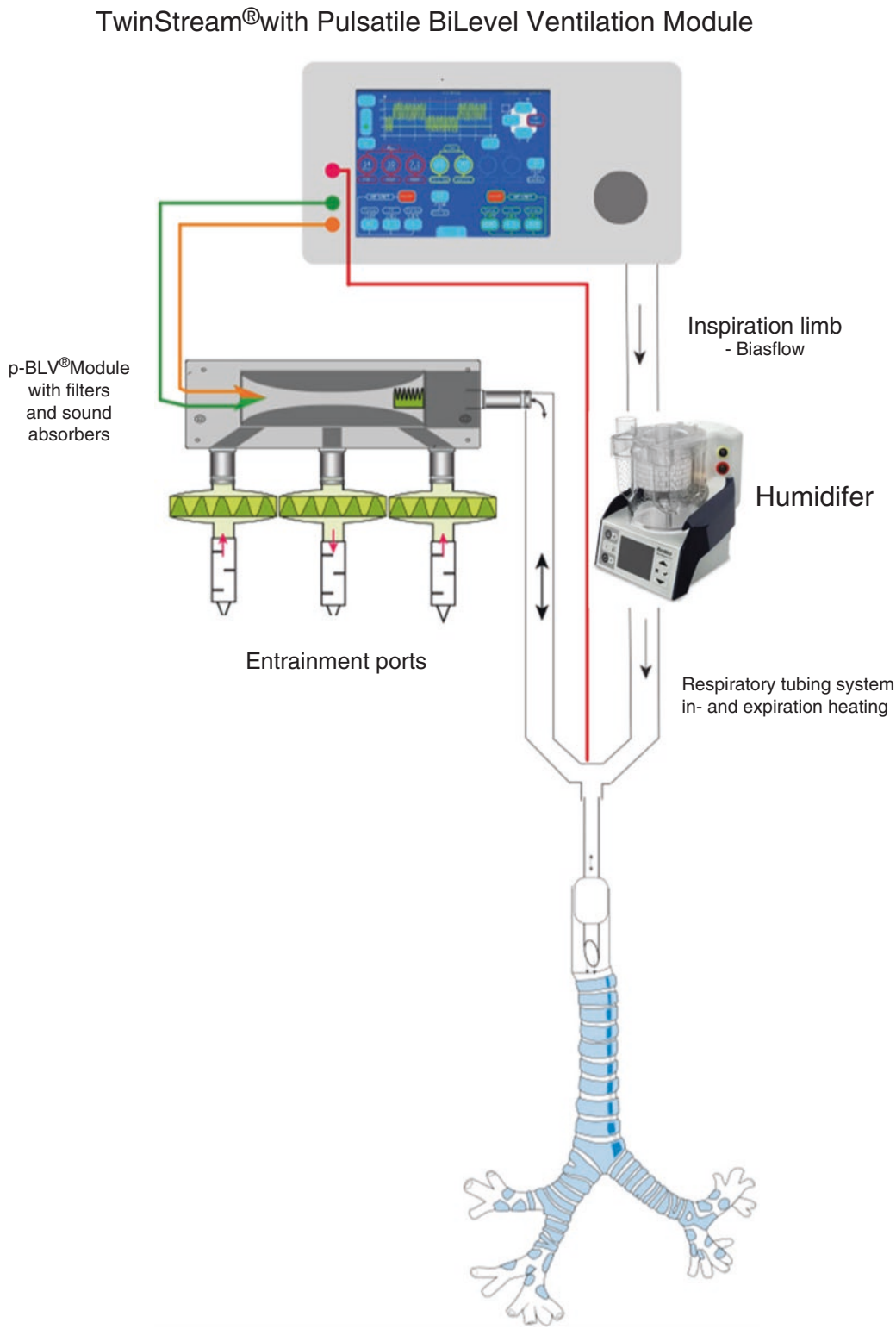

Fig. 47.1 TwinStream ventilator

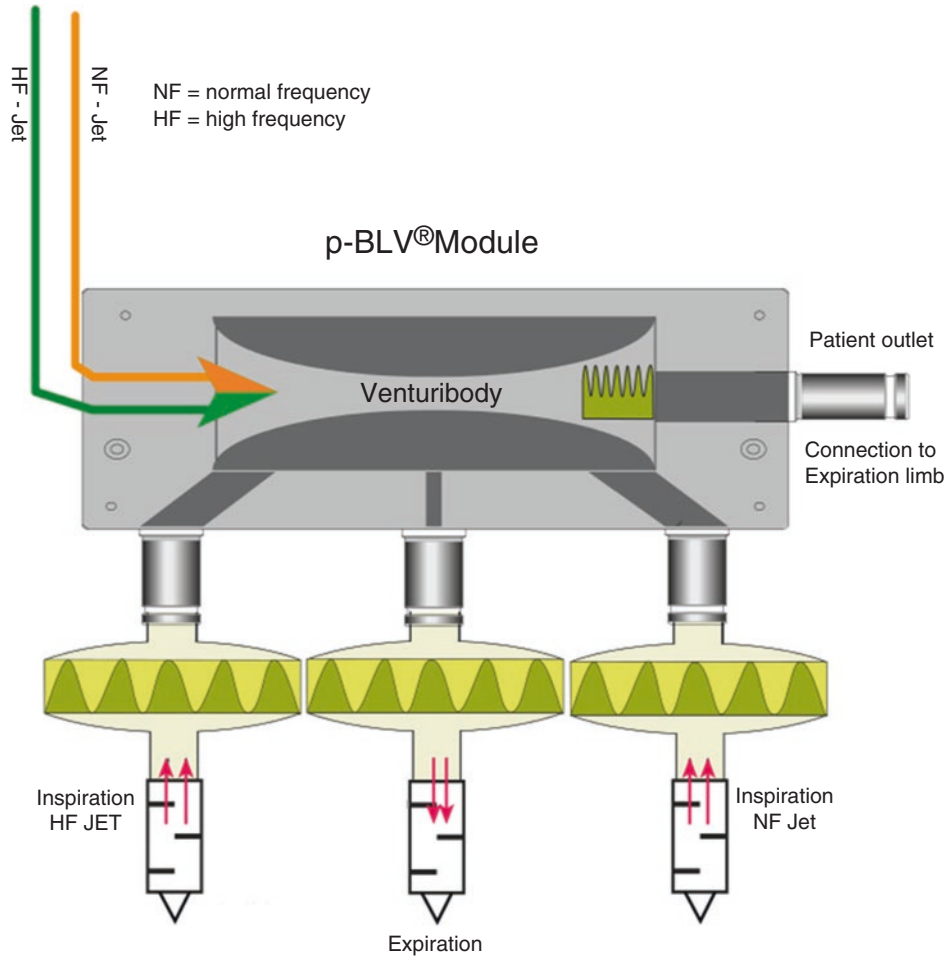

Fig. 47.2 Pulsatile BiLevel ventilation® module

C. Monitoring
   1. Pressure monitoring is achieved by the red line connected to the inspiratory limb of the ventilator circuit near the y-piece.
   2. The pressure time curve displays peak, mean, and end expiratory pressures.
   3. Two oxygen cells can measure oxygen concentrations of the jet streams and the bias flow. The FiO_2 is shown on the ventilator display (Fig. 47.3).

III. Ventilator settings
   A. Bias flow: 20 L/min (range 20–55 L/min)
   B. FiO_2: According to FiO_2 on conventional mechanical ventilation (CMV)
   C. Low frequency module
      1. Driving pressure (P_{NF}): 0.5 psi (range 0.1–2.5 psi)
         a. Adoption in steps of 0.1 psi to achieve the same peak inspiratory pressure (PIP) than under CV
         b. Goal: PIP < 30 cm H_2O
      2. Ventilatory rate: 12–20 bpm (range 1–100 bpm)
      3. I:E ratio-1:2

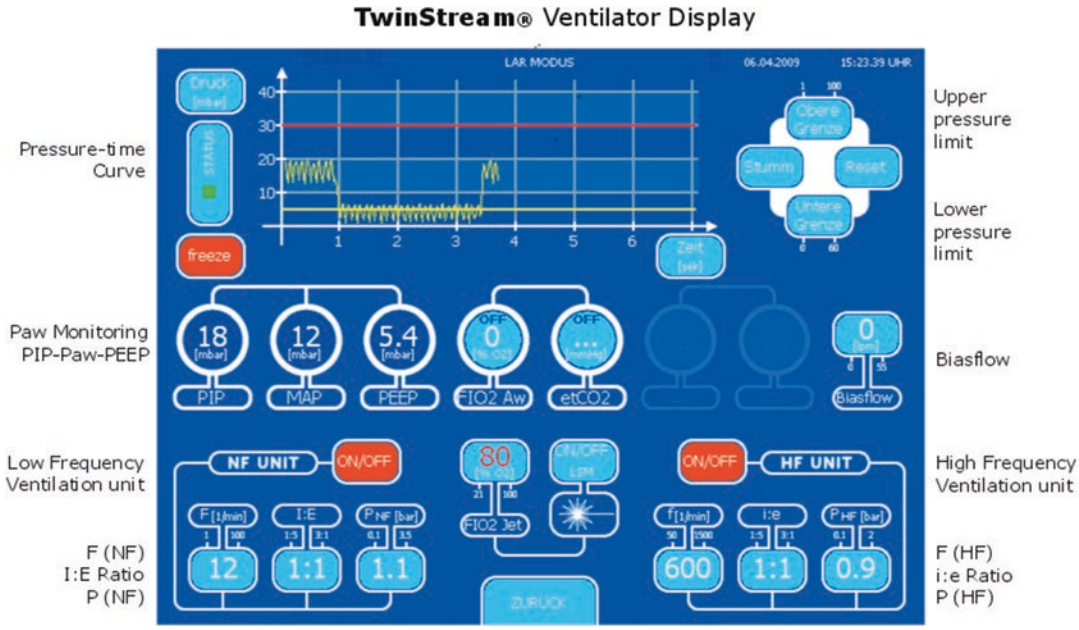

Fig. 47.3 TwinStream® ventilator display

D. High frequency module
   1. Driving pressure (P_{NF}): 0.5 psi
      Adjust in increments of 0.1 bar to achieve the PEEP (PIP) (less than in CMV)
   2. Ventilatory rate: 8–10 Hz (range 1–25 Hz)
   3. I:E ratio-1:2

E. Alarm settings
   1. High inspiratory pressure: 35 cm H_2O
   2. Low inspiratory pressure: 10 cm H_2O

IV. Optimizing oxygenation
   A. Increase PEEP by increasing driving pressure (P_{HF}) of the HF-module
   B. Increase FiO_2
   C. Increase frequency of the HF-module

V. Optimizing ventilation:
   A. Increase frequency of the NF-module
   B. Decrease frequency of the HF-module
   C. Increase pressure amplitude of the NF-module

VI. Indications for pulsatile biphasic lung ventilation
   A. ARDS—acute respiratory distress syndrome
   B. Bronchiolitis
   C. Pulmonary Baro-Volutrauma
   D. Thoracic trauma

VII. Patients
   A. At present, infants and children with a body weight more than 10 kg
   B. For the future a newly developed jet-converter will allow use of the pulsatile BLV—technique even for both neonates and small infants.

Table 47.1 Modes for the Twinstream ventilator

	Mode classification				
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	Tag
BiLevel ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pulsatile BiLevel ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pulsatile CPAP	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
CPAP	Pressure	CSV	N/A	Set-point	PC-CSVs

VIII. Advantages of the Twinstream ventilator®
- A. Effective mobilization of tracheo-bronchial secretions
- B. Improved gas exchange at lower airway pressures
- C. Increased FRC
- D. Spontaneous breathing option on both pressure plateaus

IX. Mode Map

The modes available on the Twinstream ventilator are shown in Table 47.1.

Puritan Bennett 840 and Puritan Bennett 980 Ventilators

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Robert L. Chatburn and Cyndy Miller

I. Description
The Puritan Bennett™ 840 and 980 ventilators (Covidien, Boulder, CO, USA) are designed for invasive and noninvasive ventilation of adult, pediatric, and neonatal patients. They are electrically controlled and pneumatically powered (require air and oxygen gas sources) (Fig. 48.1).

II. Operator Interface
   A. The operator interfaces for both of these ventilators use a touch screen (GUI), buttons (membrane on Puritan Bennett™ 840 and GUI keys on Puritan Bennett™ 980), and a control knob.
   B. Settings are entered by touching virtual buttons on the screen to select the desired setting, turning the knob to select the setting value, and then touching/pressing ACCEPT to finalize the setting (touching/pressing CLEAR rejects the setting).
   C. Other keys/buttons/icons provide access to the screen brightness, display lock, alarm volume, manual inspiration trigger, inspiratory pause, expiratory pause, alarm reset, alarm silence, logs, elevate oxygen percentage, help, home (Puritan Bennett™ 980 only), configure (Puritan Bennett™ 980 only), and screen capture (PB 980 only) functions.
   D. The Puritan Bennett™ 980 offers additional functions to those found on the Puritan Bennett™ 840 ventilator.
      1. The Puritan Bennett™ 980 has an advanced GUI with many options for displaying monitored data and graphics through customized displays.
      2. It also uses a separate status display for providing redundant information about the state of the ventilator: current power source (AC or DC), presence of primary and extended batteries and their charging status, relative available battery charge level, circuit pressure graph displaying pressure units, high P_{PEAK} alarm setting and current P_{PEAK} and PEEP values, connection and inlet pressures of air and oxygen, ventilator operational hours, alarm volume setting, and information related to device alerts such as the initiation and type back of ventilation and the activation of safe state.

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Fig. 48.1 Puritan Bennett™ 980 ventilator

3. There is an optional proximal flow sensor for use when ventilating neonates.
4. Capnography is available in some markets.

III. Modes

Modes are set by selecting the breath sequence and the control variables separately. The operator interface uses the term "mode" to refer to what we have described in Chap. 44 as the breath sequence (i.e., CMV, IMV, and CSV). Menu selections include "A/C" (assist/control), "SIMV" (synchronized intermittent mandatory ventilation), "SPONT" (spontaneous), "CPAP" (continuous positive airway pressure), and "BiLevel." Mandatory breath types available are "PC" (pressure control), "VC" (volume control), and "VC+" (volume control plus). Spontaneous breath types available are "PS" (pressure support), "TC" (tube compensation), "VS" (volume support), "PA" (proportional assist), and "NONE." An apnea backup mode is available with default settings based on the patient ideal body weight (entered as weight or height and gender during the setup routine), circuit type, and mandatory breath type. These settings are also applied when a manual inspiratory trigger is activated in SPONT mode. They are user adjustable.

A. Assist/Control Pressure Control
   1. Mandatory breaths: machine triggered (pre-set frequency) or patient triggered (pressure or flow sensitivity) and machine cycled (inspiratory time)
   2. Spontaneous breaths: not allowed
   3. Between-breath targets: none
B. Assist/Control Volume Control
   1. Mandatory breaths: machine triggered (pre-set frequency) or patient triggered (pressure or flow sensitivity) and machine cycled (tidal volume or additional pause time)
   2. Spontaneous breaths: not allowed
   3. Between-breath targets: none
C. Assist/Control Volume Control Plus
   1. Mandatory breaths: machine triggered (pre-set frequency) or patient triggered (pressure or flow sensitivity) and machine cycled (inspiratory time). Between-breath targets: operator set tidal volume
   2. Spontaneous breaths: not allowed
D. BiLevel (with Pressure Support)
   1. Mandatory breaths: machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine (inspiratory time) or patient cycled (% peak inspiratory flow/expiratory sensitivity).
   2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity). Spontaneous breaths are permitted both between and during mandatory breaths.
   3. Between-breath targets: none
E. BiLevel (with Tube Compensation or Pressure Support)
   1. Mandatory breaths: machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine cycled (inspiratory time) or patient synchronized (% peak inspiratory flow/expiratory sensitivity)
   2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity). Spontaneous breaths are allowed both during and between mandatory breaths. Breath delivery during the inspiratory phase is determined by the settings for % support, expiratory sensitivity, tube I.D., and tube type.
   3. Between-breath targets: none
F. SIMV Pressure Control (with Pressure Support)
   1. Mandatory breaths machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine cycled (inspiratory time).
   2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity).
   3. Between-breath targets: none
G. SIMV Pressure Control (with Tube Compensation)
   1. Mandatory breaths: machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine cycled (inspiratory time)
   2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity)
   3. Between-breath targets: none
H. SIMV Volume Control (with Pressure Support)
   1. Mandatory breaths: machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine cycled (tidal volume or additional pause time)

2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity)
3. Between-breath targets: none

I. SIMV Volume Control (with Tube Compensation)
1. Mandatory breaths: machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine cycled (tidal volume or additional pause time).
2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity). Breath delivery during the inspiratory phase is determined by the settings for % support, expiratory sensitivity, tube I.D., and tube type.
3. Between-breath targets: none

J. SIMV Volume Control Plus (with Pressure Support)
1. Mandatory breaths: machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine cycled (inspiratory time). Between-breath targets: operator-set tidal volume
2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity)

K. SIMV Volume Control Plus (with Tube Compensation)
1. Mandatory breaths: machine triggered (pre-set frequency) or patient synchronized (pressure or flow sensitivity) and machine cycled (inspiratory time). Between-breath targets: operator-set tidal volume
2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity)

L. Spont Pressure Support
1. Mandatory breaths: not allowed
2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity)
3. Between-breath targets: none.

M. Spont Proportional Assist (PAV+)
1. Mandatory breaths: not allowed
2. Spontaneous breaths: patient triggered (estimated lung flow) and patient cycled (estimated lung flow)
   a. Breath delivery during the inspiratory phase is determined by the settings for % support, tube I.D., and tube type.
   b. PAV™+ adjusts pressure delivery to offload the operatory set (%Support) of work.
3. Between-breath targets: none

N. Spont Tube Compensation
1. Mandatory breaths: not allowed
2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow). Breath delivery during the inspiratory phase is determined by the settings for % support, expiratory sensitivity, tube I.D., and tube type.
3. Between-breath targets: none

O. Spont Volume Support
1. Mandatory breaths: not allowed.
2. Spontaneous breaths: patient triggered (pressure or flow sensitivity) and patient cycled (% peak inspiratory flow/expiratory sensitivity). Between-breath targets: operator set tidal volume.

IV. Mode Map

The Puritan Bennett™ 980 modes and breath type selections are identical to those on the Puritan Bennett™ 840, however, the breath delivery and monitoring algorithms have been updated.

Table 48.1 Modes on the Puritan Bennett™ 840 and Puritan Bennett™ 980 ventilators

	Mode classification				
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
A/C volume control	Volume	CMV	Set-point	N/A	VC-CMVs
SIMV volume control with pressure support	Volume	IMV	Set-point	Set-point	VC-IMVs,s
SIMV volume control with tube compensation	Volume	IMV	Set-point	Servo	VC-IMVs,r
A/C pressure control	Pressure	CMV	Set-point	N/A	PC-CMVs
A/C volume control plus	Pressure	CMV	Adaptive	N/A	PC-CMVa
SIMV pressure control with pressure support	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
SIMV pressure control with tube compensation	Pressure	IMV	Set-point	Servo	PC-IMVs,r
BiLevel with pressure support	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
BiLevel with tube compensation	Pressure	IMV	Set-point	Servo	PC-IMVs,r
SIMV volume control plus with pressure support	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
SIMV volume control plus with tube compensation	Pressure	IMV	Adaptive	Servo	PC-IMVa,r
Spont pressure support	Pressure	CSV	Set-point	N/A	PC-CSVs
Spont tube compensation	Pressure	CSV	Servo	N/A	PC-CSVr
Spont proportional assist	Pressure	CSV	Servo	N/A	PC-CSVr
Spont volume support	Pressure	CSV	Adaptive	N/A	PC-CSVa

The mode names and classifications are shown in Table 48.1. Note: not all modes are used for neonates. For example, PAV+ is intended for use on adults whose predicted body weight is at least 25 kg (55 lb).

V. Leak Sync
   A. Leak Sync is available for neonatal, pediatric, and adult patients during both invasive and noninvasive ventilation with all modes and breath types except PAV™+ and tube compensation spontaneous breath types.
   B. Leak Sync automatically differentiates between patient and leaked flow during inspiration and also uses servo-controlled, trigger-compensated flow to stabilize baseline pressure and prevent auto-triggering during exhalation.
   C. Patient and leaked volumes and flows are identified in the patient data.
   D. Volume management for VC+ and VS breaths and flow cycling of PS and VS breaths are based on the patient data value rather than the total (patient + leak) volume and flow data values.

VI. Neonatal Ventilation

A "NeoMode" option (standard on all Puritan Bennett™ 980 Neonatal Ventilators, and Puritan Bennett™ 980 Universal Ventilators), which includes the optional use of a proximal flow sensor, provides invasive and noninvasive (including nCPAP) ventilation and monitoring for neonates from 0.3 to 7.0 kg or 0.66 to 15 lb. It supports delivered tidal volumes as low as 2.0 mL.

Suggested Reading

Chatburn RL, Khatib ME, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

Draeger VN500

49

Manuel Sanchez Luna

I. Introduction
   A. Overall benefits
      1. Complete and integrated solution that can be applied to most clinical situations
      2. Single platform supports all respiratory needs, including non-invasive, invasive conventional, and HFOV.
      3. Developed specifically for neonates and pediatric patients
   B. Interface and monitoring
      1. Individual monitoring
      2. "Help" function with context-sensitive messages
      3. Smart data visualization
   C. Decision making
      1. Smart pulmonary view (compliance, resistance, and spontaneous breathing)
      2. Trending, waveforms, and loops
   D. Workstation
      1. Screenshots downloadable
      2. Export options of logs for education and research
      3. Transport-enabled for 6 h ventilation, external gas, and power supplies
      4. Docking unit for beds for easy patient transport

II. Modes
   A. The Babylog VN500 offers a variety of conventional modes: mandatory ventilation modes (pressure-controlled) and spontaneous and assisted modes.
   B. Invasive and non-invasive ventilation
   C. Modes are patient-triggered. Flow trigger can be configured according to patient need. A neonatal flow sensor is used to trigger ventilation and measure mechanics. A very sensitive hot wire anemometer is used and located at the proximal airway.

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D. Trigger windows have been set up for many ventilation modes, inspiratory attempts to trigger the mandatory breaths are detected only within this range. In mechanically triggered modes, the parameters RR, I:E ratio, or Ti start inspiration. The expiration is flow- or time-cycled.
   1. PC-CMV
      a. Pressure-controlled, time-cycled; spontaneous breathing permitted; mandatory triggering (determined by respiratory rate)
      b. The upper pressure limit is determined by Pinsp, the duration is determined by Ti
      c. The applied tidal volume depends on the difference between PEEP and Pinsp (delta P), lung mechanics (resistance and compliance), and breathing effort for the patient.
      d. Set parameters
         (1) FiO_2
         (2) Pinsp
         (3) Ti
         (4) RR
         (5) PEEP
         (6) Slope
   2. PC-SIMV
      a. Pressure-controlled, machine- or patient-triggered, spontaneous breathing permitted
      b. The patient can breathe spontaneously at any time, but the number of mechanical breaths is specified. The mandatory breaths are synchronized to the patient's own breathing. This adaption prevents a change in the number of mandatory breaths. If no independent breath attempt is detected, the set RR triggers mandatory breaths at a back-up frequency. It can only be triggered in a certain "timing window" by the flow trigger during inspiration, which prohibits the breath being applied during expiration. During spontaneous breathing the patient can be supported with pressure support (PS).
      c. Set values:
         (1) FiO_2
         (2) Pinsp
         (3) TI
         (4) RR
         (5) PEEP
         (6) Delta P supp
         (7) Slope
   3. PC-AC
      a. Pressure control-assist control. Assist-controlled, pressure-controlled ventilation allowing spontaneous breathing during the entire respiratory cycle and a back-up control rate.
      b. Every inspiratory effort of the patient above the trigger sensitivity triggers a synchronized mandatory breath.
      c. The Ti and number of mandatory breaths are determined by the patient.
      d. A sufficient "window" for triggering is made by adjusting the control rate.
      e. Minimum mandatory respiratory frequency is controlled by the set RR.
   4. PC-PSV
      a. Pressure control-pressure support ventilation: pressure-controlled ventilation with guaranteed minimum (control) respiratory.
      b. Combined PS inspiratory pattern in the PC-AC mode.

(1) During spontaneous breathing, the patient can be supported with PS. This breath is terminated as soon as the inspiratory flow falls to 15 % of the peak inspiratory flow rate.
(2) The level of pressure support is determined by Pinsp.
(3) Every inspiratory effort of the patient that meets the trigger criteria initiates a pressure-supported breath. The Ti and frequency of pressure-supported breaths are determined by the patient's spontaneous breathing.
(4) If the patient's respiratory rate is less than the set back-up respiratory rate or there is no spontaneous breathing, the system administers time-cycled, pressure-supported breaths at the back-up RR.

5. PC-MMV
   a. Volume-guaranteed, machine- or patient-triggered, safeguarding the mandatory minute volume with permitted spontaneous breathing
   b. It ensures that the patient always receives at least the set minute volume ($V_T \times RR$)
   c. If the patient's breath is insufficient to achieve the set MV, machine-triggered breaths are applied.
      (1) These breaths are synchronized.
      (2) The set RR therefore is the maximum number of mandatory breaths.
      (3) In contrast to SIMV, which provides a pre-set number of mandatory breaths regardless of spontaneous breath frequency, the mandatory breaths in MMV are only provided if spontaneous minute ventilation is lower than the pre-set minimum ventilation. In other words, spontaneous breaths may suppress mandatory breaths.
      (4) During spontaneous breathing, the patient can be supported and synchronized with PS; breaths are terminated when the inspiratory flow falls to 15 % of the maximum inspiratory flow rate or when it reaches the maximum inspiratory time, whichever occurs first.
6. PC-APRV (optional feature)
   a. Pressure control-airway pressure release ventilation: spontaneous breathing under continuous positive airway pressure with brief pressure releases.
   b. Spontaneous breathing is possible for a certain period of time at a high pressure, and afterwards the ventilator switches to a lower pressure to allow deflation of the lungs; this time is shorter and also controlled.
   c. It is possible to add auto-release to synchronize the switch from the high to the low pressure with the expiratory flow.
7. SPN-CPAP
   Spontaneous breathing on CPAP with PS or VS
   a. Pressure support
      (1) Supported by an increased PEEP; if the trigger criterion is met during inspiration a pressure-supported breath is activated, Ti, rate, and duration are determined by the patient.
      (2) Pressure support terminates at 15 % of the maximum insp. flow or after 1.5 s inspiratory time. (In Neo. Mode, not available with NIV)
   b. Volume support
      (1) Inspiratory effort that meets criterion triggers a volume supported breath, synchronized, and determined by the patient.
      (2) Same termination criteria
8. SPN-PPS
   a. Spontaneous-proportional pressure support

b. Spontaneous breathing with flow and volume proportional pressure support.
   (1) The ventilator support is proportional to the inspiratory effort; if the patient effort is strong, the ventilator provides high pressure support.
   (2) This support can be adjusted separately depending on the resistive and elastic components.
   (3) The resistive component is supported by flow, and the elastic by pressure. Low compliance and a high resistance can be supported independently.
   (4) The amount of resistive flow assist, and elastic volume assist are determined by the user.
   (5) Support is only effective during inspiration. Maximum tidal volume can be set to prevent excessive tidal volume delivery.

9. Flow trigger
   a. Necessary for synchronization of mandatory or pressure-supported breaths. It is also used with SPN-CPAP/PS and VS.
   b. It is automatically leak compensated.
   c. Spontaneous breathing is indicated by the illuminated lung symbol.
   d. The mandatory breaths are synchronized with the inspiratory efforts.
10. Sigh
   a. Atelectasis can be prevented by activating the sigh function to provide intermittent PEEP.
   b. The purpose of the expiratory sigh is to open collapsed lungs or to keep open the more dependent regions of the lungs.
   c. It can be combined with all modes except APRV.
   d. PEEP is adjusted by the set value of intermittent PEEP.
11. Nebulization
   The medication nebulizer is supplied with compressed air, O_2, or a mixture of compressed air and O_2, depending on the set O_2 concentration.
12. Smart pulmonary view
   a. Smart pulmonary view is a qualitative graphic display of lung compliance and airway resistance.
   b. Compliance and resistance are graphically displayed to better visualize changes or modifications.
   c. A reference can be set to compare before and after different situations.
   d. Loops can also be added to better understand lung mechanics.
   e. Mandatory or spontaneous minute volume is also displayed as the movement of the diaphragm to better distinguish between spontaneous and mandatory breaths.
13. O_2 Therapy
   O_2 Therapy can be used in spontaneous breathing by a continuous flow with a mask or nasal cannula.
14. Leak compensation
   a. Leak compensation: the ventilator calculates a lung tidal volume (labeled as VT) using a sophisticated algorithm. The calculated lung tidal volume is not measured, but calculated. It is not perfectly accurate, but may be better than measuring expiratory and inspiratory tidal volume. It can stabilize the tidal volume better than any other mode. It automatically compensates for volume loss from ETT leak.
   b. Leak adaptation: automatically adjusts the trigger and termination criteria according to the measured leak.
   c. The advantage is low work of breathing and a low rate of auto-cycling.

15. Apnea ventilation
    a. Apnea is detected by the absence of expiratory flow through the neonatal flow sensor or if insufficient inspiratory gas is delivered during the set apnea alarm time.
    b. This alarm is set at a fixed I:E ratio of 1:2.
    c. When apnea ventilation is working, the spontaneous patient inspiratory effort is synchronized and the ventilator uses SIMV.
    d. Apnea ventilation concludes when the ventilation mode is modified or new settings are added.
    e. It is possible to configure an automatic return from apnea ventilation. Here, the ventilator automatically switches back to the previous ventilation mode with the same settings when sufficient spontaneous breathing resumes.
16. Automatic tube compensation
    a. In this modality, the resistance of the endotracheal tube is compensated, the ventilator calculates the pressure at the Wye piece and at the trachea level, knowing the diameter of the ETT and using a mathematical model.
    b. When it is activated, the Babylog VN500 controls the ventilation pressure so that the resistive work of breathing from the tube is compensated in accordance with the selected degree of compensation.

III. Mode Map

The modes available on the VN500 are shown in Table 49.1.

IV. Highlights

A. Conventional ventilation with focus on volume guarantee (Chap. 39) With the ventilation modes PC-SIMV, PC-CMV, PC-AC, and PC-PSV, VG can be used. In MMV and SPN-CPAP/VS, VG is always switched on.

1. Volume guarantee
    a. General explanation
        (1) In volume guarantee the mandatory breaths are volume controlled.
        (2) To apply the set tidal volume, the Babylog controls the Pinsp.
        (3) All changes in lung mechanics, such as compliance and resistance, are compensated.
        (4) The tidal volume if the mandatory breath remains constant.
        (5) The advantage is that resistance and compliance change do not have an impact on the delivered tidal volume.
        (6) If compliance increases and the patient can breathe more independently, the inspiratory pressure decreases automatically.
        (7) If the compliance decreases (e.g., pneumonia, pneumothorax, and lung fibrosis) the patient is more supported by increasing the pressure. However, it is still limited to the set Pmax.
        (8) The Babylog VN500 always sets the appropriate pressure required for the desired tidal volume.
        (9) The control occurs gradually from breath to breath. The tidal volume is measured, compared to the set value and the new plateau pressure is calculated. For neonates, the expiratory tidal volume is the reference, whereas in pediatric patients inspiratory tidal volume is used. If activated, the leak compensated values are used.
    b. Advantages of proximal flow measurement
        (1) The tubing compliance is clinically significant compared to the premature infant lung compliance.

Table 49.1 Mode map for the VN500

Mode name	Mode classification				TAG
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	
Pressure control A/C	pressure	CMV	Set-point	N/A	PC-CMVs
Pressure control A/C with volume guarantee	Pressure	CMV	Adaptive	N/A	PC-CMVa
Pressure control A/C with volume guarantee and automatic tube compensation	Pressure	CMV	Adaptive/servo	N/A	PC-CMVar
Pressure control A/C with automatic tube compensation	Pressure	CMV	Set-point/servo	N/A	PC-CMVsr
Pressure control continuous mandatory ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure control SIMV	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure control pressure support ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure control airway pressure release ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure control mandatory minute volume ventilation with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure control continuous mandatory ventilation with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure control SIMV with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure control pressure support ventilation with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure control continuous mandatory ventilation with volume guarantee and automatic tube compensation	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVar,sr
Pressure control SIMV with volume guarantee and automatic tube compensation	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVas,sr
Pressure control pressure support ventilation with volume guarantee and automatic tube compensation	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVar,sr
Pressure control continuous mandatory ventilation with automatic tube compensation	Pressure	IMV	Set-point/servo	Set-point/servo	PC-IMVsr,sr
Pressure control SIMV with automatic tube compensation	Pressure	IMV	Set-point/servo	Set-point/servo	PC-IMVsr,sr
Pressure control pressure support ventilation with automatic tube compensation	Pressure	IMV	Set-point/servo	Set-point/servo	PC-IMVsr,sr
Pressure control airway pressure release ventilation with automatic tube compensation	Pressure	IMV	Set-point/servo	Set-point/servo	PC-IMVsr,sr
Spontaneous CPAP/pressure support	Pressure	CSV	Set-point	N/A	PC-CSVs
Spontaneous proportional pressure support	Pressure	CSV	Servo	N/A	PC-CSVr

(continued)

Table 49.1 (continued)

Mode name	Mode classification				TAG
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	
Spontaneous proportional pressure support with automatic tube compensation	Pressure	CSV	Servo	N/A	PC-CSVr
Spontaneous CPAP/volume support	Pressure	CSV	Adaptive	N/A	PC-CSVa
Spontaneous CPAP/volume support with automatic tube compensation	Pressure	CSV	Adaptive/servo	N/A	PC-CSVar
Spontaneous CPAP/pressure support with automatic tube compensation	Pressure	CSV	Set-point/servo	N/A	PC-CSVsr

(2) Expiratory flow measurement as it is used in adults is not accurate enough and would not reflect the lung volume of the neonate.
(3) As the Babylog VN500 only displays the exhaled tidal volume, the amount of gas that actually participated in the gas exchange is displayed.
(4) The discrepancy between inspired and expired tidal volumes helps to identify and measure air leak, pneumothorax, inadvertent extubation, and need for a larger ET tube.

c. Clinical application
(1) Volume guarantee prevents V_T variation and helps prevent over or under ventilation.
(2) High tidal volume injures the immature lung, so volume guarantee ventilation may prevent lung injury during the initial phase of RDS when compliance changes rapidly after surfactant administration.
(3) Improvements in lung compliance will be followed by a progressive reduction in the inspiratory pressure, so the ventilator actively weans the support.
(4) The response in the respiratory rate of the patient can help to predict if the volume set is too high or too low. Adjust to the lowest volume that results in a normal RR.
(5) VG can be used in any synchronized mode of ventilation.

B. High-frequency ventilation (optional feature)
1. Operating principle
a. The VN500 in HFOV provides active inspiration and active expiration with sinusoidal waveforms. Its input parameters are frequency (fhf), amplitude (Ampl hf), mean airway pressure (MAPhf), and inspiratory to expiratory (I:E) ratio.
b. In the Babylog VN500 the flow controller ensures that the desired sinusoidal flow is delivered into the circuit.
(1) It regulates pressure in the circuit by adjusting the opening and closing mechanisms of the expiratory valve to generate the sinus pressure curve. To reach higher amplitudes at lower mean airway pressures, an ejector (suction nozzle) is integrated in the expiratory valve.
(2) The ejector actively removes air from the circuit and ensures quick pressure reduction to drain the patient's lungs to prevent intrinsic end expiratory pressure (active expiration).

c. With the VN500 different I:E ratios can be chosen related to the frequency as follows:

I:Ehf	Oscillation frequency
1:1	5–20 Hz
1:2	5–15 Hz
1:3	5–10 Hz

d. While pressure amplitudes may be considerable in the circuit, only small fluctuations occur around the mean pressure at the alveoli. Depending on the breathing circuit used, the set pressure amplitude may not be reached.
e. The inspiratory device flow is the flow that is delivered by the inspiratory valve and is based on customized settings. It may be influenced by tube leak, change in circuit resistance, and compliance. The measured value device flow only indicates the flow delivered by the ventilator. The flow from external sources is not taken into account.
f. The user can set desired mean airway pressure as well as amplitude, and these values are monitored to ensure patient safety.

C. Volume guarantee with HFO
1. The volume guarantee can be used with the HFOV mode by modifications in the amplitude pressure to maintain a desired high-frequency ventilation tidal volume.
2. If the volume option is switched on, the VThf (tidal volume on HFOV) can be set additionally.
3. If VG is activated, amplitude is automatically increased to the user-defined maximal amplitude to achieve the set VThf.
4. In this modality, variations in the tidal volume are prevented and a direct control on CO_2 clearance can be affected by adjustment in the tidal volume.
5. In this mode, the Babylog VN500 calculates the amplitudes required to reach the set VThf. The Ampl. Hf therapy control is then inactive, but a maximum amplitude needs to be set. If the VThf is not reached, the device alarms.
6. Rescue mode of ventilation in severe respiratory failure is the standard HFOV indication, activation of the VG can be done at the initial setting or after finding the desired tidal volume in each situation.
7. A tidal volume of less than the dead space is desired (<2.7 mL/kg).
8. To prevent lung trauma, lower tidal volume is desirable.

D. Non-invasive ventilation
1. Important principle: Non-invasive ventilation can be used mostly in the preterm infant with respiratory instability or failure to stabilize, wean, or prevent extubation failure.
2. Possible prevention of complications and intubation:
   a. Acute respiratory failure
   b. Acute lung injury
   c. Ventilator associated pneumonia, post-operative respiratory failure
   d. Decrease of nosocomial pneumonia
3. Non-invasive respiratory support can be achieved using nasal continuous distending pressure or nasal ventilation (n-CPAP, n-CMV) and O_2 Therapy.
   a. BabyFlow® nasal CPAP system is comprised of a complete system with circuit, housing, connector for prongs or masks, and pressure line for devices which need a proximal pressure measurement
   b. Avoid Auto-cycling.

Suggested Reading

Abubakar K, Keszler M. Effect of volume guarantee combined with assist/control vs synchronized intermittent mandatory ventilation. J Perinatol. 2005;25:638–42.

Keszler M. Update on mechanical ventilatory strategies. NeoReviews. 2013;14:e237–51. http://neoreviews.aappublications.org/content/14/5/e237.

Keszler M, Nassabeh-Montazami S, Abubakar K. Evolution of tidal volume requirement during the first 3 weeks of life in infants <800 g ventilated with volume guarantee. Arch Dis Child Fetal Neonatal Ed. 2009;94:F279–82.

Klingenberg C, Wheeler KI, Davis PG, Morley CJ. A practical guide to neonatal volume guarantee ventilation. J Perinatol. 2011;31:575–85.

Nassabeh-Montazami S, Abubakar K, Keszler M. The impact of instrumental dead-space in volume targeted ventilation of the extremely low birth weight infant. Pediatr Pulmonol. 2009;44:128–33.

Wheeler K, Klingenberg C, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in the neonate. Cochrane Database Syst Rev. 2010;CD003666.

SERVO-i Ventilator and NAVA

50

Jennifer Beck, Louis Fuentes,
and Howard McDonald

I. Introduction
   A. The SERVO-i ventilator (Maquet Critical Care AB, Solna, Sweden) has the capability to support ventilation for all patient ranges, age, size, and weight, including very low birth weight infants. Neurally Adjusted Ventilator Assist (NAVA) is a mode of ventilation available on the SERVO-i ventilator and will be described below (modes for spontaneous breathing, list item E) (Fig. 50.1, Table 50.1).
   B. The SERVO-i ventilator system consists of the following components:
      1. User Interface—for setting ventilation modes, displaying patient data, and indicating alarms
      2. Patient Unit—for mixing gases
      3. Patient Breathing System—for delivering and exchanging gases
   C. Many of the SERVO-i's features are specific for neonatal ventilation, including flow triggering in all modes, tubing compliance compensation, leak compensation, apnea delay, and apnea support with back-up ventilation.
   D. The exhalation valve on the SERVO-i is an active expiratory valve that is able to provide accurate levels of PEEP and enhances comfort for spontaneously breathing patients. The active expiratory valve utilizes a time constant valve-controlling algorithm to measure the compliance and resistance of each mechanical breath in an effort to reduce the expiratory work of breathing for the patient.
   E. The new generation exhalation valve is also necessary to use new modalities such as Bi-Vent, Non-Invasive Ventilation, and Nasal Continuous Positive Airway Pressure (CPAP) for the infant population.
   F. The SERVO-i ventilator has the capability of monitoring the electrical activity of the diaphragm (Edi) while in standby, or during all operating modes. The Edi waveform is also used

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S.M. Donn, S.K. Sinha (eds.), *Manual of Neonatal Respiratory Care*,
DOI 10.1007/978-3-319-39839-6_50

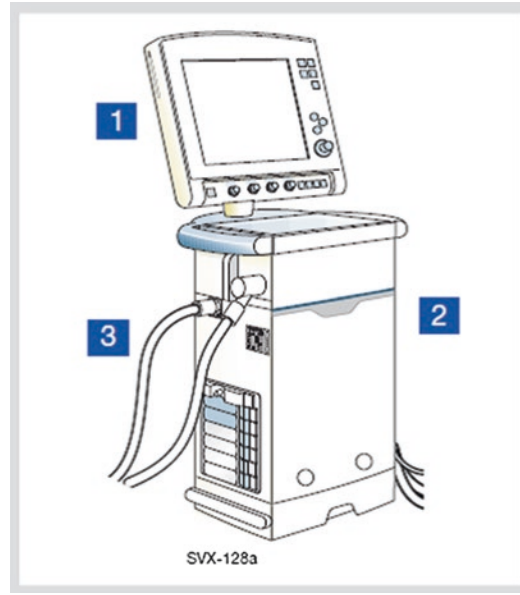


Fig. 50.1 Schematic representation of Servo-i ventilator

Table 50.1 Patient and weight ranges

Configuration	Weight range				
		Non-invasive ventilation			
	Invasive ventilation	Adult	NIV PC + PS infant	NIV-NAVA infant	NIV nasal CPAP
SERVO-i infant	0.5–30 kg	Not applicable	3–30 kg	0.5–30 kg	0.5–10 kg
SERVO-i adult	10–250 kg	10–250 kg	Not applicable	Not applicable	Not applicable
SERVO-i universal	0.5–250 kg	10–250 kg	3–30 kg	0.5–30 kg	0.5–10 kg

NIV non-invasive ventilation

to control the patient's assist during NAVA and Non-invasive Neurally Adjusted Ventilator Assist (NIV-NAVA).

G. The Servo-i has the ability for in-hospital transport with 1 hour back-up or up to 3 h with additional batteries. The SERVO-i may also be used with a Transport Kit for helicopter, airplane, or land transport.

H. In Volume Control Mode, decelerating flow is now an option.

II. Modes

A. The SERVO-i offers a variety of conventional modes as well as combination modes. The SERVO-i offers both invasive and non-invasive modes of ventilation (NIV), including NAVA and NIV-NAVA.

B. The ventilator may be set to flow or pressure trigger in all modes of ventilation. During NAVA and NIV-NAVA, the Edi serves as the principle trigger, with flow or pressure triggers providing back-up triggers if the Edi catheter is removed or out of position.

C. All modes can be patient-triggered.

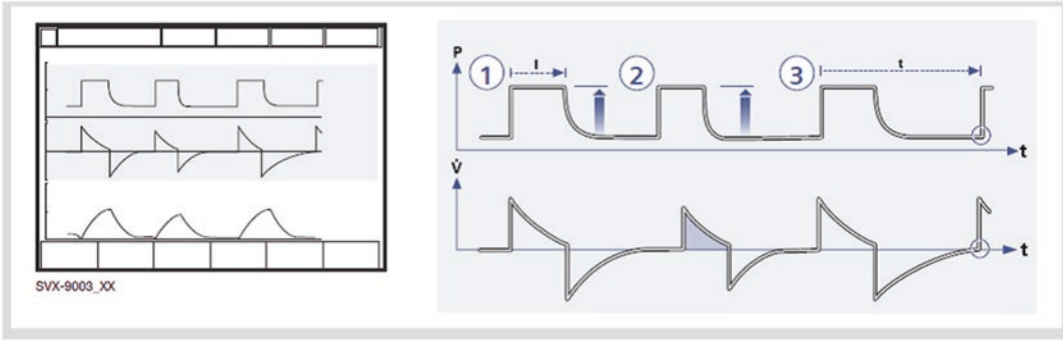
D. Control modes of ventilation. Spontaneously triggered breaths have the same characteristics (flow, inspiratory time, volume, or pressure) as the set ventilator breaths.

1. Pressure control (PC). This mode of ventilation employs a variable flow rate, which is microprocessor-controlled to provide a constant inspiratory pressure.

a. Tidal volume is variable.
b. Peak inspiratory pressure is constant.
c. Square pressure waveform
d. Decelerating inspiratory flow waveform (the variable flow rate differentiates this from time-cycled, pressure-limited ventilation, which imposes a preset peak inspiratory flow)
e. Clinician-set parameters
   (1) Peak inspiratory pressure level (above PEEP)
   (2) Inspiratory time
   (3) Ventilator rate
   (4) PEEP
   (5) FiO_2
f. High and low minute ventilation alarms
g. High pressure alarm
h. High and low respiratory rate alarms
i. High and low end expiratory pressure alarms
j. Trigger sensitivity level (Fig. 50.2)

2. Volume control (VC)
   a. Tidal volume is fixed
   b. Peak pressure is variable
   c. Square flow waveform
      (1) Flow is regulated based on set tidal volume and inspiratory time.
      (2) If flow adaptation is activated, targeting scheme switches from set-point to dual, meaning that in the presence of sufficient patient inspiratory effort, inspiration switches from volume control to pressure control and may be flow cycled instead of volume cycled (Fig. 50.3).
   d. Volume Control with decelerating flow (flow pattern can be set to end the inspiratory flow at 75, 50 (default), 25, or 0 % of the peak flow) (Fig. 50.4)
   e. Clinician-set parameters
      (1) Tidal volume
      (2) Inspiratory time (controls flow rate)
      (3) Pause time (optionally added to inspiratory time to help increase mean airway pressure, does not affect flow rate)
      (4) Ventilator rate
      (5) PEEP
      (6) FiO_2
      (7) High and low minute ventilation alarms
      (8) High pressure alarm
      (9) High and low respiratory rate alarms
      (10) High and low end expiratory alarms
      (11) Trigger sensitivity level (Fig. 50.5)

3. Pressure Regulated Volume Control (PRVC). PRVC combines a variable flow rate with the advantage of setting a targeted tidal volume. When PRVC is first initiated, the ventilator delivers a volume-controlled breath with a 10 % pause time. The measured pause pressure is used to find the plateau pressure, then uses it for the pressure level target for the next breath. PRVC is a form of pressure control with an adaptive targeting scheme. It targets the tidal volume by monitoring delivered V_T on each breath and adjusting the PIP on the subsequent breaths to achieve an average V_T equal to the set V_T. An alarm is activated if the pressure level



1. Pressure Control assures that the preset inspiratory pressure level is kept constant during the entire inspiration. Breaths are delivered according to the preset frequency, inspiration time and inspiratory pressure level resulting in a decelerating flow.
2. The preset pressure level is controlled by the ventilator. The resulting volume depends on the set pressure level, inspiration time and the patient´s lung mechanical properties during each breath with a decelerating flow.
3. Inspiration starts according to the preset frequency or when the patient triggers.

Expiration starts:

a. After the termination of preset inspiration time.

b. If the upper pressure limit is exceeded.

Fig. 50.2 Schematic representation of pressure control

Fig. 50.3 Volume control flow waveforms with and without flow adaptation

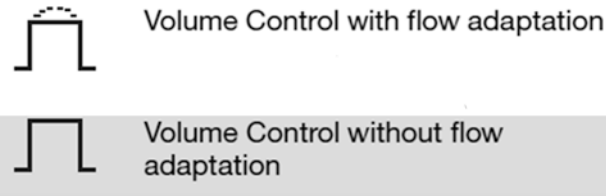
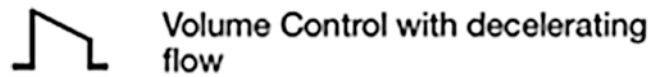


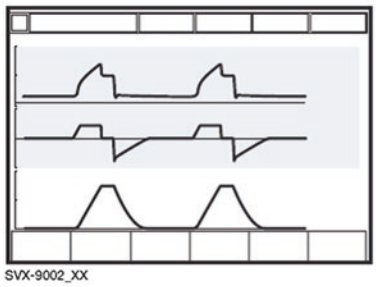
Fig. 50.4 Volume control with decelerating flow waveform

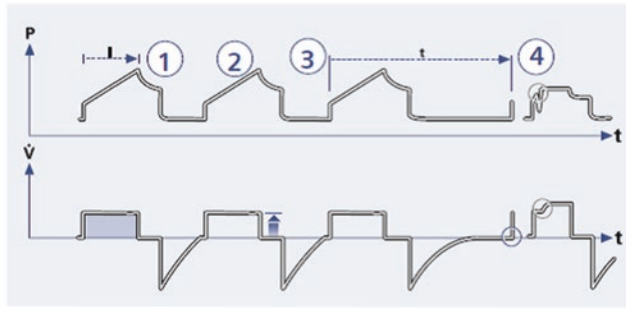


required to achieve the set target tidal volume cannot be delivered because of a lower setting of the upper pressure limit (−5 cm H_2O) (Fig. 50.6).

a. Tidal volume is set, inspiratory pressure is automatically adjusted.

b. Peak pressure is variable.





1. Volume Control assures a preset tidal volume with constant flow during a preset inspiratory time at a preset frequency.
2. The inspiratory flow is constant and depends on User Interface setting.
3. Inspiration starts according to the preset frequency or when the patient triggers.
4. If the patient makes an inspiratory effort during the inspiratory period, the ventilator will switch to Pressure Support to satisfy the patient´s flow demand.

Expiration starts:

a. When the preset tidal volume is delivered and after the preset pause time.

b. When the flow returns to the set value after the preset tidal volume is delivered and after the preset pause time (on-demand support). The patient is however always guaranteed an expiration time corresponding to at least 20% of the total breath.

c. If the upper pressure limit is exceeded.

Fig. 50.5 Schematic representation of volume control

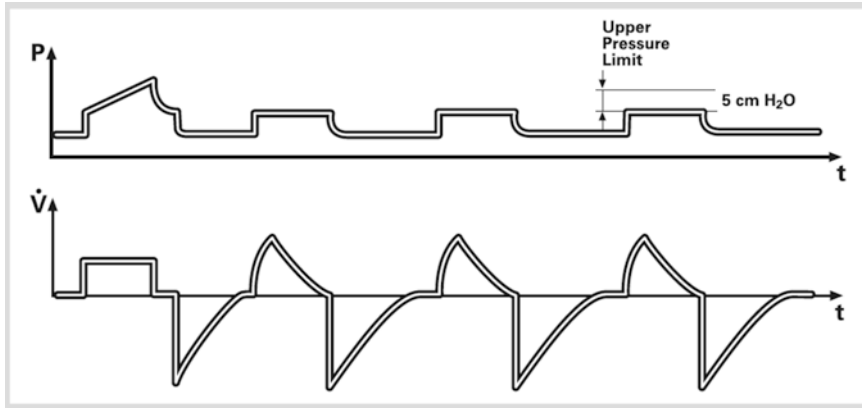
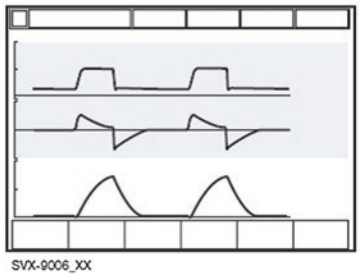
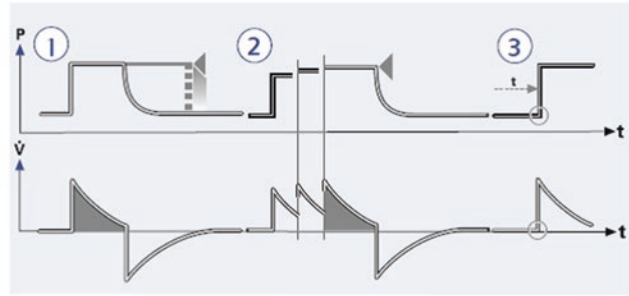


Fig. 50.6 Schematic representation of pressure regulated volume control (PRVC))

c. Decelerating flow waveform (the same as PC)
d. Square pressure waveform
e. Clinician-set parameters
   (1) Tidal volume
   (2) Inspiratory time





1. PRVC assures a set target minute ventilation to the patient. The target volume is based upon settings for Tidal Volume, frequency and inspiration time.
2. The inspiratory pressure level is constant during each breath, but automatically adapts in small increments breath-by-breath to match the patient´s lung mechanical properties for target volume delivery.
3. Inspiration starts according to a preset frequency or when the patient triggers.

Expiration starts:

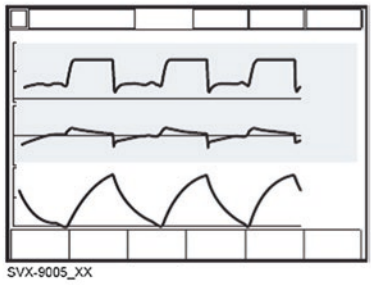
a. After the termination of preset inspiration time

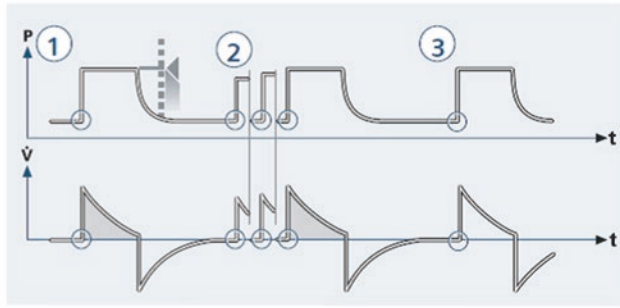
b. If the upper pressure limit is exceeded.

Fig. 50.7 Schematic representation of PRVC

(3) Ventilator rate
(4) PEEP
(5) FiO_2
(6) High and low minute ventilation alarms
(7) High pressure alarm
(8) High and low respiratory rate alarms
(9) High and low end expiratory alarms
(10) Trigger sensitivity level (Fig. 50.7)

E. Modalities for spontaneously breathing patients (where ventilator breaths are patient initiated)
   1. Volume Support (VS). Volume support is a modality for patients with an intact respiratory drive. This mode produces pressure controlled, flow-cycled inspiration with an adaptive targeting scheme to automatically adjust the inspiratory pressure to achieve an average V_T equal to the set V_T. Back-up ventilation is set so that if a patient becomes apneic, the ventilator will alarm and changeover to configurable back-up ventilation settings that are pre-determined by the clinician. Back-up ventilation is set based on an apnea time, set by the clinician, with configurable settings that will revert to the spontaneous mode once the respiratory effort is sensed by the ventilator.
      a. Tidal volume is set, inspiratory pressure is automatically adjusted.
      b. Peak pressures are variable (based on lung compliance and respiratory effort).
      c. Flow is decelerating.





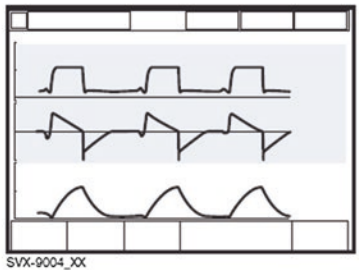
1. Volume Support assures a set target Tidal Volume upon patient effort by an adapted inspiratory pressure support.
2. The inspiratory pressure level is constant during each breath, but alters in small increments, breath-by-breath, to match the patient´s breathing ability and lung mechanical properties.
3. Inspiration with Volume Support starts

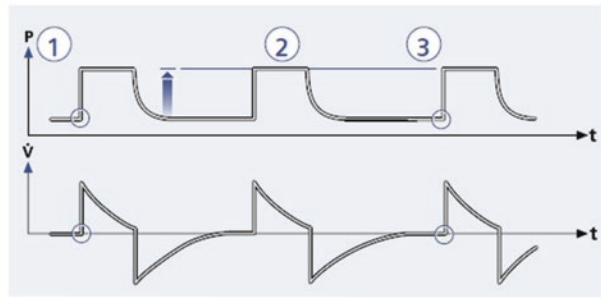
Expiration starts:

a. When the inspiratory flow decreases below a preset fraction of the inspiratory peak flow (Inspiratory cycle-off)
b. If the upper pressure limit is exceeded.
c. If the maximum time for inspiration is exceeded.

Fig. 50.8 Schematic representation of volume support

   d. Clinician-set parameters
      (1) Minimum tidal volume
      (2) Inspiratory time (for back-up ventilation should apnea occur)
      (3) Ventilator rate (for back-up ventilation should apnea occur)
      (4) PEEP
      (5) FiO_2
      (6) High and low minute ventilation alarms
      (7) High pressure alarm
      (8) High and low respiratory rate alarms
      (9) High and low end expiratory alarms
      (10) Trigger sensitivity level (Flow or Pressure)
      (11) Inspiratory cycle off (Fig. 50.8)
2. PS/CPAP (Pressure Support/CPAP). PS/CPAP is a mode for patients with an intact respiratory drive. This mode supports the patient's inspiratory effort with a set inspiratory pressure. It is pressure or flow triggered, and flow cycled. Back-up ventilation is automatic if the patient has apnea. Back-up ventilation is set based on an apnea time, set by the clinician, with configurable settings that will revert to the spontaneous mode once the respiratory effort is sensed by the ventilator.
   a. Tidal volume is variable.
   b. Peak inspiratory pressure is set.
   c. Decelerating flow
   d. Clinician-set parameters





1. Pressure Support assures that a preset inspiratory pressure level is constantly maintained upon patient effort.
2. The preset pressure level is controlled by the ventilator, while the patient determines frequency and inspiration time.
3. Inspiration starts when the patient triggers a breath, gas flows into the lungs at a constant pressure. Since the pressure provided by the ventilator is constant, the flow will decrease until the Inspiratory Cycle-off is reached.

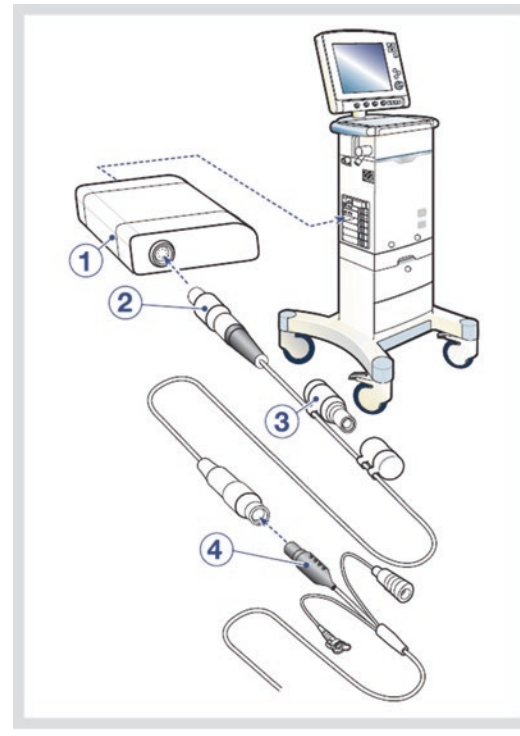
Expiration starts:

a. When the inspiratory flow decreases below a preset fraction of the inspiratory peak flow (Inspiratory cycle-off)
b. If the upper pressure limit is exceeded.
c. If the maximum time for inspiration is exceeded.
d. If the flow drops to a flow range between 25% of the peak flow and lower limit for Inspiratory Cycle-off fraction level and the spent time within this range exceeds 50% of the time spent in between the start of the inspiration and entering this range.

Fig. 50.9 Schematic representation of pressure support

(1) Inspiratory pressure
(2) FiO_2
(3) PEEP
(4) High and low minute ventilation alarms
(5) High pressure alarm
(6) High and low respiratory rate alarms
(7) High and low end expiratory pressure alarms
(8) Trigger sensitivity level (Flow or Pressure)
(9) Inspiratory cycle off (Fig. 50.9)

3. Neurally Adjusted Ventilatory Assist (NAVA). The SERVO-i offers NAVA as an option, for both invasive and non-invasive ventilation. NAVA uses the diaphragm electrical activity (Edi) to trigger, cycle off, and control the level of ventilator assist (Fig. 50.10).
   NAVA delivers assist in synchrony with and in proportion to the patient's spontaneous breathing efforts based on the measured Edi signal (Fig. 50.11). NAVA provides partial ventilatory assist, used in spontaneously breathing patients. NAVA takes advantage of pneumatic control as a back-up in case Edi fails to do so. Back-up ventilation, as in PSV, is based on an apnea time, set by the operator, and can be configured according to clinical practice. The ventilator reverts to NAVA once the apnea is over and Edi has returned.
   a. Tidal volume is variable and controlled by the patient and the NAVA level.
   b. PIP is variable and controlled by the patient and the NAVA level.



The Edi interchangeable plug-in Module slots into the module compartment in the SERVO-i Ventilator System:

- Edi Module (1).
- Edi Cable (2).
- Edi Test Plug (3).
- Edi Catheter (4).

Fig. 50.10 Schematic representation of neurally adjusted ventilatory assist (NAVA)

c. Flow is variable and controlled by the patient and the NAVA level.
d. Clinician-set parameters
   (1) NAVA level (the proportionality factor between Edi and delivered pressure above PEEP, units are cm H2O per μV)
   (2) Trigger sensitivity level (Edi, Flow, or Pressure)
   (3) Cycle off is fixed and non-adjustable. Cycle off is relative to the peak Edi per breath. The cycle off occurs at 70 % of the Edi peak for normal and high Edi signals and 40 % for low Edi signals.
   (4) FiO_2
   (5) PEEP
   (6) Pressure support level settings (see above) in the case where NAVA reverts to PSV
   (7) Back-up ventilation settings (similar to pressure control settings, see above)
   (8) High and low minute ventilation alarms (low minute volume off)
   (9) High pressure alarm (during NAVA, the ventilator limits 5 cm H_2O below this alarm value)

Fig. 50.11 Time tracings obtained during NAVA. From *top* to *bottom*: Airway pressure (*yellow*), flow (*green*), volume (*blue*), and electrical activity of the diaphragm (*green*)

(10) High and low respiratory rate alarms
(11) High and low end expiratory pressure alarms
(12) Low Edi Activity Low Alarm
(13) Percentage leakage fraction (in NIV-NAVA mode)

4. Continuous Positive Airway Pressure
   a. CPAP is a mode for spontaneously breathing patients who do not require any assistance in overcoming the work of breathing imposed by lung disease or the endotracheal tube.
   b. Clinician-set parameters
      (1) FiO_2
      (2) Pressure level
      (3) High and low minute ventilation alarms
      (4) High pressure alarm
      (5) High and low respiratory rate alarms
      (6) High and low end expiratory pressure alarms
      (7) Nasal CPAP low minute volume off
5. Bi-Vent
   a. Bi-Vent is pressure controlled breathing that allows the patient the opportunity of unrestricted spontaneous breathing. Two pressure levels are set together with the individually set duration of each level. Spontaneous breathing efforts can be assisted by pressure

support. In the Bi-Vent mode, the ventilator uses two shifting pressure levels, with the patient being able to breathe spontaneously on both these levels. Since Bi-Vent is a controlled mode of ventilation, apnea alarm and back-up ventilation are not available. It is also very important to set lower and upper alarm limits for expired Minute Volume.

b. Clinician-set parameters
   (1) Pressure high (PHigh) for the higher pressure level (cm H_2O)
   (2) PEEP for the lower pressure level (cm H_2O)
   (3) Oxygen concentration (%)
   (4) Time at the higher pressure (THigh) level (s)
   (5) Time at the lower pressure (TPEEP) level (s)
   (6) Inspiratory rise time (s)
   (7) Trigg. Flow/Trigg. Pressure
   (8) Inspiratory cycle off (%)
   (9) PS (Pressure Support level) above PHigh (cm H_2O)
   (10) PS (Pressure Support level) above PEEP (cm H_2O)
   (11) High and low minute ventilation alarms
   (12) High pressure alarm
   (13) High and low respiratory rate alarms
   (14) High and low end expiratory pressure alarms

F. Combination Modes of Ventilation. In addition, the above modes are offered in combination. This provides the clinician the ability to support ventilator delivered breaths and spontaneously triggered breaths with different parameters.
   1. SIMV Volume Control with pressure support
   2. SIMV Pressure Control with pressure support
   3. SIMV/PRVC with pressure support

G. Automode
   1. Automode is an option that senses the patient's respiratory effort and changes from a control mode (VC, PC, and PRVC) to a spontaneous mode, such as PSV or VS. In other words, the mode is a form of IMV but differs from conventional IMV in that the presence of spontaneous breaths will suppress mandatory breaths.
   2. If cessation of the respiratory drive occurs, Automode will place the patient back in control ventilation after a user-determined timeout threshold has been met during which the patient makes no detectable inspiratory efforts.
      a. Volume Control changes to Volume Support
      b. PRVC changes to Volume Support
      c. Pressure Control changes to Pressure Support

H. Mode Map (Table 50.2)

III. Control Panel and Display

A. The SERVO-i ventilator is equipped with a touch sensitive user interface, which is computer based.

B. The user interface, or the control panel, includes a continuous display of the set and measured values; graphic monitoring of flow, pressure, and volume; and 24 h trend monitoring.

C. The user interface is computer based with a luminescence screen and a combination of soft touch keys, and control knobs. This interface provides numerous menus and functions for the clinician to choose. They include:
   1. Patient Category Indicator (Table 50.3). The ventilator has a "patient category indicator" to set different internal parameters for adult/infant and infant/neonatal ventilation. These parameters control the following:

Table 50.2 Mode Map

Model	Mode name	Mode classification				TAG
		Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	
Servo-i	Volume control	Volume	CMV	Set-point	N/A	VC-CMVs
Servo-i	Volume control with flow adaptation	Volume	IMV	Dual	Dual	VC-IMVd,d
Servo-i	SIMV (volume control)	Volume	IMV	Set-point	Set-point	VC-IMVd,s
Servo-i	SIMV (volume control with flow adaptation)	Volume	IMV	Dual	Set-point	VC-IMVd,s
Servo-i	Automode (volume control to volume support)	Volume	IMV	Set-point/ adaptive	Set-point	VC-IMVd,a
Servo-i	Automode (volume control with flow adaptation to volume support)	Volume	IMV	Dual/adaptive	Dual/ set-point	VC-IMVd,a
Servo-i	Pressure control	Pressure	CMV	Set-point	N/A	PC-CMVs
Servo-i	Pressure regulated volume control	Pressure	CMV	Adaptive	N/A	PC-CMVa
Servo-i	SIMV (pressure control)	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Servo-i	Bi-vent	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Servo-i	Automode (pressure control to pressure support)	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Servo-i	SIMV pressure regulated volume control	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Servo-i	Automode (pressure regulated volume control to volume support)	Pressure	IMV	Adaptive	Adaptive	PC-IMVa,a
Servo-i	Spontaneous/CPAP	Pressure	CSV	Set-point	N/A	PC-CSVs
Servo-i	Pressure support	Pressure	CSV	Set-point	N/A	PC-CSVs
Servo-i	Neurally adjusted ventilatory assist	Pressure	CSV	Servo	N/A	PC-CSVr
Servo-i	Volume support	Pressure	CSV	Adaptive	N/A	PC-CSVa

Table 50.3 Flow triggering levels

Adult/pediatric	Infant
2.0 L/min	0.5 L/min

Table 50.4 Maximum inspiratory peak flows

Adult/pediatric	Infant
200 L/min	33 L/min

a. The level of continuous flow for flow and/or pressure triggering (Table 50.3)
b. Maximum inspiratory peak flow (Table 50.4)
c. Tidal volume range (Table 50.5)
d. Apnea alarm/Back-up ventilation ranges (Table 50.6)
e. Maximum flow rate (Table 50.7)

Table 50.5 Tidal volume ranges

Adult/pediatric	Infant
100–4000 mL	2–350 mL

Table 50.6 Apnea alarm and back-up ventilation ranges

Adult/pediatric	Infant
15–45 s, default 20 s	5–45 s, default 10 s

Table 50.7 Maximum flow rate

Adult/pediatric	Infant
200 L/min	33 L/min

2. Mode Indicator. Lists current mode of ventilation.
3. Automode Indicator. Indicates if Automode is on or off.
4. Nebulizer. This ventilator may be equipped with an ultrasonic nebulizer. When the nebulizer is connected, this indicator allows the clinician to set the time for the nebulizer to run. Optional Aerogen nebulizer is integrated into the software with an optional hardware module to plug the unit into. Nebulizer runs on batteries during transport.
5. Admit Patient. Stores and displays individual patient information, identification number, name, age, and weight.
6. Status. Provides internal information on the status of the following:
   a. General System Information
   b. O_2 cell/O_2 sensor
   c. Expiratory cassette
   d. Batteries
   e. CO_2 module (if integrated)
   f. Wye sensor measuring (if integrated)
   g. Installed options
   h. Pre-use check
   i. Patient Circuit
7. Alarm Settings
   a. High pressure
   b. Upper and lower minute ventilation
      (1) Upper and lower respiratory rate
      (2) Low end expiratory pressure (PEEP)
      (3) High and low $ETCO_2$
8. Graphic Display. When the unit is connected to a patient, there is a continuous display of four user-defined waveforms and two loops.
   a. Flow–time
   b. Pressure–time
   c. Volume–time
   d. CO_2–time
   e. Flow–volume (optional)
   f. Pressure–volume (optional)
   g. Edi (optional)

9. Digital readouts of the following are also displayed, if selected:
   a. PIP (Maximum inspiratory pressure)
   b. PPlat (Pressure during end inspiratory pause)
   c. Pāw (mean airway pressure)
   d. PEEP (end expiratory pressures)
   e. PEEP tot (Set PEEP + Intrinsic PEEP)
   f. CPAP (NIV Nasal CPAP only)
   g. RR (Respiratory Rate)
   h. FiO_2 (Measured oxygen concentration %)
   i. Ti (Inspiratory time)
   j. TC (Time constant)
   k. I:E ratio (Inspiration to expiration ratio) displayed during controlled breaths
   l. Spontaneous expiratory minute volume (Bi-Vent)
   m. Duty cycle time (Ti/Ttot) during spontaneous breaths and Bi-Vent
   n. MVe (Expired minute ventilation)
   o. Vti (Inspired tidal volume)
   p. Vte (Exhaled tidal volume)
   q. MVi (Inspired minute volume)
   r. MVe sp (Expiratory minute volume spontaneous)
   s. Leak % (only during NIV)
   t. V*EE (End inspiratory flow)
   u. $ETCO_2$ (End-tidal carbon dioxide concentration) (CO_2 Analyzer—optional)
   v. VCO_2 (Volume of expiratory CO_2 per minute) (CO_2 Analyzer—optional)
   w. $VtCO_2$ (CO_2 tidal elimination) (CO_2 Analyzer—optional)
   x. C_{dyn} (Dynamic characteristics)
   y. C_{static} (Static compliance)
   z. E (Elastance)
   aa. Ri (Inspiratory resistance)
   bb. Re (Expiratory resistance)
   cc. WOBp (Work of breathing patient)
   dd. WOB (Work of breathing ventilator)
   ee. P0.1—(Indicator for respiratory drive)
   ff. SBI—(Shallow Breathing Index)
   gg. Stress Index (optional for Volume Control only, fixed flow)
   hh. Edi Peak and Edi Minimum (optional NAVA and NIV-NAVA)
10. Trend Monitoring. The user interface has a comprehensive trend monitoring with information stored for 24 h with a time resolution of 1, 3, 6, 12, and 24 h. Data can be downloaded.
    a. Measured parameters (listed above)
    b. Ventilator changes
    c. Event log
11. Suction Support. A suction support key, when selected, offers an adjustable FiO_2 for pre- and post-oxygenation, silences the ventilator and stops flow for 60 s. If the patient is re-connected to the ventilator prior to 60 s, the ventilator resumes ventilation. It will stay at selected FiO_2 until changed or ventilator is rebooted.

IV. Additional Features
   A. CO_2 monitor. The SERVO-i is equipped with a port to monitor end-tidal CO_2 ($ETCO_2$), VCO_2, and $VtCO_2$ using the Novametrix $ETCO_2$ sensor.
   B. Nebulizer. There are two choices for this. The Servo-i has an Aerogen nebulizer that can be added to use with SOLO neb or SERVO-i using that port to run the Servo ultrasonic nebulizer. With either system, the nebulizer software has an automatic shut off, which may be set to run for a maximum of 30 min in 5 minute intervals but with the Aerogen, there is a continuous nebulization option as well.
   C. Edi monitoring is available during all modes of ventilation and when the ventilator is in Standby. The patient must have an Edi catheter and a Servo-i ventilator equipped with an Edi module. The Edi catheter serves also as a feeding tube, and is available in sizes 6 and 8 F for infant patients. (Note: catheter must be exchanged every 5 days per FDA.) The Edi catheter is not compatible with MRI.
   D. HeO_2 Heliox—A heliox enabled SERVO-i ventilator system has software that compensates monitoring flow delivery when HeO_2 is used (it compensates volumes) and an FiO_2 analyzer for heliox. HeO_2 gas is connected to the ventilator via a heliox adapter, which is connected to the Air/HeO_2 inlet and the ventilator will auto-recognize the change, or it can be changed manually.
      Available gas mixtures are:
      Helium/Oxygen mixture 80:20
      Helium/Oxygen mixture 79:21
      Helium/Oxygen mixture 78:22
   E. MR Conditional Option. The MR SERVO-i is conditionally approved for use in the MR Suite with open scanners up to 10 m (100 Gauss) and 20 m (200 Gauss) tunnel scanners. The allowable field strength of the scanner for the MR conditional option is 1.0, 1.5, and 3.0 T.
   F. Stress Index—Stress index option is intended for adults only with tidal volumes over 100 mL and in Volume control ventilation, or SIMV (VC)+Pressure support with square waveforms. The Stress Index cannot be calculated with a decelerating waveform.
   G. Open Lung Tool—Provides a breath-by-breath analysis of the following parameters to allow users to evaluate the trending of lung dynamics pre- and post-ventilator changes, therapy, and recruitment maneuvers. Parameters monitored are as follows:
      1. End inspiratory pressure
      2. PEEP
      3. Tidal volume (V_T) inspired and expired
      4. Dynamic compliance
      5. Tidal CO_2 elimination (if $ETCO_2$ option installed)
   H. Non-invasive Ventilation
      1. The SERVO-i has an optional NIV capability for all patient categories from the 500 g neonate to the 250 kg adult. NIV is ventilator support for patients who are not intubated and/or tracheotomized. This support feature is utilized with various non-invasive interfaces such as masks, nasal prongs, nasal pillows, and nasopharyngeal prongs. During NIV, the following displayed values are compensated for leak: inspired tidal volume (Vti), exhaled tidal volume (Vte), exhaled minute ventilation (MVe), and inspired minute ventilation (MVi).
      2. Available modes in NIV are Pressure Control, PS/CPAP, Nasal CPAP (infant patient category only), and NIV-NAVA. During the NIV option, the ventilator automatically adjusts for leak in the system to maintain set inspiratory and PEEP pressure. The NIV function has a variable trigger that adjusts to the variation in leak in an attempt to optimize patient-triggered support. Alarm settings are similar to the invasive modes of ventilation with the

option to silence nuisance alarms in the presence of high leak. Leak compensation in NIV can be set to low flow or high flow depending on the expected interface leak during NIV support.

Infant:

Low Flow: 7.5 LPM

High Flow: 15 LPM

Disabled: The ventilator will continue to deliver assist even when the leak is excessive

Disclosure Dr. Beck has made inventions related to neural control of mechanical ventilation that are patented. The license for these patents belongs to MAQUET Critical Care. Future commercial uses of this technology may provide financial benefit to Dr. Beck through royalties. Dr. Beck owns 50 % of Neurovent Research Inc. (NVR). NVR is a research and development company that builds the equipment and catheters for research studies. NVR has a consulting agreement with MAQUET Critical Care.

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Suggested Reading

Beck J, Emeriaud G, Liu Y, Sinderby C. Neurally adjusted ventilatory assist (NAVA) in children: a systematic review. Minerva Anestesiol. 2015. [Epub ahead of print].

Chatburn RL, Khatib ME, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

Duyndam A, Bol BS, Kroon A, Tibboel D, Ista E. Neurally adjusted ventilatory assist: assessing the comfort and feasibility of use in neonates and children. Nurs Crit Care. 2013;18(2):86–92.

Firestone KS, Fisher S, Reddy S, White DB, Stein HM. Effect of changing NAVA levels on peak inspiratory pressures and electrical activity of the diaphragm in premature neonates. J Perinatol. 2015;35(8):612–6.

http://ww2.maquet.com/pass/assets/documents/product-information/SERVO-i-Universal/en_US/SERVO-i-Universal-Data-Sheet-EN-US.pdf

Lee J, Kim HS, Jung YH, Shin SH, Choi CW, Kim EK, Kim BI, Choi JH. Non-invasive neurally adjusted ventilatory assist in preterm infants: a randomised phase II crossover trial. Arch Dis Child Fetal Neonatal Ed. 2015;100(6):F507–13.

Longhini F, Ferrero F, De Luca D, Cosi G, Alemani M, Colombo D, et al. Neurally adjusted ventilatory assist in preterm neonates with acute respiratory failure. Neonatology. 2014;107(1):60–7.

Nishimura M, Hess D, Kacmarek RM. The response of flow-triggered infant ventilators. Am J Respir Crit Care Med. 1995;152(6 Pt 1):1901–9.

Sinderby C, Beck J. Neurally adjusted ventilatory assist. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. 3rd ed. New York: McGraw Hill; 2012.

Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, et al. Neural control of mechanical ventilation. Nat Med. 1999;5:1433–6.

Stein H, Firestone K. NAVA ventilation in neonates: clinical guidelines and management strategies. Neonatol Today. 2012;7(4):1–10.

Stein H, Howard D. Neurally adjusted ventilatory assist in neonates weighing <1500 grams: a retrospective analysis. J Pediatr. 2013;160(5):786–9.

SLE5000 and SLE4000 Infant Ventilators

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David G. Tingay, Barbara Pilgrim, and Sunil K. Sinha

I. Introduction
   A. The SLE5000 is a combined conventional and high frequency oscillation ventilator with respiratory monitoring capabilities.
   B. The SLE4000 is a dedicated conventional ventilator with respiratory monitoring.
II. Ventilator Features
   A. Patented valveless technology
   B. Designed for use in neonates and infants from 350 g to 20 kg
   C. Constant flow of 8 LPM fresh gas (maximum gas flow 60 LPM)
   D. Time-cycled, pressure-limited and flow-cycled, pressure-limited
   E. Volume limiting (volume-targeted ventilation)
III. Ventilation Modalities
   A. Continuous positive airway pressure
   B. Continuous mandatory ventilation (CMV)
   C. Patient-triggered ventilation (PTV)
   D. Pressure support ventilation (PSV)
   E. Synchronized intermittent mandatory ventilation (SIMV) +/- pressure support
   F. Targeted tidal volume (TTV) on all conventional modalities
   G. High frequency oscillatory ventilation (HFOV)
   H. High frequency oscillatory ventilation combined with CMV
IV. Design Details and Principles of Operation

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A. The SLE5000 infant ventilator consists of an electronic system in the upper section of the ventilator and a pneumatic system in the lower.
B. The Electronic System
    1. The electronic system comprises three autonomous subsystems, one responsible for monitoring the patient, the other responsible for controlling the valves of the pneumatic system, and the third for the user interface (touch screen and displayed data).
    2. They are connected together by three serial communication links in a delta configuration.
    3. The ventilator has an internal battery that can power the ventilator in the event of a main power fail. If the main power fails with the battery fully charged, then operation will continue for approximately 60 min depending on ventilation mode.
C. Pneumatic System
    1. The pneumatic system comprises of the tubing and electro-mechanical valves necessary to provide the gas in conventional and oscillatory ventilation modes.
    2. The two gas controlling functions are blending and pressure generation.
    3. Blending
        a. The method used for blending air and oxygen, in known proportions, is to pressure regulate the two supplies (air and oxygen) so they produce equal flow rates. Each supply is then allowed into a mixing chamber for a time period equivalent to the proportions required.
        b. As an example, delivering oxygen at a set flow rate into a mixing chamber for 1 s and air at the same flow rate for 2 s will result in a mixture of 1 part oxygen to 2 parts air (resulting in a mix of 47.3 %).
    4. Pressure Generation: There are three jet nozzles within the exhalation block in the pneumatic subsystem.
        a. One generates negative pressure in the patient circuit.
        b. The other two generate positive pressure.
        c. The exhalation block is sterile, inserted at the time of set up and locked into place with a clamp. If the user does not secure the expiration block with the clamp at setup pressure delivery will not occur and the ventilator will alarm. Checking the exhalation block port clamp, and/or removing and reinserting the exhalation block should be part of the circuit troubleshooting procedure.
        d. The pressures generated from the three jet nozzles are controlled by three electronically controlled pressure regulators.
            (1) The negative and one of the positive nozzle pressures can also be switched on and off rapidly with in-line (high speed) solenoid valves.
            (2) The other positive nozzle (the mean jet) is used to generate steady baseline pressures in ventilation (CPAP or PEEP pressures in conventional ventilation, and mean pressures in HFO modes).
            (3) These three jets are used in various combinations to generate all ventilation modes.
    5. Conventional Ventilation
        a. In non-HFO modalities, the negative (or reverse) jet is used in a steady mode to provide a small amount of flow to offset the inadvertent patient circuit pressure generated from the fresh gas flow of 8 LPM.
        b. The mean jet is also used in a steady mode to generate the baseline pressure (CPAP or PEEP) measured relative to atmospheric pressure.
        c. The forward jet is used to generate the PIP during inspiration. The pressure amplitude is measured relative to atmospheric pressure in conventional mode.

d. The rise time of the inspiratory phase is controlled by dynamically controlling the forward jet pressure regulator rather than switching a steady pressure with the high speed valves.
   (1) This provides a smooth rise in pressure and allows user adjustable rise times rather than abrupt changes and pressure "ringing," which can result from high speed switching.
   (2) The fall of the inspiratory wave is also controlled by the forward jet pressure regulator to bring the pressure down quickly and smoothly; using the high speed valves to do this results in difficulties for the monitor subsystem in trying to detect a patient breath attempt by monitoring the pressure alone.
   (3) Once the pressure has been brought close to the base pressure, after about 100 msec, the forward jet solenoid is switched off to prevent any further artifact causing false triggering.
   (4) All jet pressures sum in the exhalation block. For example, to ventilate a patient with a PEEP pressure of 5 cm H_2O and a PIP pressure of 30 cm H_2O, the mean jet will be set to generate a continuous circuit pressure of 5 cm H_2O and the forward jet will be set to generate a circuit pressure varying between zero (exp. phase) and 25 cm H_2O (insp. phase).
   (5) Since the jet pressures will sum, this will result in the desired patient pressure.

6. HFO Ventilation. The ventilator is capable of functioning as a dedicated HFOV device with active exhalation.
   a. In pure HFO, the mean jet pressure regulator is used to set the mean pressure (relative to atmospheric pressure).
   b. The generated HFO waveform is a square wave with complex harmonics (similar to the SensorMedics 3100A, Chap. 55).
   c. The forward and reverse jet pressure regulators are used to generate steady positive and negative delta P components that will be superimposed on the mean pressure (i.e., positive and negative pressures are controlled relative to the mean pressure).
   d. These components are switched quickly using the high speed solenoid valves to generate the HFO pressures.
      (1) For example, to ventilate a patient with a mean pressure of 10 cm H_2O and a delta P pressure of 60 cm H_2O, the mean jet will be set to generate a continuous pressure of 10 cm H_2O, the forward jet will be set to generate a pressure amplitude of 30 cm H_2O and the reverse jet will be generating a pressure amplitude of −30 cm H_2O. Thus, peak airway pressure will be $30 + 10 = 40$ cm H_2O and trough pressure will be $10–30 = -20$ cm H_2O.
      (2) The HFO rate is determined by the rate of switching between the forward and reverse pressures on the high speed valves. Because the jet pressures sum, the resulting patient pressures will be switching between −20 cm H_2O and +40 cm H_2O. Thus, if mean HFO pressures up to 35 cm H_2O are required and the mean jet is only generating pressures up to about 20 cm H_2O, it will be necessary to apply a higher pressure on the forward pressure regulator and a lower pressure on the reverse pressure regulator. Using this method, the desired mean must be less than half the desired delta P pressure plus 20 cm H_2O.

7. Trigger Mechanisms
   a. Pressure Triggering. This senses the rate of change of pressure at the patient manifold when the onset of inspiration is detected. The sensitivity is adjustable within an uncalibrated range. Back-up breath rate is set in PTV ventilation to deliver a mandatory (machine triggered) breath if a trigger event is not sensed. This is recognized if

triggering breath is *not* flashing on the screen. It is sometimes difficult for the VLBW infant to consistently trigger pressure support with this mode of triggering.

b. Flow Triggering. This mechanism requires the use of a flow sensor. The SLE5000/4000 uses a heated-wire anemometer, which is calibrated at set up. The sensitivity is adjustable between 0.2 and 2.0 LPM. Back-up ventilation is delivered in the absence of a recognized trigger event. Flow triggering is easier for the VLBW infant and allows both inspiratory and expiratory synchronization using flow-cycling.

8. Alarms
   There are a large number of alarms and safety features, and users should pay attention to these while operating the machine and know how to react to alarms by referring to the operator's manual provided by the manufacturer.
9. LCD Screen displays: numerous data can be displayed, including wave forms and pulmonary mechanics, ventilator functions, and measured variables. These included expiratory tidal volume (with mandatory and spontaneous tidal volume differentiation, minute ventilation (conventional and HFOV), respiratory system compliance and resistance, and C20/C). [In accordance with European standards, the SLE5000 displays pressure in mbar; practically, this is the same as cm H_2O (1 cm $H_2O = 0.98$ mbar).]
10. Other Features
    a. A restrictor remains a feature of the SLE5000 patient circuit. As the fresh gas flow is 8 LPM, the restrictor is calibrated for this and is colored green to differentiate from the SLE2000 restrictor, which is purple. The SLE5000 restrictor is colored yellow with the Fisher and Paykel circuits.
    b. The pressure waveform modification (rise time) is located within the tools menu and allows variable setting between sine and square wave via gas flow modification.
    c. Targeted tidal volume (TTV*plus*) 50 % leak compensation. This allows the user to set a volume that is appropriate for the infant being ventilated. The leak compensation is deliberately limited to prevent overshoot on the next breath. All volume measurements are exhaled tidal volume.
    d. PSV with flow-cycling has automatic compensation in the presence of a leak thereby ensuring that all breaths are flow-triggered and flow-terminated.
    e. Complete respiratory monitoring with measurements of C20/C and DCO_2 (gas transport coefficient for carbon dioxide) and loops and waveforms.
    f. Ability to trend all measured parameters for 24 h.
    g. Ability to take a snapshot of a loop, save it, and compare future loops with this reference loop to observe changes in compliance.
    h. The user is able to deliver nitric oxide into the patient circuit and to remove and scavenge expired nitrogen dioxide through the exhalation block and scavenging system.
11. Advanced Modes of Ventilation
    a. PTV mode allows inflation pressure delivery to be synchronized with the patient's inspiratory efforts. The trigger setting defaults to 0.6 LPM but can be set by the user between 0.2 and 2.0 LPM. User selects PEEP, PIP, Ti, and back-up rate.
    b. PSV can be used in isolation, provided there is consistent respiratory effort, or together with SIMV if there is not. PSV has an algorithm to compensate for leaks, thereby ensuring that all breaths are flow-terminated.
       (1) In PSV mode all inflations are flow-cycled with settings and trigger operation as per PTV. The user selects a maximum allowable Ti.
       (2) When PSV is used together with SIMV any spontaneous breaths (i.e., triggered and cycled by the patient) between scheduled mandatory breaths (triggered and cycled by the machine) will be supported with PSV. This means that some inflations maybe

time-cycled (mandatory) and others flow-cycled (spontaneous). For example, if an infant is breathing at 60 BPM and SIMV is set at 40 inflations per minute the infant will receive 40 mandatory inflations in SIMV mode (at the set Ti) and 20 spontaneous inflations in PSV mode (flow-cycled with Ti set by infant).

(3) Unlike PSV used in isolation, in SIMV + PSV mode, the pressure support level for spontaneous breaths is set as a % of delta pressure (PIP–PEEP) used for mandatory breaths. For example, if mandatory breaths are set at PIP 20 cm H_2O and PEEP 6 cmH_2O (delta pressure 14 cm H_2O) and the PSV pressure support is set at 50%, then the pressure support level during spontaneous breaths will be $0.5 \times 14 = 7$ cm H_2O (above PEEP) and PIP (PSV inflations) will be $7 + 5 = 13$ cm H_2O (above atmospheric pressure). This mode is often used if prolonged weaning is anticipated.

c. Targeted Tidal Volume Plus (TTV^{plus})

(1) TTV^{plus} is a feature that changes set-point targeting of conventional mandatory pressure controlled breaths to adaptive targeting. This means the inspiratory pressure is automatically adjusted to achieve an average exhaled tidal volume equal to the tidal volume setting. Spontaneous breaths are not controlled in this way but the inspiratory pressure of pressure support breaths will be affected indirectly in SIMV + PS mode (because it is defined as a percentage of the mandatory breath delta P; see above).

(2) The adaptive targeting automatically accommodates to changes in resistance and compliance and patient ventilator effort.

(3) SLE5000/4000 with the latest 5.0 version of software introduces leak compensation of up to 5 L/min or 50 %, whichever happens first. Leak compensation is only active if the leak volume is 10–50 %. The TTV*plus* algorithm determines required PIP from the measured expiratory tidal volume.

(4) To avoid excessive volume delivery from active spontaneous breathing, the TTV*plus* algorithm will terminate PIP if 130 % of set tidal volume is measured during a supported inflation.

d. High Frequency Oscillatory Ventilation.

(1) The delivery of pressures in HFO in the SLE5000 is different from that of the SLE2000.

(2) It is derived from the fast switching of the high speed solenoid valves.

(3) The SLE 5000 is able to oscillate infants up to 20 kg with a maximum mean airway pressure of 45 mbar.

(4) Inspiratory:Expiratory ratios of 1:1, 1:2, and 1:3 are available.

(5) The practical principles of HFO still apply. By using a flow sensor the user has access to the DCO_2 measurement, which may be an aid to assessing alveolar ventilation and thereby CO_2 elimination. This may be helpful where there is no other form of CO_2 monitoring other than blood gas analysis.

(6) The use of the flow sensor allows accurate measurements of end tidal volumes and minute volumes.

(7) There is also the option of viewing a flow-volume loop.

(8) The SLE5000 has the option of HFOV combined with CMV. In this mode the user sets CMV parameters (PIP, PEEP, Ti, and Rate) and can also superimpose an HFOV waveform (set frequency and delta pressure) during PEEP only (expiratory phase) or during PEEP and PIP (inspiratory and expiratory phases). The benefit of this mode over HFOV or conventional modes alone has not been explored in clinical trials and should only be reserved for experienced users only.

12. Mode Map (Table 51.1)

Table 51.1 Mode Map

	Mode classification				
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	Tag
Continuous mandatory ventilation	Pressure	CMV	Set-point	N/A	PC-CMVs
Continuous mandatory ventilation with targeted tidal volume	Pressure	CMV	Adaptive	N/A	PC-CMVa
Patient triggered ventilation	Pressure	CMV	Set-point	N/A	PC-CMVs
Patient triggered ventilation with targeted tidal volume	Pressure	CMV	Adaptive	N/A	PC-CMVa
Synchronized intermittent mandatory ventilation with pressure support ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Synchronized intermittent mandatory ventilation with targeted tidal volume	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
High frequency oscillation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
High frequency oscillation with continuous mandatory ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
CPAP	Pressure	CSV	Set-point	N/A	PC-CSVs
Pressure support ventilation	Pressure	CSV	Set-point	N/A	PC-CSVs
Pressure support ventilation with targeted tidal volume	Pressure	CSV	Adaptive	N/A	PC-CSVa

Suggested Reading

SLE5000/SLE4000 User Manual Version 5.0 software (SLE Limited, South Croydon, UK). Product Brochures and data sheet (www.sle.co.uk).

Stephanie and Sophie Ventilators

52

Helmut D. Hummler and Christian F. Poets

Stephanie Ventilator

I. Introduction. The Stephanie ventilator (Fritz Stephan GmbH, Gackenbach, Germany) (Fig. 52.1) was designed as a device for newborn and pediatric patients up to 25 kg bodyweight. This review will focus only on the use in the neonatal population.

II. Description. The Stephanie ventilator (Fig. 52.2) provides volume- and pressure-controlled ventilation, proportional assist ventilation (PAV) and high frequency ventilation as well as some pulmonary function diagnostic techniques.
   A. A proximal flow sensor (pneumotachograph) can be used to detect patient effort and to provide flow-triggered synchronization for ventilator inflations as well as for proximal flow/volume measurements.
   B. Several modes for pressure- or volume-controlled ventilation are available.
   C. Synchronized ventilation can also be achieved by using patient-triggered ventilation (drop in airway pressure induced by patient effort) or with an external pressure capsule placed on the abdomen.
   D. Several mechanisms to trigger and to cycle off inspiration are available.
   E. The Stephanie has an integrated humidification system with heated tubes to prevent rainout with an automated refill system.
   F. A 10.4″ Color TFT screen allows visualization of respiratory parameters, graphics, and loops as well as measured data. Data outputs (RS232) and analog outputs are available for real time data export to patient data management systems.

III. Special Features:
   A. Non-invasive ventilation is possible, which may be synchronized using an abdominal pressure capsule.

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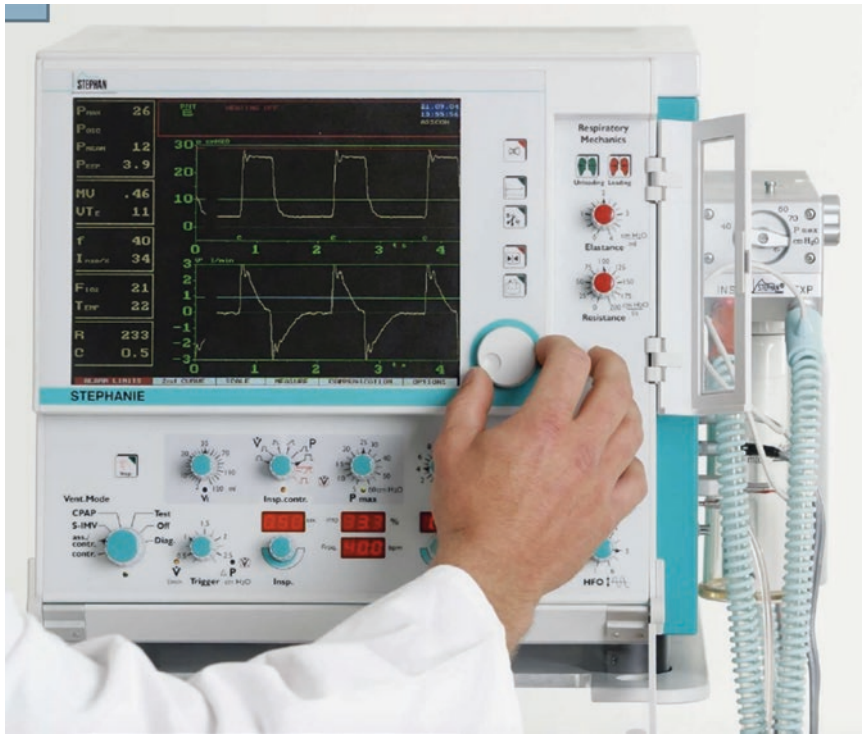

Fig. 52.1 Stephanie ventilator

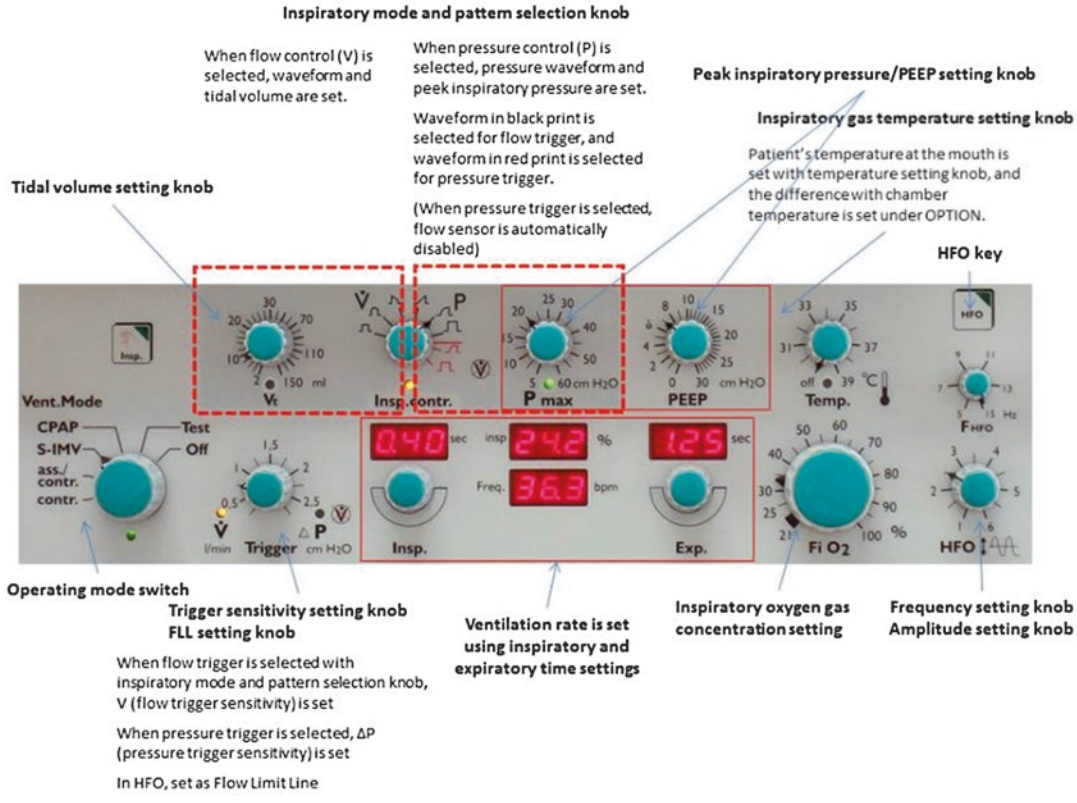

Fig. 52.2 Stephanie ventilator operator menu

B. Back-up ventilation
   1. Several back-up features for infants with variable respiratory drive are available. The interval until the back-up is initiated is adjustable from 0.5 to 15 s ("apnea duration"). Furthermore, the user can choose between an instantaneous stopping of the back-up ventilation once the patient has resumed spontaneous breathing, and a more gradual reduction of back-up inflations ("frequency controlled back-up"), which may be particularly useful in infants with a more unstable breathing pattern and/or unstable functional residual capacity (FRC). The back-up may be initiated using flow during invasive ventilation or by using an abdominal pressure capsule to detect apnea.
   2. An optional SpO_2-sensitive back-up system can initiate back-up inflations if the SpO_2 decreases below the user-adjustable lower limit and wean back-up support once recovery has occurred.

C. Proportional assist ventilation
   1. Elastic and resistive unloading may be used to support the infant's own respiratory effort. Adjusting the degree of elastic and resistive unloading is possible according to the patient's individual needs. This allows compensation for decreased compliance (i.e., increased elastance) and increased resistance of the respiratory system, allowing the patient to use his/her own respiratory control mechanisms.
   2. Combining with back-up features is possible.

D. Pneumotachograph: Several pneumotachographs with different specifications are available. Type A (PNT A) is designed to measure air flow up to 10 LPM and has a dead space of 0.5 mL. PNT B is designed to measure up to 12 LPM, dead space 0.6 mL, and PNT C measures up to 25 LPM with a dead space of 0.9 mL.

E. A special pressure port supplies continuous airflow for nebulization of drugs into the inspiratory limb of the patient circuit providing the same FiO_2 as in the regular patient circuit. If activated, the aerosol pressure line will deliver a constant gas flow, which will stop automatically after 5 min, if not manually turned off earlier.

F. Internal battery. Automatically activated back-up for the loss of electric power with a minimum operating time of 5 min. However, a larger battery with extended capacity for up to 20–30 min is available.

IV. Preparation for Operation
   A. The power supply should be connected for charging the internal battery.
   B. Connect gas supply (oxygen and pressurized air).
   C. Fill the humidifier with distillated water. The humidifier may be filled manually, requiring regular refills. Alternatively, an automated refill system is available.
   D. Connect the patient circuit to the ventilator. An expiratory filter has to be included between the expiratory limb and the ventilator to protect the valve system of the ventilator if nebulization of drugs is used (formation of crystals).
   E. The "Operating Mode Switch" is turned to the "test" position. An internal test program is started, which checks for correct function of all essential parts and for leaks. This test program can be overridden in emergency cases by turning the "Operating Mode Switch" to the desired ventilation mode straight away.

V. Settings available
   A. Ti: 0.1–2 s
   B. Te: 0.1–60 s
   C. Vt: 0.2–15 mL or 2–150 mL
   D. $P_{max.}$: 5–60 cm H_2O
   E. PEEP: 0–30 cm H_2O

F. Inspiratory pattern
   1. Pressure-controlled: square wave, half sinus, ascending ramp (linear acceleration) in pressure
   2. Flow controlled: square wave, sinus, descending ramp (decelerating) flow

G. Trigger sensitivity
   1. Flow: 0.1–2.9 LPM, activated when inspiratory air flow exceeds the set threshold
   2. Pressure: 0.1–2.9 cm H_2O, activated as a differential pressure trigger (relative to PEEP)
   3. Pressure abdominal movement: 0.1–2.9 arbitrary units (available during non-invasive ventilation only)

H. Gas temperature (30–39 ° C)

I. FiO_2 (0.21–1.0)

J. PSV
   1. Expiratory trigger: 5–40 % of peak flow
   2. Pressure during PSV: 0–100 % of P_{max}

K. High Frequency Oscillation
   1. Frequency: 5–15 Hz
   2. % Inspiratory time: 33, 40, 50 %
   3. Mean airway pressure: up to 30 cm H_2O
   4. Amplitude max: 24 mL @ 10 Hz

L. Inspiratory hold: 1–7 s. Inspiration is maintained for the duration as long as this button is pushed. The maximal inspiration hold time is user adjustable up to 7 s.

M. PAV
   1. Elastic unloading: 0–4 cm H_2O/mL
   2. Resistive unloading: 0–200 cm H_2O/L/s
   3. PAV Volume limit: 1–150 mL

VI. Monitoring

A. Almost all settings are monitored and displayed on the screen.

B. Graphic monitoring
   1. Waveform display
      a. Airway pressure is measured at the inspiratory (displayed in gray–blue) and expiratory tubing system (displayed in blue) to calculate the instantaneous mean value (displayed in yellow). Breaths automatically receive annotations with “C” for a controlled breath, “A” for an assisted breath, and “B” for a back-up breath.
      b. Flow
      c. Vt
      d. Non-invasive pressure capsule signal
   2. Mechanics
      a. Volume–pressure loop
      b. Flow–volume Loop
      c. Flow–pressure loop
   3. Trends:
      a. Airway pressure, Vt, air flow
      b. 0.5, 1, 2, 4, 12, 24 h trend intervals
   4. Pulmonary mechanics calculations: compliance of the respiratory system, resistance, and the expiratory time constant can be calculated.

VII. Alarms/Limits: The alarm limits can be adjusted manually for each monitored item, or automatically, where the device takes a certain value below and above the currently measured value as the upper and lower limit. For more information see Chap. 4 of the operator’s manual.

A. Airway pressure (high/low)

B. End-expiratory pressure (high)
C. Mean airway pressure (high/low)
D. Expiratory minute ventilation (high/low)
E. Expiratory tidal volume (high/low)
F. Inspiratory fraction of O_2 (high/low)
G. Gas temperature (high/low)
H. Oscillatory amplitude (high/low)
I. Oscillatory tidal volume (high/low)
J. Oscillatory minute ventilation (high/low)
K. Disconnection
L. Apnea

VIII. "Inspiration Control" for initial decision by the operator: Pressure- or flow-controlled ventilation:
A. Pressure-controlled ventilation
1. The pressure is controlled. In this mode a linear increase in pressure (from the PEEP level to peak inspiratory pressure (PIP)), or a "half sinus" pressure profile (steep pressure increase from PEEP initially, with a plateau towards the end of the inspiratory time to reach the desired PIP, or a "square" profile (immediate increase of airway pressure to PIP to be maintained for the remaining inspiratory time) can be chosen by the operator.
2. The half-sinus and the square wave pressure profile can be chosen without a pneumotachograph in place, which can be switched off at the inspiration control. With this setting there is no flow/tidal volume monitoring, and flow-triggered ventilation and PAV are not possible.
3. Volume varies with changes in pulmonary compliance and airway resistance.
B. Flow-controlled ventilation
1. The flow is controlled during the inspiratory phase by the ventilator. A square wave, a sinusoidal, or a decelerating flow curve can be chosen.
2. The pressure varies with changes in pulmonary compliance and airway resistance.

IX. Mechanisms for triggering and cycling off ventilator breaths
A. General comment: Synchronized breaths can be triggered by using air flow, pressure, or the abdominal pressure capsule. The thresholds can be adjusted for flow (0.1–2.9 LPM), pressure (0.1–2.9 cm H_2O), and with the pressure capsule (arbitrary units).
B. Assist/Control (A/C)
1. If the patient triggers the ventilator with a spontaneous effort, assisted mandatory breath with given characteristics (i.e., inspiratory time, pressure- or volume-controlled) is delivered. The rate of mechanical inflations is controlled by the patient's respiratory rate. After every triggered breath the trigger is suppressed for 200 ms.
2. A back-up rate may be chosen to support the patient if effort/spontaneous respiratory rate decreases below the back-up rate (safety cushion).
C. Synchronized Intermittent Mandatory Ventilation (SIMV)
1. A mandatory breath is delivered whenever the patient's effort occurs within the prespecified synchronization window. This window opens 2 s before the end of expiration time, or at the beginning of the second half of the calculated expiration time if it is <4 s. If the effort is not sensed by the time the window period elapses, a time triggered mandatory breath will be delivered.
2. SIMV can be used during both pressure- and volume-controlled modes.
3. If the patient's spontaneous effort triggers the ventilator above the set control rate, the additional breaths will be spontaneous.

D. Pressure Support Ventilation (PSV)
   1. PSV allows the patient to initiate the mechanical breath, and to end mechanical inspiration. Thus, inspiration is flow-cycled, and is synchronous with the patients' spontaneous breathing pattern.
   2. Inspiration ends at a percentage (adjustable from 5 to 40 %) of the peak inspiratory flow rather than after the set inspiratory time. Flow-cycling helps to prevent an inversed I:E ratio during rapid breathing and may reduce the risk of gas trapping. Compared to time-cycled A/C, a high spontaneous respiratory rate will reduce inspiratory time automatically. Flow-cycling enables better synchronization between the baby and ventilator.
   3. With a very high spontaneous respiratory rate the inspiratory time may become extremely short, which may result in delivery of an inadequately small tidal volume. To prevent this, a preset minimum volume (V_{min}) that must be delivered before PSV actively terminates inspiration can be set.
   4. PSV can be used as a stand-alone mode, or as an adjunct to support spontaneous breaths between mandatory (S) IMV inflations.
   5. Pressure during PSV: The peak pressure of PSV during SIMV (PPSV%) can be set at 0–100 % P_{max} of the pressure-control to support spontaneous breaths during SIMV. 0 % would result in CPAP only with no pressure support, 100 % would give a peak pressure similar to the peak pressure of the SIMV breath (fully supported).

X. Modalities of Ventilation
   A. Pressure-controlled modalities
      1. Continuous positive airway pressure (CPAP)
         a. During CPAP the patient is breathing spontaneously with a set continuous positive airway pressure (0–30 cm H_2O).
         b. CPAP may be combined with back-up ventilation to provide (synchronized) ventilator breaths to compensate for irregular breathing (apnea). Apnea duration for the back-up to start can be adjusted from 0.5 to 15 s and the duration of back-up is adjustable (5–60 s). A special frequency-controlled back-up mode is available, which allows a more gradual withdrawal of back-up breaths if the baby starts breathing within a pre-defined (5–60 s) back-up duration (BUD). Any spontaneous breath within this period would reduce the back-up frequency to 1/2, 1/3, or 1/5 of the initial rate to be switched off, if the patient continues to breathe.
         c. A special SpO_2-sensitive back-up can be switched on in the same menu. It provides back-up breaths if the actual SpO_2 of the patient is below a certain threshold (adjustable from 70 to 97 %). An upper limit for weaning of back-up may be set as well. For more detailed information see the manual.
      2. Controlled mandatory ventilation (CMV)
         a. The ventilator provides a preset rate and preset inspiratory time. The patient cannot actively influence the timing of these ventilator breaths. This mode is most often used with pressure-control, but it can be used in volume-control.
         b. In pressure-control, Vt depends on the characteristics of the respiratory system of the patient. During the expiratory phase the patient can take additional spontaneous breaths, which are not synchronized.
         c. The gas flow in the patient circuit is continuous, but will vary if leaks occur to allow for three different pressure profiles.
      3. Volume-limited pressure-controlled ventilation:
         a. The inspiratory pressure increase/decrease is adjusted automatically in steps of 2 cm H_2O until the target volume is reached (measured as the expiratory tidal volume of the preceding breath).

   b. The "P_{max}" is used to set the maximal pressure allowed. In general a Vt target of 3–6 mL/kg is chosen during this mode.
   c. Leaks up to 50 % can be compensated.
4. Pressure support ventilation
   a. A pressure-limited breath that is patient-triggered. The patient has primary control of the inspiratory time.
   b. During PSV, spontaneous breathing is supported by a pre-specified (adjustable) pressure and allows the patient to synchronize the initiation and the end of the breath. The factor for the peak inspiratory flow (called KV'max) is adjusted between 5 and 40 (%), and the minimum volume (V_{MIN}), which has to be measured via the pneumotachograph before PSV is allowed to end inspiration before the set inspiration time expires, can be set at 1–40 mL.
5. Non-invasive pressure-controlled ventilation
   a. Non-invasive modes of ventilation are available including non-invasive triggering using the abdominal pressure capsule. This signal can be displayed on the screen. The trigger threshold can be adjusted.
   b. "Expiratory Cycling" of the external trigger can be activated if desired. If the pressure is not rising any more in the abdominal pressure capsule the mechanical inflation will be terminated, even before the end of the inspiration time set by the clinician. If this change in pressure rise is not detected, inflation will end by the end of the set inspiration time. The peak pressure delivered to the lung may be lower than the desired peak pressure because of loss of gas (and pressure) secondary to large leaks.

B. Volume-controlled modality. There are several ways volume-targeted ventilation may be achieved using the Stephanie. It can be achieved by using a true volume-controlled mode, or by a pressure-controlled mode with adaptive targeting (volume limitation—see above).
1. A pre-set volume is delivered during volume-controlled ventilation with each breath (V-CMV). This mode is activated if the "Ventilation Mode" is on "control" and the "Inspiration control" is on flow-controlled inspiration (three choices of flow patterns). The pressure limit ("P_{max}") can be used to limit the maximal peak pressure, if desired. A leak could result in the desired volume not completely being delivered to the lung.
2. The volume is measured with the pneumotachograph located between the Wye-piece and the endotracheal tube.
3. The volume given by the ventilator is the independent variable and the pressure as the dependent variable will depend on the mechanical characteristic of the respiratory system (compliance and airway resistance). There will be a loss of volume secondary to compression within the tubing system, especially if the lungs are stiff.
4. With the pneumotachograph in place, the user can chose "V_{Tex} on" in the menu "Options," "Modify." With this setting, the inspiratory volume supplied is increased to compensate for leaks. The maximum permitted inspiratory volume for leak compensation corresponds to leaks that are twice the measured expiratory volume.

C. Proportional assist ventilation
1. PAV is a servo-targeting mode, which adjusts the airway pressure during each individual breath in proportion to the patient's inspiratory effort. It is based on the equation of motion: $p(t) = K_1 V(t) + K_2 V(t)$, where inspiratory pressure relative to PEEP is a function of time (t) and is the sum of two components. The first is the "volume assist" as reflected by $K_1 V(t)$, which is the amount of pressure given to compensate for elastic loads at any point in time throughout the respiratory cycle. The amount of pressure change in relation to PEEP applied during any point in time during a spontaneous breath will be higher if a higher gain (K_1) is used (Fig. 52.4).

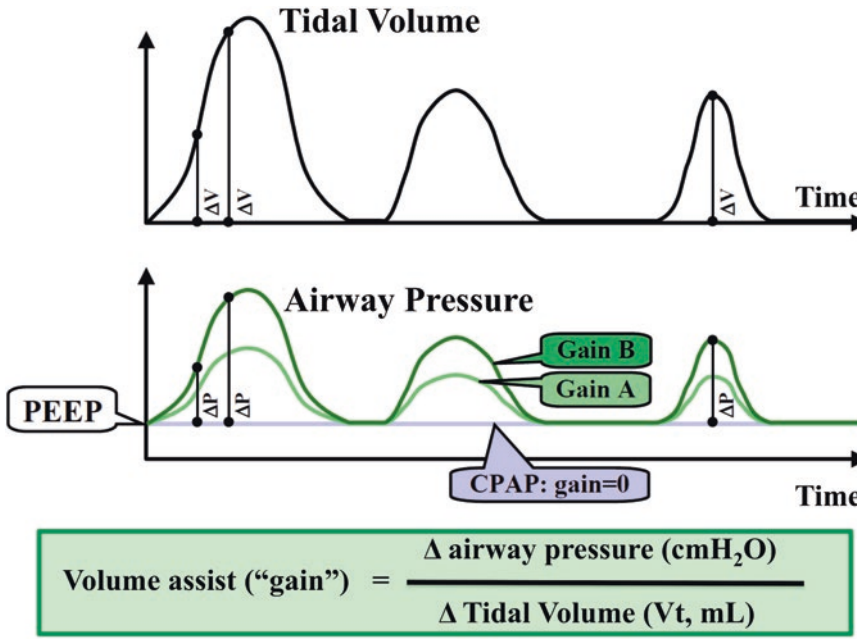

Fig. 52.3 Elastic unloading during proportional assist ventilation (Gain B > Gain A)

The second is the "flow assist" as reflected by $K_2 V(t)$, which is the amount of pressure to compensate for resistive loads, again throughout the respiratory cycle. The amount of pressure change in relation to PEEP applied during any point in time during a spontaneous breath will be higher if a higher gain (K_2) is used (Fig. 52.4). The values for K_1 and K_2 can be set by the clinician and should ideally compensate for the increased elastic and resistive loads secondary to the patient's respiratory disease.

2. PAV is initiated in a separate control panel at the Stephanie with the basic mode being CPAP. There is an option to limit the delivered tidal volume (for safety reasons) to avoid volutrauma in case K_1 is chosen arbitrarily too high. The user must always adjust the following safety limits: first the pressure knob acts as an upper pressure limit during PAV. The upper pressure limit should be a few cm H_2O above the peak inspiratory pressure observed with PAV with appropriately adjusted settings. An additional safety feature is the adjustable volume limit. If this limit is reached the airway pressure is reduced to PEEP. Again, this limit should be at least slightly above the tidal volume the clinician accepts as the upper limit. The maximum possible duration of the inspiratory time is limited to 0.7 s.
3. A detailed description on how to use PAV clinically is beyond the scope of this chapter, but is available in the manual of operations and in the references listed below. Briefly, the simplest and most practical procedure to initiate PAV is to start with the gain (K_1 and K_2)=0 (zero) and gradually increase both gains. The gain for resistive unloading may be adjusted to compensate the resistance imposed by the endotracheal tube (i.e., 25 cm H_2O/L/s with a 2.5 mm I.D. endotracheal tube). Then the gain for elastic unloading must be increased, keeping in mind that smaller infants have a higher elastance compared to more mature infants, because compliance and tidal volume are related to body weight. When PAV is properly adjusted, preterm and term infants typically show a relatively fast but comfortable breathing pattern with their own respiratory rate at approximately 60–100 breaths/min. If the degree of elastic unloading

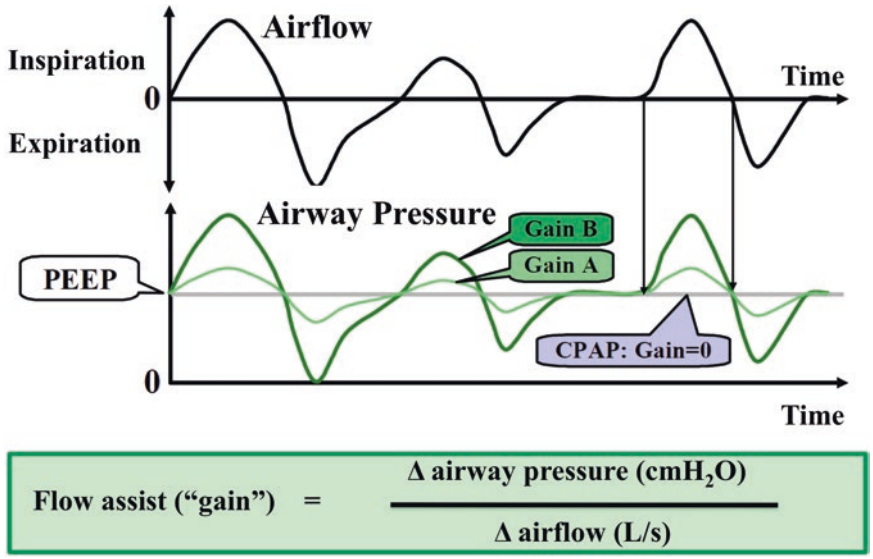

Fig. 52.4 Resistive unloading during proportional assist ventilation (Gain B > Gain A)

is chosen too high, the pressure "runs" away, and when the tidal volume or pressure limit is set properly, PAV converts to assist/control (overcompensation).

D. High frequency oscillatory ventilation
   1. Initiation of HFO. Mean airway pressure is adjusted using the CPAP/PEEP knob from 0 to 30 cm H_2O.
   2. Frequency: adjusted between 5 and 15 Hz
   3. HFO amplitude. The HFO amplitude will depend on the respiratory characteristics of the tubing system and the respiratory system of the patient. The maximal oscillatory amplitude is 24 mL at 10 Hz.
   4. Inspiratory time. The inspiration time as a percentage of the total cycle time can be adjusted between 33 and 50 %.

XI. Mode map

Mode name	Mode classification				TAG
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	
Assist/control flow controlled	Volume	CMV	Set-point	N/A	VC-CMVs
Assist/control flow controlled with pressure limit	Volume	CMV	Dual	N/A	VC-CMVd
Controlled mandatory ventilation flow controlled	Volume	IMV	Set-point	Set-point	VC-IMVs,s
Controlled mandatory ventilation flow controlled with pressure limit	Volume	IMV	Dual	Set-point	VC-IMVd,s
SIMV flow controlled	Volume	IMV	Set-point	Set-point	VC-IMVs,s
SIMV flow controlled with pressure limit	Volume	IMV	Dual	Set-point	VC-IMVd,s
Assist/control pressure-controlled	Pressure	CMV	Set-point	N/A	PC-CMVs
Assist/control pressure-controlled with volume limitation	Pressure	CMV	Adaptive	N/A	PC-CMVa
SIMV pressure-controlled	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
SIMV pressure-controlled with volume limitation	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
High frequency oscillation	Time	IMV	Set-point	Set-point	TC-IMCs,s
Pressure support ventilation	Pressure	CSV	N/A	Set-point	PC-CSVs
Proportional assist ventilation	Pressure	CSV	N/A	servo	PC-CSVr
CPAP	Pressure	CSV	N/A	Set-point	PC-CSVs

XII. Pulmonary function diagnostics
   A. Different loops can be displayed and curves can be frozen to identify points of interested during a single breath and to calculate pulmonary mechanics, such as compliance, resistance, and time constant.
   B. Virtual occlusions of the endotracheal tube at the Wye-piece can be triggered when pushing the "occlusion" button. Depending upon the selection in the "OPTIONS" menu this occlusion may be end-inspiratory or end-expiratory.
      1. Inspiratory occlusion. End-inspiratory occlusion will usually elicit a Hering–Breuer reflex and results in temporary apnea, where intrapulmonary pressure is displayed at the end of the inspiratory phase to be used to calculate compliance after measuring the exhaled tidal volume after the occlusion.
      2. Expiratory occlusion. End-expiratory occlusion can be used to measure inadvertent PEEP.
      3. Pulmonary function. Within the menu "Measure" reference cursers can be activated to for further calculations of respiratory mechanics.

Sophie Ventilator

I. Introduction. The Sophie ventilator (Fritz Stephan GmbH, Gackenbach, Germany) was designed as a device for newborn and pediatric patients up to 25 kg bodyweight (Fig. 52.5). This review will focus only on its use in the neonatal population.
II. Description. The Sophie ventilator provides pressure-controlled ventilation, volume-targeted modes, and high frequency ventilation, as well as some pulmonary function diagnostic techniques.

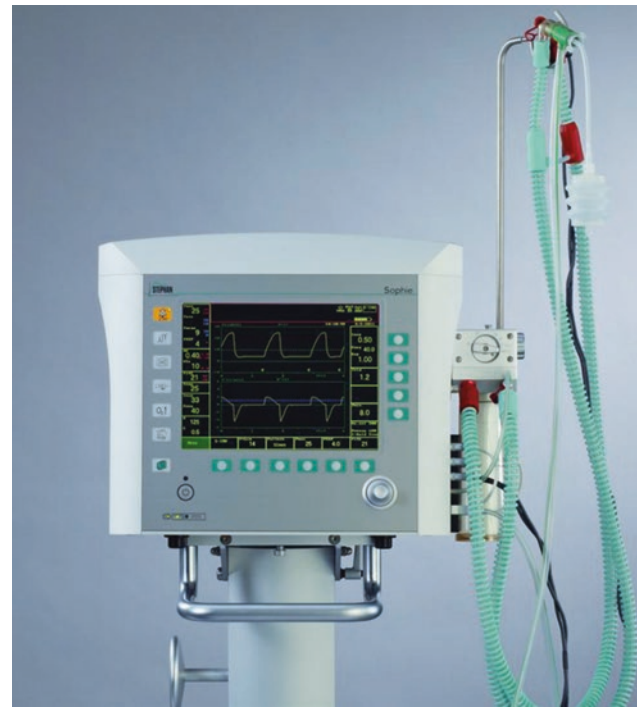

Fig. 52.5 Sophie ventilator

A. Several modes to trigger and to cycle off mechanical breaths are available.
B. A proximal flow sensor (pneumotachograph) can be used to detect patient effort and to provide flow-triggered synchronization for ventilator inflations as well as for proximal flow/volume measurements.
C. Synchronized ventilation can also be achieved by using pressure-triggered ventilation (drop in airway pressure induced by patient effort), or an external pressure capsule placed on the abdomen.
D. The Sophie has an integrated humidification system with heated tubes to prevent rainout with an automated refill system.
E. A 10.4″ color TFT screen allows visualization of respiratory parameters, graphics, and loops as well as measured data. Data outputs (RS232) are available for real time data export to patient data management systems.

III. Special Features:
A. Non-invasive ventilation is possible, which may be synchronized using an abdominal pressure capsule.
B. Back-up ventilation. Several back-up features for infants with variable respiratory drive are available. The interval until the back-up (called "apnea duration") is initiated is adjustable from 0.5 to 15 s. Furthermore, the user can choose between an instantaneous stopping of the back-up ventilation once the patient has resumed spontaneous breathing (standard back-up), and a more gradual reduction of back-up inflations (frequency controlled back-up), which may be particularly useful in infants with a more unstable breathing pattern and/or unstable FRC. The back-up may be initiated using flow during invasive ventilation, or by using an abdominal pressure capsule during non-invasive ventilation to detect apnea.
C. Pre-oxygenation: If the "Preoxy" button is pressed, a pre-configurable FiO_2 inspiratory oxygen concentration for a certain pre-set interval. The time can be set between 30 and 420 s, or switched off entirely.
D. SpO_2 controller (SPOC): An integrated, automatic SpO_2 Controller is available, which adjusts FiO_2 automatically depending on the measured SpO_2, called "Auto-FiO_2" to reduce variation of SpO_2 and to increase the patients' time with SpO_2 within the target range.
E. Pneumotachograph: Several pneumotachographs with different specifications are available: Type A (PNT A) is designed to measure air flow up to 10 LPM and has a dead space of 0.5 mL. PNT B is designed to measure up to 12 LPM, dead space 0.6 mL, and PNT C up to 25 LPM; dead space 0.9 mL.
F. A special pressure port supplies continuous airflow for nebulization of medications into the inspiratory limb of the patient circuit providing the same FiO_2 as in the regular patient circuit. If activated, the aerosol pressure line will deliver a constant gas flow, which will stop automatically after 5 min, if not turned off earlier manually.
G. Internal battery: automatically activated back-up for the loss of electric power with a minimum operating time of 60 min.

IV. Preparation for operation
A. Power supply should be connected for charging the internal battery at all times.
B. Connect gas supply (oxygen and pressurized air).
C. Fill the humidifier with distilled water. The humidifier may be filled manually, requiring regular refills. Alternatively, an automated refill system is available.
D. Connect the patient circuit to the ventilator. An expiratory filter has to be fitted between the expiratory limb and the ventilator to protect the valve system of the ventilator if nebulization of drugs is used (formation of crystals).

E. The entire "Ventilation menu" can be controlled by one central "push and turn" knob. Pup-up sub-menus appear once a specific mode is selected and allow entering all necessary settings.

V. Settings available
   A. Ti: 0.1–2 s
   B. Te: 0.1–60 s
   C. Vt: 2–150 mL (VtLim mode)
   D. $P_{max.}$: 5–60 cm H_2O
   E. PEEP: 0–30 cm H_2O
   F. Inspiration pattern: square wave, half sinus, and linear acceleration in pressure
   G. Trigger sensitivity
      1. Flow: 0.2–2.9 LPM, activated when inspiratory air flow exceeds the set threshold
      2. Pressure: 0.2–2.9 cm H_2O, activated as a differential pressure trigger (relative to PEEP)
      3. Pressure abdominal movement: 0.2–2.9 arbitrary units (available during non-invasive ventilation only)
   H. Gas temperature (33–39 °C)
   I. FiO_2 (0.21–1.0)
   J. PSV
      1. Expiratory trigger: 5–40 % peak flow
      2. Pressure of PSV breaths during SIMV/PSV: 0–100 % P_{max}
   K. High frequency oscillation
      1. Frequency: 5–15 Hz
      2. % Inspiratory time: 33–50
      3. Mean airway pressure: 0–30 cm H_2O
      4. Oscillatory amplitude max. 24 mL @ 10 Hz
   L. Inspiration hold: 1–7 s. Inspiration is maintained for the duration as long as this button is pushed. The max. inspiration hold time is user adjustable in the "Options." "Inspiratory Hold Time" menu (up to 7 s).

VI. Monitoring
   A. Almost all settings are monitored and displayed on the screen.
   B. Graphic monitoring
      1. Waveform display
         a. Airway pressure
         b. Flow
         c. Tidal volume
         d. Non-invasive pressure capsule signal
      2. Mechanics
         a. Volume–pressure loop
         b. Flow–volume loop
         c. Flow–pressure loop
      3. Trends
         a. Airway pressure, tidal volume, and air flow
         b. 0.5, 1, 2, 4, 12, 24 h trend intervals
      4. Pulmonary mechanics calculations (i.e., compliance of the respiratory system and resistance can be performed at the graphic display)

VII. Alarms/Limits: The alarm limits can be manually adjusted for each monitored item ("manual modify"), or automatically ("Auto modify"), where the device takes a certain value below and

above the currently measured value as the upper and lower limit. For more information see the operating manual.

A. Airway pressure (high/low)
B. End-expiratory pressure (high PEEP)
C. Mean airway pressure (high/low)
D. Expiratory minute ventilation (high/low)
E. Expiratory tidal volume (high/low)
F. Oscillatory amplitude (high/low)
G. Oscillatory tidal volume (high/low)
H. Oscillatory minute ventilation (high/low)
I. Inspiratory FiO_2 (high/low)
J. Gas temperature (high/low)
K. Disconnection
L. Water level humidification
M. Apnea

VIII. "Ventilation Menu" for initial choice of ventilator mode, Sophie offers pressure-controlled ventilation. Volume-controlled ventilation is not available. However, there is an option to limit tidal volume (called "Volume-limitation," or "volume-guarantee ventilation"). If "Vt Lim" is set, the volume will be targeted by adjusting the peak pressure.

A. A linearly increasing pressure profile [from the PEEP level to peak inspiratory pressure (PIP)], or a "half sinus" pressure profile (steep pressure increase from PEEP initially, with a plateau towards the end of the inspiratory time to reach the desired PIP), or a "square" profile (immediate increase of airway pressure to PIP to be maintained at this level for the rest of the inspiratory time) can be chosen by the clinician.
B. The half-sinus and the square wave pressure profile can be chosen without the pneumotachograph in place. However, no flow/tidal volume monitoring or flow-triggered ventilation is possible in this situation.
C. Volume varies with changes in pulmonary compliance and airway resistance.

IX. Modes for Triggering and Cycling off Ventilator Breaths

A. General comment. Synchronized breaths can be triggered using airflow, pressure trigger, or using the abdominal pressure. The abdominal capsule can be used during invasive and non-invasive modes. The thresholds can be adjusted for flow (0.2–2.9 LPM), pressure (0.2–2.9 cm H_2O), and with the pressure capsule (arbitrary units).
B. Assist/Control (A/C)
   1. If the patient triggers the ventilator with a spontaneous effort, an assisted breath with given characteristics (i.e., inspiratory time, pressure- or volume-controlled) is delivered. The rate of mechanical inflations is controlled by the patient's respiratory rate. After every triggered breath the trigger is suppressed for 200 ms.
   2. A back-up rate may be chosen to support the patient if effort/spontaneous respiratory rate decreases below the back-up rate (safety cushion).
C. Synchronized intermittent mandatory ventilation
   1. A pre-set number of controlled breaths are delivered (i.e., they are mandatory), whenever the patient effort occurs within a pre-specified synchronization window. This window opens 2 s before the end of expiration, or at the second half of the calculated expiration time, if it is <4 s.
   2. If the patient's spontaneous effort triggers the ventilator above the set control rate, the additional breaths will be spontaneous.
D. Assist/Control and SIMV with inspiratory time termination [ITT(PSV)]

1. During Assist/Control and during SIMV the operator can activate inspiratory time termination (ITT), which "cycles-off" the ventilator breath once the inspiratory flow has decreased to a certain percentage ("KV %", adjustable from 5 to 40 %) of the peak inspiratory flow rate rather than after the set inspiratory time (flow-cycling).
2. This mode is identical to PSV and may reduce the risk of gas trapping at higher rates. Flow-cycling enables complete synchronization between the baby and ventilator.

E. SIMV with ITT and Pressure Support
1. SIMV permits spontaneous breaths between the mandatory inflations, which can receive additional ventilator (pressure) support.
2. The degree of pressure support is adjusted with the "PPSV%" setting, which is adjustable within the range of 0–100 % of the set P_{max}.
3. If the peak pressure of the mandatory/assisted inflations is reduced by the volume limitation (volume guarantee) mode, the supporting pressure for spontaneous breaths is automatically adjusted to this new inflation pressure.

X. Modalities of Ventilation
A. Volume controlled modalities: are not available in the Sophie. However, volume-targeted ventilation may be achieved using pressure-controlled modes with volume limitation (see below).
B. Pressure-controlled modalities:
1. Continuous positive airway pressure
a. During CPAP the patient is breathing spontaneously with a set continuous positive airway pressure. The Sophie compensates for pressure level changes from leaks by providing additional flow. This leak compensation can be limited by the operator to 6–20 LPM. CPAP can be adjusted between 0 and 30 cm H_2O.
b. CPAP may be combined with back-up ventilation to provide (synchronized) ventilator breaths to compensate for irregular breathing (apnea). The apnea duration (ApD) for the back-up to start can be adjusted from 4 to 16 s. With standard back-up (BU) the first spontaneous breath that exceeds the set trigger threshold, stops back-up ventilation. A special "frequency controlled backup" mode is available which allows a more gradual withdrawal of back-up breaths if the baby starts breathing within a predefined (10, 30, or 60 s) BUD. Any spontaneous breath within this period will reduce the back-up frequency gradually to 1/3 of the set back-up rate. The duration of back-up is at least 5× the BUD. Back-up breaths can be synchronized.
2. Intermittent mandatory ventilation
a. The ventilator provides a pre-set rate and pre-set inspiratory time. The patient cannot actively influence the timing of these ventilator breaths.
b. In the pressure-controlled mode the tidal volume depends upon the characteristics of the respiratory system of the patient. During the expiratory phase the patient can take additional spontaneous breaths, which are not synchronized.
c. The gas flow in the patient circuit is continuous but will vary if leaks occur. The pressure profile (3 choices) can be adjusted. The ventilator adjusts the flow needed to obtain the desired profile, even in the presence of leak by increasing the circuit flow.
3. Volume-limited pressure-controlled ventilation
a. This mode is a volume-targeted approach. The inspiratory pressure increase/decrease is adjusted automatically in steps of 2 cm H_2O until the target volume is reached (measured as the expiratory tidal volume of the preceding breath). The minimum peak inspiratory pressure will be PEEP + 4 cm H_2O.

b. The mode is activated by adjusting "Vt Lim" to the desired value. The "P_{max}" is used to set the maximal pressure allowed. In general, a Vt target of 3–6 mL/kg is chosen during this mode.
c. Leaks up to 50 % can be compensated.

4. Assist-control, SIMV and pressure support (PS): see above
5. Non-invasive (nasal) CPAP (NCPAP)
   a. During non-invasive modes, intermittent larger leaks may lead to a drop in airway pressure and may overwhelm the capacity of the humidification system and lead to abdominal distension. The operator can limit the maximum flow to 6–20 LPM ("MaxV'").
   b. Apnea monitoring is available and back-up NIPPV is automatically activated after an (adjustable) apnea duration of 4–16 s (standard back-up). Frequency-controlled back-up (FBU) with reduction of IPPV every 10/30/60 s (adjustable) is available.
6. Non-invasive positive pressure ventilation (SNIPPV)
   a. Non-invasive modes of ventilation are available, including non-invasive triggering using the abdominal pressure capsule. This signal can be displayed on the screen. To activate synchronization, the trigger threshold (Trig) must be set.
   b. The trigger is suppressed for 150 ms after the end of inflation.
   c. "Expiratory Cycling" of the external trigger can be (de)activated. If the pressure is not rising any more in the abdominal pressure capsule, the mechanical inflation will be terminated, even before the end of the inspiratory time set by the clinician. If this change in pressure rise is not detected, inflation will end by the end of the set inspiratory time. The peak pressure delivered to the lung may be lower than the desired peak pressure because of a loss of gas (and pressure) secondary to large leaks.
   d. SNIPPV-B (SNIPPV with back-up) results in SNIPPV with the rate controlled by the patient. In case of apnea, back-up is activated if the apnea duration (ApD) is set to 4–16 s.

C. High frequency oscillatory ventilation
1. Mean airway pressure is adjusted using the CPAP pressure from 0 to 30 cm H_2O.
2. Frequency. The frequency can be adjusted in the sub-menu (5–15 Hz).
3. HFO amplitude. The HFO amplitude can be adjusted in the sub-menu. The actual amplitude (measured in airway pressure change) will depend upon the respiratory characteristics of the tubing and the respiratory system of the patient. The maximal oscillatory amplitude is 24 mL st 10 Hz.
4. Inspiratory time. The inspiration time as a percentage of the total cycle time can be adjusted in the "Options" "HFO" menu from 33 to 50 %.
5. HFO can be combined with IMV ("HFO-IMV").

XI. Mode Map

	Mode classification				
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
Assist/control pressure-controlled	Pressure	CMV	Set-point	N/A	PC-CMVs
Assist/control pressure-controlled with volume limitation	Pressure	CMV	Adaptive	N/A	PC-CMVa
Assist/control pressure-controlled with inspiratory time termination	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
SIMV pressure-controlled	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
SIMV pressure-controlled with volume limitation	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
High frequency oscillation	Time	IMV	Set-point	Set-point	TC-IMCs,s
Pressure support ventilation	Pressure	CSV	N/A	Set-point	PC-CSVs
CPAP	Pressure	CSV	N/A	Set-point	PC-CSVs

XII. Pulmonary function diagnostics
   A. Graphics and loops can be displayed and frozen at points of interested during a single breath and to calculate pulmonary mechanics, such as compliance, resistance, and time constant.
   B. Pulmonary function. Reference cursors can be activated to examine values on the graphics display for further calculations of respiratory mechanics.

XIII. SpO_2 Controller (SPOC) for automated FiO_2-Control (Auto-FiO_2) (Chap. 60)
   A. General description:
      1. An integrated, automatic SpO_2 Controller is available, which adjusts FiO_2 automatically depending on the measured SpO_2, reduces variation of SpO_2, increases the patient's time with SpO_2 within the target range, and reduces the number of necessary FiO_2 adjustments by the staff.
      2. SPOC uses SpO_2 as measured by pulse oximetry and adjusts the actual FiO_2 setting every 2 s. In general, pre-ductal SpO_2 (sensor placed at the right arm of the patient) is recommended. It takes into consideration the SpO_2 target range (adjusted by the clinician), and the actual FiO_2 (initially adjusted by the clinician) and re-adjusts automatically thereafter. If the measured SpO_2 is higher than the target, the FiO_2 will be decreased and vice versa. The SPOC systematically analyzes trends and re-adjusts FiO_2 even before the upper and lower limits of the target range are crossed. Therefore, it anticipates necessary changes in FiO_2 much earlier than a caregiver would do when responding to a neonate with the SpO_2 crossing certain alarm limits, and allows for implementation of any necessary changes of FiO_2 earlier compared to routine clinical care.
      3. SPOC uses a PID-controller (P = proportional, I = integral, D = differential). If SpO_2 falls far off the target range (looking at the difference), the response of SPOC is more pronounced. The history of this difference and the speed of change are taken into account as well for the response.
      4. In case of malfunction of the pulse oximetry signal the system will alarm and adjust the FiO_2 to an clinician-selected back-up FiO_2.
      5. If CPAP is used with back-up ventilation, SPOC can initiate back-up breaths not only with apnea, but also with the SpO_2 crossing the lower target as well.
   B. Activation of Auto-FiO_2
      1. The output of the pulse oximeter has to be connected to the Sophie. Several pulse oximeters are approved by the manufacturer of the Sophie for use in the Auto-FiO_2 mode.
      2. If Auto-FiO_2 is activated in the main menu, the left half of the screen is used to monitor trends (airway pressure, FiO_2, and SpO_2). The graphics of the right panel can be adjusted according to user preferences.
      3. An upper and lower limit of the SpO_2 target, the actual FiO_2, and the back-up FiO_2 have to be chosen by the clinician. Then, SPOC is started by activating "Auto-FiO_2."
      4. Since SPOC will adjust FiO_2 automatically, an alarm will notify the caregivers if the average FiO_2 shows an increasing trend.
   C. Special considerations
      1. If "Pre-oxygenation" is activated during use of SPOC, the increase in FiO_2 secondary to pre-oxygenation will be terminated early if SpO_2 is >88 % for more than 10 s.
      2. Caregivers can override SPOC at all times. If this is done in the usual way, the SPOC software asks if the caregiver wants to override Auto-FiO_2, and the caregiver must respond with "yes," if he/she wants to do so.
   D. Special considerations with noninvasive ventilation modes
      1. If CPAP is used along with Auto-FiO_2, desaturation events can be treated by a combined approach using Auto-FiO_2 and back-up ventilation.

2. If CPAP with regular back-up (CPAP-BU) is used along with Auto-FiO_2, the back-up ventilation will be activated if the SpO_2 drops below the lower target range (even without apnea), and switched off once the SpO_2 is above the lower target range and the patient has spontaneous respiratory activity.
3. IF CPAP is used with frequency-controlled back-up along with Auto-FiO_2, and the SpO_2 drops below the lower target range, back-up with 2/3 of the set ventilator rate is activated. If SpO_2 increases above the lower target range, weaning of the back-up rate will be accelerated. If SpO_2 increases to the mean of the target range, back-up will be stopped. In summary, apnea initiates back-up with a higher back-up rate, whereas SpO_2 triggered back-up leads to a more moderate back-up response.

Suggested Reading

Bhat P, Patel D-S, Hannam S, et al. Crossover study of proportional assist versus assist control ventilation. Arch Dis Child Fetal Neonatal Ed. 2015;100:F35–8.

Chatburn RL, Khatib ME, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

Herber-Jonat S, Rieger-Fackeldey E, Hummler H, et al. Adaptive mechanical backup ventilation for preterm infants on respiratory assist modes- a pilot study. Intensive Care Med. 2006;32:302–8.

Huang L, Mendler MR, Waitz M, et al. Effects of synchronization during noninvasive intermittent mandatory ventilation in preterm infants with respiratory distress syndrome immediately after extubation. Neonatology. 2015;108:108–14.

Hummler H, Schulze A. New and alternative modes of mechanical ventilation in neonates. Semin Fetal Neonatal Med. 2009;14:42–8.

Reyes ZC, Claure N, Tauscher MK, et al. Randomized, controlled trial comparing synchronized intermittent mandatory ventilation and synchronized intermittent mandatory ventilation plus pressure support in preterm infants. Pediatrics. 2006;118:1409–17.

Schulze A, Bancalari E. Proportional assist ventilation in infants. Clin Perinatol. 2001;28:561–78.

Schulze A, Rieger-Fackeldey E, Gerhardt T, et al. Randomized crossover comparison of proportional assist ventilation and patient-triggered ventilation in extremely low birth weight infants with evolving chronic lung disease. Neonatology. 2007;92:1–7.

Shetty S, Bhat P, Hickey A, et al. Proportional assist versus assist control ventilation in premature infants. Eur J Pediatr. 2016;175:57–61.

Leoni Plus Ventilator

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Felix Neunhoeffer and Christian F. Poets

I. Introduction

The LEONI PLUS ventilator (Heinen+Löwenstein, Bad Ems, Germany) is a pressure control ventilator designed for long-term ventilator support of preterm and term neonates and infants up to 30 kg body weight. Here, we will focus only upon neonatal applications.

II. Description

A. For the neonatal population the basic pressure control modes IPPV/IMV, SIPPV, SIMV, and CPAP are available.

B. A volume-targeted tidal volume guarantee mode is available in pressure assisted ventilation modes.

C. A volume limit function can be used to limit delivered tidal volume in modes that deliver mandatory breaths (i.e., machine triggered or machine cycled).

D. The device also features PSV ventilation modes and separate nCPAP and nIPPV modes for non-invasive respiratory support.

E. An integrated high frequency module of the diaphragmatic type can be used with standard ventilator tubes.

1. The frequency range is between 5 and 20 Hz.
2. Amplitude control is regulated and compensates for any leak or change in compliance.

F. The proximal hot-wire flow sensor enables flow-triggered synchronization of all ventilator breaths, volume measurements, and automatic readjustment of trigger sensitivity relative to the patient‘s tidal volume.

G. Control of the device can be either from a 12 inch color touch screen display or using a control knob. All essential settings, readings, alarm limits, and graphic information such as simultaneous display of up to three curves and two loops are available.

H. Triggered spontaneous breaths are displayed.

I. An internal battery provides backup for the loss of electric power for up to 2 h.

J. A novel closed-loop automatic oxygen controller is available as an optional feature.

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III. Internal Graphic Monitoring
  A. Waveforms and loops
    1. Flow
    2. Pressure
    3. Volume
    4. Flow/pressure
    5. Volume /pressure
    6. Flow/volume
  B. Mechanics
    1. Pressure–volume loop
    2. Flow–volume loop
  C. Trends: up to 72 h data storage and display
    1. Pressure
    2. Frequency
    3. Minute volume
  D. Pulmonary mechanics calculations
    1. Compliance and C_{20}/C ratio
    2. Resistance
    3. Gas transport coefficient (DCO_2)

IV. Alarms
  A. Low minute volume (LPM)
  B. High minute volume (LPM)
  C. High Vt_e (mL)
  D. Leak (%)
  E. High rate (bpm)
  F. Apnea interval (sec)
  G. Low P_{peak} (cm H_2O)
  H. High P_{peak} (cm H_2O)
  I. Low CPAP (cm H_2O)
  J. High CPAP (cm H_2O)
  K. Low FiO_2 (%)
  L. High FiO_2 (%)

V. Modalities of Ventilation
  A. Intermittent positive pressure ventilation (IPPV) (PC-CMVs): Continuous mandatory ventilation. A pre-set number of control breaths are delivered. Ventilation follows a pattern set by the ventilator without reference to any spontaneous breathing by the patient. Spontaneous breaths between mandatory breaths become possible if the expiratory time is set >1.5 s.
  B. Intermittent mandatory ventilation (IMV) (PC-IMVs,s): Additional spontaneous breaths are possible between mandatory breaths.
  C. Synchronized intermittent positive pressure ventilation (S-IPPV) (PC-IMVs,s): The respirator rate depends on the patient's breathing effort. All breaths are supported with the pre-set parameters by the ventilator. In case of apnea, ventilation is carried out at a pre-set rate.
  D. Synchronized intermittent mandatory ventilation (S-IMV) (PC-IMVs,s): A pre-set number of control breaths are delivered. Inspiratory effort of the patient within the trigger window starts with inspiration. Breaths within each trigger window are supported by variable pressure support. In case of apnea ventilation is carried out with a pre-set respiratory rate.
  E. Pressure support ventilation—Synchronized intermittent positive pressure ventilation (PSV-SIPPV) (PC-IMVs,s): Every breath is supported by the ventilator. The patient initiates the

mechanical breath (inspiration trigger) and the inspiration ends at 25 % of the peak inspiratory flow rate rather than the set inspiratory time. In case of apnea, ventilation is carried out with a pre-set respiratory rate.

F. Pressure support ventilation—Synchronized intermittent mandatory ventilation (PSV-SIMV) (PC-IMVs,s): Breath is patient-triggered like PSV-SIPPV. The ventilator only supports the pre-set respiratory rate. In case of apnea, ventilation is carried out at a pre-set respiratory rate.

G. Continuous positive airway pressure (CPAP) (PC-CSVs): CPAP is achieved by continuous gas flow through the circuit with expiratory resistance to provide the desired pressure in the intubated patient. Back-up ventilation can be chosen.

H. Nasal continuous positive airway pressure (nCPAP) (PC-CSVs): Continuous gas flow through the circuit with expiratory resistance to provide the desired pressure in the non-intubated patient via the patient interface.

I. Nasal intermittent positive pressure ventilation (nIPPV) (PC-CMVs): Continuous mandatory ventilation via patient interface. A pre-set number of control breaths are delivered without synchronization.

J. High frequency oscillation (HFO) (PC-IMVs,s): Spontaneous breathing is possible.

VI. Mode Map (Table 53.1)

VII. Special Features

A. Volume guarantee (V_{TG}): The ventilator automatically adjusts inspiratory pressure to achieve an average pre-set tidal volume (i.e., adaptive targeting). May be very useful in attempting to control ventilation in the treatment of patients with changing compliance.

Table 53.1 Mode Map

	Mode classification				
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
Intermittent positive pressure ventilation	Pressure	CMV	Set-point	N/A	PC-CMVs
Synchronized intermittent positive pressure ventilation	Pressure	CMV	Set-point	N/A	PC-CMVs
Synchronized intermittent positive pressure ventilation with volume guarantee	Pressure	CMV	Adaptive	N/A	PC-CMVa
Nasal intermittent positive pressure ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Intermittent mandatory ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Synchronized intermittent mandatory ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure support ventilation—synchronized intermittent positive pressure ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Pressure support ventilation—synchronized intermittent mandatory ventilation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
High frequency oscillation	Pressure	IMV	Set-point	Set-point	PC-IMVs,s
Synchronized intermittent mandatory ventilation with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure support—synchronized intermittent positive pressure ventilation with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
Pressure support—synchronized intermittent mandatory ventilation with volume guarantee	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
High frequency oscillation	Pressure	IMV	Adaptive	Set-point	PC-IMVa,s
CPAP	Pressure	CSV	N/A	Set-point	PC-CSVs
Nasal CPAP	Pressure	CSV	N/A	Set-point	PC-CSVs

B. Volume limitation ($V_{T\,limit}$): If the pre-set tidal volume is exceeded, the ventilator stops inspiration to avoid volume trauma (i.e., volume cycling of pressure controlled mandatory breaths).
C. Closed-loop automatic oxygen control
   1. The controller algorithm is based on a time-oriented data abstraction method, capable of deriving steady qualitative descriptions from oscillating data (e.g., SpO_2). It tends to level out SpO_2 fluctuations, thereby keeping SpO_2 in a pre-defined target range.
   2. Data are analyzed in time windows and qualified as too high, too low, or within target.
   3. The target range is further subdivided into an upper, middle, or lower target range.
   4. According to this qualification, five different FiO_2 adjustments are made (−0.02, −0.01, ±0, +0.02, +0.05).
   5. Each adjustment is followed by a wait-and-see period of 180 s during which the controller software does not affect further changes.
   6. In case of low SpO_2 values, the algorithm changes into an "alarm" mode, signals this condition, and suspends further adjustments until the SpO_2 values are again above the critical limit.

Bunnell Life Pulse High-Frequency Jet Ventilator

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Martin Keszler

I. The Bunnell Life Pulse® is the only Food and Drug Administration (FDA)-approved neonatal HFJV device currently available in the USA. Other HFJV devices manufactured abroad have been used in Europe and elsewhere.
II. The Life Pulse is a microprocessor-controlled time-cycled, pressure-controlled infant ventilator that continuously monitors airway pressure and automatically adjusts the pressure that drives pulses of gas through the injector cannula to achieve the set peak inflation pressure measured at the proximal endotracheal tube.
III. Small pulses of heated, humidified gas are injected into a special endotracheal tube adaptor (LifePort®); the pulses are generated by a pinch valve inside a patient box located close to the airway. This arrangement minimizes dampening of the pulses and allows more effective pulse delivery with unimpeded exhalation.
IV. The pressure transducer for monitoring proximal airway pressure (which approximates tracheal pressure) is also located in the patient box, resulting in a higher fidelity signal.
V. Intermittent puffs of gas purge any condensation or secretions and maintain patency of pressure monitoring line.
VI. Independently set variables:
    A. Peak inflation pressure (PIP, range 8–50 cm H_2O)
    B. Ventilator rate (240–660 cycles/min = 4–11 Hz)
    C. Jet valve "on" time [i.e., inspiratory time (T_i)], range 0.02–0.034 s
VII. PEEP and superimposed low rate IMV (when desired) are generated by a conventional ventilator used in tandem with the Life Pulse through a conventional ventilator circuit attached to the top of the LifePort® adapter.
VIII. Mean airway pressure, which is abbreviated MAP on this device, is not set directly; it is controlled primarily by adjusting PEEP. Because the I:E ratio is very short, the MAP is much closer to PEEP than to PIP. In order to achieve adequate MAP in sicker infants, PEEP levels higher than those commonly used with conventional ventilation are often needed.

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IX. ΔP or pressure amplitude is set indirectly by adjusting PIP and PEEP. Beware of inadvertent decrease in MAP when lowering PIP in order to reduce ΔP. PEEP may need to be increased at the same time as decreasing PIP, so that MAP is not lowered inadvertently.

X. The FiO_2 of the two ventilators may be adjusted separately (it should be maintained at the same level), or both ventilators can be supplied from a common source using a single blender (preferable).

XI. Displayed parameters
   A. PIP (cm H_2O)
   B. ΔP = Pressure amplitude (cm H_2O)
   C. PEEP (cm H_2O)
   D. MAP = Mean airway pressure (cm H_2O)
   E. Servo pressure (pounds/square inch, PSI)
   F. I:E ratio (this is determined by the Jet valve on time and rate)

XII. The ventilator will go through a self-check when the "Test" button is pressed to ensure all components are functioning and the circuit is intact. This should always be done when the device is initiated.

XIII. The ventilator settings start with default values of PIP 20 cm H_2O, rate 420 (7 Hz) and valve on time of 0.02 s when the device is activated; these, along with the resulting I:E ratio, will be displayed in the "NOW" row in the control panel.

XIV. The user selects "NEW" settings in the row below and activates them by pressing the "Enter" button. Please see Chap. 37 for recommended settings under a variety of circumstances.

XV. Once the measured values stabilize and the Life Pulse reaches the "Ready" state, the Servo Pressure upper and lower alarm limits, displayed in the upper right-hand side of the front panel, are automatically set 20 % above and below current levels for Servo Pressure when Servo Pressure is in the usual range of 1–5 PSI. When Servo Pressure is <1 PSI the limits are ± 0.2 and when >5 the range is ± 1 PSI. The MAP alarm limits are automatically set at ±1.5 cm H_2O. Subsequently, the alarm limits can be adjusted manually, if desired.

XVI. As a safety feature, the Servo Pressure is locked at its current value when the MAP or Servo Pressure alarm is activated. The patient will remain ventilated with that same Servo Pressure until one of the following occurs:
   A. The pressures return to the target range.
   B. The alarm limits are changed.
   C. The Reset button is pressed (not recommended until troubleshooting of the situation is done, to ensure safe operation).
   D. Settings are changed and the Enter button is pushed.

XVII. Servo Pressure or MAP alarms may resolve spontaneously if the pressures return to the target range; if the alarm condition persists, the clinician needs to examine the patient, circuit, and ventilator and correct the condition that initiated the alarm to re-establish servo-control of PIP.

XVIII. It is essential to understand the meaning of changes in Servo Pressure and to evaluate the circuit and patient before proceeding.

XIX. When more gas volume is needed to reach the set PIP, Servo Pressure increases.
   High Servo Pressure may result from the following:
   A. Improved lung compliance/increased lung volume
   B. Leak in the circuit (large leak around endotracheal tube, accidental extubation, partial disconnect, and cracked connector)
   C. Increased leak through a bronchopleural fistula

D. Partial kinking of the patient circuit (partial obstruction of jet line)
E. Partial occlusion of the pressure line leading to dampened pressure reading

XX. When less gas volume is needed to reach set PIP, Servo Pressure decreases. Low Servo Pressure may result from:
A. Worsening lung compliance (atelectasis, tension pneumothorax)
B. Right main bronchus intubation
C. Obstruction of endotracheal tube (e.g., secretions)
D. Increased airway resistance

XXI. Additional alarm messages include
A. Jet valve fault
B. Ventilator fault
C. Low gas pressure (supply gas)
D. Cannot meet PIP
E. Loss of PIP
F. High PIP

XXII. The ventilator must be in the "Ready" state with the "Ready" light illuminated before the system is stable, alarms are set, and it is safe to leave the bedside after any change in settings or after the "Reset" button is pressed.

XXIII. The "Ready" state occurs when the PIP has stabilized for 20 s within +2.0 and −1.5 cm H_2O of the set PIP. If the "Ready" condition is not met 3 min after the ENTER or RESET button is pushed, the CANNOT MEET PIP alarm will result.

XXIV. Like any servo-controlled device, the actual PIP will fluctuate around the set value, especially when the patient is breathing actively.

XXV. The "Silence" and "Reset" buttons are located close together. They serve a different function.
A. Use the "Silence" button as the primary button to silence the ventilator alarm while troubleshooting.
B. "Reset" should be reserved for:
1. Establishing new alarm limits after a change in the backup IMV setting that activates an MAP or Servo Alarm.
2. The rare situation when the ventilator has not been able to reach steady state and activate the "Ready" button secondary to a leak or partial disconnection.

XXVI. An efficient low volume humidifier is built into the device/patient circuit, assuring optimal heating and humidification of inspired gases.

XXVII. The humidifier panel allows the user to independently set the cartridge and circuit temperature within the range of 32–42 °C.

XXVIII. A water pump automatically maintains an optimal water level in the humidification cartridge.

XXIX. Temperature of the gas as it leaves the patient circuit is continuously displayed. Cartridge and circuit temperatures can be displayed by pressing the "Set" button on the humidifier panel.

XXX. Optimal positioning of the patient and endotracheal tube (ETT) are extremely important when using HFJV, because of its unique mechanism of gas flow. With HFJV, ventilating gas emerges at high velocity from the ETT and penetrates the center of the airway with minimal pressure being applied to the lateral wall, hence the ability to ventilate effectively in the presence of airway disruption. As the gas flows in, it displaces some of the gas resident in the upper airway, creating simultaneous rotational expiratory flow along the outer wall of the

trachea, resulting in clearance of secretions or aspirated material. Optimal effectiveness of HFJV depends on the jet stream penetrating the airway in an unobstructed manner.

A. Ensure that the ETT is at least 1 cm above the carina with the bevel of the tube facing anteriorly to avoid the jet stream hitting the carina, or preferentially ventilating one of the mainstem bronchi.
B. Position the infant's head midline to ensure that the ETT is aligned with the long axis of the trachea and the jet stream does not hit the wall of the trachea.

XXXI. Suctioning can be done in one of two ways.

A. The jet ventilator can be placed in STANDBY mode and suctioning done in the usual fashion, resuming ventilation as soon as possible by pressing the Enter button.
B. Alternately, suctioning may be done with the ventilator continuing to operate and constant (continuous) suction is applied while the suction catheter is withdrawn. The jet gas delivery will be partially obstructed, but may still generate enough pressure in the ETT to cause the ventilator to sense overpressure and pause gas delivery with a loud click signaling that Servo Pressure has been momentarily vented to the atmosphere. Ventilation will resume as soon as ETT pressure returns to normal. This method is NOT RECOMMENDED FOR ROUTINE USE, but may be useful in unstable infants who may not tolerate the reduction in support after suctioning while the ventilator is working up to set pressures.

XXXII. Inhaled nitric oxide can be safely and effectively delivered via the Life Pulse ventilator by splicing the INOmax® DS Injector Cartridge into the high-pressure line between the ventilator and the humidification cartridge and attaching the monitoring line to a T-connector inserted in the jet gas delivery line distal to the pinch valve.

XXXIII. Clinicians in the USA should be aware that the FDA has only approved the Life Pulse for treatment of pulmonary interstitial emphysema and for rescue of infants with refractory respiratory failure complicated by air leak.

Suggested Reading

Bunnell Life Pulse Ventilator Quick Start Guide. http://www.bunl.com/quick-start-guide.html.

Bunnell Life Pulse User Manual. http://www.bunl.com/uploads/4/8/7/9/48792141/inservicemanual.pdf.

Harris TR, Bunnell JB. High-frequency jet ventilation in clinical neonatology. In: Pomerance JJ, Richardson CJ, editors. Neonatology for the clinician Norwalk. Appleton & Lange, 1993.

Keszler M, Pillow JJ, Courtney SE. High-frequency ventilators. In: Rimensberger P, editor. Neonatal and pediatric mechanical ventilation: from basics to clinical practice. Springer; 2011.

High Frequency Oscillatory Ventilators

55

David G. Tingay

I. Physiology of high frequency oscillatory ventilation (HFOV) (Chaps. 41 and 43)
   A. Conceptual difference between conventional and high frequency ventilation
      1. With conventional ventilation, gas is moved from the upper airway to the alveoli primarily by *bulk flow* (tidal volumes pushed into and out of the alveoli).
      2. With HFOV, gas movement is achieved via a number of additional mechanisms including *mixing* of gas in the upper airway with gas in the alveoli ("shaking gas into and out of the alveoli"), pendelluft, and diffusion.
      3. Practically, unlike conventional ventilation, airway pressure transmission is attenuated through the respiratory tree between the ventilator and the alveoli during HFOV.
   B. Characterizing high frequency oscillatory (HFO) ventilators
      1. HFO ventilators can be defined by the type and method of pressure and flow wave measured at the proximal endotracheal tube. These can be considered as square or sine (triangular) waves. At an alveolar level all devices deliver some form of a sine wave. The waveform harmonics are broader and more complex with a square wave, especially at higher frequencies.
         a. The Sensormedics 3100A and 3100B are the only dedicated HFO ventilators, all other devices are hybrid devices offering conventional and high frequency ventilation options.
         b. Table 55.1 summarizes the characteristics of the different HFO ventilators available.
      2. For all devices the pressure wave is characterized by four factors, each of which can be independently adjusted.
         a. Mean airway pressure (the "average" pressure delivered to the lung throughout the respiratory cycle).
         b. Amplitude (the difference between peak inspiratory and end-expiratory pressure wave, or "height"), the principal determinant of tidal volume.

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Table 55.1 Summary of current neonatal high frequency oscillators (*Information correct as of 1 Jan 2016*)

Ventilator	Manufacturer	Principle of operation	HFOV waveform	DCO/V_T monitoring	VTV	Manufacturer stated specifications				
						Maximum weight	Maximum P_{AW} (cm H_2O)	Frequency range (Hz)	Maximum amplitude (cm H_2O)	I:E ratio
Fabian HFO	Acutronic (Switzerland)	Voice coil flow generator	Sine	Yes	No	30 kg	80	5–20	80	1:1–1:3
Sensormedics 3100A	CareFusion (USA)	Electromagnetic flow generator	Square	No	No	35 kg	45	3–15	90	1:1–1:2
Sensormedics 3100B	CareFusion (USA)	Electromagnetic flow generator	Square	No	No	>35 kg	45	3–15	90	1:1–1:2
VN500	Drägerwerk (Germany)	Expiratory valve with venturi-assisted expiration	Sine	Yes	Yes	7 kg	40	5–20	90	1:1–1:3
BabyLog 8000+	Drägerwerk (Germany)	Expiratory valve with venturi-assisted expiration	Sine	Yes	No	4 kg[a]	30	5–20	% max[b]	1:1–1:5
Leonie+	Heinen+Löwenstein (Germany)	Membrane integrated diaphragms	Sine	Yes	Yes	8 kg	40	5–20	100	1:1–1:3
SLE5000	SLE (UK)	Bi-Directional Jets	Square	Yes	No	20 kg	45	3–20	180	1:1–1:3
Sophie	Stephan (Germany)	Valve oscillator with active expiration	Sine	Yes	Yes	6 kg	30	5–20	% max[b]	1:1–1:3

VTV volume targeted ventilation mode, *DCO* diffusion coefficient of CO_2 (Frequency × V_T^2), V_T tidal volume, P_{AW} mean airway pressure

[a]Practical maximum weight 2 kg

[b]Amplitude expressed as a % of maximum possible for specific settings and patient characteristics, maximum reported amplitude in vivo settings; Sophie 80 cm H_2O and BabyLog 8000+ 35 cm H_2O (see Tingay et al. Neonatology 2015;108:220–228)

c. Frequency (the number of inflations per minute).
d. The inspiratory:expiratory (I:E) ratio. Usually 1:2 or 1:1 for most neonatal patients. Tidal volume is higher with a 1:1 ratio but expiratory time is shorter.

C. Oxygenation and ventilation
1. Oxygenation is proportional to mean airway pressure.
   a. Increasing mean airway pressure increases lung volume.
   b. The higher the mean airway pressure, the more alveoli are open throughout the respiratory cycle. This decreases atelectasis and improves ventilation/perfusion matching.
   c. Excessive mean airway pressures (above the upper inflection point of the pressure–volume relationship) may cause overdistension and impaired cardiac output with worsening oxygenation.
2. Ventilation (or CO_2 removal) is approximately proportional to (Frequency) × (Tidal Volume)^2.
   a. Tidal volume is determined by the stroke volume, and related to the size and duration of the pressure amplitude. Thus, CO_2 removal can be considered as (Frequency) × (Amplitude)^2.
   b. This means that small changes in amplitude have a greater impact on CO_2 exchange than do changes in frequency.
   c. For most patients, a frequency is chosen for the patient size and lung disease, and left constant, while CO_2 exchange is affected by changing the amplitude.
   d. I:E ratio influences the width of the pressure amplitude but, practically, is not altered often.
   e. When CO_2 clearance is not responding as expected to amplitude changes, the appropriateness of frequency and I:E ratio settings should be considered.
3. Effect of frequency on amplitude.
   a. The endotracheal tube and upper airway act as a *low pass filter*. This means that low frequency pressure waves are passed from the ventilator to the alveoli without being attenuated, while high frequency pressure waves are attenuated. The higher the frequency, the greater the attenuation.
   b. A simplified example of the attenuation of pressure amplitude at high frequencies is outlined below. Imagine a ventilator that is set to deliver an amplitude of 20 cm H_2O (e.g., PIP 25 cm H_2O, PEEP 5 cm H_2O).
      (1) At a low frequency (e.g., 30 inflations per minute; 0.5 Hz), this pressure amplitude of 20 cm H_2O is completely transmitted to the alveoli. The alveolar pressure changes from 5 to 25 cm H_2O as the ventilator cycles.
      (2) At an intermediate frequency (e.g., 120 inflations per minute; 2 Hz), the pressure amplitude will be slightly attenuated as it travels from the ventilator to the alveoli, since neither the inspiratory time nor the expiratory time is adequate for the pressure to equalize between the upper airway and the alveoli. At the alveolar level, the inflation will have a PIP of less than 25 and a PEEP of more than 5. Thus, the amplitude of the inflation will have been *attenuated* from 20 cm H_2O to something slightly less than 20 cm H_2O. This is the phenomena that causes gas trapping (sometimes called inadvertent PEEP) at inappropriately high rates on conventional ventilation.
      (3) At an even higher frequency (e.g., 600 inflations per minute; 10 Hz), the attenuation is far more significant. An inflation with an amplitude of 20 cm H_2O at the hub of the endotracheal tube may be attenuated to less than 5 cm H_2O at the alveoli.

c. Thus, if everything else is constant, *decreasing frequency will increase alveolar amplitude.* This is because at a lower frequency, more of the pressure wave will be transmitted to the alveoli. Since amplitude has a greater impact on CO_2 clearance than does frequency, *decreasing frequency will increase CO_2 clearance*.
d. This complex relationship between frequency and CO_2 exchange is one of the reasons frequency is not the primary parameter to be adjusted when optimizing ventilation.

II. Mechanics common to all HFO ventilators. There are six parameters that can be adjusted.
A. Mean airway pressure
1. Increasing mean airway pressure recruits alveoli, leading to improved ventilation–perfusion (V/Q) matching, improved oxygenation, more CO_2 removal, and increased lung inflation on chest radiography.
2. When placing a patient on HFOV consider the lung disease. If atelectasis predominates (most neonatal diseases, for example, RDS), a *high lung volume strategy* must be used.
3. For lung diseases without atelectasis (for example, pulmonary hypoplasia and congenital diaphragmatic hernia), overdistension is common and a mean airway pressure at or below conventional mean airway pressure may be more appropriate.
4. Changes in mean airway pressure.
a. Increase mean airway pressure if the lungs are underinflated and/or the patient is not oxygenating adequately.
b. Decrease mean airway pressure if the lungs are overinflated and/or if the patient's oxygenation is improving.
c. To cause a small change in lung inflation and/or oxygenation, change the mean airway pressure by 10–20 % (usually 1–2 cm H_2O).
d. To cause a larger change in lung inflation and/or oxygenation, change the mean airway pressure by 20–40 % (usually 2–5 cm H_2O).

B. Amplitude is set by adjusting the Delta (Δ) Pressure (cm H_2O). This is termed power on the Sensormedics 3100A and 3100B.
1. Increasing the ΔPressure leads to an increase in the excursion of the operating mechanism. This increases the amplitude of the pressure wave, and is reflected in an increase in the ΔPressure, which is measured at the hub of the endotracheal tube. Remember that this ΔPressure is markedly attenuated at the alveoli.
2. Most devices display amplitude in absolute units (cm H_2O). The Dräger BabyLog 8000+ and Sophie oscillators display amplitude as a percentage of the maximum ΔPressure the ventilator can generate in that patient at the set frequency, I:E ratio, endotracheal tube, and mean airway pressure. *Importantly, this means that amplitude delivery cannot be assumed to be translatable from other devices or between patients and settings.*
3. Increasing the amplitude leads to an increase in chest movement ("chest wiggle") and a decrease in $PaCO_2$.
4. Relatively small (10–20 %) changes in amplitude may result in significant changes in $PaCO_2$.
5. When placing a patient on HFOV, adjust the amplitude so that the patient is comfortable without much spontaneous respiratory effort, and so the "chest wiggle" looks appropriate.
6. Assessment of "chest wiggle" is tactile as well as visual. Feeling the chest wiggle at the right and left second intercostal spaces (mid-clavicular) simultaneously is more reliable than observing "chest wiggle," especially in larger or edematous infants. This also aids assessment of suction need and uniformity of oscillation.

7. Follow $PaCO_2$ closely (it can change dramatically), using $TcPCO_2$ or tidal volume/minute ventilation (DCO_2) monitoring to help with initial adjustments in amplitude, and prevent rapid $PaCO_2$ changes.

C. Frequency
1. Measured in Hz (1 Hz = 1 inflation/s or 60 inflations/min). For neonatal patients, frequency is usually 5–15 Hz (300–900 inflations/min).
2. Frequency setting should be determined by the time constant of the lung (similar to setting inspiratory time during conventional ventilation), and based on patient size and type of lung disease.
3. Use higher frequencies for small babies with dense atelectatic lung disease.
4. Use lower frequencies for large babies, babies with mild disease, and babies with non-uniform disease.
5. In general, use a lower frequency for patients with non-homogeneous lung disease, airway disease, or gas trapping. If a patient has an unacceptable degree of gas trapping which does not respond to decreasing mean airway pressure, consider decreasing the frequency by at least 1–2 Hz.
6. Typical frequencies
   a. Preterm infant with severe RDS: 10–12 Hz, sometimes higher (except Dräger BabyLog 8000+, 7–10 Hz)
   b. Preterm infant with mild RDS or early chronic lung disease: 8–12 Hz (except Dräger BabyLog 8000+, 7–10 Hz)
   c. Preterm infant with significant chronic lung disease and/or gas trapping: 6–8 Hz (except Dräger BabyLog 8000+, 5–7 Hz)
   d. Term infant with severe pneumonia or meconium aspiration syndrome: 8–10 Hz, and consider frequencies 6–7 Hz if severe disease and/or gas trapping (except Dräger BabyLog 8000+, which is unlikely to have the power to clear CO_2 in these infants)
   e. The Dräger BabyLog 8000+ has limited power at high frequency and amplitudes and should be reserved for preterm infants.
   f. Because of similarities in design, the Dräger VN500 may not be able to generate amplitudes >30–40 cm H_2O in some conditions at frequencies >7 Hz. In high CO_2 states it maybe more useful to use frequencies 1–2 Hz below those used on a Sensormedics 3100A.

D. Inspiratory:expiratory ratio of 1:2 is usually adequate for most neonates, and always should be if gas trapping is present. An I:E ratio of 1:1 will increase tidal volume delivery and this may be useful in severe atelectasis if operating at high amplitude and frequencies.

E. Flow, measured in liters per minute (LPM), can be set in some HFO ventilators (Sensormedics 3100A and 3100B, Fabian, Leoni). As with other types of ventilators, more flow is needed for large infants (15–20 LPM) than for premature infants (6–12 LPM).

F. Fraction of inspired oxygen (FiO_2)
Adjustments in FiO_2 have the same impact on oxygenation for a patient on HFOV as they do for a patient on other forms of ventilation.

G. Optimizing mean airway pressure in the atelectatic lung (for example, RDS) (Chap. 77).
1. In general, the approach to HFOV in the atelectatic lung requires using a *high lung volume strategy* that includes avoiding the extremes of over- and underinflation (atelectasis), minimizing oxygen exposure, and weaning as aggressively as tolerated.
2. A high lung volume strategy involves "optimizing" lung volume by use of a mean airway pressure above conventional ventilation mean airway pressure (at least at initiation),

weaning FiO_2 before weaning mean airway pressure, and considering intentional recruitment maneuvers.

3. There are multiple approaches to "optimizing" lung volume on HFOV, all of which are based on the assumption that patients are optimally ventilated when atelectasis has been reversed, and ventilation is occurring on the deflation limb of the pressure–volume relationship.
4. Achieving optimal lung volume involves progressively recruiting atelectatic alveoli by increasing mean airway pressure until FiO_2 is able to be decreased, suggesting that V/Q matching has improved.
5. Optimizing lung volume can be done only in conjunction with monitoring and careful attention to FiO_2. While increasing mean airway pressure can be very effective at recruiting alveoli and decreasing FiO_2, it can also lead to significant overdistension.
6. There is no single absolute "optimal" mean airway pressure, the value will vary between patients and as the disease state changes in a patient. In general, "optimal" mean airway pressure is usually defined as the lowest mean airway pressure that maintains the best oxygenation. In most preterm infants with respiratory distress syndrome this will be achieved with an FiO_2, which is less than 0.3–0.4.
7. For experienced users an "open lung approach" to recruit the lung and then identify the lowest mean airway pressure that maintains optimal recruitment (oxygenation) is a highly effective method of achieving a high lung volume strategy.
   a. Commence HFOV at a mean airway pressure 2–4 cm H_2O above the conventional mean airway pressure.
   b. If oxygenation does not significantly improve over 10 min, increase mean airway pressure by 2 cm H_2O every 2 min (2–5 min in meconium aspiration syndrome) and observe SpO_2.
   c. At each mean airway pressure step, wean FiO_2 if SpO_2 improves (e.g., >94–96 %). This indicates that lung recruitment has occurred.
   d. Continue a stepwise increase in mean airway pressure until either no improvement in SpO_2 over 2–3 steps or SpO_2 starts falling (overdistension). This maximum mean airway pressure is called the "opening pressure" and represents maximal lung recruitment (may be >20 cm H_2O).
   e. Keeping FiO_2 at the "opening pressure" value, mean airway pressure should now be judiciously decreased (2 cm H_2O steps every 2 min) to map the deflation limb of the pressure–volume relationship.
   f. If SpO_2 falls persistently below acceptable levels (e.g., 88 %), or clinical instability occurs after a mean airway pressure decrease, this indicates that atelectasis predominates again. The mean airway pressure has now been weaned to beyond the "closing pressure" of the lung.
   g. Mean airway pressure should be immediately increased to the "opening pressure" until SpO_2 improves (2–5 min) and FiO_2 can again be decreased.
   h. Mean airway pressure should then be immediately decreased to 2–5 cm H_2O above the "closing pressure," as this will represent the lowest safe pressure that maintained adequate SpO_2 at the lowest FiO_2. This is termed the "optimal pressure."

H. Optimizing mean airway pressure in the non-atelectatic lung.
   1. Aggressive mean airway pressures should be avoided in non-atelectatic lungs. Remember that recruitment maneuvers should only be used in lungs that need recruitment.
   2. High lung volume strategies should be avoided in pulmonary hypoplasia (prolonged ruptured membranes, congenital diaphragmatic hernia), PPHN, established cystic BPD, tracheo-esophageal fistulas, and congenital cystic lung disease.

3. Pulmonary hypoplasia
   a. Reduced FRC and risk of overdistension.
   b. Initial mean airway pressure at or below conventional ventilation mean airway pressure (usually 10–15 cm H_2O).
   c. Lung volume changes will be slow (hours) and gentle stepwise recruitment (maximum 2 cm H_2O) only if poor oxygenation and chest radiography evidence of atelectasis.
4. Congenital diaphragmatic hernia
   a. Pulmonary hypoplasia and pulmonary hypertension predominate in heterogeneous lungs.
   b. As per pulmonary hypoplasia, avoid high mean airway pressure (maximum 16 cm H_2O) and gentle stepwise recruitment only if atelectasis/collapse present.
   c. Allow permissive hypercapnia (pH >7.25–7.30) and relative hypoxia (preductal SpO_2 >85 %).
5. Established cystic BPD (or congenital cystic disease)
   a. Non-recruitable lungs with cysts and prolonged inspiratory and expiratory time constants.
   b. Gas trapping and overdistension likely, thus expiratory phase needs to be adequate (use frequency 8 Hz or less and I:E ratio 1:2). Consider positioning cystic lung "up."
   c. Use a low pressure strategy (mean airway pressure 10–14 cm H_2O).
   d. Accept higher FiO_2 and avoid all recruitment maneuvers.
   e. Lung volume changes are very slow (hours) secondary to loss of elasticity of lungs.
6. PPHN
   a. Approach is determined by the nature of the lung disease associated with PPHN.
   b. PPHN with parenchymal lung disease should be managed as per the atelectatic lung.
   c. PPHN with pulmonary hypoplasia should be managed as per pulmonary hypoplasia.
   d. High mean airway pressures should be avoided in PPHN without any lung disease. Often infants with PPHN and no lung disease are better managed with conventional ventilation.

I. Optimizing frequency
   1. Identifying the optimal frequency is an imprecise process. In most cases, the frequency range listed above is adequate.
   2. If the patient appears to have air trapping, manifested by an overinflated chest radiograph and poor oxygenation or ventilation, consider decreasing the frequency in steps of 1–2 Hz.
   3. Remember that decreasing frequency will decrease the pressure attenuation, and therefore increase the delivered pressure amplitude at the alveolar level, resulting in decreased $PaCO_2$.

J. Weaning and extubating from HFOV
   1. Weaning amplitude is done by judiciously decreasing delta pressure (usually by 10 %) for patients who have a $PaCO_2$ in their "target range." However, if a decrease in amplitude results in a significant increase in $PaCO_2$, work of breathing, or clinical lability, the amplitude has probably been weaned too far.
   2. Most patients can be extubated directly from HFOV. The approach to preparing an infant for extubation from HFOV is essentially the same as for an infant on conventional ventilation.
      a. Decrease both mean airway pressure and amplitude as the patient improves.
      b. As the patient improves, and as amplitude decreases, the patient will do more spontaneous breathing. If the amplitude decreases sufficiently, the patient will essentially be on "oscillatory CPAP" rather than oscillatory ventilation.

c. When the patient is achieving most of the CO_2 elimination by spontaneous breathing, and the mean airway pressure has been decreased sufficiently, the patient can be extubated.
d. General guidelines for extubation from HFOV are similar to those for extubation from conventional ventilation. As with conventional ventilation, clinicians have become progressively more aggressive about early extubation. The author's current approach is to extubate from HFOV using the following criteria:
   (1) Preterm infants:
      (a) There is good spontaneous respiratory effort.
      (b) Mean airway pressure is <6–8 cm H_2O.
      (c) Maintaining adequate SpO_2 in FiO_2 <0.3–0.4
      (d) pH >7.25, and acceptable CO_2 with delta pressure 10–15 cm H_2O
   (2) Term infants:
      (a) There is good spontaneous respiratory effort.
      (b) Mean airway pressure is <6–10 cm H_2O.
      (c) Maintaining adequate SpO_2 in FiO_2 <0.3–0.4
      (d) pH >7.25, and acceptable CO_2 with delta pressure 15–20 cm H_2O

III. Mechanics specific to some oscillators
   A. Volume targeted ventilation during HFOV
      1. Currently three oscillators offer volume targeted ventilation (VTV) modalities in HFOV (termed "volume guarantee" by some manufacturers); the Dräger VN500, Acutronic Fabian, and Leoni+.
      2. In principle, VTV in HFOV is similar to conventional ventilation in that the clinician sets a desired tidal volume and the ventilator algorithm adjusts amplitude to maintain the set tidal volume.
      3. The clinician also sets the maximum amplitude the oscillator is allowed to deliver (similar to the PIP maximum setting during conventional ventilation).
      4. VTV during HFOV offers the potential of less CO_2 instability, quicker weaning, and an aid during recruitment maneuvers (because of the interaction between lung volume and CO_2 clearance).
      5. Unlike conventional ventilation, the ideal target range of tidal volumes during HFOV is unknown, and there are no large clinical trials validating use in the neonatal population.
      6. Remember that tidal volume during HFOV is not only determined by the amplitude but also frequency, I:E ratio, and patient characteristics. A single tidal volume range or value is unlikely to be appropriate for all infants. More importantly, unlike conventional VTV modes, *a change in frequency or I:E ratio will alter the delivered tidal volume* in HFOV VTV modes.
      7. There are two approaches to using VTV during HFOV that have been suggested, but neither validated in clinical trials yet.
         a. Start VTV at approximately 2 mL/kg tidal volume, with a high maximum amplitude setting. Then observe chest wall movement and CO_2 clearance over the next 10–30 min. Titrate the maximum amplitude setting to be 5 cm H_2O above the amplitude required during stabilization. Increase the VTV value (mL/kg) if CO_2 clearance is not appropriate.
         b. First stabilize the infant using a "traditional" HFOV approach without VTV, and determine the amplitude required to achieve the target CO_2. During this process the tidal volume and minute ventilation needed to achieve CO_2 stability should be documented. VTV is then started at that tidal volume setting (maximum amplitude set at 5 cm H_2O above that needed to achieve stability).

c. For both methods, if frequency (or I:E ratio) is changed, this will also alter tidal volume. Remember that minute ventilation is the true determinant of CO_2 clearance. To maintain the same CO_2, the VTV setting will need to be re-adjusted to establish the same minute ventilation value prior to frequency change. If this is not done there is a possibility that CO_2 will rise or fall outside of target range despite an apparent unchanged VTV setting.

IV. Monitoring lung function during HFOV
   A. Bedside monitoring
      1. Rapid and substantial changes in oxygenation and lung mechanics (CO_2) are possible with HFOV. Continuous bedside monitoring of both should be mandatory.
      2. SpO_2 or $TcPO_2$ and cardiovascular monitoring must be used during HFOV to guide level of lung inflation and mean airway pressure.
      3. Monitoring of CO_2 clearance can be achieved using:
         a. $TcPCO_2$
         b. Tidal volume measured at the airway opening.
         c. Minute volume
            (1) Calculated from (Frequency) × (Tidal Volume)^2
            (2) As minute ventilation reflects the role of frequency, amplitude, and I:E ratio on CO_2 clearance, it is a more useful indicator than tidal volume of CO_2 trends
            (3) Absolute minute volume values are dependent on patient and device characteristics, so they cannot be translated between patients or diseases. Rather the trend in minute volume should be used (higher = more CO_2 clearance)
         d. Tidal volume and minute volume monitoring are available in all modern oscillators except the Sensormedics 3100A and 3100B. External devices that reliably monitor these parameters during HFOV, and can be used in conjunction with the Sensormedics 3100A and 3100B, are available.
         e. No method of CO_2 clearance monitoring during HFOV has been shown to be universally reliable as a trend of ventilation. It is recommended that more than one be used initially and clinicians determine the optimal method, and reliability, for each individual infant against intermittent blood gas analysis.
   B. Chest radiography (Chap. 23)
      1. Chest radiographs have been recommended as a method of determining the degree of lung inflation for more than two decades.
      2. With the availability of complex bedside monitoring during HFOV, the role of chest radiography has changed. Chest radiography is an intermittent investigation and should not be used to set HFOV parameters but rather confirm lung inflation *after* optimizing settings or to diagnose lung conditions.
      3. Chest radiography should be repeated after any major change in mean airway pressure (e.g., open lung approach recruitment), or increasing FiO_2 needs if clinical assessment of the patient and bedside monitoring cannot determine the cause.
      4. Appropriate clinical intervention (e.g., increasing mean airway pressure after suction derecruitment) should not be delayed by the need for chest radiography.
      5. Assessing lung inflation on chest radiography:
         a. Position and shape (flat) of hemi-diaphragm, radiolucency of lung fields, heart size, and intercostal shape of lung edges (eg bulging) have all been described as methods to assess lung inflation (volume) during HFOV.
         b. Individually, each has limitations and combining all within the context of the clinical bedside information is needed to assess lung inflation.

c. In most patients, the lungs should be inflated so that the top of the right hemi-diaphragm is between 8 and 10 ribs.
d. A higher location of the right hemi-diaphragm (e.g., 6–8 ribs) will represent normal lung inflation in conditions of reduced FRC (e.g., pulmonary hypoplasia).

C. Lung ultrasound
Lung ultrasound has been described as a point of care method of assessing lung volume and detecting pneumothoraces during HFOV but is currently limited to centers with expertise in the practice.

V. HFOV or "Conventional" Ventilation?
A. There are clear theoretical advantages of HFOV over "conventional" ventilation for patients with severe restrictive lung disease (severe atelectasis) when adequate mean airway pressure is used.
1. With HFOV, the alveolus never deflates to the degree that it does with conventional ventilation. Thus, surface forces are less likely to cause atelectasis. In any patient with a tendency to develop atelectasis (e.g., RDS), this should be a significant advantage, since preventing atelectasis is a key element in avoiding lung injury.
2. With HFOV, the lung is not distended as much during tidal ventilation, so there is less chance of causing alveolar or airway overdistension, a primary cause of both acute and chronic lung injury.
3. Because oxygenation and ventilation are relatively "uncoupled" during HFOV, changes in one may not affect the other, and dual changes can often be accomplished simultaneously. This is useful in complex or rapidly changing diseases.

B. Multiple animal models have shown advantages of HFOV over conventional ventilation, particularly in models of severe RDS or with severe acute lung injury.
C. The human data on the advantages of HFOV over conventional ventilation are less compelling. In general, reports and clinical trials of HFOV have focused on either the role of HFOV in patients with severe lung disease, or in preventing BPD in very preterm infants.
1. Recent meta-analyses of the clinical trials comparing "first intention" HFOV to conventional ventilation for the prevention of BPD conclude that any advantages of HFOV are relatively small.
2. Interpreting the large trials of HFOV vs. conventional ventilation is hampered by the fact that essentially all of the trials were conducted using clinical strategies that are no longer used. Extrapolating these studies to the current era of vigorously avoiding intubation, and of early extubation, is difficult.
3. HFOV has evolved in most units as a rescue therapy, after a period of conventional ventilation, rather than first intention therapy. There are no clinical trials of this practice in the modern era.

D. There are several conclusions which can be drawn from the animal and human trials of HFOV.
1. HFOV is at least as effective as conventional ventilation in supporting oxygenation and ventilation in patients with significant restrictive disease.
2. HFOV is at least as safe as conventional ventilation, when used properly (with a high lung volume strategy).
3. HFOV is superior to conventional ventilation for infants with pulmonary interstitial emphysema or broncho-pleural fistula. However, HFOV is probably not as effective as HFJV in treating patients with severe disease.
4. HFOV may be superior to conventional ventilation for patients with severe restrictive lung disease.
5. HFOV probably offers no advantages over conventional ventilation in patients with minimal lung disease.

6. In experienced hands HFOV has an important role in NICU care, but in inexperienced hands HFOV can be harmful.

E. General indications for HFOV in most centers which are experienced with HFOV include:
   1. Treatment of air leak syndromes, including pulmonary interstitial emphysema or bronchopulmonary fistula.
   2. Severe restrictive lung disease, including RDS, meconium aspiration syndrome, or pneumonia, especially in centers familiar with the use of the open lung approach.
   3. Severe lung hypoplasia, including congenital diaphragmatic hernia.
   4. Small preterm infants at high risk of developing BPD. This indication is more controversial than those listed above.

Suggested Reading

Chang H. Mechanisms of gas transport during ventilation by high-frequency oscillation. J Appl Physiol. 1984;56:553–63.

Cools F, Askie LM, Offringa M, Asselin JM, et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. Lancet. 2010;375:2082–91.

Courtney SE, Durand DJ, Asselin JM, et al. High frequency oscillatory ventilation vs conventional mechanical ventilation for very-low- birth-weight infants. N Engl J Med. 2002;347:643–52.

De Jaegere A, van Veenendaal MB, Michiels A, van Kaam AH. Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. Am J Respir Crit Care Med. 2006;174:639–45.

Froese AB, Kinsella JP. High-frequency oscillatory ventilation: lessons from the neonatal/pediatric experience. Crit Care Med. 2005;33 Suppl :S115–21.

Harcourt ER, John J, Dargaville PA, Zannin E, et al. Pressure and flow waveform characteristics of eight high-frequency oscillators. Pediatr Crit Care Med. 2014;15(5):e234–40.

Pillow JJ. High-frequency oscillatory ventilation: mechanisms of gas exchange and lung mechanics. Crit Care Med. 2005;33 Suppl :S135–41.

Tingay DG, Mills JF, Morley CJ, Pellicano A, Dargaville PA. Indicators of optimal lung volume during high-frequency oscillatory ventilation in infants. Crit Care Med. 2013;41(1):237–44.

Section IX

Adjunctive Therapies

Hemodynamic Support

56

Keith J. Barrington

I. Introduction
   A. Neonatal cardiovascular physiology differs in many ways from the physiology of the more mature human.
      1. Cardiac function
         a. Neonatal myocardium is structurally, metabolically, and functionally limited.
         b. Basal contractility is near to maximal levels, and therefore, any further demands on cardiac function, such as those resulting from increases of afterload, may not be met.
         c. Increases in afterload as a result of vasoconstriction often lead to decreases in ventricular output.
         d. Drug responses are often also quite different in the newborn; metabolic immaturity of the myocyte may lead to responses which are in a different direction in the newborn. For example, phosphodiesterase-3 inhibitors (e.g., milrinone) may lead to negative inotropic responses in the newborn, in contrast to the positive inotropic responses seen in the older subject.
         e. Only studies restricting the investigation to the newborn or the preterm newborn give adequate information.
      2. Vascular responses

         The development of vascular receptors is poorly studied. Alpha-mediated vasoconstriction is seen with the administration of catecholamine agents, even in very immature babies, but the gestational age at which other vascular responses may occur (those mediated by other catechol receptors, or other categories of responses, such as those mediated by endothelin or acetylcholine) are unknown.
      3. Shunts
         a. Because of the presence of shunts, newborn infants with normal hearts do not have a single variable called "cardiac output."
         b. Total perfusion of the body is the sum of SVC flow and IVC flow.
         c. In contrast, left ventricular output (LVO) only reflects systemic perfusion when the ductus arteriosus is closed.

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d. When the ductus is open, LVO is the sum of pulmonary venous return and any net shunting across the foramen ovale.
e. Right ventricular output (RVO) is the sum of systemic venous return and any net left-to-right shunting across the foramen ovale; as this shunt is often small, RVO can often be used as an indicator of total systemic perfusion.

B. Normal transition
1. The fetal circulation
a. In utero the pulmonary vascular resistance is very high, which keeps pulmonary blood flow low (less than 15 % of the combined ventricular output).
b. The majority of blood ejected by the right ventricle crosses the ductus and perfuses the low resistance placental circulation; thus, right ventricular afterload in utero is low.
c. Most upper body flow in utero is derived from the LVO.
2. At the time of birth the ductus arteriosus constricts and the RVO perfuses the lungs, after which pulmonary vascular resistance starts to fall; thus, right ventricular afterload transiently increases at birth, and then falls as the PVR decreases.

II. Hemodynamic problems
A. PPHN (Chap. 72)
1. Pathophysiology
a. This condition results from the failure of pulmonary vascular resistance to fall, or a recurrence of high resistance after the initial transition.
b. This may occur as a complication of meconium aspiration, pneumonia, pulmonary hypoplasia, other respiratory disorders, such as respiratory distress syndrome, or occasionally as an isolated phenomenon in babies with clear chest radiographs.
c. Right-to-left ductal shunting, although pathognomonic, is seen only in those with severe disease and an open ductus.
d. Many other infants have intracardiac shunting across the foramen ovale; such shunting depends on an inter-atrial pressure gradient. Right atrial pressures will be elevated in the presence of right ventricular failure, which may result from the high right ventricular afterload. Thus, right ventricular function is an important determinant of a good outcome in infants with PPHN.
e. Finally, hypoxemia may result from intrapulmonary shunting (that is, V/Q mismatch).
2. Clinical evaluation
a. PPHN may accompany respiratory distress, or occur in babies with little distress; such infants often need a high FiO_2 to achieve adequate saturation.
b. Pre-ductal saturation (right hand) and post-ductal saturation (a foot) may show a gradient, but its absence does not rule out the disease.
c. In most infants with severe respiratory failure there is some elevation of the pulmonary vascular resistance, which may contribute to the severity of their illness.
3. Supplementary testing
a. Echocardiography may show right-to-left or bi-directional shunts, at the ductus arteriosus or across the foramen ovale. In the presence of tricuspid regurgitation, right ventricular pressure can be estimated. Abnormal curvature of the inter-ventricular septum may give an indirect estimate of increased pulmonary arterial pressure.
b. If congenital heart disease is suspected, a hyperoxia test may be helpful, but can also be misleading.
4. Therapy
a. Supportive therapy, assisted ventilation, warmth, oxygen, and fluids are used.
b. Sedation may help in certain cases.

c. The only proven directly acting therapy is inhaled nitric oxide (Chap. 63), which can be commenced at between 2 and 20 ppm.
d. Hyperoxia should be avoided, as it may impair nitric oxide-mediated pulmonary vasodilation, and increase pulmonary vascular reactivity.
e. Hyperventilation should be avoided, as progressive systemic hypotension may occur.
f. Infusions of sodium bicarbonate should be avoided, as their use has been associated with increased need for ECMO and poorer outcomes.
g. Cardiac supportive therapy may be required, but it is unclear which agent has the best effect. Epinephrine use at low to moderate doses (0.05–0.2 mcg/kg/min) improves systemic oxygen delivery in animal models. Norepinephrine leads to pulmonary vasodilation in some animal models.

B. Septic shock
1. Pathophysiology
a. There are little data regarding the usual hemodynamic features of septic shock in the newborn.
b. Older patients with gram-negative septic shock commonly have excessive vasodilation accompanied by a normal or increased cardiac output and hypotension, so-called warm shock.
c. It is not clear if this is true in newborn infants, who often have different organisms (e.g., group B streptococcus) and have a different cardiovascular physiology. Neonatal *animals* with group B streptococcus demonstrate vasoconstrictive "cold shock," with hypotension being a pre-terminal event.
2. Clinical evaluation
a. In cold shock, signs of peripheral vasoconstriction are common: prolonged capillary filling, oliguria, and inactivity.
b. In warm shock, pulses may be bounding, but signs of inadequate tissue oxygen delivery may be seen (e.g., lactic acidosis and poor urine output).
3. Supplementary testing
a. Echocardiography may be helpful for estimating cardiac filling, contractility, and systemic blood flow, and in determining therapeutic interventions.
b. There is no clear evidence that this improves outcomes, but it does allow more rational therapy.
4. Therapy
a. There is little good evidence regarding therapeutic options in infants with septic shock.
b. A physiology-based approach would suggest that infants with clinical shock but with adequate blood pressure may benefit from dobutamine (which increases systemic perfusion without having much effect on blood pressure).
c. Infants with shock and hypotension may preferably be treated with epinephrine, which appears to increase both blood pressure and systemic perfusion. Norepinephrine may be a useful alternative.
d. Combinations of drugs have unpredictable effects. Pharmacokinetics and receptor status of babies vary considerably; therefore, dose responses are extremely variable and doses need to be individualized.
e. In adults with septic shock, there is little evidence that clinical outcomes vary according to the drug chosen; randomized trials comparing different agents show differences in short term clinical responses, but generally not in survival.
f. Fluid boluses are often administered, based on the assumption that sepsis leads to a functional hypovolemia.

(1) Although this may be true in certain cases, a recent trial in older infants and children showed an increase in mortality in children with early septic shock who received a fluid bolus.
(2) If fluid boluses are administered, crystalloids and colloids have different hemodynamic responses, with a greater and more prolonged increase in perfusion with colloids than with saline, but with little or no evidence of differential clinical outcomes, the agent of choice in the newborn is uncertain.

C. Hypovolemic shock
   1. Pathophysiology
      a. Hypovolemia can result from blood loss (e.g., ruptured vasa praevia), or occasionally in infants following placental abruption (in this situation the blood lost is usually mostly maternal).
      b. Partial umbilical cord occlusion, as may occur with a tight nuchal cord, or cord prolapse, will initially occlude the umbilical vein, prior to the arteries, reducing circulating blood volume.
      c. Large volume feto-maternal hemorrhage will also lead to hypovolemia, but is rare before 28 weeks' gestation, mostly occurring in late preterm and term infants.
      d. Neonatal animal models suggest that blood pressure and perfusion can be maintained up to the loss of about 20 mL/kg by vasoconstriction; after that, further blood loss leads to shock and hypotension.
   2. Clinical evaluation: Infants are usually pale, tachycardic, and poorly perfused with prolonged capillary refill.
   3. Supplementary testing:
      a. Echocardiographic assessment of cardiac filling may be helpful but clear indices of circulating blood volume do not exist.
      b. Central venous pressure (CVP) measurements are of limited usefulness, as they are often low in the newborn, and remain low despite volume administration. CVP may provide useful trend data.
   4. Therapy
      a. Administration of volume.
      b. Saline will temporarily restore perfusion in emergency resuscitation; blood, as soon as available, is required to restore oxygen carrying capacity.

D. Cardiogenic shock
   1. Pathophysiology
      a. Cardiomyopathy
      b. Congenital heart disease (e.g., HLHS)
      c. Asphyxial injury
   2. Clinical evaluation
      a. Poor perfusion and tachycardia are the hallmarks of primary cardiac dysfunction.
      b. Metabolic acidosis with increasing serum lactate, and oligo- or anuria are danger signs.
   3. Supplemental testing
      a. Echocardiography is essential; identification of the coronary artery origins should be considered important unless another diagnosis is likely.
      b. Structural heart disease and cardiomyopathy should be ruled out.
   4. Therapy
      a. Avoiding excessive preload and those therapies which increase afterload makes physiologic sense.
      b. Dobutamine and low dose epinephrine are reasonable first choices.

E. Extreme prematurity: Hypotension or shock?
   1. Pathophysiology
      a. Many extremely preterm infants receive cardiovascular intervention, very often for a *numerically* low blood pressure.
      b. Numerous studies show that there is no correlation between mean arterial pressure and systemic perfusion; most preterm hypotensive infants have low blood pressure for reasons of low vascular resistance and are supplying adequate oxygen to their vital tissues.
      c. Hypotensive babies with good clinical perfusion can have good outcomes without intervention.
      d. There is no clear answer regarding the appropriateness of treatment for hypotension in infants with either clinical signs of good perfusion, or those with documented normal systemic blood flow.
      e. Many centers do not intervene medically for such infants, and institute close surveillance; usually blood pressure will spontaneously rise over the subsequent few hours.
      f. Hypotension in association with poor perfusion is a very hazardous situation with poor outcomes; some babies in this situation will be found to be septic, and others may have primary cardiac dysfunction.
   2. Clinical evaluation
      a. An overall evaluation including clinical signs of poor perfusion and supplementary tests is required to determine whether an extremely preterm infant with a numerically low blood pressure has inadequate perfusion.
      b. The clinical evaluation includes capillary filling time, warmth of peripheries, urine output, and the level of spontaneous activity.
   3. Supplementary testing
      a. Echocardiography, for measurement of systemic flow (SVC flow less than 40 mL/kg/min is associated with increased risk of intraventricular hemorrhage and poor long-term outcome).
      b. An elevated or rising serum lactate is a sign of inadequate tissue oxygen delivery, as long as it is correctly sampled and processed, and a combination of an elevated lactate and a prolonged capillary refill is associated with low systemic perfusion.
      c. Near infra-red spectroscopy to measure cerebral oxygen tension has promise, but more work is required. It may also prove useful for determining intestinal perfusion.
   4. Therapy
      a. If there is no evidence of peripheral under-perfusion, then hypotension may not need to be treated.
      b. For infants with hypotension and signs of poor perfusion or poor systemic flow, therapeutic approaches are uncertain. Low to moderate dose epinephrine, (or perhaps a combination of dopamine and dobutamine) is physiologically reasonable as a way of improving cardiac function, and elevating blood pressure as well.
      c. Fluid boluses are over-used, and hypotensive extremely preterm infants are rarely hypovolemic; in the presence of a history compatible with volume loss, 10 mL/kg of normal saline can be tried empirically.

Nutritional Support in Respiratory Failure

57

David H. Adamkin

I. Introduction

Respiratory distress remains a leading cause of neonatal morbidity despite new strategies with both invasive and non-invasive mechanical ventilation. The relationship between early nutrition and its impact on severity of illness in extremely low-birthweight (ELBW) infants (birthweight <1000 g), recently studied, indicates why nutrition is so important in infants with respiratory distress syndrome (RDS).

A. Infants were divided into more critically ill (BW 734 g, mean 41 days on assisted ventilation) versus less ill (BW 842 g, mean 13 days on assisted ventilation). Using mediation framework statistical analyses data from 1366 ELBW neonates answered three questions

1. Is critical illness in the first weeks of life associated with later growth and other outcomes? Those babies defined as more ill experienced:
   a. An increase in late onset sepsis
   b. An increased risk of bronchopulmonary dysplasia (BPD)
   c. An increase in neurodevelopmental impairment
   d. Decreased growth velocity of 2 g/kg/day for weight
   e. Increased mortality
2. Is critical illness in the first weeks of life associated with early nutritional support?
   a. Those babies in the more critically ill group received less total nutritional support during the first 3 weeks of life.
   b. Over the first week of life, the less ill had total energy intake of 52.0 cal/kg/day versus the more ill babies at 42.7 cal/kg/day for the week.
   c. However, fluid intake was greater in the more ill babies versus the less ill (130 ml/kg/day compared to 123 ml/kg/day, respectively).
3. Most importantly: Is early nutritional support associated with later growth and other outcomes after controlling for critical illness in the first 3 weeks of life?
   a. It showed that nutrition could mitigate severity of illness. If the more critically ill babies received the same nutrition as the less critically ill, then for each increase of

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1 cal/kg/day in the first week of life, the following morbidities and risk of death decreased by 2 %:
(a) Necrotizing enterocolitis (NEC)
(b) Late onset sepsis
(c) BPD
(d) Death

B. The following lessons are learned from this study
1. Early nutritional decisions on ELBW are influenced by clinician perceptions of severity of illness.
2. Early Total Parenteral Nutrition (TPN) and enteral support are associated with lower rates of death, short-term morbidities, improved growth, and neurodevelopmental outcomes.
3. Early initiation of enteral nutrition was well-tolerated and associated with an earlier achievement of full enteral feeding and no increase in NEC.
4. Daily energy intake during the first 7 days of life mediates the influence of critical illness on the risk of adverse outcomes.
5. Management decisions made in the first days of life may have long-lasting effects.

C. Conclusions that can be made to optimize nutritional support for these infants
1. The first week of life is critical to promote growth.
2. Postnatal weight loss and postnatal growth failure may be limited to the first days of life in most of these infants, which emphasizes the importance of early initiation of amino acids.
3. Subsequent growth may also be optimized and catch-up growth is supported with higher protein containing human milk fortifiers, preterm formulas, and caloric-dense strategies for volume-restricted infants.

D. Nutritional strategies for these VLBW infants with respiratory distress begin within the first hours of life with stock solutions of parenteral amino acids that afford a number of benefits:
1. Limiting catabolism by achieving early positive nitrogen balance
2. Promoting growth of lean body mass
3. Reducing postnatal weight loss
4. Earlier return to birthweight
5. Preventing the co-morbidities of hyperglycemia and non-oliguric hyperkalemia
6. Synergy with early enteral feedings to maintain growth
7. Enhancing neurodevelopmental outcome

E. The guiding principle for all nutritional strategies is that undernutrition is, by definition, non-physiologic and undesirable. Any measure that diminishes undernutrition is inherently good provided that safety is not compromised.
1. Considerable evidence suggests that early growth deficits have long-lasting consequences, including short stature and poor neurodevelopmental outcomes.
2. Data linking neurodevelopmental consequences with inadequate early nutrition come from studies in preterm infants fed a preterm formula containing higher protein and energy over the first postnatal month. They had higher neurodevelopmental indices at both 18 months and 7–8 years of age compared to preterm infants fed term formula.
3. Another study demonstrated improved neurodevelopmental and growth outcomes at 18–22 months of age for ELBW infants who had higher growth velocities for weight and head circumference during their NICU hospitalization.

II. Nutritional Management

Nutritional management of these infants may be divided into three phases: exclusive TPN, transition from TPN to enteral nutrition, and finally exclusive enteral nutrition. The goal is to maintain nutrition at requirement levels during all three phases. Requirements for protein and energy are reviewed first.

Table 57.1 Enteral protein and energy requirements of preterm infants[a]

Body weight, g	Protein, g/kg/day	Energy, kcal/kg/day	P/E, g/100 kcal
500–700	4.0	105	3.8
700–900	4.0	108	3.7
900–1200	4.0	119	3.4
1200–1500	3.9	127	3.1
1500–1800	3.6	128	2.8
1800–2200	3.4	131	2.6

P/E = Ratio of protein to energy, expressed as grams of protein per 100 kcal
[a]Adapted from Ziegler, J Ped Gastro/Nutr 2007

A. Requirements for protein and energy
   1. The two methods for estimating protein intake necessary to maintain approximate in utero growth of a fetus of the same gestational age
      a. Factorial method, which includes an estimate of the amount of protein deposited in utero corrected for efficiency of absorption and deposition as well as an estimate of the inevitable urinary nitrogen losses. The main advantage of the factorial method is that it provides estimates of energy requirements, which may be applied to ELBW infants where there are no empirical estimates available.
      b. Empirical method, which determines the actual intakes that support intrauterine rates of growth and nitrogen accretion. Only the empirical method provides estimates for catch-up growth. The empirical method does not estimate energy requirements.
   2. Table 57.1 shows enteral protein and energy requirements determined by the factorial approach. Protein requirements decrease with increasing body size as does the protein to energy ratio.

B. Energy requirements are lower during parenteral nutrition compared to enteral nutrition because energy is neither utilized for thermic effect of feeding nor malabsorbed in stools.

C. Energy expenditure measurements in critically ill very low birthweight infants (VLBW, <1500 g BW) receiving assisted ventilation are extremely difficult to perform using existing measurement techniques. Collectively, studies suggest a mean energy expenditure of approximately 54 kcal/kg.
   1. Technical limitations hampered these investigations, including the minimal inspired oxygen level at which the patients could be studied.
   2. Smaller infants had lower energy intakes but lower energy expenditure of the same magnitude.
   3. Critically ill ELBW infants have limited energy stores; it is important to provide adequate energy sources early, which should also include early intravenous amino acids.
   4. In general, a total energy intake varying from 90 to 100 kcal/kg/day is sufficient for most neonates receiving mechanical ventilation as long as they are normothermic and receiving parenteral nutrition. Additional intakes ranging from 10 to 20 kcal/kg/day (120 kcal/kg/day) are indicated for infants who are premature, physically active, and receiving full enteral feedings.
   5. Intravenous carbohydrates should supply 50 % of total calories in TPN. Glucose infusion rate (GIR) will depend on the volume of fluid provided and the percent dextrose chosen. As the amount of fluid is changed, the amount of glucose infused will change. Table 57.2 provides an easy guide to determine GIR.
      a. A steady infusion of 6–8 mg/kg/min of glucose should be provided parenterally.

Table 57.2 Quick calculation rate glucose infusion rate (GIR)
Chowning R, Adamkin DH. J Perinatol. 2015;35:463

Dextrose %	5	6	7	7.5	8	9	10	11	12	13	14	15	20
mL/kg/day													
20	0.7	0.8	1.0	1.0	1.1	1.3	1.4	1.5	1.7	1.8	1.9	2.1	2.8
40	1.4	1.7	1.9	2.1	2.2	2.5	2.8	3.1	3.3	3.6	3.9	4.2	5.6
60	2.1	2.5	2.9	3.1	3.3	3.8	4.2	4.6	5.0	5.4	5.8	6.3	8.3
70	2.4	2.9	3.4	3.6	3.9	4.4	4.9	5.3	5.8	6.3	6.8	7.3	9.7
80	2.8	3.3	3.9	4.2	4.4	5.0	5.6	6.1	6.7	7.2	7.8	8.3	11.1
90	3.1	3.8	4.4	4.7	5.0	5.6	6.3	6.9	7.5	8.1	8.8	9.4	12.5
100	3.5	4.2	4.9	5.2	5.6	6.3	6.9	7.6	8.3	9.0	9.7	10.4	13.9
110	3.8	4.6	5.3	5.7	6.1	6.9	7.6	8.4	9.2	9.9	10.7	11.5	15.3
120	4.2	5.0	5.8	6.3	6.7	7.5	8.3	9.2	10.0	10.8	11.7	12.5	16.7
130	4.5	5.4	6.3	6.8	7.2	8.1	9.0	9.9	10.8	11.7	12.6	13.5	18.1
140	4.9	5.8	6.8	7.3	7.8	8.8	9.7	10.7	11.7	12.6	13.6	14.6	19.4
150	5.2	6.3	7.3	7.8	8.3	9.4	10.4	11.5	12.5	13.5	14.6	15.6	20.8
160	5.6	6.7	7.8	8.3	8.9	10.0	11.1	12.2	13.3	14.4	15.6	16.7	22.2

b. GIR (mg/kg/min) = % glucose × total mL × 100 mg ÷ 1440 (minutes/day) ÷ wt (kg) (Table 57.2).
c. Glucose intake >18 g/kg/day or >13 mg/kg/min, 60 kcal/kg/day increases CO_2 production which affects respiratory gas exchange. Excessive glucose energy induces lipogenesis, which is an inefficient process and increases energy expenditure and CO_2 production.
d. Glucose intakes at or below energy expenditure have no effect on respiratory gas exchange (CO_2 production).

D. Glucose intolerance can limit delivery of energy to the infant to a fraction of the resting energy expenditure, resulting in negative energy balance.
1. Administration of early intravenous amino acids after birth helps prevent hyperglycemia in the majority of ELBW infants. Stimulation of endogenous insulin secretion and increased insulin activity with specific parenteral amino acids explains how early amino acids prevent hyperglycemia.
2. Regular insulin may be necessary for hyperglycemia (serum glucose >180–220 mg/dL) at a GIR <4 mg/kg/min.
3. Prophylactic infusion of insulin to increase glucose utilization and energy intake in the euglycemic infant does not increase protein balance. It decreases both proteolysis and protein synthesis by approximately 20 %. It is also associated with metabolic acidosis and increases the risk of hypoglycemia.
4. Table 57.3 is a guide for using TPN.

E. Early intravenous amino acid infusion allows the transition from fetal to extrauterine life to occur with as minimal an interruption of growth and development as possible.
1. The administration of amino acids should begin within the first hours of life to avoid early malnutrition. This nutritional strategy initiates efforts at preventing growth failure in ventilated ELBW infants and neurodevelopmental outcome is enhanced.
2. A moderate increase in blood urea nitrogen (BUN) after the start of TPN is usually not adverse or a sign of toxicity; rather, it is related to metabolism of the amino acids.
3. The early administration of amino acids simulates the nutrition of the early fetus, as 50 % of amino acids provided to the fetus are used for energy. These amino acids are oxidized

Table 57.3 Parenteral nutrition guide

Nutrient	Standard	Advance by	Acceptable labs	Notes
Fluid	DOL 1–3: 80–100 mL/kg DOL 4: 100–120 mL/kg DOL 5: 130–150 mL/kg	Increase by 10–20 mL/kg/day	Na 130–145 mEq/L K 3.5–5.5 mEq/L	Adjust fluid based on I and O's and electrolytes and weight
Dextrose	Peripheral: D10–12.5 % Central: D10–15 %	Adjust to keep glucose delivery at 6–8 mg/kg/min	Glucose 45–130 mg/dL	Dextrose calories not to exceed 50 % of total calories
Lipids	3 g/kg/day	Begin with 1–2 g/kg/day and increase by 1 g/kg/day until goal is met	Triglyceride ≤200 mg/dL	Calories from fat not to exceed 40 % of total calories
Protein	3 g/kg/day	Begin with 2.0–3 g/kg and increase by 1 g/kg/day until goal is met	BUN[a] 6–40 mg/dL Creatinine 0.8–1.2 mg/dL	Calories from protein not to exceed 12 % of total calories
Cysteine	40 mg/g of amino acids			Not to exceed 100 mg/kg/day
Carnitine	8 mg/kg ≤1250 g begin on DOL 14 ≥1250 g begin on DOL 30			Carnitine is a cofactor required for the oxidation of fatty acids
Sodium	3 mEq/kg	Adjusts per labs and fluid status	Na 130–145 mg/dL	No sodium until Na level is ≤130 mg/dL
Magnesium	0.25 mEq/dL	Adjust per labs	Mg 1.7–2.1 mg/dL	Watch for increased levels in the first few days of life
Potassium	2 mEq/kg	Adjust per labs and fluid status	K 3.5–5.5 mEq/L	
Calcium	1–3 mEq/kg	Adjust per solubility and labs	Ca 7.6–10.4 mg/dL ionized Ca	Maintain a 2:1 ratio with PO_4
Phosphorus	0.5–1.5 mEq/kg	Adjust per solubility and labs	PO_4 5–7 mg/dL	Maintain a 2:1 Ca to PO_4 ratio
Chloride	1–2 mEq/kg	Adjust per labs	Cl 95–110 mEq/L	Chloride can be used to adjust acetate
Acetate	1 mEq/kg	Adjust per labs	CO_2 18–24 mEq/L	Acetate can only be manipulated by decreasing/increasing chloride
Pediatric MVI	1 mL/kg/day			Given to all infants when TPN begins
Iron	200 μg/kg			Begin if EPOGEN used or prolonged TPN (>3 weeks)
Zinc	200 μg/kg			Added to infants weighing <3 kg
Iodine				Only given to infants receiving TPN for >4 weeks (1 mcg/kg/day)
Copper[b]	30 μg/kg			Added to infants weighing ≤3 kg

(continued)

Table 57.3 (continued)

Nutrient	Standard	Advance by	Acceptable labs	Notes
Manganese[b]	6 μg/kg			Added to all TPN
Chromium	0.2 μg/kg			Added to all TPN
Selenium	2 μg/kg			Added to all TPN
Trace Pack	0.2 mL/kg			Added to all TPN
Heparin	0.5–0.7 units/mL			Maximum 1 unit/mL (100 units/kg)
Osmolarity				Not to exceed 1200 mOsm/L in a peripheral line. Adjust protein or sodium if osmolarity is too high

Adamkin, Nutritional Strategies VLBW. Cambridge Press 2009

[a]BUN: An elevated BUN may represent appropriate amino acid delivery, utilization, and subsequent oxidation, or it may represent amino acid intolerance. Modification of amino acid intake should not be based on BUN concentrations alone. A continually rising Bun value may indicate a mismatch between production and excretion

[b]Remove if evidence of TPN-associated cholestasis, D Bili. 2.2 mg/dL. Add back weekly if on long-term exclusive TPN

and generate carbon dioxide and ammonia. The ammonia is converted to urea and elevates the BUN. Therefore, with early amino acid administration, there is a rise in BUN.

4. Several controlled studies have demonstrated the efficacy and safety of amino acids initiated within the first 24 h after birth. No recognized metabolic derangements, including hyperammonemia, metabolic acidosis, or abnormal aminograms, have been observed.
5. In our experience, a minority of patients, especially those <25 weeks' gestation, may develop hyperazotemia with BUN values exceeding 50 mg/dL and occasionally the parenteral amino acid content will need to be decreased. The majority of the time the elevated BUN resolves in short order without any adjustment in dose of amino acids.
6. Amino acid dose does not directly correlate with the BUN value. An elevation in BUN is also related to acuity of illness, state of hydration, and renal function.
7. Glucose tolerance improves in infants receiving early amino acids because they stimulate insulin secretion. If TPN with amino acids is not provided soon after delivery, insulin activity falls because of an insufficiency of specific amino acids. The provision of early amino acids prevents hyperglycemia and allows the provision of more energy with less fluid because of this relationship with insulin secretion.
8. Similarly, non-oliguric hyperkalemia may be prevented. Early amino acids stimulate insulin activity and prevent intracellular energy failure. Without sufficient insulin, glucose delivery to the cell is impaired and intracellular energy failure occurs. As glucose transport is reduced at the cellular membrane level, there is a resultant decrease in Na+, K+ ATPase activity, and leakage of intracellular potassium. Therefore, non-oliguric hyperkalemia is avoided with early amino acid therapy.
9. Early TPN amino acids may be initiated with a stock solution of 4% to easily provide 2.4–3.0 g/kg/day of amino acids in the first hours of life. The dose of amino acids delivered to the infant is dependent upon the volume per kg of the 4% solution. The stock solution usually has a glucose concentration of 10%.
10. Parenteral amino acid intakes of up to 4.0 g/kg/day for ELBW infants may be used when enteral feedings are delayed or withheld for prolonged periods.
11. Intake of amino acids should not exceed 12% of total calories.

F. Intravenous lipids serve as a source of linoleic acid to prevent or treat essential fatty acid deficiency (EFAD). Larger quantities serve as a partial replacement for glucose as a major source of calories (balanced TPN).
   1. Use 20% lipid emulsion to decrease risk of hypertriglyceridemia, hypercholesterolemia, and hyperphospholipidemia.
   2. Premature infants can clear 0.15–0.2 g/kg/h. Lipid infusion hourly rate correlates best with plasma lipid concentrations. Hourly infusion should not exceed 0.15–0.20 g/kg/h. However, SGA infants and infants with sepsis may not be able to clear standard doses of intravenous lipids and will demonstrate hypertriglyceridemia.

G. Total Parenteral Nutrition
   1. TPN is the main mode of alimentation for critically ill neonates receiving mechanical ventilation, especially during the immediate neonatal period when they cannot be fed enterally.
   2. TPN is usually continued until enteral feedings are providing sufficient volume to replace TPN. The transition from TPN to enteral is critical in preventing postnatal growth failure and will be discussed below.
   3. Parenteral nutrition solutions should supply all necessary nutrients at maintenance rates, including electrolytes and minerals, to correct the common biochemical abnormalities that occur during the neonatal period (Table 57.3).
      a. Premature infants receiving parenteral nutrition are at risk of developing vitamin A deficiency because of their low hepatic stores and low serum-binding protein levels at birth.
      b. There are also significant losses of vitamin A into the delivery system used for parenteral nutrition.
         (1) In 2005, the largest randomized, controlled trial was performed in 807 premature infants with a birthweight of <1 kg who received 5000 IU of vitamin A IM three times per week for the first month of life.
         (2) The results showed a modest but beneficial effect of vitamin A supplementation in reducing the incidence of BPD.
         (3) It has become increasingly difficult to find supplies of parenteral vitamin A and its use has declined.

H. The "routine" use of intravenous lipid emulsions has not been universally accepted in critically ill ventilated ELBW infants because of potential pulmonary complications.
   1. No differences in gas exchange were found in infants randomly assigned to various lipid doses (including controls without lipids) when using lower rates and longer infusion times of intravenous lipids (<0.2 g/kg/h).
   2. For the late preterm infant with increased pulmonary vascular resistance (PVR) or any preterm infant with respiratory failure, it appears a more prudent approach with intravenous lipids should be taken.
   3. Figure 57.1 shows that the high polyunsaturated fatty acid content of lipid emulsions as linoleic acid may lead to pathways resulting in vasoactive prostaglandins, leukotrienes, and thromboxanes through their conversion from arachidonic acid. This may exacerbate pulmonary hypertension.
   4. The oxidation of fat produces less CO_2 for the same amount of oxygen consumed. This reduction in CO_2 production and its elimination may be beneficial for patients with compromised lung function. Therefore, lipids partially replace glucose as a source of energy (balanced TPN).
   5. Initiate lipids the day following birth after starting the amino acid stock solution at a dose 0.5 or 1.0 g/kg/day for ELBWs with respiratory disease.

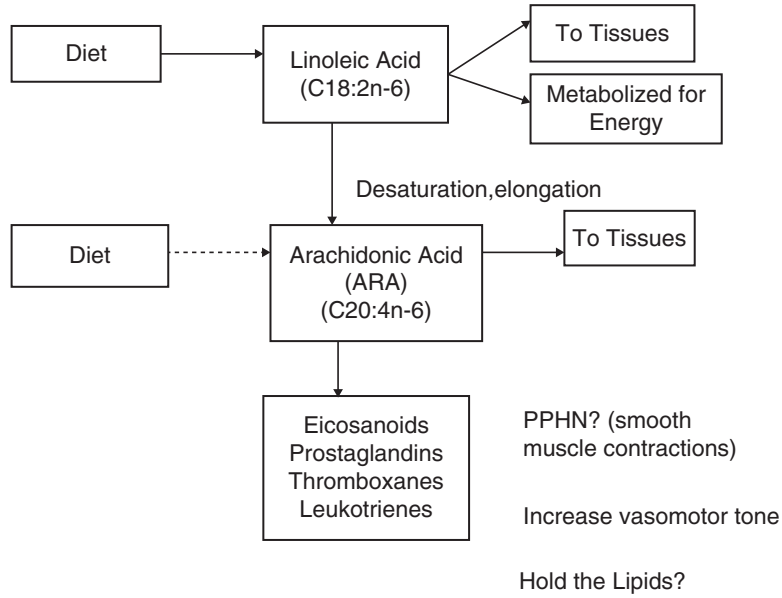

Fig. 57.1 Metabolic derivatives of linoleic acid and ARA (arachidonic acid). *Reference*: Adamkin DH. Clin Perinatol. 2006

6. Plasma triglycerides are monitored after each increase in dose, and levels are maintained <200 mg/dL.
7. Maximum lipid administration is usually 3 g/kg/day over 24 h of infusion to not exceed 0.2 g/kg/h.
8. See Table 57.3.

I. Transitioning from TPN to Enteral and the Prevention of Postnatal Growth Failure.
1. A recent study showed a high rate of postnatal growth failure among VLBW infants. The study divided nutritional management into three phases: TPN, transition, and exclusive full enteral nutrition.
2. Almost 50 % of the infants experienced growth failure and it was linked to inadequate nutrition during the transition phase from TPN to enteral nutrition.
3. The infants did not receive adequate protein during the transition from TPN to enteral nutrition. A number of suggestions can be made to avoid this period of inadequate protein and they involve both TPN amino acids and enteral feedings:
   a. Continue approximately 0.7–1.2 g/kg/day of TPN amino acids when total enteral feeds are 100–120 mL/kg/day.
   b. Fortify human milk at 40 mL/kg/day when using the human concentrated fortifier prepared from donor milk or fortifiers at 80 mL/kg/day when using the concentrated bovine fortifiers. This will increase the enteral protein during transition when the highest volumes of enteral nutrition are being fed.
   c. Determine the enteral protein that is being provided from the human milk or formula and subtract it from 4.0 g/kg/day of protein (the amount of protein that is necessary for transition with TPN at 100–120 mL/kg/day of enteral) (Table 57.4).

J. Enteral Nutrition

Enteral protein feeding requirements have been re-evaluated and emphasize the concept of protein/energy ratio and lean body mass gain. The relationships among protein and energy to promote lean body mass and limit fat accretion are shown in Fig. 57.2.

1. Additional protein is also necessary for catch-up growth. The first weeks of life are associated with an accumulated protein and energy deficit. The protein deficit is most important

Table 57.4 Protein content

Human milk and formula feeds	@ 100 mL/kg		@ 110 mL/kg		@ 120 mL/kg		@ 130 mL/kg		@ 140 mL/kg		@ 150 mL/kg		@ 160 mL/kg		@ 170 mL/kg		@ 180 mL/kg	
Breast milk																		
Breast milk (plain) (BM)	0.9	1.4	1.0	1.5	1.1	1.7	1.2	1.8	1.3	2.0	1.4	2.1	1.4	2.2	1.5	2.4 1.6	2.5	
Breast milk w/Prolacta (human) (PL)																		
BM24/ PL (80 % BM + 20 % PL + 4)	1.9	2.3	2.1	2.6	2.3	2.8	2.5	3.0	2.7	3.3	2.9	3.5	3.1	3.7	3.3	4.0	3.5	4.2
BM26/ PL (70 % BM + 30 % PL + 6)	2.4	2.8	2.7	3.1	2.9	3.3	3.2	3.6	3.4	3.9	3.6	4.2	3.9	4.5	4.1	4.7	4.4	5.0
BM28/ PL (60 % BM + 40 % PL + 8)	2.9	3.2	3.2	3.6	3.5	3.9	3.8	4.2	4.1	4.5	4.4	4.9	4.7	5.2	5.0	5.5	5.3	5.8
BM30/ PL (50 % BM + 50 % PL + 10)	3.5	3.7	3.8	4.1	4.1	4.4	4.5	4.8	4.8	5.2	5.2	5.6	5.5	5.9	5.9	6.3	6.2	6.7
Breast milk w/Enfamil HMF-AL (bovine)																		
BM22/ EHMF (50 MBM + 1 pack HMF)	1.9	2.4	2.1	2.6	2.3	2.8	2.5	3.1	2.7	3.3	2.9	3.5	3.1	3.8	3.2	4.0	3.4	4.2
BM24/ EHMF (25 MBM + 1 pack HMF)	2.6	3.0	2.8	3.3	3.1	3.6	3.4	3.9	3.6	4.2	3.9	4.5	4.1	4.8	4.4	5.1	4.6	5.4
Breast milk w/Similac HMF-HPCL (bovine)																		
BM22/ SHMF (50 MBM + 1 pack HMF)	1.8	2.3	2.0	2.5	2.2	2.7	2.4	2.9	2.5	3.2	2.7	3.4	2.9	3.6	3.1	3.8	3.3	4.1

(continued)

Table 57.4 (continued)

Human milk and formula feeds	@ 100 mL/kg		@ 110 mL/kg		@ 120 mL/kg		@ 130 mL/kg		@ 140 mL/kg		@ 150 mL/kg		@ 160 mL/kg		@ 170 mL/kg		@ 180 mL/kg	
BM24/ SHMF (25 MBM + 1 pack HMF)	2.4	2.8	2.7	3.1	2.9	3.4	3.1	3.7	3.4	4.0	3.6	4.2	3.9	4.5	4.1	4.8	4.4	5.1
Breast milk w/30 kcal/oz formula (bovine)																		
BM22 (80 % BM + 20 % SSC30)	1.3	1.7	1.5	1.9	1.6	2.1	1.7	2.2	1.8	2.4	2.0	2.6	2.1	2.8	2.2	2.9	2.4	3.1
BM24 (60 % BM + 40 % SSC30)	1.7	2.0	1.9	2.2	2.1	2.4	2.3	2.7	2.4	2.9	2.6	3.1	2.8	3.3	3.0	3.5	3.1	3.7
BM27 (30 % BM + 70 % SSC30)	2.4	2.5	2.6	2.8	2.8	3.0	3.1	3.3	3.3	3.5	3.6	3.8	3.8	4.0	4.0	4.3	4.3	4.5
Premature formula (regular or high protein)																		
24 cal	2.4	2.8	2.6	3.0	2.9	3.3	3.1	3.6	3.4	3.9	3.6	4.1	3.8	4.4	4.1	4.7	4.3	5.0
27 cal (50 % 24 cal + 50 % 30 cal)	2.7	2.9	3.0	3.2	3.2	3.5	3.5	3.7	3.8	4.0	4.1	4.3	4.3	4.6	4.6	4.9	4.9	5.2
30 cal	3.0		3.3		3.6		3.9		4.2		4.5		4.8		5.1		5.4	
Hypoallergenic formulas																		
Extensively hydrolyzed 24 cal	2.2		2.5		2.7		2.9		3.1		3.4		3.6		3.8		4.0	
Elemental 24 cal (all brands)	2.2	2.5	2.4	2.7	2.7	3.0	2.9	3.2	3.1	3.5	3.3	3.7	3.6	4.0	3.8	4.2	4.0	4.5

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Prolacta Biosciences California

Fig. 57.2 Impact of protein/energy ratio (P/E) on body composition

Table 57.5 Revised recommended protein intake and protein–energy ratio for premature infants according to postconceptional age and the need for catch-up

	Without need of catch-up growth	With need of catch-up growth
26–30 weeks PCA: 16–18 g/kg/day LBM 14 % protein retention	3.8–4.2 g/kg/day PER: ±3.0	4.4 g/kg/day PER: ± 3.3
30–36 weeks PCA: 14–15 g/kg/day LBM 15 % protein retention	3.4–3.6 g/kg/day PER: ±2.8	3.6–4.0 g/kg/day PER: ± 3.0
36–40 weeks PCA: 13 g/kg/day LBM 17 % protein retention	2.8–3.2 g/kg/day PER: 2.4–2.6	3.0–3.4 g/kg/day PER: 2.6–2.8

PCA postconceptual age, *LBM* lean body mass, *PER* protein/energy ratio
PER = gram of protein/100 cal
Based on Rigo, in Tsang, J Peds, Nov 2006;149:S80–88

and must be addressed to allow catch-up growth to occur and improve both growth and neurodevelopmental outcome.

2. An increase in the protein/energy ratio of feeding is mandatory to improve the lean body mass accretion and to limit fat mass deposition.
3. Human milk plays a significant role in promoting lean body mass and avoidance of maldistribution of adipose tissue.
4. Table 57.5 shows recommendations for protein intake and protein/energy ratio for preterm infants according to postmenstrual age and need for catch-up. Table 57.1 presents requirements based on the reference fetus. These may be taken together to address both growth and the need for catch-up growth.
5. Preterm formulas and supplemented human milk provide protein intakes of 3.6–4.8 g/kg/day at an energy intake of 120 kcal/kg/day. The "higher" protein preterm formulas with P/E ratio of 3.3–3.6 instead of the 3.0 in standard preterm formula will promote more lean body mass accretion when meeting a protein requirement of 4.0 g/kg/day than will the standard preterm formulas which must be fed at higher volumes and excessive energy to achieve 4.0 g/kg/day.
6. The higher protein levels found in the concentrated liquid bovine fortifiers and the high-protein preterm formulas allow higher protein to meet catch-up growth requirements with less energy.

K. Enteral feeding guideline practicum.

1. Begin minimal enteral/trophic (<25 mL/kg/day) feedings by the second day of life in ELBW infants after they are physiologically stable, unless contraindications exist.
2. Human milk is the definitive preference for feeds. This includes the use of donor human milk.
3. Advancing feeds in a safe standardized fashion is helpful.
   a. Each institution should have guidelines for initiation of feedings, advancement of feedings, and for stopping feeding if intolerance is identified.

b. Any situation associated with gut hypoxia or decreased intestinal blood flow may contraindicate initiation of enteral feeding until the situation resolves.
c. Nutrition advances of ≤20 mL/kg/day do not increase the incidence of NEC.
d. Dilute formulas and dilute human milk fail to provide sufficient energy intake and fail to stimulate motor activity of the GI tract and should not be used.
e. Slow bolus feeds ("compressed"), those lasting at least 30 min up to an hour or two, may be used, particularly in infants with feeding intolerance and gastroesophageal reflux.
f. Gastric residuals do not indicate NEC, or impending NEC; other signs of NEC are much more important. Clinical exam and thorough evaluation of the infant are critical when feeding intolerance is diagnosed.
g. In fact, gastric residuals may have a protective function, serving as markers of gut maturation, and help the clinician advance feeding volumes based on the volume of the residuals.

4. Human milk provides substantial benefits for the preterm infant and is the feeding of choice and may include the use of donor human milk.
   a. It should be encouraged unless contraindications exist.
   b. The substantial benefits of human milk for the preterm infant and the importance of a mother's contribution should be emphasized.
   c. Breast pumping and manual expression should be initiated within the first 6 postpartum hours.
   d. The value of colostrum should be emphasized. Fresh colostrum should be collected and used in first feeds.
   e. Lactation consultations should occur, ideally, prenatally, or on DOL 1, or when mother is available (e.g., in cases where baby has been transferred from another hospital).
5. Human milk fortification is necessary in ELBW infants and most VLBW infants to provide optimal nutrient intake.
   a. Since the composition of mother's milk varies greatly from one mother to another, and the concentration of nutrients in preterm milk changes over time, it is difficult to determine the actual intake of nutrients, particularly protein, that the VLBW infant is receiving.
   b. To confer the potential non-nutritional advantages and provide optimal nutrient intake, human milk should be supplemented or fortified, with protein, calcium, phosphorus, vitamin D, and sodium.
   c. Human milk alone does not meet the nutritional needs of VLBW infants. Assuming a protein requirement for these infants of between 4.0 and 4.3 g/kg/day, a premature infant, taking his or her own mother's milk at full volume, would receive approximately 2.5 g/kg/day. If receiving donor human milk, which has a lower protein than mother's own milk, an infant would receive only approximately 1.5 g/kg/day. It is critical in managing human milk fortification to meet the protein requirement.
   d. Regardless of donor or mother's own milk, the calcium and phosphorous provided by human milk does not come close to meeting the required calcium and phosphorous for growth and bone mineralization.
   e. The protein level assumed to present in milk from a mother delivering a preterm infant is 1.5 g/dL. However, as lactation progresses and in the same window that a fortifier is being provided, the protein level is falling. Donor human milk provides 0.8–1.0 g/dL.
   f. The high variability in nutrient content in human milk makes meeting nutrient requirements inherently imprecise.

g. Milk composition varies with volume of milk expressed, the type of milk obtained (foremilk or hindmilk), and the stage of lactation.
h. Sterile bovine concentrated liquid fortifiers which may be added to human milk have been developed providing more protein than the non-sterile powdered bovine fortifiers. The Centers for Disease Control and Prevention no longer recommend powdered formulas and fortifiers for preterm infants because of the risk of bacterial contamination and subsequent bacteremia. There is also a human milk fortifier prepared from concentrated donor human milk and provides additional protein, energy, calcium, and phosphorous. It provides an exclusive human milk diet.
i. Earlier fortification (40 mL/kg/day for human concentrate and 80 mL/kg/day for bovine concentrated liquid) is important to prevent protein deprivation during transition from TPN to enteral feedings.
j. Table 57.4 shows the protein intake of various preterm formulas and human milk fortifiers. The primary goal with human milk fortification is to support postnatal growth rates above the intrauterine growth rate of 15 g/kg/day to prevent malnutrition and allow catch-up growth.
k. To achieve this goal of growth, there must be an adequate balance between protein and energy.

L. Additional studies: Human milk versus formula feedings and BPD
1. In this study, we looked at the influence human milk vs. formula intake had on growth and outcomes in VLBW infants receiving predominantly human milk or more than 50 % of their diet the first year of life vs those predominantly formula fed.
a. Infants who received predominantly formula were larger by all anthropometrics at 6 months of life.
b. However, duration of human milk feeding correlated with significantly improved mental developmental index scores at 12 months of age after controlling for home environment and maternal intelligence.
c. Those receiving more human milk had improved visual acuity despite the fact that the formula was supplemented with DHA.
d. Those predominantly human milk-fed also had less post-discharge morbidity, including readmission to the hospital.
e. For those infants predominantly fed human milk, who also had BPD, there was a significant advantage in mental developmental scores (11 points) vs. those receiving predominantly formula.
2. Another study that looked at donor human milk versus mother's own milk or preterm formula for growth and outcomes made an observation that was surprising.
a. Those infants who received human milk had a significant reduction in the occurrence of BPD.
b. Many infants, because of poor growth on donor human milk, crossed back over to the preterm formula group.
c. These two studies demonstrate how important human milk fortification is to achieve immunologic benefits associated with human milk and also achieve catch-up growth.

III. Nutritional Management of BPD

Nutritional management of infants with BPD plays a role in prevention, amelioration, and recovery for these patients. There are no specific evidence-based guidelines for the nutritional management of infants with BPD. The best nutritional practices for any VLBW infant apply to these infants, but there are specific strategies to consider for those with a high likelihood of developing BPD or those with established BPD.

Table 57.6 Nutrient comparisons per 100 kcal formula

Nutrient	PTF 24	PTF 24 high protein	PTF 27 (PTF 24HP + PTF 30)	PTF 30	30 kcal (PTF 24 + Polycose® + MCT)
Protein (g)	3.0	3.3	3.15	3.0	2.2
Fat (g)	5.43	5.43	6.09	6.61	5.53
CHO (g)	10.3	10.0	8.9	7.73	10.73
Ca (mg)	180	180	180	180	133
P (mg)	100	100	100	100	74
Vitamin D (IU)	150	150	150	150	122
OSMOL	280	280	305	325	N/A
Volume (mL)	124	124	111	99	100

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A. Caloric-dense enteral feedings (>24 kcal/oz) are intended for use in critically ill VLBW infants unable to tolerate sufficient feeding volumes (volume restricted) to meet their needs for growth using standard premature formulas or standard fortified breast milk. The feedings should promote proportional growth, which is more important than absolute weight gain.
   1. Over half of the infants with BPD in the NICHD growth observation study grew in the lowest quartile at 12 g/kg/day from return to birthweight to discharge and had the worst growth and developmental outcomes at 18–22 months.
   2. Table 57.6 shows the nutrient comparisons among preterm formulas, and caloric-dense formulas.
   3. Before the advent of ready-to-feed 27 and 30 cal per ounce formulas, many clinicians would devise their own "recipes" to make a 30 cal milk by adding glucose polymers and MCT oil to a base 24 cal preterm formula. The resultant P/E ratio of this was 2.2 g protein/100 cal of energy. This will only promote the growth of fat and not lean mass but was the only way to make caloric-dense recipes until the new formulas and human milk fortifiers became available.
   4. Using the ready-to-feed 30 cal per ounce milk, a protein of 3.0 g/kg/day can be reached even at 100 mL/kg/day. At 130 mL/kg/day, the protein is 3.9 g/kg/day. Using the 27 cal/oz formula at 130 mL/kg/day one can provide 3.5 g/kg/day of protein with appropriate energy.
   5. There is also a caloric-dense strategy for the infant with BPD on exclusive human milk with the human milk fortifier. Using the 28 or 30 cal per ounce human donor concentrated product, a volume of 120 mL/kg/day will provide approximately 4.0 g/kg/day.
   6. In a study more than 10 years ago including 200 ELBW infants, we diagnosed BPD in 45 % of them with gestational age of 25 weeks and BW 739 g using the oxygen requirement and X-ray findings at 36 weeks' PMA to make the diagnosis.
   7. Their nutritional data included the receipt of less protein and energy over the first 14 weeks of life with more TPN than those ELBW infants who did not develop BPD.
   8. Their growth rate was slower than those who did not develop BPD and they were more likely to develop postnatal growth failure.
   9. Ten years later we examined another cohort of ELBW infants who developed BPD and discovered significant differences in growth and nutritional management had taken place for these infants over 10 years.
   10. The latest cohort from 2012 showed that two thirds of ELBW infants with BPD were growing at or above the fetal weight gain rate of 15 g/kg/day. These infants were approximately 800 g BW and 26 weeks' gestation. In fact, 40 % grew at 18 g/kg/day which matches

the goal for catch-up growth and improved neurodevelopmental outcome according to the NICHD growth observation study.

11. Those managed 10 years before had a mean postnatal weight loss of 18.5 % vs 10 % in the later group. The comparison of time to return to birthweight decreased from 20 days to 10 days, respectively.
12. There was initiation of amino acids at 3 h in the most recent cohort of ELBW with BPD vs 2 days of life for those 10 years before. Protein intake and growth velocity were greater for the later cohort.
13. The major difference in nutrition responsible for these differences over the 10 years included early initiation of amino acids, earlier initiation of enteral feedings with advancing to full feeds sooner, expanded use of human milk, using higher protein preterm formulas, and the liberal use of caloric-dense feedings for babies who were volume restricted on diuretics as part of their management for their BPD.

B. Post-discharge nutrition is another strategy with nutrient-enriched formulas and multi-nutrient fortifiers for human milk to promote catch-up growth in ELBW infants with BPD.
   1. The first postnatal year provides an important opportunity for human somatic and brain growth to compensate for earlier deprivation.
   2. Available data suggest that many smaller/sicker preterm infants are in a state of suboptimal nutrition at the time of discharge and are frequently below the tenth percentile on the growth curve (postnatal growth failure).
   3. These infants have also accumulated significant nutrient deficits for protein, energy, calcium, and phosphorus by the time of discharge.
   4. Nutrient-enriched formula for preterm infants after hospital discharge (post-discharge formula [PDF]) is generally intermediate in composition between preterm and term formulas.
   5. Compared to term formula (TF), PTF contains an increased amount of protein with sufficient additional energy (22 cal/oz) to permit utilization.
   6. PDF contains extra calcium, phosphorous, and zinc, which are necessary to promote linear growth.
   7. Studies demonstrated that the use of either PTF or PDF after discharge in preterm infants results in improved growth, with differences in weight and length persisting beyond the period of intervention.
   8. Such findings suggest that nutrition during the post-discharge period may have longer-term effects on growth trajectory.
   9. Several non-randomized controlled trials have shown that breast-fed infants do not grow as well as their formula-fed counterparts after discharge.
   10. Options include replacing some breast feeds with nutrient-enriched formula feeds or fortifying expressed breast milk.
   11. In a post-discharge feeding study in preterm infants receiving at least 80 % of their daily feedings as human milk, half of the feedings were supplemented with four packets of a powdered multi-nutrient human milk fortifier for 12 weeks. Infants demonstrated improved growth at 1 year. Also noted was the fact that for the smaller babies in the study, head circumference growth was positively affected.
   12. An important study looked at growth and body composition in preterm infants discharged on a nutrient-enriched formula or standard term formula and the infants were fed these two different diets through 6 months' corrected age.
   13. Results included the observations that all of the AGA infants demonstrated catch-up growth on the higher protein discharge formula.

14. The most important advantages for the preterm infant fed nutrient-enriched formula were the combination of increased fat-free mass at 6 months of age and a larger head circumference. Those infants <34 weeks or <1800 g at birth should be discharged on a PDF to gain these advantages for the formula-fed infant.
15. Follow anthropometrics carefully post-discharge and maintain the PDF strategy for 9–12 months' corrected age, especially for VLBW infants who were the most ill and those that developed BPD.
16. VLBW infants discharged on human milk require an individualized approach based on anthropometrics and whether or not there is evidence of osteopenia of prematurity as they approach discharge.
17. Human milk-fed babies with growth failure or evidence of osteopenia at discharge may receive fortification by alternating breast feedings with the PDF or other fortification strategies reviewed in the human milk and caloric-dense sections.
18. Growth post-discharge should be monitored with the CDC, NCHS Growth Curves, and not the IHDP Curve.

IV. Feeding Disorders
   A. Feeding disorders may develop in infants treated with mechanical ventilation, impairing long-term growth, nutritional status, and developmental outcome.
   B. In general, feeding disorders are first recognized after the patient is extubated and then fails multiple attempts to be orally fed.
   C. Oropharyngeal hypersensitivity, defined as a pathologic aversion to oral stimulation, is evidenced by an avoidance behavior to the introduction of any type of oral feeding.
      1. This disorder results from prolonged endotracheal intubation, frequent oral and nasal pharyngeal suctioning, prolonged use of nasal and oral gastric feeding tubes, and the use of nasal cannula oxygen at high flow rates.
      2. Delays in the critical time to learn how to feed may result in the loss of rooting and sucking reflexes and contribute to the feeding problem.
      3. The treatment of oropharyngeal hypersensitivity includes a program of desensitization of the infant's oral pharynx with positive stimulation and attempts to minimize negative stimuli. The latter implies replacement of nasogastric and orogastric feeding tubes with gastrostomy tubes and the use of tracheostomy instead of continuing endotracheal intubation if mechanical ventilation needs to be continued.
   D. Swallowing disorders may also be observed after prolonged courses of mechanical ventilation.
      1. These disorders may affect the three phases of swallowing: oral, pharyngeal, and esophageal.
      2. Swallowing disorders can be seen in association with congenital anomalies, such as micrognathia, choanal atresia, cleft lip and palate, tracheoesophageal fistulas, and laryngeal clefts. They can also be acquired and are seen in infants with severe laryngotracheomalacia, BPD, and neurologic insults that result in cerebral palsy.
      3. Assessment of swallow dysfunction includes a comprehensive history, physical examination, and evaluation of neurologic, pulmonary, and gastrointestinal status. Videofluoroscopy is the radiologic evaluation of choice to detect abnormalities in the different phases of swallowing and the risk of aspiration.
      4. Treatment depends on the signs, etiology, and feeding history and usually requires special therapy in five categories: positioning, oral sensory normalization, modification of food consistency, adaptation of feeding devices, and oral feeding exercises.

E. Pathologic gastro-esophageal reflux (GER) may be seen in infants who received mechanical ventilation, especially in those who develop BPD, neurologic insults resulting in cerebral palsy, and tracheomalacia or subglottic stenosis from prolonged endotracheal intubation.
   1. The clinical presentation of pathologic GER includes the presence of frequent gastric residuals, episodes of vomiting, failure to thrive, and aspiration pneumonia.
   2. Medical management has included antacids, H_2 receptor antagonists, and proton pump inhibitors. These, however, have been linked to the development of NEC. They are not used in the NICU during the first weeks or months of intensive care.
   3. In severe cases of GER that are refractory to medical management, Nissen fundoplication may be indicated.

Suggested Reading

Adamkin DH. Postdischarge nutritional therapy. J Perinatol. 2006;26 suppl 1:S27–30.

Adamkin DH. Nutritional strategies for the very low birthweight infant. Cambridge: Cambridge University Press; copyright 2009.

Adamkin DH, Radmacher PG. Fortification of human milk in very low birth weight infants (VLBW <1500 g birth weight). Clin Perinatol. 2014;41(2):405–21.

Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol. 2007;31:48–55.

Ehrenkranz RA, Younes N, Lemons J, et al. Longitudinal growth of hospitalized very-low-birth-weight infants. Pediatrics. 1999;104:280–9.

Ehrenkranz RA, Dusick AM, Vohr BR, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics. 2006;117:1253–61.

Ehrenkranz RA, et al. Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatr Res. 2011;69(6):522–9. doi:10.1203/PDR.0b013e318217f4f1.

Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics. 2001;107:270–3.

Ernst KD, Radmacher PG, Rafail ST, et al. Postnatal malnutrition of extremely low birthweight infants with catch-up growth postdischarge. J Perinatol. 2003;23:447–82.

Kuscel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants (Cochrane Review). The Cochrane Library 2005.

Leitch CA, Denne SC. Energy expenditure in the extremely low birth weight infant. Clin Perinatol. 2000;27:181.

Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ. 1998;317:1481–7.

Miller M, Vaidya R, Rastogi D, Bhutada A, Rastogi S. From parenteral to enteral nutrition: a nutrition-based approach for evaluating postnatal growth failure in preterm infants. JPEN J Parenter Enteral Nutr. 2014;38(4):489–97.

O'Connor DL, Khan S, Welshuhn K, et al. Growth and nutrient intakes of human milk-fed preterm infants provided with extra energy and nutrients after hospital discharge. Pediatrics. 2008;121(4):766–76.

Poindexter BB, Karn CA, Denne SC. Exogenous insulin reduces proteolysis nd protein synthesis in extremely low birth weight infants. J Pediatr. 1998;132:948–53.

Radmacher PG, Rafail S, Adamkin DH. Nutrition and growth in VVLBW Infants with and without bronchopulmonary dysplasia. Neonatal Intensive Care. 2004;16(1):22–6.

Rigo J, Senterre J. Nutritional needs of premature infants: current issues. J Pediatr. 2006;149:S80–8.

Stefano JL, Norman ME, Morales MC, et al. Decreased erythrocyte Na-K^+-ATPase activity associated with cellular potassium loss in extremely-low-birth-weight infants with nonoliguric hyperkalemia. J Pediatr. 1993;122:276.

Theile AR, Radmacher PG, Anshutz TW, Davis DW, Adamkin DH. Nutritional strategies and growth in extremely low birth weight infants with bronchopulmonary dysplasia over the past 10 years. J Perinatol. 2012;32(2):117–22.

Ziegler EE. Meeting the nutritional needs of the low-birth-weight infant. Ann Nutr Metab. 2011;58 suppl 1:8–18.

Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very-low-birth-weight infant. Clin Perinatol. 2002;29:225–44.

Surfactant Administration

58

Fernando Moya and Kathryn Colacchio

I. Introduction
   A. The administration of exogenous surfactant is considered one of the most significant breakthroughs in neonatology and has been the standard of care for the past 3 decades to prevent and treat respiratory distress syndrome (RDS) in preterm neonates. A recent observational study reported that the overall use of surfactant has decreased over the past decade. This study also reported an increase in the incidence of bronchopulmonary dysplasia (BPD) throughout the same time period, although no causality was suggested.
   B. Infants who develop RDS generally have a surfactant lipid pool of less than 10 mg/kg compared to surfactant lipid pool sizes in term infants of around 100 mg/kg. Furthermore, preterm infants with RDS have a lower percent of saturated phosphatidylcholine species, less phosphatidylglycerol, and fewer surfactant proteins in their pulmonary surfactant.

II. Structure and Function of Pulmonary Surfactant

The main function of pulmonary surfactant is to diminish respiratory work by reducing the surface tension at the air–liquid interface in the alveolus. It also stabilizes the respiratory tracts, improves mucociliary transport, prevents the formation of edema, and contributes to lung defense against pathogens.

   A. Surfactant phospholipids
      1. Pulmonary surfactant is a macroaggregate of about 90 % highly organized lipids (about 85 % are phospholipids) and 10 % surfactant-specific proteins (SP-A, SP-B, SP-C, and SP-D). Its components are synthesized and secreted into the alveolar spaces by type II epithelial cells. The various lipids of surfactant derive from the circulation, from de novo synthesis, or from reuptake from the alveolar pool. These lipids are routed from the endoplasmic reticulum to the lamellar body, the organelle for surfactant storage of type II cells. This process needs the presence of the protein ATP-binding cassette transporter A3 (ABCA3), which is encoded in chromosome 16. Mutations of this gene are the most common cause of hereditary respiratory failure in newborns.

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2. Dipalmitoyl phosphatidylcholine (DPPC) is the most abundant lipid (75%) and is the main surface-active species. Its structure is suited to form a stable monolayer generating the low surface tension required to prevent alveolar collapse at end-expiration. DPPC at physiologic temperature is in a crystalline gel, but because of its rigid structure is unable to adsorb and spread quickly.
3. Spreading is facilitated by the presence of surfactant proteins (see below). Also, the presence of unsaturated phospholipids gives the structure fluidity to facilitate adsorption and distribution in the air–fluid interface.

B. Surfactant proteins.
1. The hydrophobic surfactant proteins, SP-B and SP-C, promote the rapid absorption of phospholipids at the air–liquid interface and account for the sustained low surface-tension activity after dynamic compression. SP-B is required for the formation of lamellar bodies and tubular myelin as well as processing of pro-SP-C. The contribution of SP-B and SP-C to both structural organization and functional durability or pulmonary surfactant is essential given that:
   a. The amount of SP-B and SP-C is decreased in the surfactant of infants with RDS and those evolving to or with established BPD.
   b. Lethal respiratory failure occurs after birth in newborn infants with SP-B deficiency resulting from alterations in the SP-B gene located in chromosome 2. Many such mutations have now been identified, usually inherited as an autosomal recessive condition.
   c. Mutations in the SP-C gene located in chromosome 8 lead to inadequate SP-C synthesis or the accumulation of an abnormal SP-C precursor. They are usually inherited as an autosomal dominant disease, although spontaneous mutations have been described recently. The clinical manifestations are those of a form of chronic interstitial lung disease usually starting in childhood.
2. The hydrophilic surfactant proteins SP-A and SP-D are complex glycoproteins that belong to the collectin family, a sub-group of the lectin superfamily. SP-A is encoded by two genes located in chromosome 10, whereas SP-D is encoded by only one gene in the same chromosome.
   a. SP-A and SP-D are important for tubular myelin formation, whereas SP-D participates in the regulation of the surfactant lipid pool. Both of these proteins have an important role in the innate lung defense barrier against pathogenic organisms like bacteria, fungi, and viruses.
   b. Genetic mutations of their genes have been described in humans, but they do not present with respiratory failure in the newborn period.

III. Exogenous Surfactants

A. For exogenous surfactants to be effective they should be able to adsorb into the lung air–fluid interface very rapidly once administered, thereby achieving very low surface tension during expiration, as well as to re-spread efficiently during inspiration.

B. Administration of exogenous surfactant to a surfactant-deficient preterm animal or human newborn decreases the minimum pressure required to open the lung, increases the functional residual capacity and maximal lung volumes, and prevents lung collapse at low pressures.

C. Types of exogenous surfactants.
There are several exogenous surfactants currently available and a few under development. Although all exogenous surfactants are not alike, they are generally grouped into two categories depending upon whether they are derived from animal lungs or of synthetic origin. New generation synthetic surfactants contain peptides that mimic the action of SP-B and/or SP-C (Table 58.1).

Table 58.1 The different surfactants currently available or under development

Generic name (commercial name)	Origin	Characteristics	Protein	First dose, mg/kg (mL/kg)	Additional doses, maximal number, mg/kg (mL/kg)
Animal-derived surfactants					
Calfactant (Infasurf®)	Calf lung lavage	Chloroform/methanol extracted	SP-B/SP-C	105 (3)	Max 2 doses at least q12h, 105 (3)
(BLES®)	Cow lung lavage	Chloroform/methanol extracted	SP-B/SP-C	135 (5)	Max 2 doses at least q6h, 135 (5)
Beractant (Survanta®)	Minced bovine lung extract	Enriched with DPPC, tripalmitoyl-glycerol, and free fatty acids	SP-C/low SP-B content	100 (4)	Max 3 doses at least q6h, 100 (4)
Poractant (Curosurf®)	Minced porcine lung extract	No neutral lipids (liquid-gel chromatography)	SP-B/SP-C	100–200 (1.25–2.5)	Max 2 doses at least q12h, 100 (1.25)
Synthetic surfactants with no peptides					
Colfosceril palmitate (Exosurf®)[a]	Synthetic	DPPC + Hexadecanol (9 %) + Tyloxapol (6 %)	0	67 (5)	Max 2 doses at least q12h, 67 (5)
Synthetic surfactants with peptides					
Lucinactant (Surfaxin®)[b]	Synthetic	DPPC/POPG 3/1 + free fatty acids (palmitic acid)	Sinapultide (3 %)	175 (5.8)	Max 3 doses at least q6h, 175 (5.8)

[a]No longer available
[b]Not in clinical use as liquid instillate, under study in aerosolized form

D. Animal-derived surfactant preparations are purified and extracted with organic solvents from either lung minces or lung lavage from either bovine or porcine sources.
   1. Their phospholipid concentration varies but is usually at or above 80 % and all contain highly variable amounts of SP-B and SP-C, but not SP-A or SP-D.
   2. There are several significant differences in the composition of these preparations that may bear an effect on their short-term clinical performance. For instance, the concentration of SP-B is substantially lower in the lung-minced preparation compared to surfactants derived from lung lavage extracts. The porcine-derived surfactant, poractant alfa, contains the most phospholipids per unit volume of all surfactants.

E. Synthetic surfactant preparations are composed of one or two phospholipids, usually DPPC and phosphatidylglycerol.
   1. Colfosceril palmitate (Exosurf®) for almost 20 years was the most widely used synthetic, protein-free surfactant. However, it has not been available for many years, but is mentioned only because of the trials comparing animal-derived to synthetic surfactants quoted widely.
   2. Lucinactant (Surfaxin®) is a new generation FDA-approved synthetic surfactant composed of DPPC, palmitoyl-oleoyl phosphatidylglycerol (POPG), and palmitic acid. It also includes a synthetic 21 amino acid peptide (sinapultide) consisting of repeats of lysine and leucine, whose spatial structure and function resemble that of SP-B. Aerosurf® is an aerosolized form of lucinactant that is undergoing clinical trials but is not currently FDA approved. If found to be beneficial, it could potentially provide the ability to administer surfactant therapy without the need for direct laryngoscopy and endotracheal intubation.

3. Another synthetic surfactant composed of DPPC, POPG, palmitic acid, and recombinant SP-C obtained by expression in a prokaryotic system has been recently developed. However, to date there are no published experiences involving neonates.

IV. Surfactant Responses

The clinical response to exogenous surfactant administration can be divided into three stages:

A. Stage one: acute treatment response (occurs within minutes post-administration). The initial response results from the biophysical properties of surfactant and depends on its rapid distribution to distal lung areas. An improvement in oxygenation is usually the first clinical response to surfactant instillation, which seems to derive primarily from improvements in the functional residual capacity of the lung. Because of this, continuous monitoring of oxygen saturation during and after administration is essential. Moreover, the improvement in gas exchange after administration may be quite rapid and inflation pressure and tidal volume must be adjusted by observing chest expansion, monitoring tidal volume, and intermittently measuring blood gases. This acute response to surfactant is faster for preparations that contain more SP-B.

B. Stage two: sustained response to the initial surfactant dose (occurs within hours post-administration).

1. It results from improving lung mechanics and recycling of surfactant components from the air spaces into type II cells, where the lipids are, in part, diverted into lamellar bodies to be secreted again into the alveolar spaces.
2. Thus, surfactant treatment quickly increases the metabolic pool for endogenous metabolism. In general, recycling is more efficient in the preterm lung, where recycling rates as high as 80–90 % have been measured (Jobe 2006).
3. This, however, does not guarantee that only one dose of surfactant will be effective. In fact, some infants may still remain on mechanical ventilation with FiO_2 >30–40 % several hours after the first dose and may be eligible for retreatment. A poor response to a properly administered initial surfactant dose, especially if the infant was exposed to antenatal steroids, is often associated with asphyxia (shock lung), infection, or variable degrees of lung hypoplasia.
4. There is no proven benefit to giving more than two additional doses. Also, the benefit of giving surfactant beyond the first 48–72 h after birth has not been well established.

C. Stage three: continued response to the initial surfactant dosing (occurs days or perhaps weeks post-administration). It is attributed to the long half-life of both endogenous and exogenous surfactant components within the air spaces—this is estimated to be about 3 days for infants with RDS. The net balance of a slow synthesis, secretion, metabolism, and clearance of surfactant and its components allows the infant with RDS to accumulate a large amount of surfactant over many days.

V. Efficacy of Surfactant Use for RDS

A. Overall efficacy of surfactant

1. Surfactant administration for prevention or treatment of RDS is very effective as shown in many randomized trials and meta-analyses. Of note, most placebo-controlled trials of surfactant use were conducted before widespread use of antenatal steroids (most trials reported <40 % exposure) and without routine use of continuous positive airway pressure (CPAP).
2. Historically, surfactant was used either in a prophylactic or a rescue approach.
   a. The former involved administration within the first 30–60 min after birth regardless of respiratory status and usually to very preterm newborns at high risk for RDS. This

resulted in administration of surfactant to variable proportions of infants who would not have developed RDS.

b. Rescue (treatment) administration was done in infants with established signs of respiratory failure and usually radiographic confirmation of RDS. In this approach, infants who were intubated and generally requiring FiO_2 >30–35 % were deemed eligible for treatment, which often occurred several hours after birth. More contemporary trials have used a higher threshold of FiO_2 to give surfactant.

c. Several trials also assessed the benefit of an early rescue strategy (early administration to symptomatic infants before two hours of life) compared to classic rescue treatment.

d. Over time, these distinctions have become more elusive, especially more recently with the advent of widespread use of CPAP or its derivatives as the initial form of respiratory support, even in extremely preterm neonates. These points notwithstanding, a large body of data from randomized trials has demonstrated:

(1) A consistent reduction of about 40 % in the odds of neonatal death after surfactant administration of either animal-derived or synthetic products given either for prophylaxis or rescue treatment compared to placebo.

(2) Both types of surfactants and administration strategies have also resulted in a significant 30–50 % reduction in the odds of pulmonary air leaks (pneumothorax, pneumomediastinum, or interstitial emphysema).

3. In spite of widespread use of surfactant, the incidence of BPD has not consistently decreased, although it has been suggested that the severity of this condition has been ameliorated. Likewise, the occurrence of other complications of prematurity has not been significantly reduced by surfactant therapy.

4. Earlier overviews of controlled trials demonstrated reductions in mortality and pneumothorax with prophylactic administration of surfactant compared to waiting for significant RDS to develop. However, these improvements have not been shown in systematic reviews of more contemporary trials, which have incorporated routine use of CPAP during post-delivery stabilization as well as widespread use of antenatal steroids (usually over 80–90 %).

5. More recently, surfactant has been administered using the INSURE (INtubate-SURfactant-Extubate) approach in which surfactant is given after elective endotracheal intubation, followed by a variable period of mechanical ventilation. This approach is generally well tolerated and results mainly in decreases in the need for mechanical ventilation, but no overall reductions in mortality or BPD have been demonstrated. Moreover, this approach may be more suitable for infants above 25–26 weeks of gestational age not requiring intubation during delivery room resuscitation. For those infants at the highest risk for RDS, in which an endotracheal tube has already been placed during resuscitation, there is probably very little additional morbidity from giving surfactant.

6. Several recent randomized trials (COIN, SUPPORT, and CURPAP trials) have examined whether using CPAP versus the more traditional approach of intubation and giving surfactant in the delivery room reduces BPD and mortality among very preterm infants between 24 and <29 weeks.

a. These trials are quite different in design and inclusion/exclusion criteria than previous surfactant trials, which makes it harder to draw generalizable conclusions from their results. For instance, some of them only permitted surfactant administration at much higher FiO_2 than what had been previously studied and recommended (>50 % FiO_2 in SUPPORT and 60 % FiO_2 in COIN).

b. In the SUPPORT trial, the ventilation criteria for extubation, albeit different between the two groups, were much higher than parameters used in previous trials and exceeded even prior indications for surfactant re-dosing. This notwithstanding, the investigators suggested that early use of CPAP in the delivery room reduces the need for mechanical ventilation and the proportion of infants needing surfactant. Moreover, they reported a trend towards less BPD among those infants getting initial CPAP and, in post-hoc analysis, less mortality of infants between 24 and <26 weeks; however, no specific data on what proportion of these most immature infants ultimately received surfactant was reported.
c. To the contrary, delaying surfactant administration may also increase the risks of pneumothorax and overall air leaks. Moreover, given that in both, the COIN and SUPPORT trials, more than 50 % of infants <26 weeks randomized to CPAP were intubated early, it seems reasonable to consider giving surfactant to them once the endotracheal tube has been placed and they demonstrate the need for supplemental oxygen.

VI. Head-to-Head Comparisons of Surfactants
A. Many randomized trials have compared the efficacy of animal-derived surfactant to synthetic surfactants. Previous meta-analyses grouped surfactants by their origin, i.e., natural (animal-derived) versus synthetic; however, given the enormous differences in composition and mode of administration, better comparison data are derived from head-to-head comparisons of surfactants. Even though it is not the purpose of this chapter to enumerate all of these comparisons conducted to date, below are some conclusions.
B. Administration of a surfactant preparation that contains surfactant proteins or their synthetic mimics generally leads to a more rapid onset of action as determined by weaning of FiO_2 and ventilatory support. Moreover, the onset of action is faster among animal-derived surfactants that contain more SP-B compared to those with lesser amounts of this protein.
C. The aforementioned effect probably relates to the lower occurrence of air leaks when surfactants containing surfactant proteins are compared to those containing only phospholipids without any protein.
D. In spite of these findings, updated data from these head-to-head comparison trials have not demonstrated any overall differences in mortality or BPD as a result of using different surfactants. The sole exceptions to this are the trial comparing poractant to pumactant from over 2 decades ago, and a recent systematic review comparing poractant to beractant, which showed a lower mortality favoring poractant.
E. Two randomized clinical trials compared the peptide-containing synthetic surfactant lucinactant to colfosceril palmitate, beractant, and poractant. They reported more survivors without BPD with lucinactant compared to colfosceril. However, there was no significant difference in survival without BPD between the three protein-containing surfactants. Moreover, there were no differences in other common complications of prematurity. However, colfosceril is no longer available and lucinactant in its liquid form is not actively being commercialized.

VII. Administration and Practical Concerns
A. All animal-derived surfactants require warming to room temperature before administration. The FDA-approved liquid formulation of lucinactant requires a warming step at 44 °C in a heating block for 15 min before administration. Surfactant treatment should be accomplished after clinical ascertainment of proper endotracheal tube placement. Performing a chest radiograph prior to giving surfactant is only indicated among preterm infants at high risk of RDS when conditions such as pneumothorax need to be ruled out.

B. Manufacturer's recommended doses are indicated in Table 58.1.
   1. Dosing is usually divided into two aliquots (although some manufacturers recommend four aliquots) and administered via a 5-French catheter passed in the endotracheal tube while the infant is ventilated to ensure maximal dispersion.
   2. It is best to avoid disconnecting the infant from the ventilatory circuit during administration to provide continuous positive pressure. As per manufacturers' recommendations, the infant's head and torso should be rotated 30–45° to the right for the first half-dose and to the left for the remaining aliquot. Poractant can also be administered in one rapid bolus without positioning, interruption of mechanical ventilation, or the need for manual ventilation. Some studies have reported safe administration using a dual-lumen endotracheal tube.
   3. Transient oxygen desaturation and mild bradycardia are frequently observed during administration and may require adjustment of the ventilatory settings and FiO_2 or interruption of surfactant administration. Occasionally endotracheal tube obstruction and reflux of surfactant are seen.
   4. Although some head-to-head comparisons of surfactants have revealed few differences in these complications between the various preparations studied, most side effects were transient and did not lead to significant morbidity. Moreover, these differences did not seem to be related to the volume of administration and are more common with repeated dosing.

C. Administration of surfactant without endotracheal intubation will likely be more common in the near future. The two approaches currently being evaluated are administration via techniques commonly referred to as "Minimally Invasive Surfactant Therapy" (MIST) or "Less Invasive Surfactant Therapy (LIST)," or delivery via aerosolization of surfactant.
   1. Both, MIST or LIST, still require performing direct laryngoscopy and giving surfactant using either a nasogastric or another relatively rigid tube introduced past the vocal cords. Reports outlining the steps involved in these techniques have not consistently described whether infants were pre-medicated before laryngoscopy and whether CPAP was used during administration. Moreover, these techniques are not exempt from side effects and several authors have reported relatively similar complications as those observed after endotracheal intubation to administer surfactant. Furthermore, reflux of surfactant and potentially a frequent need for re-dosing remain of concern. Trials of MIST or LIST have been generally either single-center studies or experiences in relatively larger, more stable preterm infants >26–27 weeks of gestation. Recent MIST trials include the AMV (Avoidance of Mechanical Ventilation by Surfactant Administration) trial, the Take Care study, and NINSAPP (Surfactant Application During Spontaneous Breathing with Continuous Positive Airway Pressure in Premature Infants <27 Weeks) trial. In this trial surfactant therapy administered via a feeding tube was found to reduce the need for subsequent intubation and ventilation, and to improve short-term respiratory outcomes. Further studies are currently ongoing to clarify specifics of this approach.
   2. Aerosolization of surfactant. This technique, if proven clinically feasible and effective, has the potential to revolutionize surfactant administration. It has been suggested that for aerosolized surfactant to work the particles generated must be about 2 μm in diameter and be able to reach the distal airspaces. There are several types of aerosol generators, namely jet, ultrasonic, vibrating membrane, and a heated capillary system. How these systems operate has been reviewed recently. Many studies in animal models of RDS have demonstrated that aerosolized surfactant results in improvements of gas exchange and pulmonary mechanics.

There has been limited clinical experience with aerosolized surfactant in human newborns. There is only one small randomized trial of aerosolized surfactant (poractant) published to date. This trial used a jet nebulizer as the delivery method. Thirty-two infants with established RDS on CPAP were enrolled. No benefits were observed, and the authors suggested that the aerosolized surfactant delivery method needed to be optimized. A more contemporary small uncontrolled trial demonstrated the feasibility of aerosolizing lucinactant using a vibrating membrane generator to prevent RDS among preterm infants between 28 and 32 weeks of gestation.

There are many challenges that will need to be overcome before this technique comes to fruition. Not only the delivery method and particle size are critical variables, but also dosing, duration of the aerosolization, potential loss of surfactant to the upper airway and gastrointestinal tract, and the best CPAP system to use, among others, are also of major importance. A recent review of aerosol delivery to ventilated newborns discusses in detail some of these considerations.

VIII. Use of Surfactant for Other Neonatal Indications

Many experimental and clinical studies have suggested that the pathogenesis of various neonatal respiratory disorders, such as meconium aspiration syndrome (MAS), pneumonia/sepsis, BPD, and congenital diaphragmatic hernia (CDH), includes either inactivation of surfactant or deficient synthesis of its components. Therefore, these disorders have been thought as potential targets for surfactant therapy. However, the clinical evidence to support this is limited and often not evaluated in appropriately sized randomized trials.

A. Meconium aspiration syndrome

1. Several randomized trials have shown that the administration of surfactant to infants with MAS improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO).
2. There are certain caveats, though:
   a. Most infants entered in these trials were quite sick and on high levels of support as determined by an oxygenation index in excess of 15–20. The benefit of surfactant among infants with MAS who are not intubated or have moderate degrees of respiratory disease remains unknown.
   b. Primarily animal-derived surfactants have been studied when surfactant was given as a bolus. Some trials utilized a larger dose of phospholipid than that used for RDS.
   c. The beneficial effects of surfactant may not appear until more than one dose is administered.
   d. An updated meta-analysis of all trials of bolus surfactant confirmed that its administration may reduce the severity of MAS and lower the number of infants requiring ECMO (El Shahed et al. 2014).
   e. Two randomized trials have assessed the efficacy and safety of bronchoalveolar lavage with dilute bovine (beractant) or peptide-containing synthetic surfactant (lucinactant) in severe MAS. These showed some improvement in respiratory function (trend towards shorter duration of mechanical ventilation) and a decrease of the composite outcome of death or requirement for ECMO in post-hoc analysis (Dargaville et al. 2010). However, there are not enough infants studied to develop firm conclusions.

B. Pneumonia and sepsis

1. Administration of animal-derived surfactant can improve oxygenation and decrease ventilatory requirements in preterm and term infants with respiratory failure associated with group B streptococcal sepsis.

2. However, there is presently insufficient evidence to determine whether surfactant treatment improves the long-term outcome of septic newborns with respiratory failure and its use cannot be recommended for this purpose.

C. Bronchopulmonary dysplasia
   1. Data from animal studies and infants evolving to or with established BPD have demonstrated quantitative and qualitative abnormalities of surfactant.
   2. Observational studies showed transient improvements in oxygenation and ventilatory support among infants with BPD given exogenous surfactant. These have been confirmed in two recent placebo-controlled randomized trials using either lucinactant or calfactant. The latter also included administration of inhaled nitric oxide. However, no major impact on prevention of BPD has been reported to date. Therefore, administration of surfactant alone for infants evolving to BPD remains under study and cannot be widely recommended.
   3. This notwithstanding, using surfactant as a vehicle for other interventions aimed at prevention of BPD may become a viable alternative. A recent randomized trial investigated whether the addition of the steroid budesonide to surfactant given via an endotracheal tube was helpful to decrease the risk of developing BPD (Yeh et al. 2016). This study randomized 265 very low birth weight infants with significant RDS by 4 h after delivery (receiving mechanical ventilation and $FiO_2 \geq 0.5$) to surfactant alone (100 mg/kg) or with the addition of budesonide (0.25 mg/kg). The authors showed a significant reduction in the outcome of death or BPD (44 % vs 66 %) and also decreases in pro-inflammatory cytokines in tracheal aspirates. Of note, a small study in preterm lambs demonstrated that intratracheal administration of a similar dose of budesonide resulted in peak plasma concentrations that are inversely related to the oxygenation index and, very importantly, no accumulation in brain tissue.

D. Congenital diaphragmatic hernia
   1. Determinations of surfactant phospholipids or surfactant proteins in animal models of CDH, in amniotic fluid, and in some infants with this condition have implicated a quantitative deficiency of surfactant components in its pathogenesis.
   2. To date there are no randomized trials examining this important clinical question. However, evidence from large observational databases does not support its routine use in the management of these infants regardless of whether they are preterm or term.

Suggested Reading

Ballard RA, Keller RL, Black DM, Ballard PL, et al. Randomized trial of late surfactant treatment in ventilated preterm infants receiving inhaled nitric oxide. J Pediatr. 2016;168:23–9.

Berggren E, Liljedahl M, Winbladh B, Andreasson B, et al. Pilot study of nebulized surfactant therapy for neonatal respiratory distress syndrome. Acta Paediatr. 2000;89:460–4.

Blanco O, Perez-Gil J. Biochemical and pharmacological differences between preparations of exogenous natural surfactant used to treat Respiratory Distress Syndrome: role of the different components in an efficient pulmonary surfactant. Eur J Pharmacol. 2007;568:1–15.

Chong E, Greenspan J, Kirkby S, Culhane J, Dysart K. Changing use of surfactant over 6 years and its relationship to chronic lung disease. Pediatrics. 2008;122:e917–21.

Dargaville P, Copnell B, Mills J, et al. Randomized controlled trial of lung lavage with dilute surfactant for meconium aspiration syndrome. J Pediatr. 2010;158:383–9.

Dargaville PA, Aiyappan A, De Paoli AG, et al. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. Neonatology. 2013;104:8–14.

Dunn M, Kaempk J, de Klerk A, de Klerk R, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128:e1069–76.

El Shahed AI, Dargaville P, Ohlsson A, Soll RF. Surfactant for meconium aspiration syndrome in term and late preterm infants. Cochrane Database Syst Rev. 2014;12, CD002054. doi:10.1002/14651858.CD002054.pub3.
Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. J Aerosol Med Pulm Drug Deliv. 2010;23:303–9.
Gopel W, Kribs A, Ziegler A, Laux R, et al. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011;378:1627–34.
Gupta S, Donn SM. Novel approaches to surfactant administration (Neonatal Lung Disease and Respiratory Failure). Crit Care Res Pract. 2012; article ID 278483. doi:10.1155/2012/278483.
Jobe AH. Pharmacology review: why surfactant works for respiratory distress syndrome. NeoReviews. 2006;7:e95–106.
Ketko AK, Donn SM. Surfactant-associated proteins: structure, function, and clinical implications. Curr Pediatr Rev. 2014;10:162–7.
Kribs A, Roll C, Gopel W, Wieg C, et al. Nonintubated surfactant application vs conventional therapy in extremely preterm infants. JAMA Pediatr. 2015;169:723–30.
Lally KP, Lally PA, Langham MR, Hirschl R, et al. Congenital Diaphragmatic Hernia Study Group. Surfactant does not improve survival rate in preterm infants with congenital diaphragmatic hernia. J Pediatr Surg. 2004;39:829–33.
Laughon M, Bose C, Moya F, et al. A pilot randomized, controlled trial of later treatment with a peptide-containing, synthetic surfactant for the prevention of bronchopulmonary dysplasia. Pediatrics. 2009;123(1):89–96.
Mazela J, Polin R. Aerosol delivery to ventilated newborn infants: historical challenges and new directions. Eur J Pediatr 2010. doi:10.1007/s00431-010-1292-6, published on line September 28, 2010.
Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358:700–8.
Moya F, Javier MC. Myth: all surfactants are alike. Semin Fetal Neonatal Med. 2011;16:269–74.
Moya F, Maturana A. Animal-derived surfactants versus past and current synthetic surfactants: current status. Clin Perinatol. 2007;34:145–77.
Moya F, Gadzinowski J, Bancalari E, et al. A multicenter, randomized, masked comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. Pediatrics. 2005;115:1018–29.
Perez-Gil J, Keough KM. Interfacial properties of surfactant proteins. Biochim Biophys Acta. 1998;1408:203–17.
Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. Cochrane Database Syst Rev. 2007;4, CD006069.
Pfister RH, Soll R, Wiswell TE. Protein-containing synthetic surfactant versus protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. Cochrane Database Syst Rev. 2009;4, CD006180.
Polin R, Carlo W, Committee on Fetus and Newborn, American Academy of Pediatrics. Surfactant replacement therapy for preterm and term neonates with respiratory distress. Pediatrics. 2014;133:156–63.
Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2012;(3):CD000510. doi:10.1002/14651858.CD000510.pub2.
Sandri F, Plavka R, Ancore G, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics. 2010;125:e1402–9.
Singh N, Hawley KL, Viswanathan K. Efficacy of porcine versus bovine surfactants for preterm newborns with respiratory distress syndrome: systematic review and meta-analysis. Pediatrics. 2011;128:e1588–95.
Sinha SK, Lacaze-Masmonteil T, Valls I, Soler A, et al. A randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics. 2005;115:1030–8.
SUPPORT Study Group of the Eunice Kennedy Schriver NICHD Neonatal Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362:1970–8.
Whitsett JA. The molecular era of surfactant biology. Neonatology. 2014;105:337–43.
Whitsett JA, Wert SE, Weaver TE. Diseases of pulmonary surfactant homeostasis. Annu Rev Pathol. 2015;10:371–93.
Wolfson M, Wu J, Hubert T, Gregory T, et al. Lucinactant attenuates pulmonary inflammatory response, preserves lung structure, and improves physiologic outcomes in a preterm lamb model of RDS. Pediatr Res. 2012;72:375–83.
Yeh TF, Chen CM, Wu SY, Husan Z, et al. Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2016;193:86–95.

Pharmacologic Agents

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I. Pharmacologic agents (other than antimicrobials, Chap. 70 and surfactant, Chap. 58) that may be used commonly during respiratory support include analgesics, bronchodilators, corticosteroids, diuretics, inotropes, neuromuscular blocking agents, sedatives, and pulmonary vasodilators. The following is a list of frequently used drugs with recommended indications, doses, and relevant side effects. These do differ according to various sources. Individual and institutional practices, therefore, may also be different.

II. Analgesics (Chap. 62)

A. **Acetaminophen**

1. Description: for treatment of mild to moderate pain, post-operative pain, and fever. It is an analgesic and antipyretic with no anti-inflammatory properties. Well absorbed orally and, less predictably, rectally. Conjugated in the liver and excreted in urine. Half-life is about 4 h.
2. Dose: intravenous, rectal, or oral administration.
   I.V.: Loading dose: 20 mg/kg followed by 7.5–10 mg/kg/dose every 12 h (maximum daily dose 30 mg/kg/day).
   Oral: 10–15 mg/kg/dose every 6–8 h; maximum daily dose: 60 mg/kg/day.
   Rectal: Loading dose: 30 mg/kg; then 20 mg/kg/dose every 6–8 h; and maximum daily dose: 90 mg/kg/day.
3. Relevant side effects: edema (peripheral), hypertension, hypervolemia, hypotension, tachycardia, atelectasis, abnormal breath sounds, dyspnea, hypoxia, pleural effusion, pulmonary edema, stridor, wheezing, muscle spasms, and pain in extremity.

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B. **Fentanyl**

1. Description: short-acting opioid analgesic used for peri-operative pain relief. The short action is more a function of rapid redistribution into fat and muscle depots because the elimination half-life is actually quite long—4 h in the adult and probably twice as long in the newborn. Morphine may be a better alternative for sustained pain relief.
2. Dose: Intravenous, intramuscular, or intranasal administration. Fentanyl at anesthetic doses will provide good pain relief for about 1 h in the newborn.
   Anesthetic doses: 5–15 mcg/kg IV.
   Analgesic doses: 1–5 mcg/kg/dose IM/IV repeated 30–60 min later as needed. Continuous intravenous infusions of 1–3 mcg/kg/h are effective for a period, but tolerance develops rapidly and, if the infusion is continued for more than 4–5 days, serious signs of withdrawal may follow discontinuation.
   Intranasal: Children ≥10 kg: 1.5 mcg/kg once (maximum: 100 mcg/dose); reported range: 1–2 mcg/kg. Some studies that used an initial dose of 1.5 mcg/kg allowed for additional incremental doses of 0.3–0.5 mcg/kg to be administered every 5 min, not to exceed a total dose of 3 mcg/kg depending upon pain type and severity.
3. Relevant side effects: respiratory drive will usually be abolished and assisted ventilation will be needed. Respiratory depression may also occur unexpectedly, presumably following redistribution from fat or muscle depots.

C. **Morphine**

1. Description: best studied opiate analgesic for use in the newborn period. For relief of severe pain, such as necrotizing enterocolitis, or following surgery.
2. Dose: intravenous, intramuscular, and oral. IM and IV doses are the same. The absorption of morphine by the oral route is poor and should not be used for treatment of acute pain.
   Pain: For severe pain, an IV loading dose of 100–150 mcg/kg followed by an infusion of 10–20 mcg/kg per hour is probably required. For mild to moderate pain in the non-ventilated baby, an IV dose of 100 mcg/kg once every 6–12 h may be sufficient depending upon postnatal age.
   Procedures: For elective intubation IV morphine at 50–100 mcg/kg at least 2 and preferably 5 min before intubation is recommended.
3. Relevant side effects: respiratory depression, urinary retention, and diminished peristalsis can occur with normal doses, and hypotension, bradycardia, and seizures can occur at higher doses.

III. Bronchodilators and Respiratory Stimulants

A. **Aminophylline/Theophylline**

1. Description: Treatment of apnea of prematurity (AOP), though caffeine is easier and safer to use. Therapeutic range for treatment of AOP is 7–12 mcg/mL and for treatment of bronchospasm in older infants is 10–20 mcg/mL. Aminophylline is the intravenous form of theophylline, which is administered orally. When using aminophylline the dose should be increased by 20 % to account for the salt form.
2. Dose: Based on aminophylline. A loading dose of 6 mg/kg followed by 2–4 mg/kg IV every 8–12 h based on postnatal age will generally abolish AOP in most babies. Treatment can be continued with oral theophylline. Plasma concentrations must be measured to ensure therapeutic range and to avoid toxicity since the therapeutic index is narrow**.**
3. Relevant side effects: common side effects include tachycardia, hyperactivity, and gastrointestinal disturbances. Toxicity occurs at plasma levels exceeding therapeutic range and is manifested by excessive tachycardia, nausea and vomiting, and convulsions.

B. **Caffeine**
   1. Description: Drug of choice for the treatment of AOP for many clinicians. More recently, caffeine has been shown to reduce the incidence and severity of bronchopulmonary dysplasia and is used as early as day 1 in intubated infants. It has a wider therapeutic index compared to theophylline, is well absorbed orally, and only needs to be given once daily. It is most commonly given as caffeine *citrate*, 1 mg of which is equivalent to 0.5 mg of caffeine *base*.
   2. Dose: Caffeine is usually prescribed as the citrate salt.
      Administer a loading dose of 20 mg/kg of caffeine citrate orally or IV, followed by a once daily dose of 5 mg/kg. Both the loading dose and the maintenance dose can be safely doubled, if necessary. Therapeutic concentrations of caffeine range from 10 to 20 mg/L. Toxicity occurs at concentrations exceeding 50 mg/L. Since the therapeutic index is wide, routine monitoring of plasma concentration is not necessary. It should be measured, however, if toxicity or therapeutic ineffectiveness is suspected at common doses.
   3. Relevant side effects: commonly include tachycardia, hyperactivity, and gastrointestinal disturbances. Toxicity is manifested by tachycardia, nausea and vomiting, and convulsions.

C. **Albuterol (USA)/Salbutamol (UK)**
   1. Description: Selective β_2 adrenergic agonist, bronchodilator. Adult half-life is 6 h. Well absorbed orally. However, increased hyperactivity is an undesirable side effect that is more prominent with oral dosing. In clinical practice oral use is avoided to the extent possible.
   2. Dose: Albuterol/Salbutamol may be used by inhalation or orally.
      Inhaled drug may be delivered by nebulization or metered dose inhaler.
      For nebulization, 1.25 mg/dose, nebulized 3–4 times daily, is a commonly used regimen. Metered dose inhalers deliver 90 mcg/spray. 1–2 puffs administered into the ventilator circuit is the most frequently reported dose.
   3. Relevant side effects: tachycardia, tremor, and irritability (even at normal doses). **Evidence to support its routine use in BPD is lacking.**

D. **Ipratropium**
   1. Description: anticholinergic bronchodilator, synergistic with β-agonists. Ipratropium is a synthetic derivative of atropine.
   2. Dose: Ipratropium is used by inhalation only. Inhaled drug may be delivered by nebulization or metered dose inhaler. When used by nebulization, 25 mcg/kg/dose, 3 times a day, is commonly used. Metered dose inhaler provides 21 mcg/actuation. Common dose: 1–2 actuations (puffs) every 8 h.
   3. Relevant side effects: tachycardia, tremor, and irritability (even at normal doses). These side effects may be exacerbated when used concomitantly with albuterol. **Evidence to support its routine use in BPD is lacking**.

E. **Epinephrine**
   1. Description: Direct acting sympathomimetic agent with a more marked effect on β-adrenoreceptors than on α-adrenoreceptors. Used for treatment of stridor following extubation or from any other cause or bronchodilation.
   2. Dose: used by inhalation nebulization: Racemic epinephrine (2.25 % solution): 0.05 mL/kg (maximum dose: 0.5 mL) diluted in 2 mL NS; others have reported use of 0.5 mL as a fixed dose for all patients; use lower end of dosing range for younger infants.

3. Relevant side effects: tachycardia, tremor, and irritability, even at normal doses. These side effects may be exacerbated when used concomitantly with albuterol or ipratropium.

IV. Diuretics

A. **Bumetanide**

1. Description: Loop diuretic more potent than furosemide and with similar mechanism of action. Half-life in newborns is 2–6 h.
2. Dose: Intravenous, intramuscular, or oral routes of administration can be used. The dose is the same for any route. 5–50 mcg/kg q6h IV, IM, or PO.
3. Relevant side effects: causes very significant urinary losses of sodium, chloride, calcium, and bicarbonate. Overuse can cause significant contraction alkalosis with blood pH exceeding 7.55. **Evidence to support its routine use in BPD is lacking.**

B. **Chlorothiazide**

1. Description: Benzothiazide diuretic usually combined with spironolactone for additional diuretic effect although spironolactone is a weak diuretic. Spironolactone has the added advantage of conserving potassium during chronic diuretic use. This is probably the safest diuretic combination for long term control of fluid retention in congestive cardiac failure and BPD in the newborn, although it can result in considerable urinary calcium losses.
2. Dose: Intravenous and oral routes of administration may be used.
   Intravenous: For acutely ill infants who are *nil per oral* 10–20 mg/kg/day in two divided doses is used by intravenous injection.
   Oral: The usual oral dose is 20–40 mg/kg/day (usually combined with 1–2 mg/kg of spironolactone) administered orally in two divided doses.
3. Relevant side effects: contraction alkalosis and electrolyte disturbances are extremely common and should be closely monitored during initial stages of treatment. Potassium supplements are not usually needed if both drugs are given together. However, if BOTH potassium supplements and spironolactone are used together, serum potassium should be monitored closely. **Evidence to support its routine use in BPD is lacking.**

C. **Furosemide (USA)/frusemide (UK)**

1. Description: A loop diuretic which inhibits active chloride reabsorption in the loop of Henle and the distal tubule resulting in reduced passive sodium reabsorption and diuresis. Causes significant urinary losses of sodium, chloride, potassium, bicarbonate, and calcium. Stimulates renal synthesis of prostaglandin E_2 and may increase the risk of patent ductus arteriosus. It is ototoxic and enhances the ototoxic effect of aminoglycosides. Chronic use may cause nephrolithiasis or nephrocalcinosis. There is some evidence for a direct effect improving short term lung function in BPD if nebulised furosemide is given.
2. Dose: Intravenous, oral, and nebulization are acceptable routes of administration.
   Intravenous: For acute treatment of fluid overload, 1 mg/kg IV given once or twice a day (or more frequently as indicated by the clinical condition). While there is no defined maximum dose suggested in the literature, excessive use may lead to acute contraction alkalosis, severe electrolyte abnormalities, and hypotension. In renal failure, a single 5 mg/kg dose may help to reduce ischemic tubular damage.
   Oral: 2–4 mg/kg orally two or more times a day for symptomatic control of fluid overload is commonly used.
   Nebulization: although not a common route of administration, furosemide may be used by nebulization in BPD, 1 mg/kg of the IV preparation diluted in 2 mL of 0.9 % saline

and given by nebulizer once every 6 h may improve pulmonary compliance without affecting renal function.

3. Relevant side effects: electrolyte disturbances are extremely common especially with higher doses. Patients on long term treatment should receive potassium chloride to prevent hypokalemia. May lead to nephrolithiasis, nephrocalcinosis, and osteopenia with chronic use. **Evidence to support its routine use in BPD is lacking.**

D. **Spironolactone**

1. Description: Competitive inhibitor of aldosterone resulting in potassium sparing diuresis. Usually used in combination with a thiazide diuretic such as chlorothiazide, since spironolactone itself is a weak diuretic.
2. Dose: 1 mg/kg orally twice daily. Up to 4 mg/kg/24 h may be safely used, if necessary, but should be closely monitored.
3. Relevant side effects: hyperkalemia is the most common side effect. Serum potassium should be closely monitored. **Evidence to support its routine use in BPD is lacking.**

V. Inotropes (see also hydrocortisone) (Chap. 49)

A. **Dobutamine**

1. Description: A synthetic inotropic catecholamine with primarily β_1 adrenergic activity, but in high doses it exhibits both α and β_2 effects. It stimulates myocardial contractility and increases cardiac output. Because it has less effect than dopamine on systemic vascular resistance, it has less effect in raising blood pressure (however, effectively increasing tissue perfusion is likely to be a more important goal than reaching a specific blood pressure target). Tachycardia may occur at high dosage and tissue ischemia may occur if the infusion infiltrates.
2. Dose: Intravenous route only.
   Start with a dose of 5 mcg/kg/min by continuous IV infusion, increasing to 10–20 mcg/kg/min if needed. Do not give bicarbonate or other alkaline solutions through the same catheter, as this will inactivate dobutamine. *Never give this through an arterial catheter.*
3. Relevant side effects: tachycardia is most common.

B. **Dopamine**

1. Description: A naturally occurring catecholamine precursor of noradrenaline.
2. Dose: Intravenous route only. At low doses (2–5 mcg/kg/min), dopamine causes coronary, mesenteric, and renal vasodilation (though it is questionable whether this is of clinical significance), while at high doses (6–20 mcg/kg/min) it causes vasoconstriction. It is best given via a central vein and it is inactivated by bicarbonate or other alkaline solutions. *Never give this through an arterial catheter.*
3. Relevant side effects: hypertension, tachycardia, and irregular heart beat are most common.

C. **Milrinone**

1. Description: A selective phosphodiesterase inhibitor, which works by increasing cyclic AMP concentration. It acts as an inotrope but also has some vasodilator action resulting in increased cardiac output. Used only for short periods as long term oral use in adults was associated with an unexplained increase in mortality. The volume of distribution in infancy is much higher than in adults, thus it is necessary to use a loading dose.
2. Dose: Intravenous route only. Term neonates: Loading dose: 50–75 mcg/kg administered over 15–30 min followed by a continuous infusion of 0.5 mcg/kg/min; titrate to effect; range: 0.25–0.75 mcg/kg/min has been used.

3. Relevant side effects: ventricular arrhythmias including ventricular ectopic activity, ventricular tachycardia, and ventricular fibrillation, supraventricular arrhythmias, hypotension, rarely angina/chest pain, and torsade de pointes (polymorphic ventricular tachycardia). Hypokalemia, thrombocytopenia, and abnormal liver function tests have also been reported with prolonged use.

D. **Noradrenaline (norepinephrine)**
   1. Description: Sympathomimetic vasoconstrictor. Mainly causes increased cardiac contractility, increased heart rate, and increased myocardial oxygen consumption (β_1 stimulation). High dose infusion can also increase peripheral vasoconstriction (α_1 stimulation), resulting in significantly increased cardiac afterload and a decrease in cardiac output.
   2. Dose: Intravenous route of administration only. In acutely hypotensive infants, the starting dose is 0.1 mcg/kg/min of noradrenaline base via a central vein. This may be increased to a maximum of 1.5 mcg/kg/min as long as extremity perfusion and urine output are carefully monitored. *Never give this through an arterial catheter.*
   3. Relevant side effects: respiratory distress, cardiac arrhythmias, palpitations, bradycardia, tachycardia, hypertension, chest pain, pallor, local organ ischemia (from vasoconstriction of renal and mesenteric arteries), ischemic necrosis and sloughing of superficial tissue after extravasation.

E. **Adrenaline (epinephrine)**
   1. Description: Direct acting sympathomimetic agent with a more marked effect on β-adrenoceptors than on α-adrenoceptors. Used in the treatment of cardiac arrest secondary to electromechanical dissociation or as an infusion to treat serious hypotension (though this may cause significant vasoconstriction and is likely to affect renal perfusion).
   2. Dose: Intravenous, endotracheal, intraosseous, and intracardiac.
      Dosing: Neonatal.
      Cardiopulmonary resuscitation:
      IV: 0.01–0.03 mg/kg (0.1–0.3 mL/kg of *1:10,000* solution) every 3–5 min as needed.
      Endotracheal: (Note: *IV route preferred*) ET: 0.05–0.1 mg/kg (0.5–1 mL/kg of *1:10,000* solution) every 3–5 min until IV access established or return of spontaneous circulation. Current AHA Guidelines (2015) recommend ET route only if vascular or intraosseous route not available. Only one dose should be given and attempts to achieve central venous access should be made.
      Post-resuscitation infusion to maintain cardiac output or stabilize: Continuous IV/IO infusion rate: 0.1–1 mcg/kg/min; doses <0.3 mcg/kg/min generally produce β-adrenergic effects and higher doses (>0.3 mcg/kg/min) generally produce alpha-adrenergic vasoconstriction; titrate dosage to desired effect.
      Inotropic support: Continuous IV infusion rate: 0.1–1 mcg/kg/min; titrate dosage to desired effect.
      Hypotension/shock, fluid-resistant: Continuous IV infusion: 0.1–1 mcg/kg/min; doses up to 2 mcg/kg/min may rarely be necessary, may be combined with inotropic support. *Never give this through an arterial catheter.*
   3. *Relevant side effects*: cardiac arrhythmias, palpitations, bradycardia, tachycardia, hypertension.

VI. Mucolytics—**Doronase-Alpha**
   A. Description: Enzyme inhalant to thin secretions following respiratory infections.
   B. Dose: 2.5 mg/day through selected nebulizers in conjunction with a Pulmo-Aide®, Pari Proneb®, Mobilaire™, Porta-Neb®, or Pari Baby™ compressor system. Should not be diluted or mixed with any other drugs in the nebulizer, this may inactivate the drug.
   C. Relevant side effects: Fever, rash, dyspnea, and infection.

VII. Skeletal Muscle Relaxants

Indicated for clinical situations requiring skeletal muscle relaxation or need to reduce oxygen consumption.

A. **Atracurium**

1. Description: Atracurium besylate is a non-depolarizing competitive antagonist of acetylcholine at the motor end plate of voluntary muscle. Its effect can be reversed by anticholinesterases such as neostigmine. A major advantage is that it *does not depend on either renal or hepatic function for degradation*.
2. Dose: Intravenous route of administration only.
   A single dose of 0.25–0.4 mg /kg IV will cause complete paralysis lasting about 20 min. For sustained paralysis, this dose must be followed by repeat intravenous doses of 0.25 mg/kg as needed to maintain paralysis or a continuous intravenous infusion of 400 mcg/kg/h may be used for sustained paralysis.
3. Relevant side effects: cardiovascular effects are minimal and transient. Occasionally, wheezing or increased bronchial secretions may be seen.

B. **Cis-atracurium**

1. Description: Cis-atracurium besylate is a non-depolarizing competitive antagonist of acetylcholine at the motor end plate of voluntary muscle. It is an isomer of atracurium. Its effect can be reversed by anticholinesterases such as neostigmine. A major advantage is that it *does not depend on either renal or hepatic function for degradation.*
2. Dosing: For intravenous route only.
   IV: Initial: 0.1 mg/kg followed by maintenance dose of 0.03 mg/kg as needed to maintain neuromuscular blockade.
   Continuous infusion: 1–4 mcg/kg/min (0.06–0.24 mg/kg/h).
3. Relevant side effects: cardiovascular effects are minimal and transient. Occasionally, wheezing or increased bronchial secretions may be seen.

C. **Pancuronium**

1. Description: a non-depolarizing competitive antagonist of acetylcholine similar to atracurium. This effect extends to autonomic cholinergic receptors as well as those in skeletal muscle. It is partially metabolized in the liver and excreted by the kidneys and has a variable duration of action in the newborn of the order of 2–4 h. Its effects can be reversed with atropine and neostigmine.
2. Dose: Intravenous route of administration only.
   0.1 mg/kg to produce complete paralysis within a couple of minutes and adjust repeat doses of 0.05–0.15 mg/kg based on the duration of the observed effect may be given. Dose must be adjusted for renal failure. While continuous infusions of 0.02–0.04 mg/kg/h are occasionally used, in neonates the half-life is prolonged, eliminating the need for continuous infusions in most cases.
3. Relevant side effects: tachycardia, hypotension, wheezing, bronchospasm; skeletal muscle atrophy with prolonged use.

D. **Suxamethonium (Succinylcholine)**

1. Description: acts as a depolarizing competitive agonist of acetylcholine. Brief muscle contraction is seen before paralysis occurs. These contractions are reported as painful by adults. Used to produce skeletal muscle relaxation in procedures of short duration, such as endotracheal intubation or endoscopic exams.
2. Dose: *Intravenous route is preferred*. Intramuscular route is used for non-emergent intubation where IV access is not available.
   IV: 1–2 mg/kg/dose.
   IM: 2 mg/kg/dose if no IV access available.

These doses will provide paralysis for 5–10 min. A dose of atropine (15 mcg/kg) is often given before any dose of suxamethonium and should certainly be given before a second dose.

3. Relevant side effects: because of the risk of malignant hyperthermia, use of continuous infusion is *not* recommended. Rare reports of acute rhabdomyolysis, with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death have been reported in children with myopathies. Avoid use in patients with serum potassium >5.5 mEq/L.

E. **Vecuronium**

1. Description: A non-depolarizing competitive antagonist of acetylcholine similar to pancuronium. Metabolized by the liver and excreted in urine. Vecuronium, unlike pancuronium, is cardiostable, lacking side effects such as tachycardia, hypertension, or hypotension. Vecuronium is more cardiostable than atracurium, even at high doses. Vecuronium is preferred in patients with renal failure.
2. Dose: intravenous route of administration only.
   IV: 0.1 mg/kg/dose. These doses will cause complete paralysis lasting 1–2 h. Maintenance doses of 0.03–0.15 mg/kg/dose every 1–2 h may be used as needed. May be administered as a continuous infusion at 1–1.5 mcg/kg/min (0.06–0.09 mg/kg/*h*).
3. Relevant side effects: arrhythmias, tachycardia, hypotension, hypertension, respiratory insufficiency, bronchospasm, and apnea.

VIII. Steroids

A. **Budesonide**

1. Description: Potent corticosteroid used, most often administered by inhalation to treat advanced chronic lung disease.
2. Dose: Inhalation route preferred in neonates and infants.
   Limited neonatal and infant data.
   Initial: 0.25 mg twice daily or 0.5 mg once daily; maximum daily dose: 1 mg/day.
3. Relevant side effects: Respiratory tract infection generally related to local administration. Systemic absorption of locally administered budesonide has the potential to cause hypertension, hyperglycemia, and adrenocortical insufficiency in very young children. Growth suppression and osteopenia are common with chronic use if significant systemic absorption is present in the very young.

B. **Dexamethasone**

1. Description: Potent glucocorticoid similar to betamethasone. It is used in similar fashion to promote fetal lung maturation, although there is some evidence to suggest it is less effective. It appears to be beneficial in treating severe BPD, but the ideal treatment regimen has not yet been established and high-dose treatment in the neonatal period appears to be associated with an increased incidence of cerebral palsy in survivors. Treatment of babies with dexamethasone causes increased protein catabolism, which affects growth. Hypercalciuria, hypertension, hyperglycemia, gastrointestinal hemorrhage, left ventricular outflow tract obstruction, hypokalemia, and increased risk of infection are other well recognized adverse effects.
2. Dose: Intravenous route preferred.
   a. Traditional regimen: 0.25 mg/kg base orally or IV twice daily for 7 days followed if necessary by a 9 day course of tapering dosage.
   b. Durand regimen: 100 mcg/kg orally or IV twice daily for 3 days then 50 mcg/kg twice daily for 4 days.
   c. DART Trial regimen: 60 mcg/kg orally or IV twice daily on days 1–3, then 40 mcg/kg twice daily on days 4–6, 20 mcg/kg twice daily days 7–8, and 8 mcg/kg on days 9 and 10.

d. Post-intubation airway edema: IV: 0.25 mg/kg/dose given 2–4 h prior to scheduled extubation then every 8 h for a total of 3 doses; others have used 0.5 mg/kg/dose every 8 h for 3 doses with last dose administered 1 h prior to scheduled extubation; range: 0.25–0.5 mg/kg/dose for 1–3 doses; maximum dose: 1.5 mg/kg/day. A longer duration of therapy may be needed with more severe cases.

3. Relevant side effects: gastrointestinal perforation, hyperglycemia, leukocytosis, and hypertension. Hypothalamic–pituitary–adrenal axis suppression, sodium and water retention, growth suppression, glucose intolerance, hypokalemia, and gastrointestinal bleeding. Prolonged use may cause muscle weakness, bone mineral density reduction, and fractures.

C. **Hydrocortisone**

1. Description: Glucocorticoid with minimal mineralocorticoid effect. Primarily used for physiologic replacement, but can also be useful in the treatment of acute hypotension.
2. Dose: Intravenous and oral administration possible.
   BPD prevention (preterm neonates with prenatal inflammatory exposure): PNA ≤48 h: IV: 1 mg/kg/day divided every 12 h for 9 or 12 days, followed by 0.5 mg/kg/day divided every 12 h for 3 days; dose may be needed during acute illness. Doses of 2 mg/kg IV followed by 1 mg/kg every 8–12 h are effective in treating hypotension. The AAP suggests that for neonates with prenatal inflammatory exposure, low-dose hydrocortisone therapy (1 mg/kg/day) during the first 2 weeks of life may improve survival without BPD and without adverse neurodevelopmental outcomes.
   Hypoglycemia (refractory to continuous glucose infusion of >12–15 mg/kg/min): oral or IV: 5 mg/kg/day divided every 8–12 h or 1–2 mg/kg/dose every 6 h.
3. Relevant side effects: Gastrointestinal perforation, hyperglycemia, leukocytosis, hypothalamic–pituitary–adrenal axis suppression, sodium and water retention, growth suppression, glucose intolerance, hypokalemia, and gastrointestinal bleeding. Prolonged use may cause muscle weakness, bone mineral density reduction, and fractures.

IX. Sedatives (Chap. 62)

A. **Chloral hydrate**

1. Description: sedative, well absorbed orally, metabolized in the liver, and excreted in urine. Acts within 30 min, half-life of active metabolite is 36 h.
2. Dose: Oral or rectal route of administration. 45 mg/kg as a single dose. Higher doses (75 mg/kg) have been used for sedation for imaging but can produce respiratory depression. 30 mg/kg orally every 6 h can be helpful in babies with cerebral irritability. Drug accumulation may occur if used for more than 48 h.
3. Relevant side effects: respiratory depression, apnea, and gastric irritation.

B. **Lorazepam**

1. Description: Benzodiazepine anxiolytic and sedative. Metabolized in the liver and excreted in urine. Does not have any active metabolites. Longer acting than midazolam.
2. Dose: IV and oral routes of administration. Usual: 0.05 mg/kg/dose (maximum dose: 2 mg/dose) every 4–8 h; range: 0.02–0.1 mg/kg.
3. Relevantside effects: risk of propylene glycol toxicity. Monitor closely if using for prolonged periods of time or at high doses. Bradycardia, circulatory collapse, hypertension or hypotension, respiratory depression, and apnea.

C. **Midazolam**

1. Description: Benzodiazepine anxiolytic and sedative. Metabolized in the liver and excreted in urine. 1-hydroxy midazolam is an active metabolite. Drug and metabolite accumulation may occur with repeated doses. IV infusion or rapid bolus dosage has been reported to produce seizures in some babies.

2. Dose: Intravenous, intramuscular, and intranasal routes. 0.15 mg/kg IV, IM, or intranasally produces rapid sedation and can be used for induction of anesthesia. (*Midazolam does not relieve pain*.)
   Procedures: 0.1 mg/kg IV may be used for sedation prior to elective intubation (together with morphine for pain relief and atracurium for paralysis).
   Sedation: 0.1 mg/kg loading dose infused over 15–30 min is followed by 10–60 mcg/kg/h IV infusion can be used for sedation of ventilated babies for 3–4 days.
3. Relevant side effects: cardiac arrest, hypotension, and bradycardia.

X. Pulmonary Vasodilators

A. **Bosentan**

1. Description: Used for persistent pulmonary hypertension, it is a competitive antagonist of endothelin-1 at the endothelin-A (ET-A) and endothelin-B (ET-B) receptors. Under normal conditions, endothelin-1 binding of ET-A or ET-B receptors causes constriction of pulmonary blood vessels. By blocking this interaction, bosentan decreases pulmonary vascular resistance.
2. Dose: Very limited data.
   Full term neonate:
   Oral: 1 mg/kg/dose twice daily (for short term use 2–6 days).
3. Relevant side effects: edema, flushing, hypotension, palpitations, syncope, pruritus, anemia, hepatic insufficiency, and respiratory tract infections.

B. **Epoprostenol**

1. Description: PPHN refractory to inhaled nitric oxide. Epoprostenol causes direct vasodilation of pulmonary and systemic arterial vascular beds.
2. Dose: Epoprostenol is administered by continuous IV infusion.
   Continuous IV infusion: Doses are expressed in units of **nanograms** (ng)/kg/min.
   Low-dose regimen: Initial: 2 ng/kg/min slowly titrated by 1–2 ng/kg/min every 15–30 min as tolerated to 20 ng/kg/min over ~3 h.
   High-dose regimen: Initial: 20 ng/kg/min, slowly titrated (according to oxygenation) at 30 min intervals over 4–12 h to a mean dose of 60 ng/kg/min (range: 30–120 ng/kg/min).
   Administer through a central venous catheter; peripheral infusion may be used temporarily until central line is established. Epoprostenol should be infused using an infusion pump through a dedicated lumen exclusive of any other drugs. (Refer to package insert for storage, stability, and further administration instructions prior to use.)
3. Relevant side effects: Flushing, hypotension, tachycardia, agitation, infection, pain, pulmonary edema, and thrombocytopenia.

C. **Nitric oxide** (Chap. 63)

1. Description: Acts on receptors within the muscle of blood vessel walls to produce vasodilation. Rapidly inactivated by hemoglobin producing methemoglobin. Half-life less than 5 s. Vasodilator effect is therefore limited to the pulmonary circulation. Methemoglobin levels need to be monitored and kept below 2.5 %.
2. Dose: Given as a gas by inhalation. In babies and those more than ≥34 weeks' gestation start at 20 parts per million (ppm). If this produces a rise in post-ductal PaO_2 of at least 20 Torr (3 kPa) with no alteration in ventilator settings, reduce the concentration to the lowest compatible with a sustained response, usually 5 ppm. Stop treatment quickly if there is no response. Once started on nitric oxide babies are extremely sensitive to any interruption in supply.
3. Relevant side effects: methemoglobinemia, pulmonary edema, pulmonary hemorrhage, and toxicity from nitrogen dioxide formation.

D. **Sildenafil**
   1. Indications: Treatment of pulmonary hypertension (***off label use***).
   2. Dose: Oral administration only.
      Pulmonary hypertension: Initial dose: 0.5 mg/kg/dose every 8 h; doses are increased by 0.25 mg/kg/dose every 24 h if needed and if tolerated to maximum of 2 mg/kg/dose every 6–8 h.
   3. Relevant side effects: cerebrovascular hemorrhage, edema, flushing, hypotension, pulmonary hemorrhage, tachycardia, ventricular arrhythmia, dyspnea, epistaxis, nasal congestion, rhinitis, rhinorrhea, and sinusitis. **Evidence for both safety and efficacy is lacking.**

Suggested Reading

Neonatal formulary. 6th ed. Oxford: Wiley Blackwell Publications/BMJ Books; 2011.

Weinge G, editor. Textbook of neonatal resuscitation. 7th ed. Elk Grove Village: American Academy of Pediatrics; 2016.

Takemoto CK, Hodding JH, Kraus DM (eds). Pediatric and Neonatal Dosage Handbook. 21st ed, Hudson, OH, Lexi-Comp Inc, 2014.

Automatic Control of the Fraction of Inspired Oxygen

60

Nelson Claure and Eduardo Bancalari

I. Introduction and rationale
   A. Supplemental oxygen is required to maintain adequate oxygenation in most preterm infants with hypoxic respiratory failure and this can be prolonged.
   B. Frequently, the fraction of inspired oxygen (FiO_2) is excessive resulting in hyperoxemia and an increased risk of ROP and oxidative damage to the lungs and CNS.
   C. Arterial oxygen saturation is monitored continuously by pulse oximetry (SpO_2) and FiO_2 is titrated by the caregivers to maintain a clinically prescribed target range of SpO_2.
   D. In one multicenter study, SpO_2 was found to be kept within the target range only around 50 % of the time in preterm infants who required supplemental oxygen. SpO_2 exceeded the target range for about one third of the time and was below the target range nearly a fifth of the time. Maintenance of SpO_2 within the target range is more difficult in infants with chronic underlying lung disease and with increased infant to nurse ratio and workload.
   E. In this population, hyperoxemia is induced by excessively high FiO_2 whereas hypoxemia predominantly results from spontaneous hypoxemia spells. The severity and duration of hypoxemia spells is in part dependent on the staff responsiveness. In most instances, the response to hypoxemia consists of an increase in FiO_2 but this is often excessive and frequently FiO_2 is not returned to baseline after the hypoxemia episode ends, which results in hyperoxemia.
   F. Systems of automatic FiO_2 control have been developed to improve maintenance of SpO_2 within a target range selected by the clinician and thereby, to reduce exposure to hypoxemia, hyperoxemia, and exposure to supplemental oxygen.
II. General description
   A. Systems of automatic FiO_2 control consist of a pulse oximeter, the gas delivery device (i.e., ventilator, CPAP, hood, or cannula), and the closed loop control algorithm that continuously reads SpO_2 and determines the FiO_2 to be delivered.
   B. In general, algorithms of automatic FiO_2 control a target SpO_2 range or level and continuous adjustments of FiO_2 are inversely related to the difference between the measured and target

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SpO_2. The timing, magnitude, and frequency of adjustment determine the automatic response to gradual or rapid changes in SpO_2.

III. Effects on oxygenation, oxygen exposure, and workload
   A. Short term clinical studies have consistently shown that automatic FiO_2 control improves the maintenance of SpO_2 within a target range compared to manual adjustments made by the clinical staff and comparable or better than a fully dedicated nurse (Fig. 60.1).
   B. These studies showed automatic FiO_2 control can achieve substantial reductions in time at hyperoxemia and can wean the inspired O_2 more consistently than manual control.
   C. Spontaneous hypoxemia episodes are a significant challenge to the staff. Automatic FiO_2 control does not prevent these episodes but it has been shown to reduce the more severe and prolonged episodes.
   D. During routine care SpO_2 is frequently kept above the target range in an attempt to prevent or attenuate hypoxemia spells. A more consistent weaning by automatic FiO_2 control can reduce hyperoxemia but this may result in mild episodes of low SpO_2 in particular when the target range is low. Whether these mild episodes have adverse consequences or offset the benefits of less hyperoxemia is not known.
   E. Studies under routine clinical conditions showed considerably fewer manual adjustments necessary during automatic FiO_2 control. This suggests potential reductions in workload or the ability to redirect the staff effort to other areas of patient care.

IV. Practical considerations and possible limitations
   A. The potential benefits of automatic FiO_2 control are relative to the efficacy of manual control in targeting SpO_2. Hence, advantages of automatic FiO_2 may be greater in centers with staff limitations and large workload as well as among infants with greater oxygenation instability.
   B. In addition to SpO_2 monitoring similarly to what is done with standard pulse oximeters, systems of automatic FiO_2 control offer the ability to monitor FiO_2. These additional monitoring capabilities can warn the clinician when the currently delivered FiO_2 has exceeded or fallen below specific high or low thresholds or if the baseline FiO_2 has exceeded a high threshold level, indicating a deterioration in patient condition reflected by an increased need for supplemental oxygen to maintain SpO_2 within the targeted range. These automatic systems can also monitor the reliability of SpO_2 and adopt a fail-safe state when its accuracy is questionable.
   C. Automatic FiO_2 control can potentially lead to reduced attentiveness and mask conditions that can otherwise result in severe hypoxemia. Because, in some situations, increasing FiO_2 may not be the most appropriate response, automatic warnings when higher FiO_2 is consistently needed to keep SpO_2 in range should prompt the clinician's intervention. On the other hand, the automatic response can avert more severe hypoxemia until corrective measures are taken. Adequate monitoring of ventilation to recognize these conditions should be part of standard staff training and more particularly prior to the use of automatic FiO_2 control.
   D. SpO_2 is used for automatic FiO_2 control because it provides continuous and non-invasive measurements, but certain conditions can affect its reliability. In routine care, clinicians do not use SpO_2 for patient management if the signal is deemed unreliable. The same or stricter criteria must be applied when automatic FiO_2 control is being used. Automatic FiO_2 control algorithms can include steps to recognize reduced SpO_2 reliability.
   E. The most important parameter in automatic FiO_2 control is the target range of SpO_2 prescribed by the clinician. Because the optimal range of SpO_2 for preterm infants has not been yet defined, cautious selection of the target range with the goal of avoiding extreme SpO_2 values is recommended. SpO_2 ranges currently targeted during routine clinical care may have important consequences that become evident only when the ranges are maintained more effectively over time by the automatic systems.

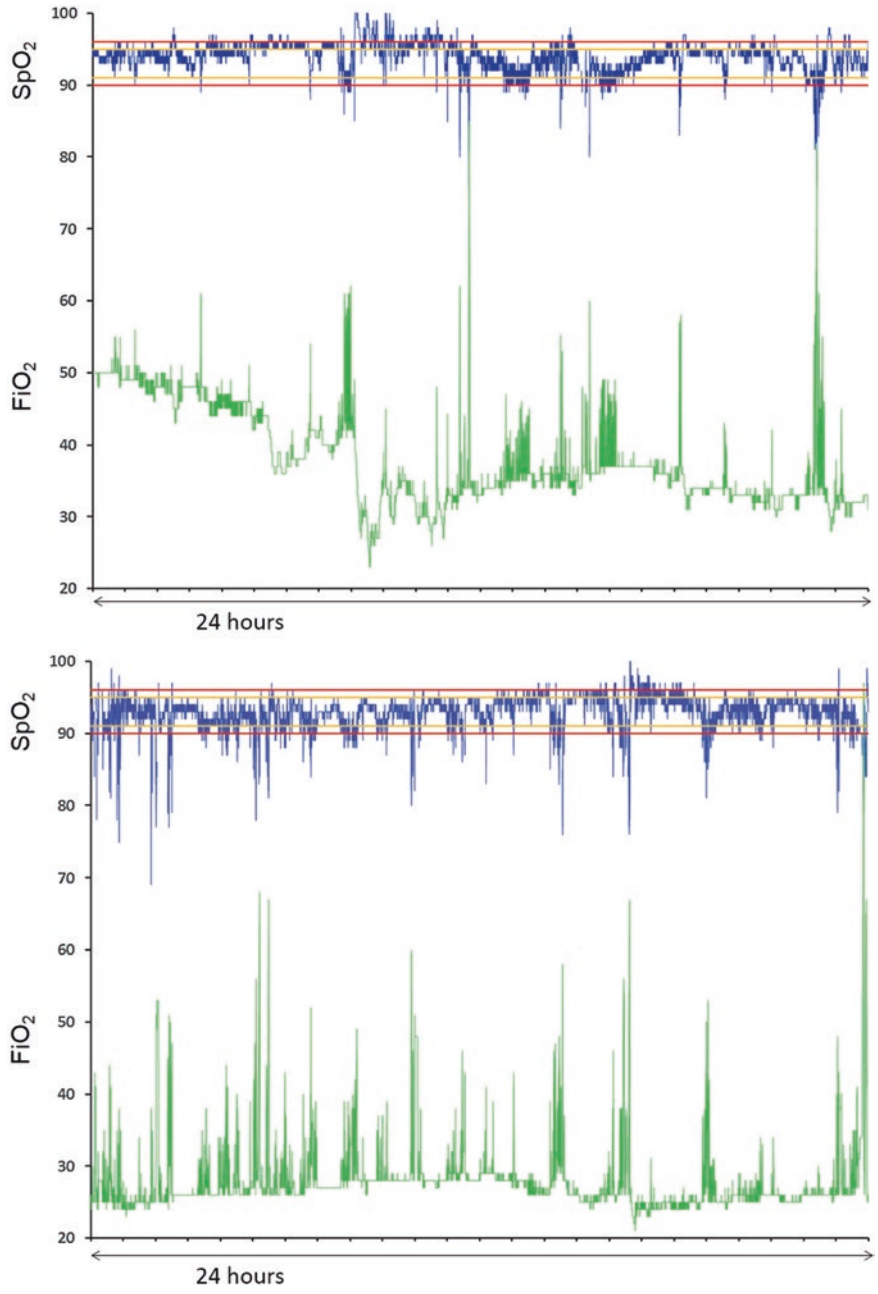

Fig. 60.1 Recordings from preterm infants undergoing 24 h of automatic FiO_2 control. Recordings illustrate automatic adjustments of FiO_2 to maintain SpO_2 within the relatively narrow target range of 91–95 % (*orange lines*) in infants with different degrees of oxygenation instability. Alarm limits are marked by *red lines*. Panel **a** shows a consistent weaning of FiO_2 with relatively few increases during episodes of hypoxemia followed by rapid return to baseline. Panel **b** shows a small and gradual changes in the baseline FiO_2 and more frequent increases in response to hypoxemia episodes. Panel **c** shows frequent automatic increases in FiO_2 in response to frequent hypoxemia episodes. In spite of the high episode frequency, in a relatively few episodes SpO_2 declines below 80 %

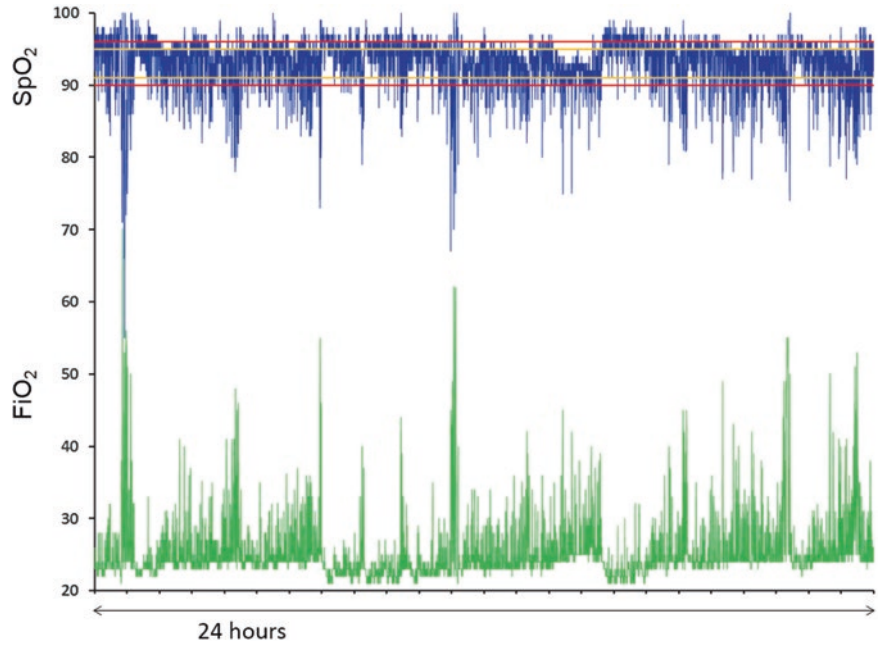

Fig. 60.1 (continued)

F. Comprehensive training and understanding of the advantages and limitations of automatic FiO_2 systems is recommended prior to their adoption for routine use.

V. Summary

A. Important detrimental effects can be associated with hyperoxemia and excessive inspired O_2 exposure as well as with insufficient oxygenation in the preterm infant. At present, these conditions are frequently observed because manual FiO_2 control does not adapt to the continuous changing needs of preterm infants. This can be overcome but requires considerable human resources.

B. Automatic FiO_2 control is an alternative to improve the maintenance of oxygenation and minimize exposure to extreme SpO_2 ranges and FiO_2. Short term studies have shown its feasibility and efficacy in achieving these goals.

C. Maintaining a balance between the avoidance of hypoxemia without inducing hyperoxemia or increased oxygen exposure may improve survival, long term respiratory, ophthalmic and neurodevelopmental outcomes in preterm infants. The extent to which automatic FiO_2 control can achieve this balance and improve these competing outcomes needs to be determined by large clinical trials.

Suggested Reading

Claure N, Bancalari E. Closed-loop control of inspired oxygen in premature infants. Semin Fetal Neonatal Med. 2015;20(3):198–204.

Claure N, Gerhardt T, Everett R, Musante G, Herrera C, Bancalari E. Closed-loop controlled inspired oxygen concentration for mechanically ventilated very low birth weight infants with frequent episodes of hypoxemia. Pediatrics. 2001;107:1120–4.

Claure N, D'Ugard C, Bancalari E. Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation: a pilot clinical trial. J Pediatr. 2009;155:640–5.

Claure N, Bancalari E, D'Ugard C, Nelin L, Stein M, Ramanathan R, Hernandez R, Donn SM, Becker M, Bachman T. Multicenter crossover study of automated adjustment of inspired oxygen in mechanically ventilated preterm infants. Pediatrics. 2011;127:e76–83.

Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, Cole CH, AVIOx Study Group. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. Pediatrics. 2006;118:1574–82.

Hallenberger A, Poets CF, Horn W, Seyfang A, Urschitz MS, CLAC Study Group. Closed-loop automatic oxygen control (CLAC) in preterm infants: a randomized controlled trial. Pediatrics. 2014;133:e379–85.

Lal M, Tin W, Sinha S. Automated control of inspired oxygen in ventilated preterm infants: crossover physiological study. Acta Paediatr. 2015;104:1084–9.

Lim K, Wheeler KI, Gale TJ, Jackson HD, Kihlstrand JF, Sand C, Dawson JA, Dargaville PA. Oxygen saturation targeting in preterm infants receiving continuous positive airway pressure. J Pediatr. 2014;164:730–6.

Sink DW, Hope SA, Hagadorn JI. Nurse:patient ratio and achievement of oxygen saturation goals in premature infants. Arch Dis Child Fetal Neonatal Ed. 2011;96:F93–8.

Urschitz MS, Horn W, Seyfang A, Hallenberger A, Herberts T, Miksch S, Popow C, Müller-Hansen I, Poets CF. Automatic control of the inspired oxygen fraction in preterm infants: a randomized crossover trial. Am J Respir Crit Care Med. 2004;170:1095–100.

van Kaam AH, Hummler HD, Wilinska M, Swietlinski J, Lal MK, Te Pas AB, Lista G, Gupta S, Fajardo CA, Onland W, Waitz M, Warakomska M, Cavigioli F, Bancalari E, Claure N, Bachman TE. Automated versus manual oxygen control with different saturation targets and modes of respiratory support in preterm infants. J Pediatr. 2015;167:545–50.e2.

van Zanten HA, Tan RN, Thio M, de Man-van Ginkel JM, van Zwet EW, Lopriore E, te Pas AB. The risk for hyperoxaemia after apnoea, bradycardia and hypoxaemia in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2014;99:F269–73.

Zapata J, Gómez JJ, Araque Campo R, Matiz Rubio A, Sola A. A randomised controlled trial of an automated oxygen delivery algorithm for preterm neonates receiving supplemental oxygen without mechanical ventilation. Acta Paediatr. 2014;103:928–33.

Aerosolization and Nebulization

61

Jan Mazela

I. Introduction
   A. Aerosols have proven to be an effective form of drug delivery. Nevertheless, the development of devices as well as medical agents designed for aerosolization to treat intubated and non-intubated infants with any kind of breathing support still presents a significant challenge.
   B. Low tidal volumes and functional residual capacity, high respiratory rates, a shortened particle residence time, and smaller airway diameters account for the diminished delivery of inhaled aerosols to the lower airways in these infants.
   C. There is a limited number of clinical deposition studies in the neonatal population because of the inability to use radio-labeled aerosols, which makes assessment of effectiveness of inhalational therapies in this population very difficult.
   D. Despite the paucity of clinical data, aerosols have been used to treat critically ill newborn infants without a clear understanding of the optimal aerosol delivery system, the drug deposition pattern in the lung, and the dose/response relationship for aerosolized medications.
   E. Aerosolized medications are administered to infants with ventilator support as part of routine therapy. Historically, regulatory approvals for use of nebulizer and delivery systems in the neonatal intensive care unit (NICU) have been based on adult studies or in vitro simulations.
      1. In September 2007, US Congress passed Title III of the FDA Amendments Act, The Pediatric Medical Device Safety and Improvement Act, which requires that new applications or protocols submitted to the FDA for use and approval of a medical device must include a description of any pediatric sub-population that suffers from the condition that the device is intended to treat, diagnose, or cure.
      2. This Act is supposed to prompt the development of new aerosol generators for infants requiring ventilator support, as the nebulizers and aerosol delivery systems in use prior to implementation of this Act were not designed solely for this population. Nevertheless, there has not been a single device developed and approved for the neonatal population.

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II. Terminology and Equipment
  A. Terminology
    1. Aerosolization is the process or act of converting some physical substance into the form of particles small and light enough to be carried in the air, i.e., into an aerosol.
    2. Nominal dose—total dose of drug prescribed. The amount of drug loaded onto the drug reservoir. This dose is device-specific, as recommended doses are different for different devices.
    3. Emitted dose—the total amount of drug emitted from the inhaler device and hence available to the user.
    4. Inhaled dose—amount of the drug available to the patient under breathing conditions (measured in in vitro settings including lung or upper airway model).
    5. Lung dose—the mass of drug delivered to the lung. The effect of a lung dose depends on several factors, including:
       a. Site of deposition
       b. Rate of clearance of the drug from airway
       c. Site of action of the drug
       d. The lung dose can be presented as follows:
          (1) Percentage of the nominal dose
          (2) Percentage of the mass of drug leaving the aerosol-generating device
          (3) Percentage of the mass of drug entering the mouth or nose
    6. Mass Median Aerodynamic Diameter (MMAD) is defined as the diameter at which 50 % of the particles by mass are larger and 50 % are smaller.
    7. Geometric Standard Deviation (GSD) is a measure of the spread of an aerodynamic particle size distribution (PSD). Typically calculated as follows:

$$\mathrm{GSD} = \left(d_{84} / d_{16}\right)^{1/2}$$

       where d_{84} and d_{16} represent the diameters at which 84 % and 16 % of the aerosol mass are contained, respectively, in diameters less than these diameters.
    8. Respirable fraction (RF) or fine particle fraction (FPF)—the mass fraction of inhaled particles penetrating into the non-ciliated airways.
    9. Laser diffraction—a popular method for particle size analysis. Laser diffraction consists of scattering laser light off an assembly of particles and collecting the scattered light using a special array of detectors. The signal from the detectors is really a pattern of scattered/diffracted light vs. angle. The scattered light pattern requires a complex mathematical algorithm to obtain an approximate representation of the PSD.
    10. Next Generation Impactor (NGI)—a unit commissioned by a consortium of pharmaceutical manufacturers for use by the industry as a tool for assessing aerosol particle size.
  B. Equipment (Table 61.1)
    1. Inhalers—devices which require active inhalation by a patient in order to entrain the aerosolized drugs.
    2. Metered Dose Inhalers (MDI)—are handheld aerosol devices that utilize propellant to deliver the therapeutic agent. MDI consists of a pharmacologic agent in suspension or solution, surfactant, propellant, and metering valve. Chlorofluorocarbon (CFC) propellants have been replaced by the hydrofluoroalkane propellant to decrease ozone depletion.
    3. Dry Powder Inhalers (DPI)—are breath-actuated devices which deliver drugs in powder form, stored in the capsule or blister, which is punctured prior to use. This inhaler requires active inspiratory flow to achieve proper drug delivery.

Table 61.1 Characteristics of different aerosol generators used for ventilated infants

	Comparison of different aerosol generators			
	Jet	Vibrating mesh	Ultrasonic	MDI
Principle of aerosol generation	Pressurized gas forms a jet passing over a capillary tube that draws liquid formulation into the jet stream	Aerosol is produced by micropumping action of the vibrating mesh containing 1000 funnel-shaped holes	Piezoelectric crystal converts an electrical signal into high frequency vibrations, creates a standing wave in the medication, and produces aerosol	Active drug is suspended in propellant which provides the force to generate the aerosol cloud when released from the canister
Gas flow	Active	Passive	Passive	Passive
Location within circuit	Inspiratory arm	Inspiratory arm or between "Y" and ET tube	Inspiratory arm	Inspiratory arm or between "Y" and ET tube
Residual volume	Large	Small	Small	HC size
Aerosol particle size	Depend on gas flow and formulation	Depend on mesh and formulation	Depend on formulation	Depend on HC size and type
Aerosol temperature	Low	Ambient	Ambient	Ambient
Efficacy expressed as inhaled dose % of nominal dose	Lower	Higher	Mid	Mid

Mazela, J. and R. Polin (2011). "Aerosol delivery to ventilated newborn infants: historical challenges and new directions." Eur J Pediatr **170**(4): 433–444

ET endotracheal, "*Y*" wye ventilator circuit connector, *HC* holding chamber

Table 61.2 Factors influencing inhaled dose in mechanically ventilated infants

Factors influencing effectiveness of inhalation therapies in mechanically ventilated infants					
Mechanical ventilation dependent		Aerosol generator dependent		Formulation dependent	
↑ Inhaled dose	↓ Inhaled dose	↑ Inhaled dose	↓ Inhaled dose	↑ Inhaled dose	↓ Inhaled dose
CPAP	IMV	MMAD = 1–3 μm	MMAD <1 and >3 μm	Aqueous solutions	Viscous solutions
Bigger VT	Smaller VT	Small residual volume	Large residual volume	Solutions	Suspension
Lower RR	Higher RR	MDI with VHC	MDI without HC	Temperature = 36 °C	Temperature <36 °C
Longer IT	Shorter IT	Detergent coated VHC	Non-coated HC		
Larger ET tube	Smaller ET tube	Aerosol flow = PIF	Aerosol flow > or < PIF		
Dry gas	Humid gas	Synchronized actuations/release	Non-synchronized actuations/release		
Low ventilator bias flow	High ventilator bias flow				

Mazela, J. and R. Polin (2011). "Aerosol delivery to ventilated newborn infants: historical challenges and new directions." Eur J Pediatr **170**(4): 433–444

CPAP continuous positive airway pressure, *IMV* intermittent mechanical ventilation, *MMAD* mass median aerodynamic diameter, *VT* tidal volume, *RR* respiratory rate, *MDI* metered dose inhaler, *HC* holding chamber, *ET* endotracheal, *PIF* peak inspiratory pressure

4. Holding Chamber—an extension add-on device that permits the aerosol plume from the MDI to expand and slow down, turning it into a very fine mist instead of a high-pressure actuation spray. Holding chambers can be equipped with one-way valves to avoid reverse air flow.
5. Nebulizers—devices which transform solutions or suspensions of medications into aerosols that are optimal for deposition in the lower airways.
   a. Ultrasonic nebulizer—it generates high frequency ultrasonic waves from electric energy via a piezoelectric element in the transducer. The ultrasonic waves are conducted into the surface where small particles are generated. It produces rather large particles compared to other nebulizers.
   b. Jet nebulizer—delivers compressed gas through a jet, causing an area of negative pressure, and draws the liquid up the tube by the Bernoulli effect. The downside of this nebulizer is adding additional flow and substantial cooling of the drug during nebulization. It produces small particles.
   c. Vibrating Mesh Nebulizer—stand-alone nebulizer which does not require any additional gas flow. Aerosol is generated by mesh vibrations, which push the solution through small pores and generate mist. It produces small particles.
   d. Capillary Aerosol Generator (CAG)—this is the newest class of nebulizers, which utilizes high pressures and energy in the form of heat to generate fine and well controlled aerosols, both from solutions as well as suspensions. Because of the small diameter of the capillary, the pharmaceutical agent is briefly exposed to high temperature, which evaporates water content without destroying the drug structure.

III. Factors Influencing Effectiveness of Inhalational Therapies (Table 61.2)
   A. Type and Location of The Nebulizer
      1. There are only a few options for aerosol entrainment within the ventilator circuit.
         a. Placement of the nebulizer within the inspiratory limb of the circuit
         b. Introducing the aerosol between the wye connector and patient interface
      2. Connecting the nebulizer to the inspiratory arm via a "T" shape connector is recommended for MDI, vibrating mesh nebulizers, and jet nebulizers. Entraining the aerosol between the wye connector and patient interface is used mainly for MDIs with a holding chamber (HC), although some recent studies have also suggested the utility of placement of vibrating mesh nebulizers in this location whenever a nebulizer with a low residual volume is used.
      3. The general overview of clinically used aerosol generators, as well as most critical variables influencing effectiveness of aerosolized formulations used for mechanically ventilated infants are included in Table 61.1.
      4. Fok et al. compared different aerosol generators in delivering salbutamol labeled with technetium 99 m (^{99m}Tc) to infants with bronchopulmonary dysplasia (BPD). The aerosols delivered to the infants by jet nebulization were significantly finer than those delivered by MDI ($p = 0.005$). Despite the larger particle size, the MDI was associated with significantly higher pulmonary deposition relative to the jet nebulizer, when results were expressed as a percentage of initial nebulizer reservoir activity (nominal dose) (0.19 % vs. 0.08 %, resp., $p = 0.009$).
         a. These data suggest that for intubated infants, smaller particle size at the aerosol generator does not insure superior pulmonary deposition and that type and location of the nebulizer may also influence the lung deposited dose.
         b. Dubus et al. showed that the vibrating mesh nebulizer (Aeroneb Pro; Aerogen, Dungan, Ireland) was superior in pulmonary deposited dose compared to a jet nebulizer (MistyNeb; Airlife Inc., Montclair, CA), when both nebulizers were placed in the same

location (inspiratory limb of the ventilator circuit) with an MMAD of 1.4 μm measured at the tip of the ET tube.
   c. This finding indicates that device characteristics, such as residual volume and output rate, may drive clinical outcomes.
5. Based on Fok's and Dubus's findings, it appears that aerosol entrainment into the ventilator circuit is as important as particle size in lung deposition.
   a. In these studies, the jet and vibrating mesh nebulizers were placed within the inspiratory limb of the ventilator circuit, whereas the MDI was connected to the HC between the wye connector and the ET tube.
   b. Entraining the aerosol into the inspiratory arm of the circuit resulted in considerable dilution of the aerosol, because inspiratory flows were much lower than ventilator circuit flow, especially when a jet nebulizer was used with an additional 6 L/min gas driving flow.
   c. Furthermore, the use of higher air flows in the ventilator circuit can lead to the impaction of aerosol within the ventilator circuit before reaching the patient.
   d. It is also possible that very small particles (below 1 μm) generated by the jet nebulizer (with relatively low inspiratory flows) were exhaled, leading to reduced lung deposition.
6. Holding chambers are used to optimize aerosol particle size generated by MDIs. The HC allows time and distance for particle shrinkage and also acts as a large particle filter.
   a. Removing the chamber may increase the impaction of aerosol within ET tube (up to 90 % of the aerosolized dose). However, it is important to remember that placement of an HC, or even a T-connector between the wye connector and patient interface, can increase ventilation dead space.
   b. HCs can also be placed within the inspiratory limb of the ventilator circuit. Using a lung model, O'Doherty et al. demonstrated that such placement of the chamber increased aerosol delivery because of continuous filling of the chamber with aerosol during expiration, but had no effect on particle size.
   c. It has also been shown that electrostatic charge can have a major influence on delivery of salbutamol generated by an MDI. Coating the plastic chamber with an ionic detergent solved the problem of electrostatic charge by the build-up of a conducting layer on the chamber surface and improved aerosol delivery from plastic HCs.
7. Placement of the nebulizer closer to the patient (between the ET tube and wye connector) avoids potential dilution of the aerosol by the higher ventilator gas flow rates.
   a. Using a neonatal lung model, Turpeinen et al. demonstrated that placement of the nebulizer at the ET tube level improved drug delivery compared to in-line nebulizer placement within the inspiratory limb of the ventilator circuit.
   b. Clinical studies with sodium cromoglycate did not show improvement in aerosol lung deposition (less than 1 % of the nominal dose) with placement of the nebulizer closer to the patient.
   c. Other studies have demonstrated enhanced lung deposition with placement of the nebulizer <30 cm from wye connector within the inspiratory limb. This suggests that ventilator tubing can assume the function of an aerosol reservoir.
8. In summary, if an MDI is used, the HC can be placed either in the inspiratory limb of the circuit or between the wye and ET tube. If a jet or vibrating mesh nebulizer is used, it should be placed within the inspiratory limb. However, the optimal location should be determined by well designed clinical trials; the ventilator setting should be adjusted if additional nebulizer driving gas flow is used. The vibrating mesh nebulizer results in

superior lung deposition of the drug, most likely from smaller residual volume and low operational gas flows.

B. Particle Size
   1. Recent studies of aerosol lung deposition in term and preterm infants have used an indirect method to assess lung deposition using a marker substance, sodium cromoglycate, which can be measured in the urine.
   2. Kohler et al. compared aerosol delivery to non-intubated spontaneously breathing infants using three different nebulizers: jet nebulizer (LC Star®; Pari, Starnberg, Germany), ultrasonic nebulizer (LS 290®; Systam, Villeneuve sur Lot, France), and ultrasonic nebulizer (Projet®; Artsana, Grandate, Italy). Although the LC Star had the highest lung deposition among the other nebulizers, only 0.89 % of the nominal dose was deposited in the lungs after inhalation via LC Star.
   3. This finding is supported by other studies on infants showing pulmonary deposition of less than 1 % of the nominal dose for spontaneously breathing and mechanically ventilated patients.
   4. Significantly greater direct lung deposition was reported in an in vivo study done on intubated and mechanically ventilated macaque monkeys with the use of the Aeroneb Pro and ^{99m}Tc diethylenetriamine pentaacetate. In this study, Dubus and colleagues reported aerosol with MMAD of 1.4 μm at the tip of the ET tube for both tested devices but 25-fold greater lung deposition of radiolabeled aerosol when generated by the Aeroneb Pro and synchronized with inspiration vs. Misty Neb in a continuous mode (14 % vs. 0.5 % of the nominal dose, respectively).
   5. These observations from clinical and non-clinical studies indicate that fine particle sizes that bypass artificial airways and upper airways can be effectively delivered into the lungs of ventilated patients, and that differences in residual volumes between nebulizers can drive deposition rates if they are expressed as percent of nominal dose.
   6. Small particles in combination with short inspiratory times and low inspiratory flow rates increase the risk for exhalational drug losses.
      a. Fok et al. demonstrated inferior lung deposition in infants with BPD treated with smaller aerosol particles (MMAD of 0.83 ± 0.01 μm) vs. larger aerosol particles (MMAD of 1.88 ± 0.01 μm).
      b. It has been shown that small particles (<1 μm) are less dependent on gravitation and can be exhaled without deposition in the lungs.
      c. Calculations, as well as actual measurements based on adult models, have indicated that particles between 2 and 6 μm are deposited in central airways and those above 6 μm are deposited in the oropharynx.
      d. Studies evaluating particle size delivery to the upper airway of the preterm infants are limited.
         (1) Minocchieri et al. using an upper airway model comparable to a 32 week gestation infant reported similar results. In this study the average MMAD of budesonide particles which passed upper airways was 1.6 μm.
         (2) However, model-based studies do not account for amounts of exhaled drug and the results are reflecting only theoretical assumptions that should be supported by in vivo experiments.
   7. O'Riordan et al. showed that the majority of the deposition within a tracheostomy tube occurs during exhalation, suggesting that a significant fraction of inhaled aerosol was actually exhaled.

a. Intubated adults were mechanically ventilated and treated with saline labeled with ^{99m}Tc bound to human serum albumin.
b. Aerosol was generated with jet nebulizer AeroTech II and entrained into the inspiratory limb of the ventilator circuit with MMAD of 1.1 μm and GSD of 1.8 μm.
c. The study reported that 53 % of the total inhaled dose was deposited in the lung, with the remainder of the dose exhaled and deposited in the tracheostomy tube or expiratory limb of the circuit.
d. Although this study was conducted in ventilated adults, the results might be of importance for ventilated infants in whom short inspiratory times are likely to increase the risk for exhalation losses.
e. Heyder et al. demonstrated that only 20–30 % of the sub-micron aerosol passing beyond the main bronchi was ultimately retained in the lungs; the remainder was expired.

8. In summary, for intubated and non-intubated infants who require breathing support, the most critical variable influencing particle size is the patient interface.
   a. The particles should be small enough to bypass that interface with minimal impaction losses but should not be too small in order to avoid significant exhalation losses.
   b. It is important to remember that particle size is only one of many variables that can influence pulmonary drug deposition.

C. Ventilation Gas Conditions
1. Jet nebulizers use air flow to generate the aerosol. Different commercially available jet nebulizers have different air flow parameters in order to reach optimized performance.
2. Ultrasonic or mesh vibrating nebulizers need gas flow in order to entrain and carry aerosol toward the patient, although air flow is not required to generate the aerosol.
   a. Coleman et al., tested different nebulizer air flows in combination with mechanical ventilation in a lung model with settings selected to simulate a 4 kg infant with moderate to severe pulmonary disease.
   b. A jet nebulizer (Airlife™ Misty-Neb™; Baxter, Valencia, CA) was used in this study and was positioned in the inspiratory limb of the ventilator circuit.
   c. The study demonstrated that as the nebulizer air flow increased, delivery to the lung model significantly decreased in a linear fashion; the mean percent delivery at 5 L/min was 4.8 ± 1.3 % whereas increasing the flow to 6.5 L/min significantly decreased the mean percent delivery to 3.7 ± 1.1 %. Further increasing the flow to 8.0 L/min resulted in a significant decrease in the mean percent delivery to 2.7 ± 1.1 % ($p < 0.015$ vs. 5 L/min).
   d. This study also demonstrated higher aerosol deposition within the inspiratory arm of the ventilator circuit with higher air flows, which was most likely related to impaction.
   e. A similar relationship between aerosol inhaled dose and ventilator bias flow was also reported by Ari et al.
   f. Using a premature infant nose-throat model, Minocchieri et al. showed that higher aerosol flows lead to reduced lung deposition. There was a statistically significant decrease in aerosol delivery from 61.8 ± 5.3 % to 26.0 ± 1.5 % and 9.0 ± 0.8 % of nominal dose for 1, 5, and 10 L/min of inspiratory flow, respectively.
3. These in vitro studies have demonstrated that increased air flow presumably leads to increased aerosol impaction in the upper airways, resulting in decreased drug delivery and deposition in the lungs.
4. Density is another gas condition, which may influence the effectiveness of inhalation therapy.

a. Any gas density lower than air or oxygen can reduce air-flow turbulence through the narrow airways of the neonate.
b. Fink et al. found that aerosol delivery via an MDI showed a linear increase when the gas density within the ventilator circuit was decreased.
c. The use of an 80 % helium and 20 % oxygen mixture in a dry ventilator circuit resulted in a 50 % increase in the amount of drug delivered to the lower respiratory tract (LRT), compared with that observed with 100 % oxygen (46.1 % vs. 30.4 %), respectively. However, it is important to remember that air-flow based jet nebulizers may potentially exhibit decreased output rates when used with helium–oxygen mixtures.
d. Interestingly, non-invasive heliox ventilation has been shown to decrease resistive work of breathing and ventilator support requirements, as well as improve gas exchange in premature infants.

5. Humidity is another variable which potentially can influence the effectiveness of inhalational therapies.
   a. Standard ventilator support requires delivery of humidified and heated gas to patients to avoid drying the airway mucosa.
   b. Several in vitro studies have investigated the relationship between humidification and aerosol lung deposition.
      (1) Miller et al. using different jet nebulizers (AeroTech II®, CIS-US, Bedford, MA) and (Portex®, SIMS Portex, Inc., Fort Myers, FL) and three different ventilators designed for adults (with a driving flow of 8 L/min.) demonstrated that aerosol delivery increased nearly twofold ($p < 0.0001$) by turning off and bypassing the humidifier. In addition, humidity increased the particle size at the tip of ET tube from 1.5 ± 0.1 μm to 2.3 ± 0.2 μm ($p = 0.0006$) by hygroscopic growth, suggesting greater particle impaction in the ventilator tubing.
      (2) Other studies showed an approximate 40 % decrease in aerosol lung deposition when humidified and heated air was used. Although studies were conducted under ventilated adult conditions, conclusions related to humidity are applicable to mechanically ventilated infants.

D. Patient Interface
   1. The patient interface can also act as a significant site of aerosol impaction.
   2. In an in vitro study, Ahrens et al. investigated the influence of different neonatal ET tube sizes and flows on aerosol deposition in a test lung.
      a. The results suggested that aerosol flows were more important than ET tube size on aerosol deposition of conventional aerosols in clinical use (MMAD = 3.95 μm).
      b. The study also showed that test lung deposition significantly improved when submicronic aerosol (MMAD = 0.54 μm) was delivered (Ahrens et al. 1986).
   3. Crogan et al. showed that the percentage of aerosolized metaproterenol (Alupent®, Boehringer Ingelheim, Ingelheim, Germany) exiting the ET tube almost doubled for a 9.0 mm vs. 6.0 mm ET tube (Crogan and Bishop 1989).
   4. Everard and co-workers showed a drop in drug delivery when using a smaller ET tube (2.5 vs 3.0 mm) during in vitro testing of a Draeger Babylog neonatal ventilator circuit and Dubus et al. reported that regardless of different aerosol particles at the nebulizer outlet, the PSD at the end of the 3.0 mm ET tube was similar with an MMAD of 1.4 μm across all tested nebulizers.
   5. A recent in vitro study based on a lung model showed that a novel aerosol connector (Afectair, Discovery Laboratories, Inc., Warrington, PA) used for Albuterol delivery under breathing support increased the delivered dose by five-fold to nine-fold. Such significant

improvement in aerosol delivery was achieved from two factors: avoidance of aerosol dilution by the ventilator bias flow and avoidance of high air flow, and thus aerosol impaction in the artificial airways.

6. As mentioned earlier, these findings show that the patient interface can be a critical variable determining the particle size delivered to a mechanically ventilated patient. There are limited data on the influence of neonatal ET tube size on aerosol characteristics and lung deposition in in vivo studies.

E. Mode of Breathing Support
   1. Ventilator settings may also play a role in aerosol lung deposition.
   2. Fink et al. studied the effect of different modes of ventilation on aerosol delivery from an MDI using an in vitro model.
      a. This allowed for comparison of controlled mechanical ventilation, assist/control, pressure support, and continuous positive airway pressure (CPAP) modes.
      b. The study demonstrated significantly higher aerosol deposition within the lower respiratory tract (LRT) with spontaneous breaths using CPAP. Moreover, LRT deposition was linearly related to the duty cycle (inspiratory time/total breath duration).
   3. Other studies clearly show that CPAP is more efficient in aerosol delivery compared to intermittent positive pressure.
      a. Hess et al. studied the relationship between albuterol delivery and pressure-control vs. volume-control ventilation in vitro. Their study showed that albuterol delivery using a nebulizer (continuous aerosol generation) was affected by the inspiratory time and inspiratory flow pattern. However, when a pressurized MDI (pMDI) (intermittent aerosol generation) was used, aerosol delivery was not influenced by inspiratory flow pattern, inspiratory time, or lung mechanics.
      b. The use of synchronized nasal intermittent positive pressure ventilation (NIPPV) might lead to improvement in aerosol delivery to the LRT, although this has not been proven in an in vivo study.
   4. High Flow Nasal Cannula (HFNC) is the latest breathing support utilized in the NICUs for premature infants requiring prolonged support.
      a. High flows used in the artificial airways could potentially decrease the efficiency of aerosol delivery.
      b. Longest et al. tested the new type of aerosol called submicrone aerosol, which is generated by evaporating the output of the small-particle aerosol generator, which has low deposition in the delivery device. Consequently, small particles in the presence of the humidified air beyond the nasal cavity start to grow, securing optimal lower airways deposition. This same group also improved patient interfaces by a streamlining effect, which they tested extensively under a computational fluid dynamic (CFD) study.
      c. These approaches establish the potential for much higher dose delivery of aerosols during HFNC if a clinically applicable system can be developed. Sunbul et al. tested the streamlined OptiFlow HFNC system (OptiFlow, Fisher & Paykel, New Zealand), and showed superior lung deposition compared to SiPAP or bubble CPAP under in vitro conditions when a vibrating mesh nebulizer was placed just prior to the humidifier with bias flow of 3 L/min.

F. Inhaled Dose Calculations
   1. Aerosolized agents are not dosed only by the patient's weight or size; the delivered dose depends upon the patient's breathing conditions.
   2. Each aerosolization system has its own characteristics of the emitted dose (E_d) and aerosol concentration (C).

Table 61.3 Relationship between peak inspiratory flows, tidal volumes, minute ventilations, and inhaled aerosol

	PIF (L/min)			Tidal Vol. (mL/kg)			V_m (mL/kg/min)			Inhaled aerosol (mg/kg/min)[a]		
Percentiles Weight (g)	10th	50th	90th	10th	50th	90th	10th	50th	90th	10th	50th	90th
500–1000	0.8	1.3	2.1	3.2	5.4	8.3	230	400	600	1.15	2.0	3.0
1000–2500	1.3	2.3	3.5	3.4	5.7	8.1	250	400	600	1.25	2.0	3.0
2500–5000	1.8	3.2	5.2	2.4	4.7	7.2	170	300	500	0.85	1.5	2.0

Modified from: Mazela, J., et al. (2007). "Aerosolized surfactants." Curr Opin Pediatr **19**: 155–162
PIF peak inspiratory flow, *Tidal Vol.* tidal volume, V_m minute ventilation, *Surf del. to LRT* surfactant delivered to lower respiratory tracts
[a]– Calculations of inhaled aerosol are based on following assumptions:
– Aerosol flow is equal to 5.2 L/min, which is the highest PIF.
– There is no diluting effect at the level of patient interface.
– Emitted dose is 26 mg/min. So with flow of 5.2 L/min the aerosol concentration is 5 mg/L.
– No losses in the oropharynx, e.g., use of endotracheal tube, single naso-paharyngeal tube, or laryngeal mask

a. The delivered dose is the amount of the drug dispensed to the patient (available to the patient) per minute.
b. Aerosol concentration is the amount of the drug per gas carrier volume, which depends on inspiratory flow.
c. Assuming that the aerosol generator has a constant output rate, the amount of the drug available to the patient can be regulated by the duration of treatment, and reducing the dilution effect by the carrier gas.
d. The variables that will determine the amount of drug deposited in the lower airways include: minute ventilation (V_m) (tidal volume respiratory rate), and potential losses at the upper airways. Table 61.3 shows that V_m increases with patient size, which indicates that lung function can be a direct driver of appropriate dosing of the drug deposited in the LRT. This is feasible only with a delivery system that provides intact aerosol concentration during inhalations.

3. Theoretically, the most efficient drug inhalational system should use an aerosol flow equal to peak inspiratory flow (PIF) or a volume of aerosol equal to V_m to avoid dilutions, or at least flow and/or volume as close to these values as possible. Most of the neonatal clinical studies used nebulizers and delivery systems with much higher aerosol flows and volume, which resulted in only part of the aerosol flow inhaled by the patient. Theoretical inhaled dose is a function of the concentration of the aerosol, the amount of aerosol inhaled by the subject (estimated by the subject's minute ventilation, assuming that all gas inhaled by the subject contains the same concentration of aerosol), and the duration of exposure to the aerosol. Thus, the dose can be estimated using the following equation:

$$\text{Inhaled Dose} = C \times \left({}^{V_m}\!/_{\text{kg}} \right) \times T$$

C = Concentration of aerosol (in mg/L)
Vm/kg = Minute ventilation normalized to body weight (L/min/kg)
T = Dose duration (in minutes)

4. Concentration of aerosol (C) is a function of emitted dose per flow (preferably inspiratory flow). Each nebulizer in device characterization contains information regarding E_d. Nevertheless, when a nebulizer is used for a mechanically ventilated patient, one should assume that E_d at the nebulizer will not be this same as it is at the patient interface. Thus,

in order to properly assess the amount of inhaled drug, one should measure E_d at the endotracheal tube or at nasal prongs under inspiratory flow conditions, which can be replicated with a controlled lung simulator.

5. The concentration of aerosolized therapeutic agent (C) is therefore the emitted dose rate [mg/min] divided by the carrier gas flow rate [L/min] (Table 61.3).

$$C = \frac{E_d\left[\text{mg / min}\right]}{V\left[\text{L / min}\right]} = \text{mg / L}$$

6. The above calculations should be accurate if one eliminates aerosol upper respiratory tract deposition and obtains an appropriate particle size. Upper airways aerosol impaction can be avoided by using some type of bypass of this anatomical region, e.g., by using a nasopharyngeal tube or laryngeal mask. The nasal cavity with or without ciliated epithelium acts like a filter, and can limit the aerosol deposition into the lower airways.

G. Summary
   1. Inhalational therapy has not been proven to be effective for infants supported with mechanical ventilation in phase III prospective clinical studies.
   2. Future trials of aerosolized medications should address the technical and physiologic variables presented in this chapter.
   3. Drugs, as well as nebulizers and delivery systems, should meet the needs and account for the physiologic limitations of the smallest patients.
   4. Device manufacturers provide nebulizers which can be used in the NICU settings with off-label drugs.

H. Recommendations:
   1. SIMV, AC, VG, VC, and CPAP:
      a. Clean the artificial airways before nebulization.
      b. Remove the ventilator flow sensor from the wye connector.
      c. Nebulizer type: vibrating mesh (Aeroneb, Pari e-flow); MDI with HC
      d. Placement: in the inspiratory limb of the circuit 20 cm from the wye connector
      e. Breathing support variables:
         (1) Increase inspiratory time as much as possible.
         (2) Decrease respiratory rate as much as possible.
         (3) Bypass the humidifier, but maintain air-flow heating during nebulization.
   2. HFNC:
      a. Clean the artificial airways before nebulization.
      b. Make sure to use streamlined prongs design.
      c. Nebulizer type: vibrating mesh (Aeroneb, Pari e-flow); MDI with HC
      d. Placement: just prior to humidifier
      e. Breathing support variables: no need to switch off humidifier

IV. Clinical Studies With Aerosolized Agents in the NICU

A. Surfactants
   1. Aerosolized drugs have been used routinely in the NICU for several decades; however, the results of clinical studies have been generally disappointing.
   2. Aerosolized agents were first used in critically ill infants more than 40 years ago by Robillard and co-workers, who administered aerosolized dipalmitoyl-phosphatidylcholine (DPPC) directly into the incubators of premature infants with established RDS. In this non-controlled study, they found that respiratory effort decreased in 8 of 11 infants.

3. In contrast, investigators at the University of California, San Francisco and the University of Singapore were unable to demonstrate a physiologic benefit with aerosolized phosphatidylcholine.
4. Other studies in which dipalmitoyl lecithin aerosol was administered to infants with RDS were also "negative" and discouraged the use of aerosolized surfactant therapy for many years. However, in the 1990s, clinicians once again became interested in aerosolized surfactant therapy, as non-invasive mechanical ventilation became more prevalent in the neonatal population.
5. The first study in neonates using nasal continuous positive airway pressure (nCPAP) in combination with aerosolized surfactant for treatment of RDS was conducted in 1997. This was a pilot feasibility study, in which preterm newborns with moderate RDS requiring pharyngeal CPAP received nebulized SF-RI1 (Alveofact®, Boehringer Ingelheim, Ingelheim, Germany). The procedure was shown to be safe and the study demonstrated that ventilation and oxygenation improved, once nebulization of surfactant was initiated.
6. The following year, Arroe et al. tested the efficacy and safety of nebulized colfosceril palmitate (Exosurf®, GlaxoSmithKline, Brentford, UK) delivered via nCPAP in preterm newborns. The study reported no adverse effects, but did not demonstrate any improvement in clinical efficacy.
7. Berggren et al. treated 34 newborns (28–33 weeks' post-conceptional age and 1015–2370 g) with RDS using nCPAP and aerosolized poractant alfa (Curosurf®, Chiesi Pharmaceutici SpA, Parma, Italy). The investigators were also unable to demonstrate the superiority of aerosolized surfactant delivery over nCPAP alone.
8. Finer et al. in a clinical study with aerosolized lucinactant (Aerosurf®, Discovery Laboratories Inc., Warrington, PA) tested the feasibility and safety of delivering a peptide-containing synthetic surfactant to newborns with early signs of RDS, within 1 h of birth.
   a. This study used a clinically approved vibrating mesh nebulizer, the Aeroneb® Pro (Aerogen, Dangan, Galway, Ireland) with a specially designed CPAP adaptor, which allowed for aerosol administration just below the "Y" connector.
   b. The procedure was shown to be safe with a low occurrence of "peri-dosing events" and some efficacy.
9. The latest conducted clinical study was reported by Pillow et al. and was aimed at administering aerosolized poractant alfa nebulized by vibrating membrane generator (Pari e-flow). The full report of this study is still to be published.
10. Another dose escalation clinical study with inhaled lucinactant is underway.

B. Corticosteroids
1. There have been 18 clinical studies focused on the effectiveness of different aerosolized corticosteroid formulations in preventing BPD. A total of 1170 infants were treated with aerosolized flunisolide, fluticasone, beclomethasone, or budesonide in the 1990s and early 2000s.
2. One study by Gupta et al. showed a significant decrease in moderate BPD with aerosolized beclomethasone versus placebo.
3. Another study by Fok et al. showed a decrease in intubation at 14 days of life, but did not show a difference in BPD when comparing fluticasone vs. placebo.
4. Only two studies (by Townsend et al. and Kovacs et al.) used a jet nebulizer, whereas other studies utilized MDI. Most of the studies placed a holding chamber (HC) between the ET tube and flow-inflating or self-inflating bag. The studies by Townsend et al., Jangaard

et al., and Fok et al. activated the nebulizer during standard ventilator support without disconnecting or using bagging. The other three studies utilized placement of the HC within the inspiratory limb. Interestingly, none of the studies evaluated the effect of the additional dead space caused by the presence of HC.

5. Only one study reported aerosol deposited lung dose, which was based on direct radiolabeling. The lung deposited dose was equal to 0.98 % of the MDI emitted dose (E_d).
6. Groneck et al. cited two different studies to support the dosing regimen, whereas Everard et al. showed 3.2 % deposited dose of the MDI E_d based on a rabbit model, and Grigg et al. showed 1.7 % deposited dose of the MDI E_d in infants based on the sodium cromoglycate excreted in the urine.
7. Cole et al. based the dosing schedule on the dose emitted from the ET tube, being 1.7 μg, which was 4 % of the MDI E_d.
8. One study presented an estimated deposited dose at 10 % of the nominal dose to target a deposited dose of 0.2 mg/kg/day.
9. The remainder of these studies did not include any information regarding dosing and presented nominal doses based on the MDI active drug concentrations and dispensed volumes.
10. Because most of the trials used MDIs, the reported E_d was the value provided by the MDI manufacturer. Except for the studies of Cole et al. and Rozycki et al., these studies did not report the E_d at the patient interface, which might be influenced by the type and size of the patient interface, the residual volume of the HC used, as well as the presence of the HC between the wye and ET tube. Some studies used different dosing strategies depending on patient size.
11. The studies by Fok et al., Cole et al., and Rozycki et al. were the only ones that provided detailed description of the particle size at the tip of the ET tube. There was a significant difference in MMAD of the aerosol emitted directly from the MDI compared to aerosol emitted from the tip of the ET tube. This study, as well as other published reports, showed that patient interface, the final component of the aerosol delivery system, can have a detrimental effect on particle size and thus influence the deposited lung dose.
12. Thirteen of 17 reports analyzed above did not address the particle size of the aerosol used in the clinical study; a key aspect of aerosol characterization.
13. A recently published study by Bassler et al. tested early treatment (within first 24 h of life) with inhaled budesonide to infants 23–27 weeks' gestational age. The incidence of BPD was 27.8 % in the budesonide group versus 38.0 % in the placebo group (relative risk, stratified according to gestational age, 0.74; 95 % CI, 0.60–0.91; $P = 0.004$). Budesonide was dispensed from an MDI placed with an HC between the wye connector and ET tube.
14. Current Cochrane meta-analysis does not recommend use of inhaled corticosteroids for treatment or prevention of BPD, when used after the first week of life.
    a. Eight trials randomizing 232 preterm infants were included in the meta-analysis. Inhaled corticosteroids did not reduce the separate or combined outcomes of death or BPD.
    b. It did not impact short-term respiratory outcomes, such as failure to extubate and total duration of mechanical ventilation or oxygen dependency. There was a trend toward a reduced use of systemic corticosteroids in favor of inhaled corticosteroids (TRR 0.51; 95 % CI 0.26–1.00).
    c. The authors concluded that because of paucity of data on short-term and long-term adverse effects and the small number of randomized patients the procedure cannot be recommended.

C. Bronchodilators
   1. Aerosolized bronchodilators comprise another group of pulmonary drugs used to treat infants with signs of BPD and to improve the effectiveness of inhaled corticosteroids.
   2. The largest of 7 clinical studies enrolled 169 infants, but one of the studies showed effectiveness of inhaled salbutamol or ipratropium bromide in decreasing airway resistance and/or improving lung compliance.
   3. Only the study by Denjean et al. did not show effectiveness, as the end point was not short-term pulmonary mechanics, but the incidence of BPD.
   4. Four studies used jet nebulizers and four utilized MDIs with HC (one study tested two different forms of bronchodilators). Placement of the jet nebulizer was described in all studies except one. The jet nebulizer was located below the wye connector or within the inspiratory limb of the circuit. Most of the studies utilized MDIs with an HC placed between the ET tube and wye, where a self-inflating bag was used in two studies.
   5. Only one study reported the lung deposited dose to be 1.7 % of the MDI E_d. The rest of the studies recommended dosing based on the nominal dose. Salbutamol daily nominal doses varied from 200 to 1200 μg/day. One study utilizing a jet nebulizer lacked information related to nebulizer output rate or E_d from the nebulizer. None of the studies reported E_d at the patient interface. The analysis of PSD of the aerosols was performed in only one.
   6. The Cochrane Library also reviewed the use of aerosolized bronchodilators for the prevention and treatment of CLD. Only one study, in which CLD was a key clinical outcome, met criteria for inclusion in the analysis. This double masked, multicenter randomized trial compared inhaled beclomethasone in combination with salbutamol vs. beclomethasone alone. There were no statistically significant differences in mortality, CLD, need for parenteral dexamethasone, respiratory infections, or positive blood cultures between groups. Furthermore there were no statistically significant differences in duration of ventilatory support, duration of oxygen supply, or age of weaning from respiratory support (defined as assisted ventilation or oxygen supplementation).

D. Diuretics
   1. Seven published studies evaluated a total of 78 premature infants treated with inhaled furosemide for BPD treatment or prevention. All of these studies are included in a Cochrane review, which concluded that for infants older than 3 weeks of age with clinical signs of BPD, aerosolized furosemide at a nominal dose of 1 mg/kg/day improves pulmonary mechanics, but in view of the lack of data from randomized trials concerning effects on important clinical outcomes, routine or sustained use of aerosolized loop diuretics in infants with (or developing) BPD cannot be recommended. Nevertheless, when pulmonary function was analyzed as the end point, 5 of 8 studies showed efficacy of the nebulized diuretics.
   2. There is limited information regarding nebulizer type used in these studies. Only four studies included information regarding nebulizer type used. Most used jet nebulizers, only Ohki et al. used an ultrasonic nebulizer. Nebulizers were placed within the inspiratory limb of the circuit in four studies, and three studies did not report placement of the nebulizer.
   3. There is no information regarding emitted or delivered dose at the patient interface. All dosing regimens were based on the daily nominal doses of furosemide, which varied from 0.1 to 2 mg/kg/day. Only one study included information regarding particle size (1–2.1 μm).

E. Antiviral (Ribavirin)
   1. RSV is one of the most common infectious pathogens of the lower airways among infants and children. The high risk population for RSV infection includes premature infants and very low birth weight (VLBW) infants with BPD. The current standard of care for the prevention of RSV is administration of palivizumab, a specific monoclonal antibody, during the RSV season.

2. Treatment of RSV has included an antiviral agent, ribavirin (1-beta-D-ribafuranosyl-1,2,4-triazole-3-carbxamide), which is a synthetic nucleoside that possesses antiviral properties. Aerosolized ribavirin is approved for ventilated patients with diagnosed RSV pneumonia, despite the non-supportive results of the Cochrane systematic review. Interestingly, ribavirin is the only approved inhalation therapy in intensive pediatric pulmonary medicine that requires the use of a specific nebulizer, a Collison aerosol generator, known as a small particle aerosol generator (SPAG), which has been specifically designed to be used in combination with mechanical ventilation.
3. There are two studies of interest that utilized aerosolized ribavirin for treatment of RSV infection among 28 infants.
   a. The therapeutic aerosolized ribavirin has been well characterized with an MMAD of 1.3 μm and aerosol concentration (Ca) of 190 μg/L.
   b. Estimated lung deposited dose was based on direct deposition studies from adult patients.
   c. There was a slight difference between both studies in dosing time, 20 vs. 12 h, which according to the authors could be responsible for less significant treatment difference observed by Taber et al.
   d. Nevertheless, both studies showed significant improvement in severity of RSV bronchiolitis after treatment with inhaled ribavirin, while Hall et al. demonstrated decreased viral shedding.

F. Vasoactive agents
1. PPHN can be caused by an abnormally constricted pulmonary vasculature from lung parenchymal diseases or by circulating vasoactive mediators, such as thromboxane in sepsis; remodeled pulmonary vasculature, also known as idiopathic PPHN; or by the hypoplastic vascular bed seen in congenital diaphragmatic hernia or pulmonary hypoplasia.
2. Treatment of PPHN aims at the reduction of pulmonary vasoconstriction through pulmonary vasodilator therapy, including oxygen, assisted ventilation, inhaled nitric oxide (iNO), and in the most severe cases extracorporeal membrane oxygenation. Systemic vasodilators are not useful, because they have no selective effect on the pulmonary vasculature. In order to achieve pulmonary selectivity, drugs must be delivered by inhalation or nebulization.
3. Aerosolized therapeutic agents studied among infants with PPHN include prostaglandin (PGE_1), prostacyclin (PGI_2), and sodium nitroprusside.
   a. Three small clinical trials published to date examined the effects of these aerosolized agents in 46 infants diagnosed with PPHN.
   b. In all three studies the clinical effects of treatment were comparable with that of iNO. It is important to note that of these three studies, only the delivery system used by Kelly et al. was optimized for the ventilated infant. This study utilized the above-mentioned SPAG-2 device, which produced an aerosol with MMAD of 1.3 μm and an inhaled dose of 20–30 ng/kg/min.
   c. In all three studies dosing of PGE_1, PGI_2, and sodium nitroprusside was based only on nominal doses and not on inhaled, nor lung deposited doses. Although different aerosol generators were utilized in each study, placement of the nebulizer was within the inspiratory limb of the circuitry and two of the studies included information on PSD.
4. In summary, in 43 clinical studies performed thus far on premature or term infants receiving inhalational therapies and requiring mechanical ventilation, there is very limited information related to performance of the nebulizers, aerosol generators, and aerosol delivery systems. Aerosol particle size was assessed in less than half of published studies, delivered aerosol dose in a third, and there was no information regarding the nebulizer used in a sixth (Table 61.4).

Table 61.4 Summary of the clinical studies on newborns treated with aerosolized agents combined with breathing support

Inhalational therapies for ventilated infants	No. of studies	No. of patients	% of studies								
			Type of nebulizer used						Particle size	Nominal/Deliv. dose	Achieved endpoint
			Jet	MDI	Ultrasonic	VM	SPAG	Unknown			
Corticosteroids	17	733	12	88					18	100/35	18
Beta agonists	7	169	50	50					14	100/14	86
Diuretics	7	78	43		14			43	14	100/0	57
Ribavirin	2	28					100		100	100/100	100
PGE1, I2, sodium nitr.	3	46	33				33	33	50	100/33	100
Surfactants	7	109	43		29	14		14	57	71/27	14
Total	43	1163	30	23	7	2	22	15	42	95/35	63

Suggested Reading

Ahrens R et al. The delivery of therapeutic aerosols through endotracheal tubes. Pediatr Pulmonol. 1986;2:19–26.
Crogan S, Bishop M. Delivery efficiency of metered dose aerosols given via endotracheal tubes. Anesthesiology. 1989;70:1008–10.

Sedation and Analgesia

62

Jenna Deeming and Elaine M. Boyle

I. Definitions
   A. Stress: a normal adaptive physiologic response generated by certain external stimuli. There may be no conscious awareness and thus no associated suffering.
   B. Distress: suffering or maladaptive behavior resulting from emotional effects of excessive stress that may be affected by past experience. In newborn infants, an observer is only able to infer this from behavioral cues.
   C. Pain: a particular form of distress, easily described by adults in terms of a hurtful experience or emotion.
   D. Nociception: behavioral and physiologic effects of a noxious stimulus independent of associated psychological and emotional responses. This most accurately describes neonatal "pain."

II. Potential Causes of Pain or Distress (Table 62.1)
   A. Invasive interventions
   B. Repeated invasive or non-invasive interventions
   C. Pathologic conditions
   D. Environmental factors

III. Indicators of Pain in the Newborn
   A. Behavioral responses
      1. Audible cry (not applicable to intubated infants)
      2. Facial expression (characteristic brow bulge, eye squeeze, naso-labial furrowing, mouth or lip purse, tongue tautness, and chin quiver)
      3. Withdrawal of affected limb or extremity
      4. Changes in tone (general increase in activity, flexion of trunk and extremities, "fetal" posturing or arching, leg extension, finger splaying, or hand clenching)
      5. Sleep cycle disturbances accompanied by twitches, jerks, irregular breathing, grimaces, or whimpers
      6. Self-regulatory or comforting behaviors such as lowered behavioral state, postural changes, hand-to-mouth movements, sucking, or an expression of "focused alertness"

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Table 62.1 Causes of possible distress or pain in the newborn infant

1. *Ventilation*
Endotracheal intubation
Presence of endotracheal tube and fixation devices
Distress of mandatory ventilator breaths
Restriction of movement and posture required for ventilation
2. *Repeated acute invasive procedures*
Arterial/venous/capillary blood sampling
Venipuncture
Endotracheal suctioning
3. *Minor surgical procedures*
Chest drain insertion
Suprapubic aspiration of urine
Lumbar puncture
Ventricular tap
4. *Co-existing infective/inflammatory conditions*
Necrotizing enterocolitis
Osteomyelitis
Meningitis
Generalized sepsis
5. *Complications of necessary procedures*
Cellulitis or abscess from infiltrated intravenous infusion
Cutaneous probe burns
6. *Post-operative following major surgery*
Patent ductus arteriosus ligation
Laser therapy for retinopathy of prematurity
Bowel repair/resection following perforation or necrotizing enterocolitis
7. *Disruptive handling*
Positioning for radiographs
Ultrasound scans
General care-giving procedures
8. *Environmental stress*
Excessive light, either daylight or from phototherapy
Excessive and distressing sound from monitor alarms, incubator doors, etc.
Unfamiliar tactile environment without physical containment
9. *Physiologic stress*
Drug withdrawal
Respiratory insufficiency/air hunger
Nutritional, i.e., hunger
10. *Repeated relatively non-invasive procedures*
Transcutaneous gas monitoring probe changes
Bolus feeds
Drug administration
Blood pressure measurement using inflatable cuffs

B. Physiologic
   1. Increase in heart rate
   2. Increase in blood pressure
   3. Changes in respiratory rate
   4. Changes in oxygenation
   5. Fluctuations in skin color and temperature
   6. Increase in palmar sweating (applicable after 37 weeks' gestation)
   7. Fluctuation in cerebral circulation and intracranial pressure
   8. Gastrointestinal disturbances

IV. Assessment of Pain or Distress
  A. General
    1. Acute distress: based largely on behavioral or physiologic measures
    2. Sub-acute distress: difficult to assess
      a. Increased activity or "thrashing"
      b. "Frozen" or motionless; withdrawn behavior
  B. Specific
    1. Clinical Tools
      a. More than 40 pain assessment tools available
      b. Designed for use in clinical practice and research
      c. Uni-dimensional or multi-dimensional
      d. Examples (Table 62.2)
        (1) Neonatal facial coding system
        (2) Premature infant pain profile
        (3) Neonatal pain, agitation, and sedation score
    2. Research Tools
      a. Neuro-endocrine markers (e.g., cortisol, adrenaline, and endorphins)
      b. Metabolic-biochemical markers of catabolism (e.g., 3—methyl-histidine)
      c. Computerized analysis of physiologic data (e.g., changes in vagal tone, heart rate variability)
  C. Pain Assessment in Ventilated or Preterm Infants
    1. Behavioral responses are influenced by:
      a. Degree of prematurity
      b. Behavioral state (level of arousal)
      c. Severity of illness
    2. Cry is inaudible in intubated infants.
    3. Presence and fixation of endotracheal tube or non-invasive respiratory support devices alter facial expression.
    4. Monitoring devices and restraints for infusions change posture and restrict limb movement.
    5. Agitation or distress may be secondary to a process other than pain (e.g., respiratory insufficiency, drug withdrawal).
    6. Habituation to pain or stress can occur.
V. Non-Pharmacologic Interventions to Prevent or Reduce Distress
  A. Environmental
    1. Control of light, temperature, and noise
    2. Positioning, swaddling, minimal handling, and containment
    3. Positive touch, massage, especially from parents
    4. Music as a therapeutic intervention
  B. Behavioral: non-nutritive sucking, breastfeeding
VI. Indications for Pharmacologic Management (Table 62.3)
  A. Observed behavioral and physiologic indicators of pain
  B. Anticipated procedural pain
  C. Asynchronous respiration interfering with ventilation
  D. Physiologic instability
  E. Failure of non-pharmacologic interventions
  F. Distress associated with therapeutic hypothermia

Table 62.2 Validated pain assessment scores for use in the newborn

1. Neonatal facial coding system: (NFCS) (Grunau and Craig 1987)						
Facial response to heel-stick (i.e., acute and obvious pain) in different sleep-wake states. 10 features scored:						
1. Brow bulge						
2. Eye squeeze						
3. Naso-labial furrow						
4. Open lips						
5. Vertical stretch mouth						
6. Horizontal mouth						
7. Lip purse						
8. Tongue taut						
9. Chin quiver						
10. Tone exaggeration with startling or twitching						

2. Premature infant pain profile: (PIPP) (Stevens et al. 1996)

Process	Indicator	0	1	2	3	Score
Chart	Gestational age	≥36 weeks	32–35 weeks	28–31 weeks	≤ 28 weeks	
Observe Infant 15 s *Observe baseline;* *Heart rate SaO_2*	Behavioral state	Active/Awake Eyes open Facial movements	Quiet/awake Eyes open No facial movements	Active/asleep Eyes closed Facial movements	Quiet/asleep Eyes closed No facial movements	
Observe Infant 30 s	Heart rate Max	0–4 beats/min. increase	5–14 beats/min. increase	15–24 beats/min. increase	25 beats/min. or more increase	
	SaO_2 Min	0–2.4 % decrease	2.5–4.9 % decrease	5.0–7.4 % decrease	7.5 % or more increase	
	Brow bulge	None 0–9 % of time	Minimum 10–39 % of time	Moderate 49–69 % of time	Maximum 70 % of time or more	
	Eye squeeze	None 0–9 % of time	Minimum 10–39 % of time	Moderate 49–69 % of time	Maximum 70 % of time or more	
	Naso-labial furrow	None 0–9 % of time	Minimum 10–39 % of time	Moderate 49–69 % of time	Maximum 70 % of time or more	

3. Neonatal pain, agitation, and sedation score (Hummel 2008)					
Assessment criteria	Sedation		Normal	Pain/agitation	
	−2	−1	0	1	2
Crying Irritability	No cry with painful stimuli	Moans or cries briefly with painful stimuli	Little crying Not irritable	Irritable or crying at intervals Consolable	High pitched or silent continuous cry Inconsolable
Behavior state	Does not arouse to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	Appropriate for gestational age	Restless sleep Awakens frequently	Constantly awake or arouses minimally (not sedated)
Facial Expression	Mouth is lax No expression	Minimal expression with stimuli	Relaxed	Any pain expression (intermittent)	Any pain expression (continual)
Extremities Tone	No grasp reflex Flaccid tone	Weak grasp reflex Decreased muscle tone	Relaxed hands and feet Normal tone	Intermittent clenched toes/fists or finger splay Body is not tense	Continual clenched toes/fists or finger splay Body is tense
Vital Signs HR, RR, BP, Sats	No variability with stimuli Hypoventilation or apnoea	<10 % variability from baseline with stimuli	Within baseline or normal for gestational age	Increase 10–20 % from baseline SpO_2 decrease to 76–85 % with stimulation, quick increase	Increase >20 % from baseline SpO_2 decrease to ≤75 % and slow to increase on stimulation Out of synch with vent

Table 62.3 Use of analgesics and sedatives

Relatively minor procedures		
Procedure	Comment	Suggested approach
Heel prick	Affected by technique and heel perfusion EMLA is not effective	Automated lancets Pacifier/sucrose/glucose Avoid EMLA
Venous and arterial puncture		Pacifier/sucrose/glucose Topical anesthetic cream
Suprapubic urine aspiration		Pacifier/sucrose/ Topical anesthetic cream
Insertion of naso-gastric tube	Discomfort with gag Vagal reflex	Insert slowly

Moderate/major procedures		
Procedure	Issues	Suggested approach
Lumbar puncture	Pain or skin puncture Stress of restraint	Pacifier/sucrose/glucose/topical anesthetic Correct positioning/technique Lidocaine infiltration of skin (avoid deep infiltration as risk of spinal injection) Consider opiate if ventilated
Thoracostomy tube insertion	Skin, muscle, pleural pain	Opiate slow bolus Lidocaine infiltration of skin and pleura—if time
Chest tube (in situ)		Opiate infusion if distressed
Ventricular tap	Pain of skin penetration	Topical anesthetic Consider opiate if ventilated

Moderate/major procedures		
Procedure	Issues	Suggested approach
Elective intubation	Discomfort Gag/cough Vagal reflex	Opiate slow bolus with muscle relaxant
Laser/cryotherapy for retinopathy of prematurity	Discomfort/restraint Eyeball pain Vagal reflex (Re-establish full monitoring before procedure)	Ventilation Oxybuprocaine eye drops Topical anesthesia Opiate loading and infusion or inhaled anesthetic before intubation Muscle relaxant to abolish eye and other movements (after intubation) Atropine to prevent bradycardia (oculocardiac reflex)

Persistent/ongoing pain or distress	Issues	Suggested approach
Mechanical ventilation/neonatal intensive care	Presence of ETT and fixation devices Ventilation asynchrony Possible associated muscle relaxation	Optimize environmental factors Minimal handling Opiate infusion if obvious distress continues despite environmental and behavioral interventions
Therapeutic hypothermia for hypoxic ischemic encephalopathy	Usually term infants May be distress associated with cooling and shivering	Opiate infusion if distressed Avoid benzodiazepines

VII. Pharmacologic Interventions (Chap. 59)
- A. Sucrose/Glucose
  1. Reduces behavioral responses to minor painful stimuli
  2. Effects mediated by sweet taste
  3. Only effective by oral route
  4. Administer 2 min before procedure onto anterior tongue
  5. Dose 0.05–2 mL sucrose/glucose 20–30 %
  6. Duration of action 5–8 min
- B. Opioids
  1. Reduce endocrine stress response
  2. Reduce asynchronous respiration during ventilation (sedative effect)
  3. Side effects
     a. Hypotension
     b. Respiratory depression
     c. Bronchospasm (theoretical)
     d. Decreased gut motility
     e. Chest wall rigidity (caused by stimulation of excitatory pathways in spinal cord; give boluses slowly)
     f. Withdrawal. Wean gradually if given for more than 5 days. Late rebound respiratory depression may occur from enterohepatic recirculation or release from fat stores.
  4. Specific agents
     a. Morphine sulfate
        (1) Most widely used
        (2) Loading dose: 100–150 mcg/kg over 30 min
        (3) Maintenance: 10–20 mcg/kg/h
        (4) Dose for procedures: 50–100 mcg/kg over 30 min (higher doses may be needed)
     b. Fentanyl
        (1) Synthetic opioid
        (2) Less histaminic effect than morphine
        (3) Tends to reduce pulmonary vascular resistance; may be preferable in PPHN, CDH, CLD, during ECMO
        (4) Large doses tolerated without adverse hemodynamic effects
        (5) Chest wall rigidity if given quickly
        (6) Loading dose: 5–15 mcg/kg over 30 min
        (7) Maintenance: 1–5 mcg/kg/h
  5. Weaning
     a. Depends on duration of treatment
     b. Signs of withdrawal
        (1) Irritability
        (2) Inconsolable cry
        (3) Tachypnea
        (4) Jitteriness
        (5) Hypertonicity
        (6) Vomiting
        (7) Diarrhea
        (8) Sweating
        (9) Skin abrasions
        (10) Seizures

(11) Yawning
(12) Nasal stuffiness
(13) Sneezing
(14) Hiccups
c. If treatment <48 h days, stop without weaning
d. If 3–7 days, reduce by 25–50 % of maintenance dose daily
e. If > 7 days, reduce by 10–20 % every 6–12 h as tolerated

C. Non-opioids
1. Acetaminophen (Paracetamol)
a. Analgesic and antipyretic. Analgesia is additive to opioid effect.
b. Newborn relatively resistant to liver toxicity with no respiratory or cardiovascular depression, G-I irritation, or platelet dysfunction
c. Useful in inflammatory and post-operative pain
d. Dose
(1) Oral: 10–15 mg/kg q4-6h (may load with 24 mg/kg)
(2) Rectal: 20–25 mg/kg q4-6h (maximum daily dose 60 mg/kg)
(3) Intravenous: 7.5 mg/kg q6h (maximum daily dose 30 mg/kg)
2. Ibuprofen
a. Non-steroidal anti-inflammatory agent
b. Recommended dose as for PDA closure (no information available regarding analgesic dose): 10 mg/kg IV/PO, then 5–10 mg/kg q24h

D. Sedative drugs
1. Adjuvant to analgesic, but no pain relief
2. May be useful for long-term ventilation
3. Useful when tolerance to opioids develops
4. May allow weaning from opioids
5. May help older babies with severe BPD
6. Specific agents
a. Midazolam
(1) Benzodiazepine
(2) Routine use not recommended
(3) IV bolus for procedures, infusion for background sedation, if required
(4) Respiratory depression and hypotension; synergistic with opioids
(5) Withdrawal (agitation, abnormal movements, and depressed sensorium) after prolonged use
(6) Loading dose: 0.1 mg/kg over 15–30 min
(7) Maintenance: 0.17–1 mcg/kg/min (10–60 mcg/kg/h)
b. Chloral hydrate
(1) Causes generalized neuronal depression
(2) Does not appear to produce respiratory depression
(3) May be given orally or rectally
(4) Onset of action in 30 min., duration 2–4 h
(5) Slow development of tolerance
(6) Dose
(a) Sedation: 25–50 mg/kg
(b) Hypnosis: Up to 100 mg/kg

E. Local anesthetics
1. Lidocaine
a. Infiltrate skin/mucous membranes.
b. 0.5 % solution, maximum dose 1.0 mL/kg
c. With overdosage, systemic absorption may cause sedation, cardiac arrhythmia, cardiac arrest, and seizures.
2. Topical anesthetic creams
a. Apply pea-sized amount with occlusive dressing 30–60 min before procedure.
b. EMLA (eutectic mixture of Lidocaine and Prilocaine as 5 % cream)
(1) Vasoconstrictor
(2) Minimal risk of methemo-globinemia
c. Amethocaine (Ametop): less vasoconstriction

VIII. Assessing Adequacy of Analgesia and Sedation
A. Challenging because of lack of self-reporting
B. Need for analgesia and sedation varies among infants
C. Difficult to differentiate between analgesic and sedative effects of opiates

IX. Experience of Pain in the Newborn
A. The preterm infant
1. Increased sensitivity to pain (reduced pain threshold)
2. Hypersensitivity develops as a result of repeated tissue damage.
3. Hyperalgesia
a. More pain neurotransmitters in spinal cord
b. Delayed expression of inhibitory neurotransmitters
4. Higher plasma concentrations of analgesic and anesthetic agents required to obtain clinical effects, compared to older age groups
5. Non-painful handling (e.g., care giving) may activate pain pathways and be experienced as pain
B. Sources of pain and distress
1. Painful conditions
a. Necrotizing enterocolitis
(1) Low threshold for analgesia
(2) Intravenous treatment needed
(3) Non-steroidal anti-inflammatory agents contraindicated (G-I side effects)
b. Meningitis/osteomyelitis
(1) Consider morphine if distressed
(2) Acetaminophen/paracetamol to relieve pain, fever
2. Ventilation
a. Use environmental and behavioral measures and synchronized ventilation.
b. Routine use of opiates not recommended for ventilation
c. Beware of hypotension with morphine use in extremely preterm infants.
3. Medical/Surgical procedures (Table 62.3)
C. Short-term consequences of pain and inadequate analgesia
1. Acute pain
a. Physiologic and behavioral changes (Sections IIA, IIB) to limit the duration of "protest" against painful experience
b. These involve great energy expenditure.
2. Continuing (chronic) pain: the body re-orients its behavioral and physiologic expression of pain to conserve energy and expresses "despair."

a. Passivity
b. Little or no body movement
c. Expressionless face
d. Decreased variability in heart rate and respiration
e. Decreased oxygen consumption

X. Clinical Implications of Pain or Inadequate Analgesia
A. Responses to pain may be extreme enough to have an adverse effect on clinical state. Evidence from research:
1. Short-term consequences
a. Frequent invasive procedures soon after birth in the extremely immature infant may contribute to physiologic instability.
b. Cardiac surgery causes extreme metabolic responses. Clinical outcome can be improved by analgesia—reduced incidence of post-operative sepsis, metabolic acidosis, disseminated intravascular coagulation, and death.
c. Circumcision without analgesia in term boys causes increased irritability, decreased attentiveness and orientation, poor regulation of behavioral state and motor patterns, altered sleep and feeding patterns lasting up to 7 days.
d. Babies born at 28 weeks' gestation, compared to those born at 32 weeks' gestation, show reduced behavioral and increased cardiovascular responsiveness at 4 weeks of age. The magnitude of the changes correlates with the total number of invasive procedures experienced.
2. Long-term consequences
a. Neonatal circumcision results in increased behavioral responses to vaccination at 4–6 months, which can be attenuated by the use of anesthetics.
b. Stressful conditions at birth are associated with an increased cortisol response to vaccination at 4–6 months.
c. Increased behavioral reactivity to heelstick sampling in term newborns correlates with increased distress to immunizations at 6 months.
d. Former preterm infants showed increased somatization at 4½ years. The strongest predictor was duration of neonatal intensive care.
B. Therapeutic interventions and outcome
1. Analgesia
a. Acute physiologic and behavioral changes can be attenuated with opioid analgesia.
b. Routine use of morphine analgesia in preterm infants does not reduce the risk of intraventricular hemorrhage (IVH).
2. Individualized developmental care
a. Aims to minimize stress and pain and support neurobehavioral development
b. Has been suggested to reduce the incidence of IVH and lead to improved developmental outcomes but further investigation required to clarify potential benefits of developmental care

XI. Areas of ongoing research
A. Pharmacologic Interventions
1. Dexmedetomidine
a. Alpha agonist, opioid sparing
b. Causes sedation without respiratory depression
2. Remifentanil
a. Ultra short acting synthetic opioid

   b. Metabolised by esterases in tissue and plasma leading to very short half life and no accumulation
   c. Not suitable for long-term use
B. Assessment of pain or distress—non-invasive technologies
   1. Near infra-red spectroscopy
   2. EEG
C. Long-term consequences of morphine use (e.g., behavior, neurodevelopment)

Suggested Reading

Anand KJS, Hall RW, Desai N, et al. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. Lancet. 2004;363:1673–82.

Grunau RV, Johnston CC, Craig KD. Neonatal facial and cry responses to invasive and non-invasive procedures. Pain. 1990;42:295–305.

Grunau RVE Craig KD. Pain expression in neonates: facial action and cry. Pain. 1987; 28: 395–410.

Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain. J Perinatol. 2008;28(1):55–60.

Johnston CC, Stevens B, Craig KD. Developmental changes in pain expression in premature, full-term, two and four month old infants. Pain. 1993;52:201–8.

Johnston CC, Fernandes AM, Campbell-Yeo M. Pain in neonates is different. Pain. 2011;152 3 Suppl:S65–73.

Pillai Riddell RR, Racine NM, Gennis HG, Turcotte K, Uman LS, Horton RE, Ahola Kohut S, Hillgrove Stuart J, Stevens B, Lisi DM. Non-pharmacological management of infant and young child procedural pain. Cochrane Database Syst Rev. 2015;12:CD006275.

Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. Clin J Pain. 1996;12(1):13–22.

Stevens BJ, Pillai Riddell RR, Oberlander TE, Gibbins S. Assessment of pain in neonates and infants In: Anand KJS, Stevens BJ, McGrath PJ editors. Pain in neonates and infants. 3rd ed. Pain Research and Clinical Management Series. Amsterdam: Elsevier Science Publishers B.V.; 2007. pp. 67–90.

Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev. 2013;1:CD001069.

Taddio A: Evidence for systemic morphine and fentanyl analgesia. In: Anand KJS, Stevens BJ, McGrath PJ editors. Pain in neonates and infants. 3rd ed. Pain Research and Clinical Management Series. Amsterdam: Elsevier Science Publishers B.V.; 2007. pp. 141–154.

Inhaled Nitric Oxide Therapy

63

John P. Kinsella

I. Introduction
   A. Inhaled nitric oxide (iNO) therapy for the treatment of newborns with hypoxemic respiratory failure and pulmonary hypertension has dramatically changed management strategies for this critically ill population.
   B. iNO therapy causes potent, selective, and sustained pulmonary vasodilation and improves oxygenation in term newborns with severe hypoxemic respiratory failure and persistent pulmonary hypertension.
   C. Multicenter randomized clinical studies have demonstrated that iNO therapy reduces the need for extracorporeal membrane oxygenation (ECMO) treatment in term neonates with hypoxemic respiratory failure.
   D. The potential role of iNO in the preterm newborn is currently controversial and its use remains investigational in this population.

II. Rationale for iNO Therapy
   A. The physiologic rationale for iNO therapy in the treatment of neonatal hypoxemic respiratory failure is based upon its ability to achieve potent and sustained pulmonary vasodilation without decreasing systemic vascular tone.
   B. Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome associated with diverse neonatal cardiac and pulmonary disorders that are characterized by high pulmonary vascular resistance (PVR) causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and/or foramen ovale (Chap. 72).
   C. Extrapulmonary shunting from high PVR in severe PPHN of the newborn can cause critical hypoxemia, which is poorly responsive to inspired oxygen or pharmacologic vasodilation.
   D. Historically, vasodilator drugs administered intravenously, such as tolazoline and sodium nitroprusside, were often unsuccessful because of systemic hypotension and an inability to achieve or sustain pulmonary vasodilation.
   E. The ability of iNO therapy to selectively lower PVR and decrease extrapulmonary venoarterial admixture accounts for the acute improvement in oxygenation observed in newborns with PPHN.

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F. Oxygenation can also improve during iNO therapy in some newborns who do not have extrapulmonary right-to-left shunting. Hypoxemia in these cases is primarily the result of intrapulmonary shunting caused by continued perfusion of lung units that lack ventilation (e.g., atelectasis), with variable contributions from ventilation/perfusion (V/Q) inequality. Low dose iNO therapy can also improve oxygenation by re-directing blood from poorly aerated or diseased lung regions to better aerated distal air spaces ("microselective effect").

G. The clinical benefits of low dose iNO therapy may include reduced lung inflammation and edema, as well as potential protective effects on surfactant function, but these effects remain clinically unproven.

H. The diagnostic value of iNO therapy is also important, in that failure to respond to iNO raises important questions about the specific mechanism of hypoxemia. Poor responses to iNO should lead to further diagnostic evaluation for "unsuspected" anatomic cardiovascular or pulmonary disease.

III. Evaluation of the Term Newborn for iNO Therapy

A. The cyanotic newborn

1. History

a. Assess the primary cause of hypoxemia. Marked hypoxemia in the newborn can be caused by lung parenchymal disease with intrapulmonary shunting, pulmonary vascular disease causing extrapulmonary right-to-left shunting, or anatomic right-to-left shunting associated with congenital heart disease.

b. Assessment of risk factors for hypoxemic respiratory failure

(1) Prenatal ultrasound studies

(a) Lesions such as diaphragmatic hernia and congenital pulmonary airway malformation are frequently diagnosed prenatally.

(b) Although many anatomic congenital heart diseases can be diagnosed prenatally, vascular abnormalities (e.g., aortic coarctation, total anomalous pulmonary venous return) are more difficult to diagnose.

(c) A history of a structurally normal heart by fetal ultrasonography should be confirmed with echocardiography in the cyanotic newborn.

c. Maternal historical information

(1) History of severe and prolonged oligohydramnios causing pulmonary hypoplasia

(2) Prolonged fetal brady- and tachyarrhythmias and marked anemia (caused by hemolysis, twin-to-twin transfusion, or chronic hemorrhage) may cause congestive heart failure, pulmonary edema, and respiratory distress.

(3) Maternal illness (e.g., diabetes mellitus), medications (e.g., aspirin causing premature constriction of the ductus arteriosus), and drug use may contribute to disordered transition and cardiopulmonary distress in the newborn.

(4) Risk factors for infection causing sepsis/pneumonia should also be considered, including premature or prolonged rupture of membranes, fetal tachycardia, maternal leukocytosis, uterine tenderness, and other signs of intra-amniotic infection.

d. Events at delivery

(1) If positive pressure ventilation is required in the delivery room, the risk of pneumothorax increases.

(2) History of meconium-stained amniotic fluid, particularly if meconium is present below the vocal cords, should raise the suspicion of meconium aspiration syndrome (Chap. 71).

(3) Birth trauma (e.g., clavicular fracture and phrenic nerve injury) or acute feto-maternal/feto-placental hemorrhage may also cause respiratory distress in the newborn.

2. Physical examination
   a. The initial physical examination provides important clues to the etiology of cyanosis (Chap. 13).
   b. Marked respiratory distress in the newborn (retractions, grunting, and nasal flaring) suggests the presence of pulmonary parenchymal disease with decreased lung compliance.
   c. Recognize that airway disease (e.g., tracheo-bronchomalacia) and metabolic acidemia can also cause severe respiratory distress.
   d. In contrast, the newborn with cyanosis alone ("non-distressed tachypnea") typically has cyanotic congenital heart disease (e.g., transposition of the great vessels) or idiopathic PPHN.
3. Interpretation of pulse oximetry measurements
   a. Right-to-left shunting across the ductus arteriosus causes post-ductal desaturation.
   b. Interpretation of pre-ductal (right hand) and post-ductal (lower extremity) saturation by pulse oximetry provides important clues to the etiology of hypoxemia in the newborn.
   c. If the measurements of pre- and post-ductal SpO_2 are equivalent, this suggests either that the ductus arteriosus is patent and PVR is sub-systemic (i.e., the hypoxemia is caused by parenchymal lung disease with intrapulmonary shunting or cyanotic heart disease with ductal-dependent pulmonary blood flow), or that the ductus arteriosus is closed (precluding any interpretation of pulmonary artery pressure without echocardiography).
   d. It is exceptionally uncommon for the ductus arteriosus to close in the first hours of life in the presence of supra-systemic pulmonary artery pressures.
   e. When the post-ductal SpO_2 is lower than pre-ductal SpO_2 (>5 % gradient), the most common cause is supra-systemic PVR in PPHN, causing right-to-left shunting across the ductus arteriosus (associated with meconium aspiration syndrome, surfactant deficiency/dysfunction, congenital diaphragmatic hernia, pulmonary hypoplasia, or idiopathic).
   f. Ductal-dependent systemic blood flow lesions (hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, and aortic coarctation) may also present with post-ductal desaturation.
   g. Anatomic pulmonary vascular disease (alveolar capillary dysplasia, pulmonary venous stenosis, and anomalous venous return with obstruction) can cause supra-systemic PVR with right-to-left shunting across the ductus arteriosus and post-ductal desaturation.
   h. The unusual occurrence of markedly lower pre-ductal SaO_2 compared to post-ductal measurements suggests one of two diagnoses: transposition of the great vessels with pulmonary hypertension, or transposition with coarctation of the aorta.
4. Laboratory and radiologic evaluation
   a. One of the most important tests to perform in the evaluation of the newborn with cyanosis is the chest radiograph (CXR).
   b. The CXR can demonstrate the classic findings of RDS (air bronchograms, diffuse granularity, and underinflation), meconium aspiration syndrome, or congenital diaphragmatic hernia.
   c. The important question to ask when viewing the CXR is whether the severity of hypoxemia is out of proportion to the radiographic changes. Marked hypoxemia despite supplemental oxygen in the absence of severe pulmonary parenchymal disease radiographically suggests the presence of an extrapulmonary right-to-left shunt (idiopathic PPHN of the newborn or cyanotic heart disease).

d. Other essential measurements include an arterial blood gas analysis, a complete blood count to evaluate for infection, and blood pressure measurements in the right arm and a lower extremity to determine aortic obstruction (interrupted aortic arch, coarctation).

5. Response to supplemental oxygen (100 % oxygen by hood, mask, or endotracheal tube).
   a. Marked improvement in SpO_2 (increase to 100 %) with supplemental oxygen suggests an intrapulmonary shunt (lung disease) or reactive PPHN of the newborn from vasodilation.
   b. The response to mask CPAP is also a useful discriminator between severe lung disease and other causes of hypoxemia.
   c. Most patients with PPHN of the newborn have at least a transient improvement in oxygenation in response to interventions such as high inspired oxygen and/or mechanical ventilation. If the pre-ductal SpO_2 never reaches 100 %, the likelihood of cyanotic heart disease is high.
6. Echocardiography (Chap. 25).
   a. The definitive diagnosis in newborns with cyanosis and hypoxemic respiratory failure often requires echocardiography (Fig. 63.1).
   b. The initial echocardiographic evaluation is important to rule out structural heart disease causing hypoxemia.
   c. It is critically important to diagnose congenital heart lesions for which iNO treatment would be contraindicated.
   d. Congenital heart diseases that can present with hypoxemia unresponsive to high inspired oxygen concentrations (e.g., dependent upon right-to-left shunting across the ductus arteriosus) include critical aortic stenosis and coarctation, interrupted aortic arch, and hypoplastic left heart syndrome. Decreasing PVR with iNO in these conditions could lead to systemic hypoperfusion and delay definitive diagnosis.
   e. PPHN of the newborn is defined by the echocardiographic determination of extrapulmonary veno-arterial admixture (right-to-left shunting at the foramen ovale and/or ductus arteriosus), not simply evidence of increased PVR.

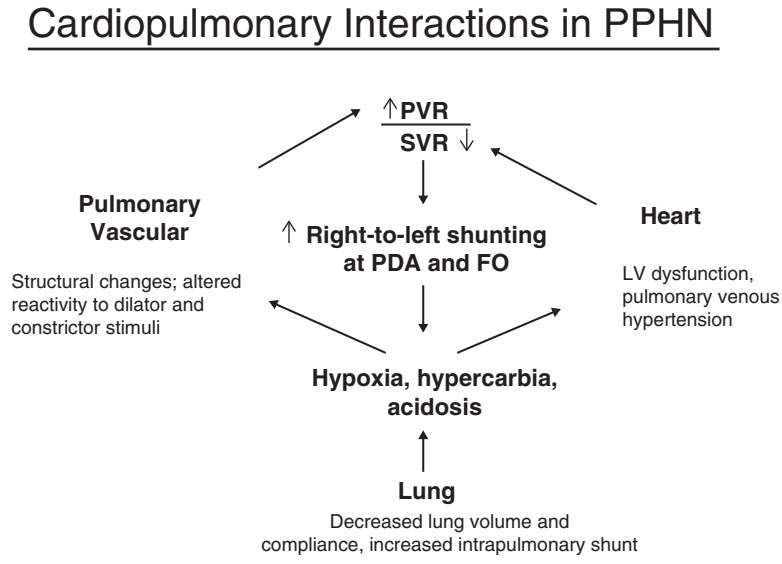

Fig. 63.1 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn

f. Doppler assessments of atrial and ductal level shunts provide essential information when managing a newborn with hypoxemic respiratory failure.
g. Left-to-right shunting at the foramen ovale and ductus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should be directed at optimizing lung inflation.
h. In the presence of severe left ventricular dysfunction and pulmonary hypertension, pulmonary vasodilation alone may be ineffective in improving oxygenation. The echocardiographic findings in this setting include right-to-left ductal shunting (caused by supra-systemic PVR), and mitral insufficiency with *left-to-right* atrial shunting.

IV. Candidates for iNO Therapy
A. Several pathophysiologic disturbances contribute to hypoxemia in the newborn infant, including cardiac dysfunction, airway and pulmonary parenchymal abnormalities, and pulmonary vascular disorders.
1. In some newborns with hypoxemic respiratory failure, a single mechanism predominates (e.g., extrapulmonary right-to-left shunting in idiopathic PPHN), but more commonly, several of these mechanisms contribute to hypoxemia.
2. MAS has complicated cardiopulmonary pathophysiology. Meconium may obstruct some airways decreasing V/Q ratios and increasing intrapulmonary shunting. Other lung segments may be overventilated relative to perfusion and cause increased physiologic dead space. Moreover, the same patient may have severe pulmonary hypertension with extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale, and LV dysfunction.
3. The effects of iNO may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease. Atelectasis and air space disease (pneumonia, pulmonary edema) will decrease effective delivery of iNO to its site of action in terminal lung units.
4. The effects of inhaled NO on ventilation–perfusion matching appear to be optimal at low doses (<20 ppm).
5. In cases complicated by homogeneous (diffuse) parenchymal lung disease and underinflation, pulmonary hypertension may be exacerbated because of the adverse mechanical effects of underinflation on PVR. In this setting, effective treatment of the underlying lung disease is essential (and sometimes sufficient) to cause resolution of the accompanying pulmonary hypertension.

B. Clinical criteria
1. Gestational and postnatal age
a. Available evidence from clinical trials supports the use of iNO in late preterm (>34 weeks' gestation) and term newborns.
b. Clinical trials of iNO in the newborn have incorporated ECMO treatment as an endpoint. Therefore, most patients have been enrolled in the first few days of life.
c. Although one of the pivotal studies used to support FDA approval of iNO therapy included as an entry criterion a postnatal age up to 14 days, the average age at enrollment in that study was 1.7 days.
d. Currently, clinical trials support the use of iNO before treatment with ECMO, usually within the first week of life.
e. Clinical experience suggests that iNO may be of benefit as an adjuvant treatment after ECMO therapy in patients with sustained pulmonary hypertension (e.g., congenital diaphragmatic hernia). Postnatal age alone should not define the duration of therapy in cases where prolonged treatment could be beneficial.

C. Severity of illness
   1. Studies support the use of iNO in infants who have hypoxemic respiratory failure with evidence of PPHN requiring mechanical ventilation and high inspired oxygen concentrations.
   2. The most common criterion employed has been the oxygenation index (OI Chap. 20). Although clinical trials commonly allowed for enrollment with OI >25, the mean level at study entry in multicenter trials approximated 40.
   3. There is no evidence that starting iNO therapy at a lower OI (i.e., <25) reduces the need for treatment with ECMO.
   4. Current multicenter studies suggest that indications for treatment with iNO may include an OI >25 with echocardiographic evidence of extrapulmonary right-to-left shunting.

V. Treatment Strategies
   A. Dose
      1. The first studies of iNO treatment in term newborns reported initial doses that ranged up to 80 ppm. Early laboratory and clinical studies established the boundaries of iNO dosing protocols for subsequent randomized, clinical trials in newborns.
      2. Recommended starting dose for iNO in the term newborn is 20 ppm.
      3. *Increasing the dose to 40 ppm does not generally improve oxygenation in patients who do not respond to the lower dose of 20 ppm.*
      4. Although brief exposures to higher doses (40–80 ppm) appear to be safe, *sustained treatment with 80 ppm NO increases the risk of methemoglobinemia.*
   B. Duration of treatment
      1. In multicenter, clinical trials, the typical duration of iNO treatment has been <5 days, which parallels the clinical resolution of PPHN.
      2. Individual exceptions occur, particularly in cases of pulmonary hypoplasia.
      3. If iNO is required for >5 days, investigations into other causes of pulmonary hypertension should be considered (e.g., alveolar capillary dysplasia), particularly if discontinuation of iNO results in supra-systemic elevations of pulmonary artery pressure by echocardiography.
      4. It is reasonable to discontinue iNO if the F_iO_2 is <0.60 and the PaO_2 is >60 without evidence of rebound pulmonary hypertension or an increase in $F_iO_2 > 15\%$ after iNO withdrawal.
   C. Weaning
      1. After improvement in oxygenation occurs with the onset of iNO therapy, strategies for weaning the iNO dose become important.
      2. Numerous approaches have been employed, and few differences have been noted until final discontinuation of iNO treatment.
      3. In one study, iNO was reduced from 20 to 6 ppm after 4 h of treatment without acute changes in oxygenation. In another trial, iNO was reduced in a stepwise fashion to as low as 1 ppm without changes in oxygenation.
   D. Monitoring
      1. Electrochemical devices accurately monitor NO and NO_2 levels.
      2. NO_2 levels remain low at delivered iNO doses within the recommended ranges.
      3. Methemoglobinemia occurs after exposure to high concentrations of iNO (80 ppm). This complication has not been reported at lower doses of iNO ($\leq$20 ppm).
      4. Because methemoglobin reductase deficiency may occur unpredictably, it is reasonable to measure methemoglobin levels by co-oximetry within 4 h of starting iNO therapy and subsequently at 24 h intervals.

E. Ventilator management
   1. Along with iNO treatment, other therapeutic strategies have emerged for the management of the term infant with hypoxemic respiratory failure.
   2. Considering the important role of parenchymal lung disease in specific disorders included in the syndrome of PPHN, pharmacologic pulmonary vasodilation alone should not be expected to cause sustained clinical improvement in many cases.
   3. Patients not responding to iNO can show marked improvement in oxygenation with adequate lung inflation alone.
   4. In newborns with severe lung disease, HFOV is frequently used to optimize lung inflation and minimize lung injury (Chap. 43).
   5. In clinical pilot studies using iNO, the combination of HFOV and iNO caused the greatest improvement in oxygenation in newborns who had severe pulmonary hypertension complicated by diffuse parenchymal lung disease and underinflation (e.g., RDS, pneumonia).
   6. A randomized, multicenter trial demonstrated that treatment with HFOV + iNO was often successful in patients who failed to respond to HFOV or iNO alone in severe pulmonary hypertension, and differences in responses were related to the specific disease associated with the various complex disorders.

VI. The Preterm Newborn
   A. Background
      1. The effectiveness of iNO in the late preterm and term newborn is largely from its properties as a selective pulmonary vasodilator; however, numerous laboratory studies also demonstrate other important effects, such as decreasing lung inflammation, reducing oxidant stress, and enhancing alveolarization and lung growth.
      2. These observations formed the basis for studying iNO in premature newborns at risk for developing bronchopulmonary dysplasia (BPD).
      3. Numerous randomized, controlled trials of iNO in premature newborns have been conducted over the last 2 decades. Meta-analyses of these studies reported no net improvement in either BPD or developmental sequelae. iNO therapy also was not associated with an increased risk of adverse events.
      4. The NIH Consensus Development Conference concluded that the use of iNO to prevent BPD is not supported by available evidence, and that "there are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks' gestation" and that "use in this population should be left to clinical discretion."
      5. Recent joint guidelines from the American Heart Association and American Thoracic Society supported the role of iNO in treating severe pulmonary hypertension in premature newborns.
   B. Current status of iNO treatment in premature newborns.
      1. Inhaled NO therapy should not be used in premature infants for the prevention of BPD, as multicenter studies have failed to consistently demonstrate efficacy for this purpose.
      2. Inhaled NO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily from PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios.
      3. Inhaled NO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention.

Suggested Reading

Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015;132:1–66.

Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med. 2006;205:343–53.

Clark RH, Kueser TJ, Walker MW, et al. Low-dose inhaled nitric oxide treatment of persistent pulmonary hypertension of the newborn. N Engl J Med. 2000;342:469–74.

Cole FS, Alleyne C, Barks JD, et al. NIH consensus development conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics. 2011;127: 363–9.

Davidson D, Barefield ES, Kattwinkel J, et al. Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension. Pediatrics. 1999;104:231–6.

Gerlach H, Rossaint R, Pappert D, Falke KJ. Time-course and dose-response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Euro J Clin Invest. 1993;23:499–502.

Gersony WM. Neonatal pulmonary hypertension: pathophysiology, classification and etiology. Clin Perinatol. 1984; 11:517–24.

Hallman M. Molecular interactions between nitric oxide and lung surfactant. Biol Neonate. 1997;71:44–8.

Kinsella JP, Abman SH. Clinical approach to inhaled nitric oxide therapy in the newborn. J Pediatr. 2000;136:717–26.

Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. 1992;340: 819–20.

Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high frequency oscillatory ventilation in severe persistent pulmonary hypertension of the newborn. J Pediatr. 1997;131:55–62.

Kinsella JP, Walsh WF, Bose CL, et al. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial. Lancet. 1999;354:1061–5.

Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med. 2006;205:354–64.

Kinsella JP, Steinhorn RH, Krishnan US, et al. Recommendations for the use of inhaled nitric oxide therapy in premature newborns with severe pulmonary hypertension. J Pediatr. 2015. doi:10.1016/j.jpeds.2015.11.050.

Levin DL, Heymann MA, Kitterman JA, et al. Persistent pulmonary hypertension of the newborn. J Pediatr. 1976;89:626.

Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med. 1997;336:597–604.

Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. 1992;340:818–9.

Schreiber MD, Gin-Mestan K, Marks JD, et al. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. N Engl J Med. 2003;349: 2099–107.

Wessel DL, Adatia I, Van Marter LJ, et al. Improved oxygenation in a randomized trial of inhaled nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics. 1997;100:e7.

Extracorporeal Membrane Oxygenation

64

Robert E. Schumacher

I. Description
   A. Extracorporeal membrane oxygenation (ECMO) is a treatment for an infant (usually term or late preterm) with *reversible* lung failure, which affords a period of "lung rest" by the use of heart–lung bypass and an artificial lung. Such a period of rest may allow for lung recovery and ultimately survival of the infant. The circulation is diverted from the body and is pumped through a membrane oxygenator.
   B. Oxygen delivery is determined by oxygen content and cardiac output. Veno-venous (V-V) ECMO increases oxygen content (think of it as "intravenous oxygen"). Veno-arterial (V-A) ECMO increases oxygen content and can increase cardiac output (which is equivalent to "pump flow").
   C. Ventilation is determined by gas flow (equivalent to respiratory rate x tidal volume (liters per unit of time)) through the artificial lung.

II. ECMO circuit (Fig. 64.1)
   A. For V-A bypass, venous blood is passively or actively (depending upon pump type) drained via the right atrium and passed via a pump to a venous capacitance reservoir (bladder box—optional), an artificial lung, a heat exchanger, and an arterial perfusion cannula. The right internal jugular vein and common carotid artery are commonly used as access points and are often ligated as part of the bypass procedure.
   B. For V-V bypass, a double lumen cannula is used. In this isovolemic procedure, blood is removed from and returned to the right atrium, the remainder of the circuit is the same as in V-A ECMO (Fig. 64.2).
   C. To prevent thrombotic complications while on ECMO, the baby is treated with systemic heparinization.

III. Patient selection
   A. For "standard" neonatal ECMO the baby should:
      1. Be of a gestational age such that the risk of intracranial hemorrhage is relatively low (≥35 weeks' gestation is often used, but registry data suggest there is no absolute gestational age below which hemorrhage will occur)

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Fig. 64.1 Typical ECMO circuit and equipment

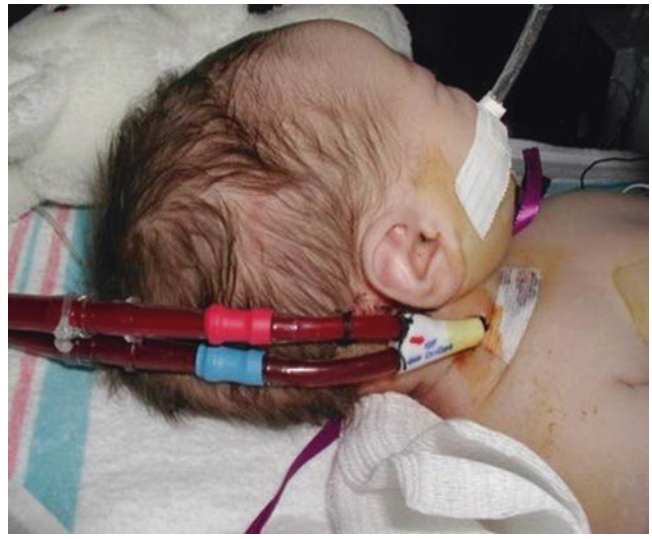

Fig. 64.2 Term infant cannulated for veno-venous ECMO

2. Have a cranial sonogram with no IVH (to many, grade I is a relative contraindication)
3. Have no major bleeding problem (isolated pulmonary hemorrhage is not a contraindication)
4. Have *reversible* respiratory failure (ECMO does not grow lung)
5. Be "failing" conventional medical management

B. Failure of conventional medical management is a definition that should be "individualized" for each ECMO center.
1. Guidelines (based on experience with populations) are used, but the ultimate decision is up to those caring for the individual infant. Cut point values (i.e., ECMO/NO ECMO) should

be chosen taking into account probabilities for mortality and long-term morbidity. Since different disease processes have different outcome probabilities, it is rational to also take that into account when applying criteria. General criteria provide guidance.

2. Oxygenation index (OI) criterion:
   a.
$$\mathrm{OI} = \frac{\text{mean airway pressure} \times \mathrm{FiO_2}}{\mathrm{P_aO_2\,(post-ductal)}} \times 100$$
   b. *After* stabilization, if the OI is ≥40 on 3 of 5 occasions (each value separated by >30 and <60 min), ECMO criteria have been met (OI >40 is University of Michigan "absolute" criterion; OI >25 is used as "consider" criterion).
   c. V-V ECMO may not provide the same cardiac support that veno-arterial ECMO does.
      (1) Infants with severe cardiac compromise may not tolerate V-V ECMO. How to identify such patients is difficult; results from the Extracorporeal Life Support Organization registry suggest V-V ECMO is effective even in infants requiring substantial blood pressure support.
      (2) Because the risk of carotid artery ligation is not present, consideration for V-V ECMO is sometimes made at a lower OI.
3. Other criteria include the A-aDO_2 (generally above 600–610 Torr), "acute deterioration," "intractable air leaks," hemodynamic instability (refractory hypotension), and "unresponsive to medical management."

IV. Management

A. Initial bypass problems
   1. Hypotension
      a. Hypovolemia: ECMO circuit has high blood capacitance; treat this with volume. The technician/specialist may/should have blood or colloid available from circuit priming procedure.
      b. Sudden dilution of vasopressors, especially with V-V ECMO; treat by having separate pressor infusion pumps to infuse into circuit.
      c. Hypocalcemia from stored blood (sometimes an issue): circuit can be primed with calcium to prevent this.
   2. Bradycardia: from vagal stimulation by catheter(s), this should be atropine-responsive.
   3. Consequences of catheter misplacement. Correct catheter placement must be documented radiographically.
   4. Once on initial bypass there should be no blood squirting, no pumping air through circuit, and there should be "blue blood going in and red blood coming out" of the circuit.

B. Initial management
   1. V-A bypass: wean ventilator rapidly (10–15 min) to "rest" settings (FiO_2 0.3, pressures 25/4 cm H_2O, rate 20 bpm, T_I 0.5–1.0 s). CPAP/High PEEP (10–12 cm H_2O) to maintain FRC can often shorten bypass time. Inotropes can usually be quickly discontinued. The use of a saturation monitor to measure blood returning to the circuit provides a clinician with an accurate measure of mixed venous oxygen saturation (SvO_2). Under most circumstances, O_2 consumption (reflected by the difference in mixed venous O_2 and arterial O_2 values) equals O_2 delivery. Since this can be measured in ECMO patients, the caregiver has a measure of "pump" oxygen delivery/cardiac output.
   2. "Hot water-cold water." With V-A ECMO there are two hearts (pump and patient) and two lungs operating in parallel. Oxygen delivery has been likened to the delivery of hot water through a faucet equipped with both a hot (ECMO lung) and cold (native "sick"

lung) water valve. The temperature of the water coming out of the spigot can be adjusted by turning either faucet handle. An example to make one think: If a baby is transfused and the ECMO flow is not adjusted, flow through the "sick lung" will increase and the SaO_2 of arterial blood will decrease, but the total oxygen delivery will increase! When this makes sense, one is "thinking ECMO."

3. V-V bypass: wean with caution; infant is still dependent on innate myocardial function for O_2 delivery. With V-V ECMO both blood intake and output occur in the right atrium and the potential for some recirculation of blood exists. Because of this, S_VO_2 is useful only for trends at the same pump flow rate. Innate lung still provides gas exchange. High CPAP with V-V ECMO may impede cardiac output or pulmonary blood flow; if desired, use end-tidal CO_2 to optimize PEEP (use Vd/V_T). Inotropes must be weaned with caution.
4. Caution: avoid large swings in pCO_2 and blood pressure; can be associated with unwanted rapid changes in cerebral blood flow.
5. Infants have "self-decannulated"; *restraints are mandatory*.
6. Head position is critical; head turned too far left will functionally occlude the left jugular vein (the right is already ligated). Such a scenario may lead to CNS venous hypertension.
7. Analgesia and sedation are usually required. Narcotics are used for analgesia; if patient needs additional sedation, benzodiazepines are reasonable choices.
8. Heparin management
   a. Prior to cannulation, load with 100 U/kg.
   b. Typical start drip concentration is 50 U/mL [5 mL heparin (1000 U/mL) in 95 mL D_5W].
   c. Usual consumption is 20–40 U/kg/h (although values vary widely). At 60 U/kg/h consider fresh frozen plasma q6h. It is affected by blood-surface interactions in circuit, infant's own clotting status, and heparin elimination (renal excretion).
   d. Titrate heparin to keep activated clotting time (ACT) in desired range.

C. Daily management, patient protocols, problems:
   1. Chest radiograph: daily.
   2. Cranial sonogram: obtain the first day after cannulation, after every change in neurologic status, and regularly thereafter (every 2–3 days). Some centers prefer a daily study when on V-A ECMO.
      a. Brain hemorrhage includes both typical and atypical (including posterior fossa) hemorrhages. If seen and patient is able to come off ECMO, do so. If patient is likely to die if removed from bypass, has stable hemorrhage, or is neurologically stable, consider continuing bypass with strict attention to lower ACT values, and keeping platelet counts higher (e.g., 125,000–200,000/mm^3).
      b. Cranial sonography is not as good as MRI/CT for demonstrating lesions such as posterior fossa hemorrhage.
   3. Fluids: follow I/O, weights; the membrane lung provides an additional area for evaporative losses.
      a. Total body water (TBW) is high: a common problem, etiology probably multi-factorial. A problem arises when TBW is high but intravascular volume is low (capillary leak); early vigorous attempts at diuresis in this instance will usually not help and can be harmful. Some argue that vigorous attempts at diuresis can hasten lung recovery; others state that spontaneous diuresis is a marker for improvement and attempts to hasten it are of no avail. If diuresis is deemed advisable, use diuretics first, mechanical support (e.g., hemofiltration) last. (Furosemide in combination with theophylline may be helpful). Expect decreased urine output when a hemofilter is used.

b. K^+: serum values often low and require replacement, check for alkalosis. (Low K^+ may be related to the use of washed RBCs "thirsty" for K^+.)
c. Pump is primed with banked blood; depending upon the preservative, ionized Ca^{++} can be low. Checking and correcting the circuit can prevent this.

4. Hemostasis/hemolysis
   a. Obtain appropriate studies (e.g., fibrinogen, serum hemoglobin) and follow trends. Some use serum Hgb values of 50 mg/dL as action thresholds (suggest creating local values/plans) and regular platelet counts (q8h) daily.
   b. Clots are common, especially if using a venous capacitance reservoir (bladder). Pre-lung clots are usually left alone. Those post-lung are handled by ECMO specialist/technician. When clots appear, review platelet/heparin consumption, etc.
   c. Bleeding
      (1) From neck wound: treated with cannula manipulation, light pressure, or fibrin glue.
      (2) Hemothorax/pericardium will present with decreased pulse pressure and decreased pump filling. Treated by drainage first. (A more common problem if previous surgery has been done, e.g., CDH, thoracostomy tube placement.)
      (3) Treat with blood replacement, keep platelet counts high (>150,000/mm^3), lower target ACT values.
5. TPN: a *major* benefit of ECMO can be immediate provision of TPN and adequate caloric/low volume intake (use high dextrose concentrations).
6. Blood products:
   a. Minimize donor exposures, give only when indicated.
   b. Excessive PRBC administration without increasing pump flow (V-A ECMO) leads to lower aortic PO_2 but greater oxygen delivery (see above). In ECMO circles, when one responds to this by transfusing again one is said to be "chasing his/her tail."
7. Hypertension is a known complication. The final mechanism by which it is achieved is usually high total body water. It is almost always transient and resolves near the end of a run. Use population norms for blood pressure (a useful working definition for hypertension is MAP >75 mmHg) Initial treatment is usually with diuretics.
8. WBC often low, probably from peripheral migration of WBCs
9. Infections not a common problem. Suspect infection if unanticipated increasing ECMO support required.
10. Bilirubin can be elevated especially with sepsis or long ECMO runs. A cholestatic picture is typical; phthalate in plastic tubing may be hepatotoxic. Hepatosplenomegaly is common.
11. Cardiac stun: once on ECMO, a dramatic decrease in cardiac performance is seen in up to 5 % of patients. Seen more in V-A patients, may be ECMO-induced from increased afterload and decreased coronary artery oxygen content. The stun phenomenon usually resolves, but patients with it do have higher overall mortality rates. Treatment is supportive.

D. Circuit problems (selected more common problems)
1. Air in circuit: treatment depends upon location, can often be aspirated.
2. Pump "slowdowns or cutouts:" kinked tube, malposition, low volume, low filling pressure (pneumothorax, hemopericardium), and agitated infant (these are all preload/afterload issues).
3. Pump
   a. Electric failure: can be cranked by hand
   b. With roller pumps: if occlusion set too loose: false high flow readings; if set too tight: hemolysis

4. Lung pathophysiology: the membrane lung can get "sick," and have pulmonary embolus, edema, etc. Treatment depends upon specific problem.

E. Weaning
1. Use serial measures of oxygen content (on V-A ECMO easiest to follow S_VO_2) and wean by preset parameters.
2. Chest radiograph is very helpful.
   a. Usually shows initial complete opacification
   b. Starts to clear prior to "re-ventilating" the lungs and serves as a marker for lung recovery. Anticipate a trial off with this early sign.
3. Pulmonary mechanics tests: compliance becomes poor hours after going on and improvement is an early marker of lung recovery.
4. $ETCO_2$: increasing exhaled CO_2 indicative of return of lung function

F. Trial off
1. Valuable information can be obtained from "trialing off" even if you do not expect to be successful.
2. Lung conditioning: lungs are periodically (hourly) inflated using a long (≥5 s) sustained inflation.
3. Turning up the ventilator F_iO_2 and following S_VO_2 will give a feel for whether or not there is any effective pulmonary gas exchange.
4. Increased ventilator settings to achieve adequate tidal volumes 30–60 min before trial off appears to allow for recruitment of lung units.
5. V-A: obtain blood gas analyses frequently to assess ventilation. Wean FiO_2 aggressively per oximetry.
6. V-V: halt gas flow to membrane lung, keep pump flowing. Since infant is still on bypass but with no effective gas exchange through membrane, use venous line S_VO_2 to wean FiO_2, as it is now a true venous saturation. Residual O_2 in membrane lung may falsely elevate O_2 content for 20–30 min.
7. A successful trial off depends upon the individual patient. In general, baby should be stable on FiO_2 ≤0.4, and receiving reasonable ventilator settings.

G. Inability to wean from ECMO (non-CDH)
1. With prolonged need for bypass (e.g., 7 days) and little to no improvement, consider an underlying "rare" lung disease.
2. Bronchoscopy and lavage and/or biopsy may allow for the diagnosis of rare lung disease (e.g., surfactant protein deficiencies, alveolar capillary dysplasia).

H. Decannulation
1. Notify surgeon as soon as possible.
2. Give skeletal muscle relaxant.
3. Need for repair of carotid artery or jugular vein controversial.

V. Post-ECMO Follow-Up
A. Neck: sutures removed in 7 days.
B. Platelets will continue to fall post-ECMO. Serial counts are necessary until stable (24–48 h).
C. CNS:
1. MRI: obtained because of relative insensitivity of sonography for posterior fossa and near field parenchymal lesions.
2. BAER: because of high incidence of sensorineural hearing loss with PPHN, hearing screening is recommended. Delayed onset loss has been described and repeated screening advised.

D. Airway: Vocal cord paresis seen in approximately 5 % of infants post-ECMO; acute respiratory deterioration has occurred. If persistent stridor is noted, flexible bronchoscopy is recommended. Hoarseness has usually resolved clinically (days to months).
E. Long-term follow-up
   1. Neurodevelopmental follow-up should be provided: 10–20 % show major problems.
   2. Medical problems include lower respiratory tract infections in many.

Suggested Reading

Annich G, Lynch W, MacLaren G, et al., editors. Extracorporeal cardiopulmonary support in critical care. 4th ed. Ann Arbor: Extracorporeal Life Support Organization; 2012.

Ijsselstijn H, van Heijst AF. Long-term outcome of children treated with neonatal extracorporeal membrane oxygenation: increasing problems with increasing age. Sem Perinatol. 2014;38(2):114–21.

Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. Cochrane Database Syst Rev. 2008;(3).

Liquid Ventilation for Neonatal Respiratory Failure

65

Ronald B. Hirschl

I. Description: Liquid ventilation refers to the process of enhancing pulmonary function through the instillation of perfluorocarbon liquid into the lungs.
   A. Partial liquid ventilation (PLV): the achievement of gas exchange through the delivery of gas tidal volumes to lungs which have been filled with perfluorocarbon liquid
   B. Total liquid ventilation (TLV): the achievement of gas exchange through the delivery of tidal volumes of perfluorocarbon liquid to the lungs using a specialized mechanical liquid ventilator

II. Physiology of Perfluorocarbon Ventilation
   A. Perfluorocarbons (PFC): inert liquids which are produced by the fluorination of common organic hydrocarbons. The carbon chain length and any additional atom give unique properties to each perfluorocarbon molecule.
   B. Physical properties of perfluorocarbons
      1. Density: denser than hydrocarbon counterparts with levels approaching twice that of water (1.75–1.95 g/mL at 25 °C).
      2. Surface tension: have weak intermolecular forces and remarkably low surface tensions (15–20 dyn/cm at 25 °C).
      3. Respiratory gas solubility: solubilities of the respiratory gases in perfluorocarbons are significantly greater than their corresponding solubilities in water or non-polar solvents.
         a. O_2 solubility at 37 °C = 44–55 mL gas/100 mL liquid
         b. CO_2 solubility at 37 °C = 140–210 mL gas/100 mL liquid
      4. An ideal PFC for respiratory application should have the properties of high gas solubility and moderate vapor pressure and viscosity. These properties, however, might not be found in a single pure perfluorocarbon. Thus, recent studies are focusing on PFC combinations that may optimize the fluid properties to better suit a particular application.
      5. Vapor pressure: perfluorocarbons are relatively volatile (vapor pressures range from 11 to 85 Torr at 37 °C). This property is important because it governs the evaporation rate of perfluorocarbons from the lungs during and after both types of liquid ventilation; high vapor pressure liquid would need more frequent supplementation than a low vapor pressure one.

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C. Basis for the use of liquid ventilation in neonatal ventilator-dependent respiratory failure
   1. Gas exchange
      a. Dependent portion of the lungs tends to be collapsed or filled with inflammatory exudate during severe pulmonary inflammation leading to ventilation-perfusion (V/Q) mismatching and hypoxemia.
      b. The high densities of perfluorocarbon liquids facilitate their distribution to the dependent portions of the lungs where atelectatic lung appears to be recruited.
      c. Perfluorocarbons have also been shown to redistribute pulmonary blood flow to the better-inflated, non-dependent segments.
      d. These effects, combined with the high respiratory gas solubilities of perfluorocarbons, lead to improvements in V/Q matching and arterial oxygenation.
   2. Pulmonary compliance
      a. Perfluorocarbons lead to an increase in pulmonary compliance secondary to their density-related recruiting effect on collapsed, inflamed alveoli. However, during PLV an increase in the perfluorocarbon dose can be associated with a reduction in compliance. This is related to the heterogeneous distribution of gas in the partially liquid-filled lungs.
      b. Perfluorocarbons act as an artificial surfactant and increase the stability of small airways.
      c. The regions of the lung that are filled with perfluorocarbon liquid (all regions for TLV, the dependent regions for PLV) exhibit a reduction of the gas–liquid interface in the distal airway which also reduces surface active forces tending to alveolar collapse.
      d. The result of these effects is enhanced alveolar recruitment at lower inflation pressures.
   3. Reduction of lung injury
      a. Effects may relate to improved alveolar inflation and better displacement and lavage of inflammatory mediators and debris from the affected portions of the lungs or to a limitation of excessive ventilator pressures from improvements in compliance.
      b. Perfluorocarbons have been shown to have in vitro anti-inflammatory activities, such as reduction in neutrophil chemotaxis and nitric oxide production, as well as decreased LPS-stimulated macrophage production of cytokines. Neutrophil infiltration also appears to be reduced following lung injury in liquid ventilated animals. In vivo evaluation has shown a reduction in the release of TNF-α, IL-1, and IL-6 in human alveolar macrophages in perfluorocarbon exposed lungs.

D. Uptake, biodistribution, elimination, and toxicology
   1. Uptake: absorbed in small quantities from the lungs during liquid ventilation, reaching a steady state at 15–30 min of liquid breathing
   2. Biodistribution: have preferential distribution to tissues with high lipid content. These compounds are cleared most quickly from vascular, lipid-poor tissues such as muscle.
   3. Elimination: do not undergo significant biotransformation or excretion. PFCs are primarily eliminated by evaporation from the lungs and are scavenged by macrophages in both the lungs and other tissues.
   4. Toxicology: pulmonary, metabolic, hematologic, and clinical effects of liquid ventilation have been studied extensively in laboratory animals with no significant pulmonary or systemic toxicity noted. Clinical studies have identified transient hypoxemia during PFC dosing and the development of pneumothorax as potential short term complications of PLV in humans.

III. Partial Liquid Ventilation
  A. A hybrid method of gas exchange, achieved through the delivery of conventional gas tidal volumes to perfluorocarbon-filled lungs
    1. Methods
      a. Lungs are filled with PFC liquid to an estimated fraction of FRC (approximately 5–30 mL/kg, depending on disease process, age, and weight) and conventional ventilation superimposed to achieve gas exchange.
      b. Adequate filling of the lungs is judged by the presence of a fluid meniscus in the endotracheal tube at a PEEP of 0, by the opacification of the dependent portions of the lungs on lateral chest radiography, and by the adequacy of gas tidal volumes. Fluid may be added or withdrawn.
    2. Theoretical basis for use of PLV in RDS
      a. PLV has relative simplicity as the need for a complex mechanical liquid ventilator is eliminated.
      b. The presence of dense perfluorocarbon fluid in the dependent regions of the lungs allows the recruitment of severely inflamed airways for the purpose of gas exchange. Oxygenation during PLV can occur either by the gas ventilation of these airways directly or by the oxygenation of the liquid as it equilibrates with the inspired gas.
      c. Carbon dioxide elimination is enhanced by increased gas tidal volumes.
      d. Compliance is enhanced secondary to alveolar recruitment and the surfactant-like activity of the perfluorocarbons. Because the gas–liquid interface is not completely eliminated during PLV, compliance improvement is not as dramatic as that seen during TLV and can actually deteriorate if the lungs are overfilled with perfluorocarbon liquid.
  B. Clinical studies of PLV in neonatal ventilator-dependent respiratory failure
    1. Leach reported significantly improved gas exchange and pulmonary compliance during PLV in 13 premature infants (24–34 weeks' gestation at birth) with refractory RDS as part of a multicenter, non-controlled trial. Significant complications occurring during the trial were limited to the development of Grade IV intraventricular hemorrhage in one patient. Of the ten patients completing at least 24 h of PLV, survival to a corrected gestational age of 36 weeks was 60 %.
    2. Pranikoff evaluated the use of PLV in four newborn patients maintained with extracorporeal life support for respiratory failure secondary to congenital diaphragmatic hernia (CDH). During 5–6 days of PLV therapy, patients exhibited significant increases in arterial oxygen tension and static pulmonary compliance compared to pretreatment values. The therapy was well tolerated and significant complications were limited to the development of pulmonary hemorrhage in one patient 4 days after the final dose of PFC.
    3. Migliori et al. evaluated the use of high-frequency PLV in two infants with chronic lung disease and severe respiratory failure. Both patients showed improved gas exchange with reduction in oxygen indices.

IV. Total Liquid Ventilation
  A. Lungs are completely filled with perfluorocarbon and a liquid tidal volume is perfused into and drained from the lungs for the purpose of gas exchange using a specialized mechanical liquid ventilator.
  B. Clinical studies of TLV
    1. The feasibility and potential of liquid ventilation as treatment for severe respiratory distress was reported in 1990 by Greenspan.
    2. Liquid ventilation was performed in 3 preterm neonates in whom conventional treatment had failed.

3. Improvement of pulmonary mechanics without hemodynamic impairment was reported in all three neonates.
4. The severity of pulmonary injury before the initiation of liquid ventilation precluded a successful outcome.

V. Perfluorocarbon-induced lung growth (PILG)
   A. Different studies have demonstrated the effectiveness of perfluorocarbon to induce lung growth in neonates with CDH on ECMO.
   B. A multicenter, prospective, randomized pilot study showed a higher mortality for the PILG group (75 %) compared to patients treated with conventional ventilation (40 %), though the number of patients in the study was very small.

VI. *At present*, *liquid ventilation is not yet an approved therapy for clinical use and remains investigational*.

Suggested Reading

Avoine O, Bosse D, Beaudry B, Beaulieu A, Albadine R, Praud JP, Robert R, Micheau P, Walti H. Total liquid ventilation in an ovine model of severe meconium aspiration syndrome. Crit Care Med. 2011;39(5):1097–103.

Furhman BP, Paczan PR, DeFancisis M. Perfluorocarbon-assisted gas exchange. Crit Care Med. 1991;19:712–22.

Greenspan JS, Wolfson MR, Rubenstein SD, et al. Liquid ventilation of human preterm neonates. J Pediatr. 1990;117:106–11.

Hirschl RB, Pranikoff T, Gauger P, et al. Liquid ventilation in adults, children and neonates. Lancet. 1995;346: 1201–2.

Hirschl RB, Croce M, Gore D, et al. for the Adult PLV study group. Prospective, randomized controlled pilot study evaluating the safety and efficacy of partial liquid ventilation in adult patients with the acute respiratory distress syndrome (ARDS). Am J Respir Crit Care Med. 2002;165(6):781–7.

Ivascu FA, Hirschl RB. New approaches to managing congenital diaphragmatic hernia. Semin Perinatol. 2004;28(3):185–98.

Leach CL, Greenspan JS, Rubenstein SD, et al. Partial liquid ventilation with perflubron in infants with severe respiratory distress syndrome. N Engl J Med. 1996;335:761–7.

Migliori C, Bottino R, Angeli A, et al. High frequency partial liquid ventilation in two infants. J Perinatol. 2004;24(2):118–20.

Mychaliska G, Bryner B, Dechert R, Kreutzman J, Becker M, Hirschl R. Safety and efficacy of perflubron-induced lung growth in neonates with congenital diaphragmatic hernia: results of a prospective randomized trial. J Pediatr Surg. 2015;50(7):1083–7.

Pranikoff T, Gauger P, Hirschl RB. Partial liquid ventilation in newborn patients with congenital diaphragmatic hernia. J Pediatr Surg. 1996;31:613–8.

Shaffer TH, Moskowitz GD. Demand-controlled liquid ventilation of the lungs. J Appl Physiol. 1974;36:208–13.

Shaffer TH, Douglas PR, Lowe CA, et al. The effects of liquid ventilation on cardiopulmonary function in preterm lambs. Pediatr Res. 1983;17:303–6.

Shaffer TH, Wolfson MR, Clark C. Liquid ventilation (state of the art review). Pediatr Pulmonol. 1992;14:102–9.

Tredici S, Komori E, Funakubo A, et al. A prototype of a liquid ventilator using a novel hollow fiber oxygenator in a rabbit model. Crit Care Med. 2004;32:2104–9.

Wolfson MR, Shaffer TH. Liquid ventilation during early development: theory, physiologic processes and application. J Appl Physiol. 1990;13:1–12.

Wolfson MR, Shaffer TH. Liquid ventilation: an adjunct for respiratory management. Pediatr Anesth. 2004;14:15–23.

Wolfson MR, Tran N, Bhutani VK, et al. A new experimental approach for the study of cardiopulmonary physiology during early development. J Appl Physiol. 1998;65:1436–43.

Section X

Management of Common Neonatal Respiratory Diseases

Mechanisms of Respiratory Failure

66

Anne Greenough and Anthony D. Milner

I. Respiratory failure is present when there is a major abnormality of gas exchange.
   A. In an adult, the limits of normality are a PaO_2 of >60 Torr (8 kPa).
   B. In the newborn, the oxygen tension needed to maintain the arterial saturation above 90 % varies between 40 and 60 Torr (5.3–8 kPa) depending upon the proportion of hemoglobin that is fetal and the arterial pH (a drop in pH of 0.2 eliminates the left shift produced by 70 % of the hemoglobin being fetal). Thus, in the newborn period, respiratory failure is best defined in terms of oxygen saturation. There are, however, no agreed criteria (see below).
   C. Hypoxia may be associated with hypercarbia ($PaCO_2$ >6.7 kPa or 55 Torr)

$$PaCO_2 \approx \frac{CO_2 \text{ production}}{\text{Alveolar ventilation}}$$

   Alveolar ventilation = (tidal volume − dead space × frequency)
   D. Respiratory failure associated with hypercarbia will occur, therefore, in situations associated with reduction in tidal volume and/or frequency.
   E. Respiratory failure in the neonatal period may be defined as:
   PaO_2 <50 Torr (6.7 kPa) in an inspired oxygen of at least 50 % with/without $PaCO_2$ >50 Torr (6.7 kPa)

II. Hypoxemia in the neonatal period can result from multiple causes
   A. Ventilation/perfusion (V/Q) mismatch
      1. Distinguished by a good response to supplementary oxygen (intrapulmonary shunting)
      2. Increased physiologic dead space, (i.e., loss of gas exchange surface area) found in the following conditions:
         a. Respiratory distress syndrome (RDS)
         b. Pneumonia
         c. Meconium aspiration syndrome
         d. Bronchopulmonary dysplasia
         e. Pulmonary hemorrhage

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B. Extrapulmonary (right-to-left) shunts are distinguished by relatively little improvement with supplementary oxygen and are found in:
   1. Pulmonary hypertension*
   2. Cyanotic congenital heart disease*
C. Methemoglobinemia*
D. Inadequate inspired oxygen*

*Note: although these situations produce cyanosis, this is not from respiratory failure. Cyanosis appears when the reduced hemoglobin concentration of the blood in the capillaries is >5 g/dL. Cyanosis, therefore, does not occur in severe anemic hypoxia (hypoxia is oxygen deficiency at the tissue level).

III. Hypoventilation (reduced alveolar ventilation, reduction in tidal volume and/or frequency) distinguished by a high $PaCO_2$ in association with hypoxemia
   A. Reduced respiratory compliance found in the following conditions:
      1. RDS
      2. Pneumonia
   B. Reduced lung volume found in the following conditions:
      1. RDS
      2. Pulmonary hypoplasia
   C. Compressed lung, found in the following conditions:
      1. Pneumothorax
      2. Congenital diaphragmatic hernia
      3. Pleural effusion
      4. Lobar emphysema
      5. Congenital pulmonary airway malformation
      6. Asphyxiating thoracic dystrophy
IV. Ventilatory pump failure. The ventilatory pump consists of the rigid thoracic cage, the respiratory muscles acting as force generators, and the central nerve system, which coordinate the respiratory muscle activity. Ventilatory pump failure occurs when there is:
   A. Reduced central drive
      1. Maternal opiate treatment (high levels of sedation)
      2. Cerebral ischemia
      3. Intracerebral hemorrhage
      4. Apnea of prematurity
      5. Central alveolar hypoventilation syndrome
   B. Impaired ventilatory muscle function
      1. Drugs (corticosteroids, paralytics—synergism with aminoglycosides)
      2. Disuse atrophy (first signs occur after 1–2 days mechanical ventilation)
      3. Protein calorie malnutrition
      4. Disadvantageous tension–length relationship (e.g., hyperinflation)—diaphragm must contract with a much higher than normal tension. When completely flat, contraction of the diaphragm draws in the lower rib cage, producing an expiratory rather than inspiratory action
      5. Neuromuscular disorders (Werdnig–Hoffman disease, myotonic dystrophy, etc.)
      6. Diaphragmatic problems (e.g., hernia, eventration)
      7. Phrenic nerve palsy (traumatic birth—Erb's palsy)
   C. Increased respiratory muscle workload
      1. Chest wall edema (hydrops)
      2. Upper airway obstruction/endotracheal tube with insufficient compensatory ventilatory support

3. Pulmonary edema, pneumonia
4. Intrinsic (inadvertent) PEEP

V. Disorders affecting the alveolar-capillary interface, distinguished, if incomplete, by a good response to increased supplementary oxygen
   A. Diffusion abnormalities (interstitial lung disease), e.g., pulmonary lymphangiectasia (Noonan syndrome)
   B. Anemia
   C. Alveolar capillary dysplasia

Suggested Reading

Aldrich TK, Prezant DJ. Indications for mechanical ventilation. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw-Hill Inc; 1994. p. 155–89.

Bazzy-Asaad A. Respiratory muscle function: implications for ventilatory failure. In: Haddad GG, Abman SH, Chernick V, editors. Basic mechanisms of pediatric respiratory disease. 2nd ed. Hamilton: BC Decker; 2002. p. 250–71.

Greenough A, Milner AD. Pulmonary disease of the newborn; Part 1 Physiology. In: Rennie JM, Roberton NRC, editors. Textbook of neonatology. 5th ed. Edinburgh: Churchill Livingstone; 2012

Marini JJ, Slutsky AS. Physiological basis of ventilatory support. In: Lenfant C, editor. Lung biology in health and disease, vol. 188. New York: Marcel Dekker Inc; 1988.

Roussos C, Macklem PT. The respiratory muscles. N Engl J Med. 1982;307:786–97.

Tissue Hypoxia

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Anne Greenough and Anthony D. Milner

I. Definition
   A. Tissue hypoxia occurs when oxygen transport is reduced below a critical level (i.e., below the metabolic demand), at which point either metabolism must be maintained anaerobically or tissue metabolic rate must be reduced.
   B. Under experimental conditions, if demands are kept constant, there is a biphasic response in oxygen consumption as oxygen transport is progressively reduced.
      1. Initially, oxygen consumption is independent of oxygen transport.
      2. Subsequently, oxygen consumption becomes dependent upon oxygen transport and declines in proportion (physiologic supply dependency).

II. Evaluating Tissue Oxygenation
   A. Mixed venous saturation identifies global tissue hypoxia, but tissue hypoxia can exist with a normal mixed venous saturation.
   B. Blood lactate levels; elevation can be present in the absence of tissue hypoxia, particularly in patients with sepsis.
   C. Fractional oxygen extraction (FOE) increases as oxygen transport is progressively compromised. FOE can be measured by near infrared spectroscopy (NIRS). Using spatially resolved spectroscopy, it is possible to measure regional tissue oxygen saturation in different organs (e.g., brain, kidney, liver, muscle or body regions, pre-ductal, and post-ductal peripheral tissue). The ratio of the oxygenated hemoglobin (Hb) to the total Hb can be measured, which expressed as a percentage equates to the oxygen saturation of the interrogated tissue. Peripheral muscle NIRS measurements can be used to recognize early states of (compensated) shock when arterial oxygen saturation (measured by pulse oximetry) or blood pressure may still be normal.
   D. When assessment of regional cerebral tissue oxygen saturation is combined with assessment of arterial oxygen saturation it is possible to calculate the fractional tissue oxygenation extraction, which reflects the balance between the cerebral oxygen supply and consumption.

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III. Oxygen Transport
  A. Determinants
    1. Cardiac output
    2. Hemoglobin concentration
    3. Hemoglobin saturation (to a lesser extent)
  B. Oxygen–hemoglobin dissociation curve (Fig. 20.1)
    1. The quaternary structure of hemoglobin determines its affinity for oxygen. By shifting the relationship of its four component polypeptide chains, and hence a change in the position of the heme moieties, it can assume:
      a. A relaxed (R) state—favors O_2 binding
      b. A tense (T) state—decreases O_2 binding
    2. When hemoglobin takes up a small amount of the oxygen, the R state is favored and additional O_2 uptake is facilitated.
    3. The oxygen–hemoglobin dissociation curve (which relates percentage oxygen saturation of hemoglobin to PaO_2) has a sigmoidal shape.
  C. Factors affecting the affinity of hemoglobin for oxygen:
    1. Temperature
    2. pH
    3. 2, 3 Diphosphoglycerate (2,3-DPG)
      a. A rise in temperature, a fall in pH (Bohr effect, elevated $PaCO_2$), or an increase in 2,3-DPG all shift the curve to the right, liberating more oxygen.
      b. The P_{50} is the PaO_2 at which the hemoglobin is half saturated with O_2; the higher the P_{50}, the lower the affinity of hemoglobin for oxygen.
      c. A right shift of the curve means a higher P_{50} (i.e., a higher PaO_2 is required for hemoglobin to bind a given amount of O_2).
  D. 2,3-DPG
    1. Formed from 3-phosphoglyceride, a product of glycolysis
    2. It is a high charged anion, which binds to the β chains of deoxygenated hemoglobin, but not those of oxyhemoglobin.
    3. 2,3-DPG concentration
      a. Increased by
        (1) Thyroid hormones
        (2) Growth hormones
        (3) Androgens
        (4) Exercise
        (5) Ascent to high altitude (secondary to alkalosis)
      b. Decreased by
        (1) Acidosis (which inhibits red blood cell glycolysis)
        (2) Fetal hemoglobin (HbF) has a greater affinity for O_2 than adult hemoglobin (HbA); this is caused by the poor binding of 2,3-DPG to the δ chains of HbF. Increasing concentrations of 2,3-DPG have much less effect on altering the P_{50} if there is HbF rather than HbA.

IV. Response to Reduced Oxygen Transport
  A. From low cardiac output; if chronic, 2,3-DPG increases unless there is systemic acidemia
  B. From anemia
    1. Cardiac output and oxygen extraction increase.
    2. If chronic, the HbO_2 dissociation curve shifts to the right.

C. From alveolar hypoxemia
   1. Increased cardiac output and oxygen extraction
   2. Increased hemoglobin

V. Oxygen Extraction Increases Progressively as Oxygen Transport is Reduced if Oxygen Consumption Remains Constant.
   A. Alterations in vascular resistance with adjustments to the microcirculation—opening of previously closed capillaries. This has three positive effects:
      1. The increase in capillary density decreases the distance for diffusion between the blood and site of oxygen utilization.
      2. It increases the lateral surface area for diffusion.
      3. The increase in cross-sectional area of the capillaries reduces the blood linear velocity and increases the transit time for diffusion.
   B. Changes in hemoglobin–oxygen affinity
      1. Increase in hydrogen (H^+) concentration results in a right shift of the dissociation curve.
      2. Changes in the 2,3-DPG concentration
      3. The concentration of 2,3-DPG is regulated by red blood cell H^+ concentration (as the rate-limiting enzyme is pH sensitive)—a high pH stimulates 2,3-DPG synthesis.
      4. Deoxyhemoglobin provides better buffering than oxyhemoglobin and thereby raises red cell pH; thus low venous oxygen promotes DPG synthesis.
         Note: this adaptive mechanism is less prominent in young infants with high levels of HgF, as HbF binds 2,3-DPG poorly and its synthesis is inhibited by unbound DPG.

VI. Consequences of Tissue Hypoxia
   A. Reduced oxidative phosphorylation
   B. Electron transport chain slows.
   C. Reduced phosphorylation of adenosine-5'-diphosphate (ADP) to adenosine-5'-triphosphate (ATP)
   D. Increased adenosine-5'-monophosphate (AMP), which is rapidly catabolized to inosine, hypoxanthine, xanthine, and finally uric acid during hypoxia
   E. Creatinine phosphate acts as a "supplementary" energy reservoir if creatinine kinase is available, but becomes rapidly depleted
   F. ADP can be phosphorylated anaerobically, but this is much less efficient than aerobic metabolism. During aerobic glycolysis, production of ATP is 19 times greater than it is under anaerobic conditions (i.e., production of 38 versus 2 mmol of ATP). Lactic acid accumulates.
   G. Adverse effect on immune function and inflammation
      1. Increased neutrophil sequestration
      2. Increased vascular permeability
      3. Decreased cellular immune function

Suggested Reading

Austin T. Measurement of cerebral oxygenation in preterm infants: is it useful? Dev Med Child Neurol. 2015;57:401–9.

Holler N, Urlesberger B, Mileer L, Baik N, Schwaberger B, Pichler G. Peripheral muscle near-infrared spectroscopy in neonates: ready for clinical use? A systematic qualitative review of the literature. Neonatology. 2015;108:233–45.

Lister G. Oxygen transport and consumption. In: Gluckman PD, Heymann MA, editors. Pediatrics and perinatology - the scientific basis. 2nd ed. London: Edward Arnold; 1996. p. 778–90.

Lister G, Farhey J. Oxygen transport. In: Haddad GG, Abman SH, Cherick V, editors. Basic mechanisms of pediatric respiratory disease. 2nd ed. Hamilton: BC Decker Inc; 2002. p. 184–99.

Van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. Neonatology. 2008;94:237–44.

Victor S, Weindling MA. Near-infrared spectroscopy and its use for the assessment of tissue perfusion in neonates. In: Kleinman CS, Seri L, editors. Haemodynamics and cardiology. Philadelphia: Elsevier Health Sciences; 2008. p. 111–30.

Indications for Mechanical Ventilation

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Anne Greenough and Anthony D. Milner

I. Absolute Indications
   A. In the delivery room
      1. Failure to establish adequate spontaneous respiration immediately after delivery despite adequate face mask ventilation.
      2. A large diaphragmatic hernia. Affected infants should be intubated and ventilated. In some centers, infants are paralyzed from birth to stop them from swallowing, which can increase the dimensions of the bowel and worsen respiratory failure.
   B. In the neonatal intensive care unit
      1. Sudden collapse with apnea and bradycardia, with failure to establish satisfactory ventilation after a short period of face mask ventilation.
      2. Massive pulmonary hemorrhage. Such infants should be intubated, usually paralyzed, and ventilated with high positive end expiratory pressure.

II. Relative Indications
   A. In the delivery room
      1. Infants of extremely low gestational age may be electively intubated to receive prophylactic surfactant therapy, in some centers; infants will then be immediately extubated to CPAP. In other centers, continuous positive airway pressure is used as an alternative to elective intubation and mechanical ventilation and surfactant is given as "rescue" therapy.
      2. Infants <24 weeks of gestational age should be electively intubated and ventilated unless very vigorous at birth.
   B. In the NICU
      1. Worsening respiratory failure—the criteria will depend upon the gestational age of the infant
         a. <28 weeks' gestation: arterial carbon dioxide tension ($PaCO_2$) >45–55 Torr (6.0–7.3 kPa), the lower limit if associated with a pH <7.25 and/or arterial oxygen tension (PaO_2) <50–60 Torr (6.7–8 kPa) in a fractional inspired oxygen (F_iO_2) of greater than 0.50, although if the infants only has poor oxygenation, nasal CPAP may be tried first.

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   b. 28–32 weeks' gestation: $PaCO_2$ >45–55 Torr (6.0–7.0 kPa), the lower limit being used if the pH is <7.25 and/or PaO_2 <50–60 Torr (6.7–8 kPa) in an F_iO_2 of greater than 0.6, if nasal CPAP has failed to improve blood gas tensions.
   c. ≥33 weeks' gestation: if the $PaCO_2$ exceeds 60 Torr (8 kPa) with a pH below 7.25 and/or PaO_2 <45 Torr (6 kPa) in an F_iO_2 of >0.80. CPAP is usually less well tolerated in mature infants. (N.B., in centers which prefer to use CPAP rather than intubation and mechanical ventilation, more severe blood gas abnormalities may be used as criteria for intubation).
2. Stabilization of infants at risk for sudden collapse
   a. Small preterm infants with recurrent apnea unresponsive to nasal CPAP and administration of methylxanthines
   b. Severe sepsis
   c. Need to maintain airway patency
3. To maintain control of carbon dioxide tension:
   a. Infants with pulmonary hypertension (e.g., congenital diaphragmatic hernia)
   b. Hyperventilation of infants to prevent cerebral edema (e.g., hypoxic ischemic encephalopathy).

Suggested Reading

Donn SM, Sinha SK. Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal-perinatal medicine: diseases of the fetus and infant. 8th ed. St. Louis: Elsevier/Mosby; 2011. p. 1116–40.

Greenough A, Milner AD. Acute respiratory disease. In: Rennie JM, editor. Roberton's textbook of neonatology. 4th ed. Edinburgh: Elsevier Churchill Livingstone; 2005. p. 468–553.

Lista G, Fontana P, Castoldi F, Cavigioli F, Bianchi S, Bastrenta P. ELBW infants: to intubate or not to intubate in the delivery room? J Matern Fetal Neonatal Med. 2012;25:63–5.

Sant'Anna GM, Keszler M. Developing a neonatal unit ventilation protocol for the preterm baby. Early Hum Dev. 2012;88:925–9.

Respiratory Distress Syndrome

69

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I. Description
   A. Respiratory distress syndrome (RDS) is a primary pulmonary disorder that accompanies prematurity, specifically immaturity of the lungs, and to a lesser extent the airways. It is a disease of progressive atelectasis, which in its most severe form can lead to severe respiratory failure and death.
   B. The incidence and severity of RDS is generally inversely related to gestational age. Approximate incidence:
      1. 24 weeks—>80 %
      2. 28 weeks—70 %
      3. 32 weeks—25 %
      4. 36 weeks—5 %

II. Pathophysiology
   A. Biochemical abnormalities
      1. The major hallmark is a deficiency of surfactant, which leads to higher surface tension at the alveolar surface and interferes with the normal exchange of respiratory gases.
      2. The higher surface tension requires greater distending pressure to inflate the alveoli, according to LaPlace's law:

$$P = 2T / r$$

         where P = pressure, T = surface tension, and r = radius of curvature.
      3. As the radius of the alveolus decreases (atelectasis), and as surface tension increases, the amount of pressure required to overcome these forces increases.
   B. Morphologic/anatomic abnormalities
      1. The number of functional alveoli (and thus the surface area available for gas exchange) decreases with decreasing gestational age.

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2. With extreme prematurity (23–25 weeks), the distance from the alveolus or terminal bronchiole to the nearest adjacent capillary increases, thus increasing the diffusion barrier and interfering with oxygen transport from lung to blood.
3. Septal wall thickness is also inversely proportional to gestational age.
4. The airways of the preterm infant are incompletely formed and lack sufficient cartilage to remain patent. This can lead to collapse and increased airway resistance.
5. The chest wall of the preterm newborn is more compliant than the lungs, tending to collapse when the infant attempts to increase negative intrathoracic pressure and increasing the work of breathing.

C. Functional abnormalities
1. Decreased compliance
2. Increased resistance
3. Ventilation/perfusion abnormalities
4. Impaired gas exchange
5. Increased work of breathing

D. Histopathologic abnormalities
1. The disorder was originally referred to as hyaline membrane disease as a result of the typical postmortem findings in non-survivors.
2. Macroscopic findings
   a. Decreased aeration
   b. Firm, rubbery, "liver-like" lungs
   c. Decreased lung volumes
3. Microscopic findings
   a. Air spaces filled with an eosinophilic-staining exudate composed of a proteinaceous material, with and without inflammatory cells
   b. Edema in the air spaces
   c. Alveolar collapse
   d. Squamous metaplasia of respiratory epithelium
   e. Distended lymphatics
   f. Thickening of pulmonary arterioles

III. Clinical Manifestations of RDS

A. Tachypnea. The affected infant breathes rapidly, attempting to compensate for small tidal volumes by increasing respiratory frequency and minute ventilation to remove carbon dioxide.

B. Flaring of the ala nasi. This increases the cross-sectional area of the nasal passages and decreases upper airway resistance.

C. Grunting. This is an attempt by the infant to produce positive end-expiratory pressure (PEEP) by exhaling against a closed glottis. Its purpose is to maintain some degree of alveolar volume (distention) so that the radius of the alveolus is larger and the amount of work needed to expand it further is less than if the radius were smaller.

D. Retractions (recessions). The infant utilizes the accessory muscles of respiration, such as the intercostals, to help provide the increased pressure required to inflate the lungs.

E. Cyanosis. This is a reflection of impaired oxygenation, when there is >5 g/dL of deoxygenated hemoglobin.

IV. Radiographic Findings

A. The classic description is a "ground glass" or "reticulo-granular" pattern with air bronchograms (Chap. 23).

B. Severe cases with near total atelectasis may show complete opacification of the lung fields ("white out").

C. Extremely preterm infants with a minimal number of alveoli may actually have clear lung fields.
D. Most cases will show diminished lung volumes (unless positive pressure is being applied).

V. Laboratory Abnormalities
A. Arterial oxygen tension is usually decreased.
B. Arterial carbon dioxide tension may be initially normal if the infant is able to compensate (tachypnea), but it is usually increased.
C. Blood pH may reflect a respiratory acidosis (from hypercarbia), metabolic acidosis (from tissue hypoxia), or mixed acidosis.

VI. Diagnosis
A. Clinical evidence of respiratory distress
B. Radiographic findings
C. Laboratory abnormalities from impaired gas exchange

VII. Differential Diagnoses
A. Sepsis/pneumonia, especially Group B streptococcal infection, which can produce a nearly identical radiographic picture
B. Transient tachypnea of the newborn
C. Pulmonary malformations (e.g., congenital pulmonary airway malformation, congenital lobar emphysema, and diaphragmatic hernia)
D. Extra-pulmonary abnormalities (e.g., vascular ring, ascites, and abdominal mass)

VIII. Treatment
A. Establish adequate gas exchange
1. If the infant is only mildly affected and has reasonable respiratory effort and effective ventilation, only an increase in the FiO_2 may be necessary. This can be provided by an oxygen hood or nasal cannula.
2. If the infant is exhibiting evidence of alveolar hypoventilation ($PaCO_2$ >50 Torr or 6.7 kPa), or hypoxemia (PaO_2 <50 Torr or 6.7 kPa in FiO_2 ≥0.5), some form of positive pressure ventilation is indicated.
a. Consider the use of continuous positive airway pressure (CPAP) if the infant has reasonable spontaneous respiratory effort and has only minimal hypercapnia (Chap. 29). A level of 4–8 cm H_2O should be used.
b. Consider endotracheal intubation and mechanical ventilation (Chap. 68) if:
(1) Hypercapnia ($PaCO_2$ >60 Torr or 8 kPa)
(2) Hypoxemia (PaO_2 <50 Torr or 6.7 kPa)
(3) Decreased respiratory drive or apnea
(4) Need to maintain airway patency
(5) Plan to administer surfactant replacement therapy
c. Mechanical ventilation
(1) The goal is to achieve adequate pulmonary gas exchange while decreasing the patient's work of breathing.
(2) Either conventional mechanical ventilation or high frequency ventilation can be used.
(3) RDS is a disorder of low lung volume, so the approach should be one that delivers an appropriate tidal volume while minimizing the risks of complications (see below).

B. Surfactant replacement therapy (Chap. 58)
1. The development and use of surfactant replacement therapy has revolutionized the treatment of RDS.
2. Numerous preparations (natural, synthetic, and semi-synthetic) are now available.

3. Types of intervention
   a. Prophylaxis—infant is immediately intubated and given surfactant as close to the first breath as possible
      (1) One option is intubation, administration of surfactant, and continued mechanical ventilation until the baby is ready for extubation.
      (2) Another option is to intubate, administer surfactant, and extubate to CPAP. Referred to as ENSURE, it is gaining popularity as an alternative to continued mechanical ventilation.
   b. Rescue—infant is treated after the diagnosis is established
4. Dose and interval are different for each preparation.
5. Although there is little doubt as to efficacy, the treatment is still very expensive.

C. Adjunctive measures
1. Maintain adequate blood pressure (and hence pulmonary blood flow) with judicious use of blood volume expanders and pressors.
2. Maintain adequate oxygen carrying capacity (Hgb) in infants with a high oxygen (FiO_2 >0.4) requirement.
3. Maintain physiologic pH, and do not give sodium bicarbonate if hypercarbia is present.
4. Maintain adequate sedation/analgesia (Chap. 62) but avoid respiratory depression, which will delay weaning.
5. Provide adequate nutrition (Chap. 57), but avoid excessive non-nitrogen calories, which can increase CO_2 production and exacerbate hypercapnia.
6. Observe closely for signs of complications, especially infection.

IX. Complications
A. Respiratory
1. Air leaks
   a. Pneumomediastinum
   b. Pulmonary interstitial emphysema
   c. Pneumothorax
   d. Pneumopericardium
   e. Pneumoperitoneum (trans-diaphragmatic)
   f. Subcutaneous emphysema
2. Airway injury
3. Pulmonary hemorrhage (Chap. 84)
4. Bronchopulmonary dysplasia (Chaps. 79, 80, and 81).

B. Cardiac
1. Patent ductus arteriosus (Chap. 83)
2. Congestive heart failure
3. Pulmonary hypertension (Chap. 63)
4. Cor pulmonale

C. Neurologic (Chap. 86)
1. Relationship to intraventricular hemorrhage
2. Relationship to periventricular leukomalacia
3. Neurodevelopmental impact

D. Infectious
1. Nosocomial and acquired pneumonia (Chap. 70)
2. Sepsis

X. Prenatal Treatments and Conditions which Impact RDS
   A. Antenatal treatment of the mother with corticosteroids has been demonstrated to reduce the incidence and severity of RDS, particularly if given between 28 and 32 weeks' gestation.
      1. Betamethasone
      2. Dexamethasone
   B. Other agents have been explored but results are thus far unconvincing.
      1. Thyroid hormone
      2. Thyrotropin
   C. Accelerated pulmonary (i.e., surfactant system) maturation is seen in:
      1. Intrauterine growth retardation
      2. Infants of substance-abusing mothers
      3. Prolonged rupture of the membranes
   D. Delayed pulmonary maturation is seen in:
      1. Infants of diabetic mothers
      2. Rh-sensitized fetuses
      3. Infants of hypothyroid mothers
      4. Infants with hypothyroidism

Suggested Reading

Cotton RB. Pathophysiology of hyaline membrane disease (excluding surfactant). In: Polin RA, Fox WW, editors. Fetal and neonatal physiology. 2nd ed. Philadelphia: W.B. Saunders; 1998. p. 1165–74.

Hamvas A. Pathophysiology and management of Respiratory Distress Syndrome. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Neonatal-perinatal medicine. Diseases of the fetus and infant. 9th ed. St Louis: Elsevier Mosby; 2015. p. 1106–16.

Kattwinkel J. Surfactant: evolving issues. Clin Perinatol. 1998;25:17–32.

Martin GI, Sindel BD. Neonatal management of the very low birth weight infant: the use of surfactant. Clin Perinatol. 1992;19:461–8.

Nelson M, Becker MA, Donn SM. Basic neonatal respiratory disorders. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk: Futura Publishing Co.; 1998. p. 253–78.

Robertson B, Halliday HL. Principles of surfactant replacement. Biochim Biophys Acta. 1998;1408:346–61.

Walsh MC, Carlo WA, Miller MJ. Respiratory diseases of the newborn. In: Carlo WA, Chatburn RL, editors. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers; 1988. p. 260–88.

Pneumonia in the Newborn Infant

70

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I. Background
   A. An estimated 800,000 deaths occur worldwide from respiratory infections in newborn infants.
   B. Four varieties of pneumonia occur in newborn infants (differ in pathogens and routes of acquisition):
      1. Congenital pneumonia: acquired by transplacental transmission of infectious agents (usually one manifestation of a generalized infection)
      2. Intrauterine pneumonia: associated with intrauterine bacterial infection (chorioamnionitis/choriodeciduitis); may be non-infectious and associated with fetal asphyxia
      3. Pneumonia acquired during birth: caused by organisms colonizing the genital tract
      4. Pneumonia acquired after birth: in the nursery (healthcare-associated infection) or at home
   C. Lung host defenses
      1. Local and systemic host defenses are diminished in newborn infants.
         a. Lack of secretory IgA in the nasopharynx and upper airway at birth (detectable by 1–2 weeks of age)
         b. Immature mucociliary function
         c. Neonatal T cells are naïve with reduced expression of T cell receptor, decreased adhesion molecule expression, and diminished cytokine production.
         d. Immature NK cell function
         e. Diminished number of lung alveolar macrophages at birth (increase rapidly after birth)
         f. Diminished expression of human beta defensin-2
         g. Developmental differences in expression of toll-like receptors
         h. Diminished levels of serum IgG in preterm neonates; lack of IgM at birth (rises post-birth)
         i. Absence of protective antibody for common bacterial pathogens [e.g., group B *Streptococcus* (GBS)]

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j. Diminished ability to generate antibody to capsular polysaccharides (e.g., GBS capsule)
k. Lower serum complement levels (classic and alternative pathway) and abnormalities in complement function
l. Diminished phagocyte function (chemotaxis, phagocytosis, and killing) especially in stressed neonates
m. Limited ability to accelerate neutrophil production
n. Slower development of inflammatory responses

2. Endotracheal tubes promote colonization of the trachea and injure the mucosa (portal for entry); oxygen interferes with ciliary function and mucosal integrity.

II. Congenital Pneumonia
A. Toxoplasmosis
1. Transmission: result of primary maternal parasitemia during pregnancy
2. Pathology
a. Widened and edematous alveolar septa infiltrated with mononuclear cells
b. Walls of small blood vessels are infiltrated with lymphocytes and mononuclear cells.
c. Parasites may be found in endothelial cells and the epithelium lining small airways.
d. In many cases a bronchopneumonia is present, which may be caused by a superinfection.
3. Manifestations
a. Four varieties of infection: (1) neonatal disease, (2) a mild or severe disease occurring in the first months of life, (3) sequelae or a relapse of a previously undiagnosed infection during infancy, childhood, or adolescence, and (4) subclinical infection.
b. Infected infants may: (1) be asymptomatic (>80%), (2) exhibit neurologic findings (chorioretinitis, hydrocephalus, seizures, and calcification), or (3) demonstrate a generalized systemic illness (IUGR, hepatosplenomegaly, pneumonia, etc.).
c. Neurologic findings and chorioretinitis may have a delayed presentation.
d. Pneumonia is observed in 20–40% of infants with generalized disease. Infants exhibit signs of respiratory distress/sepsis along with other manifestations of systemic disease (e.g., hepatosplenomegaly).
4. Diagnosis
a. Infants with a suspected infection from *Toxoplasma* should have ophthalmologic, auditory, and neurologic examinations including lumbar puncture and cranial imaging.
b. CSF demonstrates mononuclear pleocytosis and elevated protein; some infants exhibit eosinophilia.
c. Demonstration of tachyzoites in tissue (placenta, umbilical cord, body fluids, or blood specimen from the infant) by mouse inoculation is definitive.
d. Peripheral white blood cells, CSF, and amniotic fluid specimens can be assayed by PCR in a reference laboratory.
e. Thrombocytopenia and eosinophilia are commonly noted in the newborn infant.
f. There is a high prevalence of antibodies to *Toxoplasma gondii* among normal women of childbearing age; therefore a high antibody titer in the newborn infant may represent recent or past infection in the mother.
g. Quantification of IgM in cord blood is not a useful screening tool.
h. The presence of IgM, IgA, or IgE antibodies against *T. gondii* in the blood of a newborn baby is diagnostic (if contamination with maternal blood has not occurred). Those tests are best drawn 5–10 days after birth.
i. Persistence of IgG titers to *T. gondii* beyond 12 months is diagnostic.

j. The absence of IgG antibodies against *T. gondii* (capable of producing IgG antibodies) at any age rules out congenital toxoplasmosis.
k. There is a high incidence of false negative results with the IgM indirect immunofluorescent antibody (IFA) test.
l. The double-sandwich IgM capture ELISA and the IgM immunosorbent agglutination assay (ISAGA) have a sensitivity of 75–80 % and a lower incidence of false positive reactions. The ISAGA is the most sensitive method.

5. Treatment and prognosis
   a. Spiramycin (available through the US FDA in consultation with the Palo Alto Medical Foundation Toxoplasmosis Laboratory) has been used to decrease maternal to infant transmission. It is not effective for the treatment of congenital toxoplasmosis.
   b. Once congenital toxoplasmosis is confirmed in the fetus, pyrimethamine and sulfidiazene (plus folinic acid) should be used during pregnancy. *Pyrimethamine should be avoided in the first trimester because of teratogenic effects.*
   c. All infected newborns should receive pyrimethamine and sulfidiazene (plus folinic acid) up to 1 year.
   d. Prednisone (0.5 mg BID) is added for infants with very high CSF protein (>1 g/dl) or active chorioretinitis.
   e. When the diagnosis is uncertain, drug treatment can be postponed until a definitive diagnosis is made.
   f. Prevention strategies should be used for pregnant women (cook meat to well done, avoid handling or eating raw meat, and avoid contact with material potentially contaminated with cat feces).
   g. Untreated infants with congenital toxoplasmosis have a poor outcome. Infants with CNS manifestations at birth have worse outcomes.
   h. Infants with subclinical congenital infections can also develop sequelae.
   i. Most infants survive with good supportive care; however, up to 30 % develop chorioretinitis at a mean age of 3.1 years. Most patients with chorioretinitis have good visual outcomes. Neurologic sequelae are less common.

B. Cytomegalovirus
1. Transmission
   a. CMV transmission can occur *during pregnancy* by transplacental viral passage, *at birth* by exposure to CMV in cervical secretions, or *postnatally* by ingestion of contaminated breast milk. The latter two modalities of transmission usually do not result in a symptomatic infection.
   b. CMV transmission to preterm infants, by any route, including exposure to CMV-positive blood products, can be associated with systemic infections, including pneumonia.
2. Pathology
   a. Pneumocytes contain characteristic intranuclear inclusions. When type II pneumocytes are infected, surfactant production may decrease.
   b. Minimal inflammatory reaction
3. Manifestations
   a. Most common congenital infection (0.2–2.2 % of all newborns)
   b. Congenital infection can occur secondary to a primary infection or reactivation/reinfection during pregnancy.
   c. Women who are seropositive can become reinfected with a different strain of CMV leading to congenital infection.

d. With primary maternal infection, the overall risk of transmission to the fetus is 30–40 %.
e. Ninety percent of infants with congenital CMV are asymptomatic at birth.
f. Primary infections are more likely to be associated with fetal damage than recurrent infection.
g. Exposure to CMV in the genital tract can result in a 30–50 % rate of perinatal infection.
h. 70–90 % of seropositive women excrete virus in their breast milk.
i. Transmission from breast milk occurs in 30–70 % of breastfed infants, if nursing lasts more than 1 month.
j. A diffuse interstitial pneumonitis occurs in <1 % of congenitally infected, symptomatic infants.
k. Common signs of congenital infection at birth include intrauterine growth restriction, microcephaly, intracerebral calcifications, retinitis, hepatosplenomegaly, jaundice, and purpura.
l. Common sequelae include developmental delay and hearing loss.

4. Diagnosis
   a. Virus isolation from urine or other infected fluids is best.
   b. To confirm congenital CMV infection, virus isolation must be attempted in the first 2 weeks of life.
   c. CMV-DNA PCR on blood specimens may be useful in infants with viral sepsis.
   d. Serology is not helpful.
5. Treatment and prognosis
   a. There are limited data on the use of ganciclovir or valganciclovir in neonates However, use of these drugs in symptomatic infants has been associated with improved survival and reduction in hearing loss.
   b. Sequelae develop in 8–15 % of congenitally infected, asymptomatic infants and 60–80 % of symptomatic infants.

C. Herpes simplex virus
1. Epidemiology—There are three varieties of neonatal HSV infections:
   a. Intrauterine HSV infections are rare with an estimated incidence of 1/250,000 live births,
   b. Perinatal infections account for 85 % of neonatal infections, and
   c. Postnatal infections represent 10 % of infections.
2. Transmission
   a. Estimated incidence of 5–33 infants/100,000 live births in the USA.
   b. Infection in the mother can be classified as recurrent, primary, or first episode non-primary infections. In primary infections, the mother experiences an infection with HSV and has never been exposed to HSV 1 or 2. In non-primary infections, first episode infections, the mother experiences an infection with HSV-1 or HSV-2 and has pre-existing antibodies to the other HSV type.
   c. Infants most commonly acquire HSV through an infected maternal genital tract, or by an ascending infection with intact membranes.
   d. The risk of transmission is ~50 % for infants born to mothers with primary infection, 25 % for infants with non-primary first episode infections, but only 1–2 % with viral reactivation.
   e. Transmission by contact (hands) in the nursery is unlikely.
3. Pathology: Diffuse interstitial pneumonitis, which progresses to a hemorrhagic pneumonitis

4. Manifestations
   a. Most HSV infections in the neonate are symptomatic, but 20 % of infants never develop vesicles.
   b. Three varieties: localized disease (skin, eye, or mouth—45 % of neonatal HSV infections), encephalitis with or without localized disease (33 % of neonatal HSV infections), or disseminated infection (25 % of neonatal HSV infections); commonly affects liver and lungs.
   c. Half the infants are born prematurely. *RDS must always be a consideration.*
   d. Infants with disseminated infection usually present between the first and second week of life, with signs like those of bacterial sepsis or shock, liver dysfunction (hepatitis), and respiratory distress.
   e. Infants with CNS involvement typically present in the 2nd or 3rd week of life, but occasionally up to 6 weeks.
5. Diagnosis
   a. Positive viral cultures (oropharyngeal and respiratory secretions, conjunctiva and rectum, skin vesicles, blood, and CSF), obtained 12–24 h after birth, are suggestive of infection.
   b. Direct immunofluorescence of skin lesion specimens and PCR assay on cerebrospinal fluid are useful (sensitivity of 75–100 % and specificity of 71–100 %).
6. Treatment and prognosis
   a. Women with active lesions at delivery and a history of genital herpes should have cultures, serologic testing, and tests to differentiate HSV-1 and HSV-2. In that way the infection can be categorized as primary or recurrent.
   b. If there is a history of recurrent genital HSV infections, acyclovir or valacyclovir is recommended for suppressive therapy at 36 weeks' gestation.
   c. When active lesions are present at the time of delivery, cesarean section is recommended.
   d. Infants born to women with genital lesions at delivery and no history of genital herpes should be treated with acyclovir after appropriate testing (surface cultures; HSV blood PCR; serum ALT; and CSF cell count, chemistries, and PCR) at ~24 h of age.
   e. Well appearing infants born to women with active genital lesions at delivery and history of genital HSV in a preceding pregnancy do not require treatment. However at ~24 h of age viral cultures and HSV blood PCR should be obtained from the infant.
   f. Disseminated disease is treated for 21 days.
   g. Skin, eye, and mouth (SEM) disease should be treated for 14 days.
   h. All infant with SEM disease should be evaluated for CNS and disseminated disease.
   i. For babies with CNS disease, repeat CSF analysis and CSF HSV PCR should be obtained prior to stopping treatment. If the CSF has detectable DNA by PCR, treatment with parenteral acyclovir should be continued until the PCR is negative.
   j. For infants with proven HSV infection, oral acyclovir should be given for 6 months (after the course of parenteral acyclovir is completed).
   k. With antiviral therapy, the mortality rates for infants with disseminated disease or CNS disease are 29 % and 4 %, respectively.
   l. Antiviral therapy improves the prognosis for infants with disseminated disease (80 % normal) but not CNS disease (30 % normal).

D. *Treponema pallidum*
1. Transmission
   a. Congenital syphilis is generally acquired transplacentally.

   b. The rate of transmission increases with advancing gestation.
   c. Transmission rates are highest for early primary syphilis (60–90 %) and lower for early latent infections (40 %) or late, latent infections (<10 %).
   d. *T. pallidum* cannot be transmitted through breast milk.
   e. Untreated maternal syphilis can result in abortion, hydrops fetalis, fetal demise, stillbirth, prematurity, congenital infection, or perinatal death.
2. Pathology
   a. Overt infection can be observed in the fetus, newborn, or later in childhood.
   b. The placenta is often described as large, thick, and pale.
   c. Syphilitic rhinitis ("snuffles") may herald the onset of congenital syphilis.
   d. "Pneumonia alba" is characterized grossly as heavy, firm, yellow—white enlarged lungs.
   e. Marked increase in connective tissue in the interalveolar septa and the interstitium with collapse of the alveolar spaces.
3. Manifestations
   a. Infants with early congenital syphilis present between birth and 3 months of age.
   b. Two-thirds of infected infants are asymptomatic at birth.
   c. Early congenital syphilis should be suspected in any infant with unexplained prematurity, hydrops, or an enlarged placenta.
   d. Pneumonia is an uncommon manifestation.
   e. Common manifestations of "early congenital syphilis" include hepatosplenomegaly, anemia, leukopenia or leukocytosis, generalized lymphadenopathy, rhinitis, nephrotic syndrome, maculopapular rash, bony abnormalities, and leptomeningitis.
4. Diagnosis
   a. Most women are screened in pregnancy using non-treponemal antibody tests (RPR/VDRL) in the first trimester. Treponemal tests are only used for confirmation.
   b. In primary syphilis during pregnancy, non-treponemal tests are negative in a quarter to a third of cases.
   c. All infants with a titer > four-fold the maternal titer should have a lumbar puncture for a CSF VDRL, cell count, and protein.
   d. Congenital syphilis is considered *confirmed* by demonstration of *T. pallidum* using dark-filed microscopy.
   e. Congenital syphilis is considered *highly probable* if the infant has signs of congenital syphilis and a titer > four-fold the maternal titer or a positive CSF VDRL.
   f. Congenital syphilis is considered *probable* when the infant is asymptomatic, the titers are < four-fold the maternal titers, but maternal treatment did not occur, was inadequate, not documented, or failed.
   g. Congenital syphilis is considered *possible* when the infant is asymptomatic, the titers are < four-fold the maternal titer, treatment occurred during the pregnancy, and titers remained low or stable.
   h. Congenital syphilis is considered *unlikely* if the infant's physical examination is normal, RPR/VDRL titers are < four-fold the maternal titer, and the mother was adequately treated before pregnancy and her titers remained low or stable.
   i. PCR tests have been developed, but are not widely available.
5. Treatment and prognosis
   a. Infants with *proven or highly probable* congenital syphilis should receive 10 days of parenteral penicillin.

b. For infants with *probable* congenital syphilis, most experts recommend a 10-day course of parenteral penicillin. If appropriate follow-up can be guaranteed, some experts recommend a single dose of IM benzathine penicillin.
c. For infants with *possible* congenital syphilis, most experts would recommend a single dose of IM benzathine penicillin. A full evaluation may be unnecessary. Alternatively, these infants can be followed monthly, until their non-treponemal testing becomes negative.
d. Infants with congenital syphilis considered *unlikely* require no evaluation or treatment. However, they can be treated with a single dose of IM benzathine penicillin when follow-up is uncertain.
e. The earlier the treatment is initiated, the greater the likelihood of a good outcome (prevention of stigmata).

III. Pneumonia Acquired In Utero, During Birth, or Early in Life
A. Background: Time of presentation varies
1. The onset of respiratory distress immediately after birth suggests aspiration of infected amniotic fluid in utero.
2. A "delayed" presentation (1–3 days) likely results from colonization of mucoepithelial surfaces and seeding of the blood stream.
B. Pathology
1. Dense cellular exudate, congestion, hemorrhage, and necrosis
2. *Staphylococcus aureus* and *Klebsiella* may cause micro-abscesses and pneumatocoeles.
3. Hyaline membranes are common (especially in preterm infants), and bacteria may be seen within the membranes.
C. Pathophysiology of lung injury
1. Direct invasion of lung tissue by bacteria (bacterial pathogens secrete enzymes and toxins that disrupt cell membranes, disturb metabolism, and interfere with the supply of nutrients)
2. Indirect injury secondary to the host inflammatory response (cytokines, complement, and coagulation)
3. Airway obstruction from inflammatory debris
4. Alteration in surfactant composition and function (secondary to binding by secreted bacterial/inflammatory protein and direct signaling of infectious byproducts on pneumocytes)
D. Disturbances in lung function
1. Increased airway resistance from inflammatory debris and airway smooth muscle constriction
2. Decreased lung compliance (atelectasis and parenchymal inflammation)
3. Ventilation–Perfusion (V/Q) abnormalities (intrapulmonary shunts)
4. Pulmonary hypertension secondary to release of vasoactive mediators
5. Impaired alveolar diffusion
E. Epidemiology
1. Identical to that for early onset bacterial sepsis
2. Risk factors
a. Prematurity and low birth weight
b. Low socioeconomic status
c. Male gender
d. Colonization with a known pathogen (e.g., GBS)
e. Prolonged rupture of membranes >18 h

f. Galactosemia; increased susceptibility to infections with Gram-negative organisms
g. Premature rupture of membranes
h. Signs of chorioamnionitis (maternal fever >38° C, abdominal tenderness, and foul smelling or cloudy amniotic fluid)
(1) Chorioamnionitis can be subclinical or clinical.
(2) Subclinical chorioamnionitis may be a risk factor for BPD (see "Ureaplasma" below).

F. Pathogenesis
1. Infection begins with colonization of the maternal genital tract.
2. Organisms that colonize the cervix, vagina, or rectum spread upward into the amniotic cavity through intact or ruptured membranes (causing amnionitis).
3. The fetus either inhales infected amniotic fluid (and exhibits immediate onset of respiratory distress) or becomes colonized and later symptomatic.

G. Bacterial pathogens
1. *Streptococcus agalactiae* (GBS)
a. Most common bacterial pathogen in term infants
b. 15–40 % of women are colonized with GBS.
c. Women who are "culture positive" are ten times more likely to deliver an infant with early onset sepsis than "culture negative" women.
d. Intrapartum antibiotics have reduced the incidence of early onset GBS sepsis by 80 %, but have not substantially changed the incidence of late-onset GBS sepsis.
e. In the absence of intrapartum antibiotics, the vertical transmission rate is ~50 % and the risk of infection (sepsis and pneumonia) in colonized infants is 1–2 %.
2. *Escherichia coli*
a. Most common pathogen in preterm infants
b. Most strains causing sepsis are resistant to ampicillin
c. Associated with a higher mortality than infection from Gram-positive organisms
3. *Listeria monocytogenes*
a. Most infections are caused by three serotypes (1a, 1b, and 4b)
b. Almost all cases originate from ingestion of contaminated food.
c. May cause acute bacterial sepsis (when acquired during labor and delivery), a widely disseminated granulomatous infection (when acquired in utero) or late-onset disease (frequently meningitis).
d. Listeria can be transmitted to the fetus transplacentally or via an ascending infection.
e. Commonly results in preterm delivery
f. Maternal "influenza-like" infection precedes delivery in 50 % of cases.
g. Two-thirds of infants who survive delivery from a woman with Listeriosis will develop neonatal infection.
4. Other pathogens: *S. aureus*, *Haemophilus* species, *Enterococcus*, *Streptococcus viridans*, *Klebsiella*, *Enterobacter* species, Group A Streptococcus, and Coagulase negative Staphylococcus

H. Clinical history (suggestive of sepsis/pneumonia).
1. Prolonged rupture of membranes >18 h
a. Maternal signs and symptoms of intrauterine infection/inflammation (III or "triple I"), defined as maternal fever plus at least one of the following: sustained fetal tachycardia >160 bpm, maternal WBC >15,000/mm^3 (without steroid treatment), purulent vaginal discharge, laboratory evidence of amniotic fluid infection/inflammation (Table 70.1). Isolated maternal fever is not a significant risk factor for sepsis/pneumonia.

Table 70.1 Features of isolated maternal fever, and triple I with classification

Terminology	Features and comments
Isolated maternal fever (documented)	Maternal oral temperature ≥39.0 °C (102.2 °F) on any one occasion is "documented fever." If the oral temperature ≥38.0 °C (100.4 °F) but ≤39.0 °C (102.2 °F), repeat the measurement in 30 min; if the repeat value remains ≥38.0 °C (100.4 °F), it is "documented fever."
Suspected triple I	Fever without a clear source plus any of the following: Baseline fetal tachycardia (>160 bpm for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability) Maternal WBC >15,000/mm^3 in the absence of corticosteroids Definite purulent fluid from the cervical os
Confirmed triple I	All of the above plus amniocentesis-proven infection through a positive Gram stain, a low glucose or positive amniotic fluid culture, and later supported by placental pathology revealing diagnostic features of infection

2. Colonization with GBS (adequate intrapartum therapy lowers the risk of infection by 85–90 %)
3. Maternal urinary tract infection
4. Preterm premature rupture of membranes
5. Preterm labor
6. Meconium (decreases the antibacterial properties of amniotic fluid)

I. Clinical presentation
1. Signs of sepsis/pneumonia can be subtle (tachypnea) or overt (grunting flaring, retracting).
2. Pulmonary findings
   a. Tachypnea (respiratory rate > 60/min)
   b. Grunting
   c. Flaring
   d. Retractions
   e. Rales or rhonchi
   f. Cyanosis
   g. Change in the quality of secretions (serosanguinous or purulent)
3. Systemic findings (non-pulmonary)
   a. Apnea
   b. Lethargy
   c. Irritability
   d. Hypothermia, hyperthermia, or temperature instability
   e. Poor perfusion or hypotension (manifest as oliguria or metabolic acidosis)
   f. Pulmonary hypertension
   g. Abdominal distention

J. Diagnosis
1. General concepts
   a. Laboratory testing (in general) is not useful for identifying infants that are likely to have bacterial sepsis/pneumonia (i.e., most laboratory tests have a low positive predictive value).
   b. Testing is helpful in deciding which infants are <u>not likely</u> to be infected and who do not require antibiotics (high negative predictive value).

c. In infants with proven sepsis/pneumonia, laboratory tests (e.g., white blood count, neutrophil indices, acute phase reactants) obtained at birth are frequently normal. Tests obtained 8–12 h following birth have a higher likelihood of being abnormal.
d. The only absolute way to make the diagnosis of bacterial sepsis/pneumonia is to recover an organism from a normally sterile site (blood, urine, cerebrospinal fluid, pleural fluid). The presence of bacteria from a tracheal aspirate obtained *immediately after intubation* is presumptive evidence of infection
e. Infants with evolving sepsis/pneumonia can be asymptomatic at the time of birth.
f. All symptomatic infants should be cultured and treated. Some infants exhibit transient signs that resolve quickly (within a few hours of birth) and these infants may not require treatment.
g. Recommendations for evaluation and management of newborns with history of maternal fever have undergone several recent revisions. Figure 70.1 provides guidelines developed by a workshop on chorioamnionitis in 2015.
h. Validated online sepsis risk calculators can be useful tools in deciding whether or not to initiate empiric treatment.

2. Cultures
   a. A positive blood culture is the "gold standard" for detection of bacteremia in the newborn.
   b. Urine cultures are rarely positive in infants with early onset bacterial sepsis and should not be routinely obtained.
   c. A lumbar puncture should be performed in all infants with a positive blood culture *or* in symptomatic infants with a high probability of infection based on adjunct laboratory

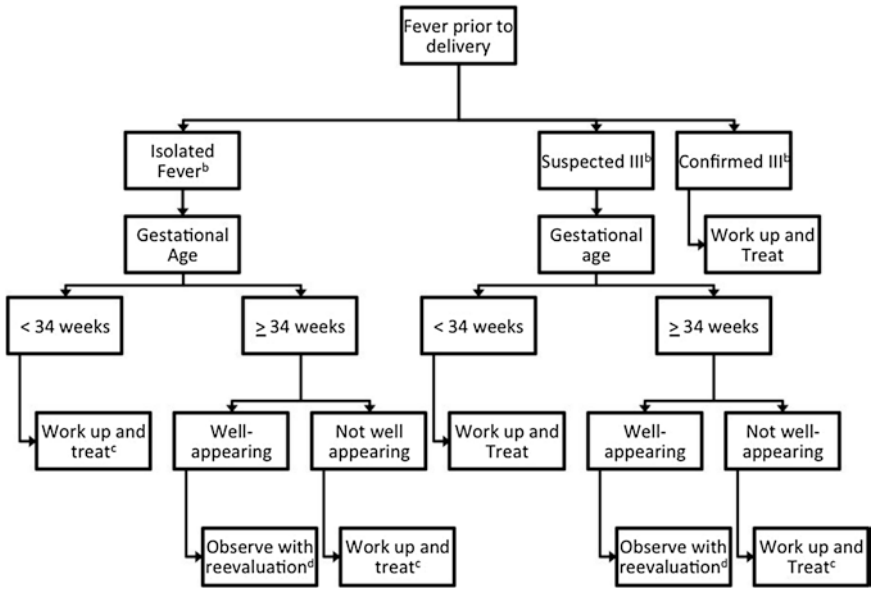

Fig. 70.1 Suggested algorithm for management of neonates with maternal history of fever[a]. [a]Guidelines should be considered a starting point. Additional factors may warrant alternative management. [b]III = intrauterine infection/inflammation. See text and Table 70.1 for details. [c]Work up should include blood culture at birth, complete blood count with differential, and C-reactive protein, the latter two at 6–12 h of life. Treatment should consist of broad-spectrum antibiotics for at least 48 h, with the ultimate duration depending on laboratory test results and clinical course. [d]Frequent observation and reevaluation by members of the medical team may take place on an appropriately staffed postpartum unit

studies, *or* infants with a poor response to conventional antimicrobial treatment. The lumbar puncture should be deferred in any infant who is clinically unstable or who has an uncorrected bleeding diathesis.

3. Adjunct laboratory tests
   a. Neutrophil indices (absolute neutrophil count, absolute band count, and immature-to-total neutrophil (I/T ratio) are more useful than total leukocyte counts.
   b. The most sensitive index is the I/T ratio and the most specific index is neutropenia.
      (1) There is no consensus on the neutrophil indices suggestive of infection; however, an absolute band count $\geq 2000/mm^3$ or an I/T ratio ≥ 0.2 are both suggestive of neonatal sepsis.
      (2) Lower limits for the absolute neutrophil count vary with gestational age (suggested cut-off values at 8–12 h of postnatal age are $<8000/mm^3$ in late preterm and term infants and $<2200/mm^3$ in very low birth weight infants.
   c. Infants delivered by cesarean section without labor have lower total neutrophil counts and infants delivered at high altitude may have higher absolute neutrophil counts.
   d. C-reactive protein (CRP), an acute phase reactant, is a useful adjunctive test.
      (1) A CRP value of ≥ 1 mg/dL is considered positive.
      (2) Values rise slowly in infected infants (therefore, a CRP obtained at birth is not as useful as one obtained at 8–12 h of life).
      (3) A CRP determination obtained 12–24 h following birth has a high negative predictive accuracy and is most useful for excluding the diagnosis of sepsis.
      (4) Maternal CRP does not cross the placenta, so any neonatal elevation is from endogenous production.
4. Chest radiographs
   a. In preterm infants the radiographic appearance of pneumonia may be indistinguishable from RDS (i.e., ground glass appearance and air bronchograms).
   b. In term infants, pneumonia more commonly causes hyperinflation with increased central peribronchial infiltrates and scattered subsegmental atelectasis.
   c. Other findings include effusions/empyema, hyperinflation, and pneumatocoeles (suggestive of *S. aureus*).

K. Management
1. Broad-spectrum antibiotics
   a. Choice depends on the predominant pathogen causing sepsis and the antibiotic sensitivity patterns for the microorganisms causing early onset sepsis in a given NICU.
   b. Empiric therapy must cover both Gram-positive and Gram-negative organisms.
   c. The most commonly used combination is ampicillin and an aminoglycoside (frequently gentamicin). Ampicillin and cefotaxime is an effective alternative, but resistance to cefotaxime develops quickly; therefore, cefotaxime should be reserved for infants with Gram-negative meningitis.
   d. None of the third generation cephalosporins are active against *L. monocytogenes* or *Enterococcus*.
   e. After an organism has been identified the antibiotic therapy should be tailored according to the sensitivities.
      (1) *L. monocytogenes* is treated with ampicillin. If meningitis is present, ampicillin should be administered in combination with an aminoglycoside antibiotic.
      (2) Enterococci are treated either with ampicillin and an aminoglycoside or vancomycin and an aminoglycoside depending upon sensitivities.

(3) *Pseudomonas aeruginosa* infections are commonly treated with either piperacillin–tazobactam or a carbapenem, but most are also sensitive to ceftazidime.
(4) Most other Gram-negative infections can be treated with aminoglycoside antibiotics or cefotaxime.

f. Duration of therapy is usually 7–10 days (3 weeks or longer for a pneumonia secondary to *S. aureus*).

2. Supportive care
a. Hemodynamic support (volume and pressors) to assure adequate systemic perfusion.
b. Nutritional support; parenteral nutrition for any infant who will not be able to tolerate enteral feedings.
c. Respiratory support:
(1) Oxygen to maintain SpO_2 91–95 %
(2) Use the least invasive form of respiratory support to achieve adequate oxygenation and ventilation.
(3) Chest physiotherapy (vibration and percussion) once the infant is clinically stable
(4) Judicious use of suctioning
(5) Drainage of pleural effusions if lung function is compromised
d. Nitric oxide for term and late preterm infants with persistent hypoxemia despite maximal ventilatory support.
e. ECMO for term and late preterm infants unresponsive to above measures if criteria are met.
f. Surfactant treatment improves oxygenation and reduces the need for ECMO in neonates with pneumonia.

3. Prevention
a. The incidence of early onset sepsis/pneumonia from GBS can be diminished by intrapartum administration of antibiotics.
b. The following "high risk" women should be treated:
(1) Previous infant with invasive disease
(2) GBS bacteriuria during pregnancy
(3) Positive GBS screening culture during pregnancy
(4) Unknown GBS status (culture not done, incomplete, or results unknown) and any of the following
(5) Delivery at <37 weeks' gestation
(6) Amniotic membrane rupture ≥18 h
(7) Intrapartum temperature ≥100.4 °F (≥38 °C)

L. Atypical Pneumonia: *Ureaplasma urealyticum*
1. Transmission
a. Although *U. urealyticum* is a frequent inhabitant of the lower genital tract of asymptomatic women, isolation of *U. urealyticum* from the chorion or amnion has been associated with premature labor and chorioamnionitis.
b. The vertical transmission rate varies by study (18–88 %), but is highest in preterm infants.
c. Transmission occurs in utero by ascending infection, even with intact membranes, by the hematogenous route through placental infection, or at delivery by contact with a colonized vaginal canal.

2. Pathology
a. Patchy exudate of polymorphonuclear cells and swollen vacuolated macrophages are found in bronchioles and alveoli.
b. Prominent interstitial fibrosis of lung tissue (possible association with BPD)

3. Manifestations
   a. *U. urealyticum* infection of the newborn is associated with pneumonia, meningitis, and hydrops fetalis.
   b. Radiographs: radiating streakiness, coarse patchy infiltrates, subtle haziness, or diffuse granularity indistinguishable from RDS
4. Diagnosis
   a. Cultures (blood, urine, nasopharyngeal secretions, and endotracheal aspirates) require special media and long incubation times.
   b. PCR has a better sensitivity than culture and results are available in less than 24 h.
   c. Serologic tests (*U. urealyticum* IgG and IgM) have limited value.
5. Treatment and prognosis
   a. Prophylactic treatment of colonized women in preterm labor does not decrease mortality or morbidity and is not recommended.
   b. Erythromycin is the drug of choice for infections that do not involve the CNS (a risk of hypertrophic pyloric stenosis has been reported with use of erythromycin).
   c. Long-term morbidities include increased stay in the NICU, and a possible association with BPD.

M. Atypical Pneumonia: *Chlamydia trachomatis*
1. Transmission
   a. In women colonized with *C. trachomatis*, 50 % of offspring become colonized at the time of delivery, of which 40–50 % develop conjunctivitis and 20–25 % develop pneumonia between 1 and 3 months of life.
   b. Systematic screening and treatment of chlamydial infection during pregnancy markedly decreases perinatally acquired infections.
2. Pathology
   a. Intra-alveolar inflammation with a mild degree of interstitial reaction
   b. Alveolar lining cells contain intracytoplasmic inclusions.
3. Manifestations
   a. *C. trachomatis* pneumonia in newborn presents between 2 and 19 weeks of age with repetitive staccato cough, tachypnea, rales, and rarely wheezing or fever. Purulent conjunctivitis can be observed.
   b. Significant laboratory findings include eosinophilia and elevated serum immunoglobulins. Chest radiography demonstrates hyperinflation and bilateral diffuse nonspecific infiltrates.
4. Diagnosis
   a. Definitive diagnosis is made by culture (conjunctiva, nasopharynx, vagina, or rectum) or by nucleic acid amplification on nasopharyngeal or endotracheal aspirates. Because *Chlamydia* is an obligate intracellular organism, culture specimens must contain epithelial cells.
   b. In infants with pneumonia, the detection of specific IgM ($\geq$1:32) is diagnostic.
5. Treatment and prognosis: Erythromycin is the treatment of choice (risk of hypertrophic pyloric stenosis).

IV. Ventilator-Associated Pneumonia (VAP)

A. General concepts
1. In the absence of mechanical ventilation, pneumonia is an uncommon presentation for hospital-acquired infections.

2. The organism gains entry to the respiratory tract by colonizing the endotracheal tube and the upper airway, by tracheal suctioning, or by direct aspiration of gastrointestinal contents.
   a. Oropharyngeal colonization plays a critical role in the pathogenesis of VAP.
   b. Endotracheal tubes and suctioning can disrupt mucosal integrity and promote dissemination.
   c. Microaspiration of secretions commonly occurs.
   d. Contaminated oral and gastric secretions can leak around uncuffed endotracheal tubes.
   e. On rare occasions, microorganisms may be transmitted from contaminated equipment.

B. Epidemiology
1. VAP accounts for 6.8–32.2 % of healthcare-associated infections
2. The true rate of neonatal VAP is difficult to establish, but appears to be decreasing. It is estimated at 0.3–1.6 per 1000 ventilator days in US level II/III NICUs
3. Risk factors include:
   a. Prematurity (most important)
   b. Parenteral nutrition and central venous catheters (general risk factor for a healthcare-associated infection)
   c. Mechanical ventilation
   d. Frequent endotracheal tube suctioning
   e. Reintubation
   f. Treatment with opiates
   g. Use of H2 blockers and antacids

C. Diagnosis
1. The diagnosis in neonates is problematic. Procedures commonly used to diagnose VAP in adults (e.g., bronchoscopy, lung biopsy, protected brush specimen, and bronchoalveolar lavage) are rarely used in the neonatal population.
2. The current definition used by the Centers for Disease Control and Prevention (CDC) and National Healthcare Safety Network requires new and persistent radiographic infiltrates, worsening gas exchange in infants who are ventilated for at least 48 h, and at least 3 of the following criteria:
   a. Temperature instability with no other recognized cause
   b. Leukopenia
   c. Change in the characteristic of respiratory secretions
   d. Respiratory distress
   e. Bradycardia or tachycardia
3. Blood cultures may or may not be positive in infants with VAP.
4. Tracheal aspirates for culture are not helpful, because they merely identify microorganisms colonizing the airway (not necessarily those causing disease). Knowledge of antimicrobial sensitivity may be useful in targeting therapy.
5. The value of quantitative cultures or the presence of intracellular bacteria has not been adequately studied in neonates.
6. Chest radiographs may indicate new or focal infiltrates, but in infants with chronic lung changes, the distinction from atelectasis is difficult.
7. Adjunctive laboratory studies are not generally helpful; however, infants with serious bacterial or fungal infections commonly exhibit an increase in total white blood count, an increased percentage of immature forms, and thrombocytopenia.
8. Bronchoscopy is not recommended for neonates with suspected VAP.

D. Bacterial and fungal pathogens
   1. VAP is frequently polymicrobial.
   2. *S. aureus* and enteric organisms (*P. aeruginosa, Klebsiella* spp., *E. coli*, *Enterobacter cloacae*, *Acinetobacter* spp., *Citrobacter* spp., and *Enterococcus*) are most common.
   3. *Candida* spp.

E. Management
   1. Broad-spectrum antibiotics targeting Gram-positive and Gram-negative organisms (including *Pseudomonas* and *Staphylococcus*) are commonly used (e.g., piperacillin–tazobactam or ticarcillin–clavulanate).
   2. If extended spectrum beta-lactamase producing organisms are identified, carbapanems may be more appropriate.
   3. When there is an outbreak of pneumonia from a resistant microorganism, empiric therapy should target those pathogens. Any cluster of infections or an infection secondary to an unusual pathogen (e.g., *Citrobacter*) should be investigated by the infection control service.
   4. Amphotericin or fluconazole is used for fungal infections.
   5. Hemodynamic and respiratory support as noted above.

F. Prevention
   1. Hand hygiene practices, including the use of gloves when in contact with secretions
   2. Avoidance of mechanical ventilation
   3. Minimize days of ventilation
   4. Other strategies and recommendations (evidence less clear):
      a. Positioning (elevating head of bed, lateral positioning)
      b. Suctioning oropharyngeal secretions before an endotracheal tube is removed or repositioned
      c. Oral hygiene
      d. Change ventilator circuit only when visibly soiled or malfunctioning.
      e. Remove condensate from the ventilator circuit.
      f. Trim excessive endotracheal tube length.

V. Respiratory Syncytial Virus (RSV)

A. Background
   1. Although RSV infections are rare in the first weeks of life, epidemics in newborns have been described.
   2. In the USA, RSV is the leading cause of hospital admission in children under 1 year of age. Approximately 1–3 % of all children in the first 12 months of life will be hospitalized because of RSV infection.
   3. RSV-related mortality has decreased in the twenty-first century (3–4/10,000 admissions in the USA).
   4. RSV is spread by direct or close contact with infected secretions. The virus can live up to 7 h on countertops, gloves, and cloths, and up to 30 min on skin.
   5. Risk factors for severe RSV infection in infants include prematurity, chronic lung disease, and complex congenital heart disease (CHD).

B. Pathology: Necrosis of the bronchiolar epithelium and peribronchiolar infiltrate of lymphocytes and mononuclear cells.
   1. Filling of alveolar spaces with fluid
   2. Multinucleated giant cells circumscribed by large syncytia

C. Manifestations
   1. Upper respiratory tract infection, pneumonia, and bronchiolitis.

2. Clinical signs of RSV infection include lethargy, irritability, poor feeding, apnea, and respiratory distress with tachypnea and wheezing.
3. RSV infection increases the infant's risk for wheezing or asthma up to 7 years of age and has been associated with sudden infant death syndrome.

D. Diagnosis
1. Rapid diagnostic assays (immunofluorescence and enzyme immunoassay) using nasopharyngeal specimens are reliable
2. Molecular diagnostic tests using reverse transcription-PCR (RT-PCR) assays are available commercially and increase RSV detection rates over viral isolation or antigen detection assays.
   a. Many commercial tests are designed as multiplex assays to facilitate testing for multiple respiratory viruses with one test.
   b. As many as 25 % of asymptomatic children test positive for respiratory viruses using RT-PCR assays in population-based studies.
3. Viral isolation in cell culture (3–5 days) on nasopharyngeal specimens using specific methods of collection and transport
4. Serologic tests cannot be relied upon for confirmation.

E. Prevention
1. In the absence of a safe and effective vaccine, passive immunization has been licensed for prevention of RSV infection. Palivizumab, a humanized monoclonal antibody, is the product of choice.
2. Palivizumab is not approved for treatment of the disease.
3. Palivizumab is recommended for RSV prophylaxis during the first year of life by the AAP for all high-risk infants including:
   a. Infants born before 29 weeks, 0 days' gestation
   b. Preterm infants with CLD of prematurity, defined as birth at <32 weeks, 0 days' gestation and a requirement for >21 % oxygen for at least 28 days after birth
   c. Infants with hemodynamically significant cyanotic or acyanotic CHD. Highest risk groups include infants with cyanotic CHD, those requiring medications for congestive heart failure, and infants with pulmonary hypertension.
   d. Children younger than 24 months who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.
4. Clinicians may administer up to a maximum of 5 monthly doses of palivizumab during the RSV season to infants who qualify for prophylaxis in the first year of life.
5. Palivizumab prophylaxis is not recommended in the second year of life except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical intervention (supplemental oxygen, chronic corticosteroids, or diuretic therapy).

F. Treatment and prognosis
1. Primary treatment is supportive (hydration, oxygen, and ventilatory support as needed).
2. Ribavirin has antiviral activity in vitro; however, it has not been shown to decrease the need for mechanical ventilation or length of hospitalization.
3. Ribavirin is not recommended for routine use but may be considered for use in selected patients with documented, potentially life-threatening RSV infection.
4. ECMO for refractory cases.

VI. Human Metapneumovirus (hMPV)

A. Background
1. Paramyxovirus discovered in 2001 recognized only recently because of new diagnostic methods

2. Affects all age groups, but most children are infected by age 5 years
3. Seasonal distribution similar to RSV (greatest number in early late winter or early spring)
4. May co-infect with RSV, possibly increasing the severity of the disease

B. Pathology
1. Primarily affects airway epithelium leading to cell degeneration or necrosis
2. Pathological findings similar to RSV

C. Manifestations: Causes both upper and lower respiratory infections:
1. Rhinopharyngitis
2. Bronchiolitis
3. Bronchitis
4. Pneumonia
5. May have concomitant otitis media

D. Diagnosis
1. hMPV replicates poorly in traditional cell cultures.
2. RT-PCR is the method of choice for diagnosis.
3. Immunofluorescence assays using monoclonal antibodies for hMPV antigen also are available.
4. Serologic tests permit only a retrospective diagnosis.

E. Treatment:
1. Supportive (hydration, use of supplemental oxygen, and mechanical ventilation as needed).
2. Use of antiviral agents is not recommended.

Suggested Reading

AAP Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for Palivizumab prophylaxis among infants and young children at increased risk of hospitalization for Respiratory Syncytial Virus infection. Pediatrics. 2014;134 (2):415–20.

Ablow RC, Gross I, Effman EL, et al. The radiographic features of early onset group B streptococcal neonatal sepsis. Radiology. 1977;127:771–7.

American College of Obstetricians and Gynecologists. Practice bulletin no. 151: Cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. Obstet Gynecol. 2015;125(6):1510–25.

Avila C, Willins JL, Jackson M, et al. Usefulness of two clinical chorioamnionitis definitions in predicting neonatal infectious outcomes: a systematic review. Am J Perinatol. 2015;32(11):1001–9. doi:10.1055/s-0035-1547325.

Barker JA, McLean SD, Jordan GD, et al. Primary neonatal Herpes simplex virus pneumonia. Pediatr Infect Dis J. 1990;9:285–9.

Barton L, Hodgman JE, Pavlova Z. Causes of death in the extremely low birth weight infant. Pediatrics. 1999;103: 446–51.

Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol. 2010;37(2): 421–38.

Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr. 2015;166(4):1070–4. doi:10.1016/j.jpeds.2014.12.023.

Benjamin Jr DK, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics. 2010;126(4):e865–73.

Bertsche A, Wagner MH, Bollmann R, Obladen M, Felderhoff-Mueser U. An unusual manifestation of a neonatal Chlamydia. J Child Neurol. 2008;23:948–9.

Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. Arch Dis Child Fetal Neonatal Ed. 2006;91(3):F208–12.

Bizzarro MJ, Shabanova V, Baltimore RS, Dembry L-M, Ehrenkranz RA, Gallagher PG. Neonatal sepsis 2004–2013: the rise and fall of coagulase-negative staphylococci. J Pediatr. 2015;166(5):1193–9. doi:10.1016/j.jpeds.2015.02.009.

Cernada M, Brugada M, et al. Ventilator-associated pneumonia in neonatal patients: an update. Neonatology. 2014;105(2):98–107.

Chapman E, Reveiz L, Illanes E, Bonfill Cosp X. Antibiotic regimens for management of intra-amniotic infection. Reveiz L, editor. Cochrane Database Syst Rev. 1996. doi:10.1002/14651858.CD010976.pub2.

Cohen-Wolkowiez M, Moran C, Benjamin DK, Cotten CM, Clark RH, Smith PB. Early and late onset sepsis in late preterm infants. Pediatr Infect Dis J. 2009;28(12):1052–6. doi:10.1097/INF.0b013e3181acf6bd.

Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA 98109, USA. N Engl J Med. 2009;361(14):1376–85.

de Jong EP[1], Vossen AC, Walther FJ, Lopriore E. How to use neonatal TORCH testing. Arch Dis Child Educ Pract Ed. 2013;98(3):93–8.

Edell DS, Davidson JJ, Mulvihill DM, Majure M. A common presentation of an uncommon cause of neonatal respiratory distress: Pneumonia alba. Pediatr Pulmonol. 1993;15:376–9. Epidemiol Infect. 2010;138(10):1503–9

Garland JS. Ventilator-associated pneumonia in neonates: an update. Neoreviews. 2014;15:e225–35.

Gronek P, Schmale J, Soditt V, et al. Bronchoalveolar inflammation following airway infection in preterm infants with chronic lung disease. Pediatr Pulmonol. 2001;31:331–8.

Hammerschlag MR. Chlamydia trachomatis and Chlamydia pneumoniae infection in children and adolescents. Pediatr Rev. 2004;25:43–51.

Heath PT, Jardine LA. Neonatal infections: group B streptococcus. BMJ Clin Evid. 2014.

Jackson KA, Iwamoto M, Swerdlow D. Pregnancy-associated listeriosis. Epidemiol Infect. 2010;138(10): 1503–9. Epub 2010 Feb 17.

Kim CJ, Romero R, Chaemsaithong P, Chaiyasit N, Yoon BH, Kim YM. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am J Obstet Gyn. 2015;213(4 Suppl):S29–52. doi:10.1016/j.ajog.2015.08.040.

Kimberlin DW, Baley J, Committee on Infections Diseases and Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital Herpes lesions. Pediatrics. 2013;131(2): e635–48.

Langlet C, Gaugler C, Castaing M, et al. An uncommon case of disseminated neonatal herpes simplex infection presenting with pneumonia and pleural effusions. Eur J Pediatr. 2003;162:532–3.

Larsen JW, Sever JL. Group B Streptococcus and pregnancy: a review. Am J Obstet Gynecol. 2008;198: 440–50.

Liu J. Lung ultrasonography for the diagnosis of neonatal lung disease. J Matern Fetal Neonatal Med. 2014;27(8):856–61. doi:10.3109/14767058.2013.844125.

Mazur MJ, Matinón-Torres F, Baraldi E, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. Lancet Resp Med. 2015;3:888–900.

Merrill JD, Ballard RA. Pulmonary surfactant for neonatal respiratory disorders. Curr Opin Pediatr. 2003; 15(2):149–54.

Mishra UK, Jacobs SE, Doyle LW, Garland SM. Newer approaches to the diagnosis of early onset neonatal sepsis. Am J Obstet Gynecol. 2008;198(4):440–8. discussion 448–50.

Nissen MD. Congenital and neonatal pneumonia. Paediatr Respir Rev. 2007;8(3):195–203. doi:10.1016/j.prrv.2007.07.001.

Numazaki K, Asanuma H, Niida Y. Chlamydia Trachomatis infection in early neonatal period. BMC Infect Dis. 2003;3:2.

Panda S, Mohakud NK, Pena L, et al. Human metapneumovirus: review of an important respiratory pathogen. Int J Infect Dis. 2014;25:45–52. doi:10.1016/j.ijid.2014.03.1394. Epub 2014 May 17.

Pinninti SG, Kimberlin DW. Preventing herpes simplex virus in the newborn. Clin Perinatol. 2014;41(4):945–55.

Principi N, Bosos S, Esposito S. Human metapneumovirus in paediatric patients. Clin Microbiol Infect. 2006;12:301–8.

Resch B, Paes B. Are late preterm infants as susceptible to RSV infection as full term infants? Early Hum Dev. 2011;87S:S47–9.

Romero R, Gotsch F, Pineles B, Kusanovic JP. Nutr Rev. 2007;65(12 Pt 2):S194–202. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. Pediatr Res. 2009;65(5 Pt 2):84R–90R.

Rudd PT, Carrington D. A prospective study of chlamydial, mycoplasmal, and viral infections in a neonatal intensive care unit. Arch Dis Child. 1984;59(2):120–5.

Schachter J, Holt J, Goodner E, Grossman M, Sweet R. Prospective study of chlamydial infection in neonates. Lancet. 1979;314(8139):377–80. doi:10.1016/s0140-6736(79)90400-8.

Sgro M, Shah PS, Campbell D, et al. Early-onset neonatal sepsis: rate and organism pattern between 2003 and 2008. J Perinatol. 2011;31(12):794–8. doi:10.1038/jp.2011.40.

Skevaki C, Kafetzis DA. Ureaplasma Urealyticum airway colonization and pulmonary outcome in neonates. Expert Rev Anti Infect Ther. 2003;1:183–91.

Stoll BJ, Hansen N, Fanaroff AA, Wright LL, et al. Changes in pathogens causing early-onset sepsis in very-low-birthweight infants. N Engl J Med. 2002;347(4):240–7.

Stoll BJ, Hansen NI, Sánchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011;127(5):817–26. doi:10.1542/peds.2010-2217.
Verani JR, Schrag SJ. Group B streptococcal disease in infants: progress in prevention and continued challenges. Clin Perinatol. 2010;37(2):375–92.
Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease–revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59(RR-10):1–36.
Vicencio AG. Susceptibility to bronchiolitis in infants. Curr Opin Pediatr. 2010;22:302–6.
Viscardi RM, Hasday JD. Role of Ureaplasma species in neonatal chronic lung disease: epidemiologic and experimental evidence. Pediatrics. 2005;116(3):595–602.
Viscardi RM, Manimtim WM, Sun CJ, et al. Lung pathology in premature infants with Ureaplasma urealyticum infection. Pediatr Dev Pathol. 2002;5:141–50.
Waites KB, Katz B, Schelonka RL. Mycoplasmas and Ureaplasmas as neonatal pathogens. Clin Microbiol Rev. 2005;18:757–89.
Waites KB, Schelonka RL, Xiao L, Grigsby PL, Novy MJ. Congenital and opportunistic infections: Ureaplasma species and Mycoplasma hominis. Semin Fetal Neonatal Med. 2009;14:190–9.
Weiss LM, Dubeyb JP. Toxoplasmosis: a history of clinical observations. Int J Parasitol. 2009;39(8):895–901.
Wolfs TGAM, Jellema RK, Turrisi G, Becucci E, Buonocore G, Kramer BW. Inflammation-induced immune suppression of the fetus: a potential link between chorioamnionitis and postnatal early onset sepsis. J Matern Fetal Neonatal Med. 2012;25(S1):8–11. doi:10.3109/14767058.2012.664447.
Woods CR. Congenital syphilis–persisting pestilence. Pediatr Infect Dis J. 2009;28:536–7.
Wynn J, Cornell TT, Wong HR, Shanley TP, Wheeler DS. The host response to sepsis and developmental impact. Pediatrics. 2010;125(5):1031–41.

Meconium Aspiration Syndrome

71

Thomas E. Wiswell

I. Overview
   A. Meconium-stained amniotic fluid (MSAF).
      1. Occurs in approximately 10–15 % of all deliveries
      2. Meconium passage may be a marker of antepartum or intrapartum compromise (such as hypoxemia or umbilical cord compression).
      3. Passage of meconium is likely more often a maturational event. MSAF is rarely noted before 37 weeks' gestation, but may occur in 35 % or more of pregnancies ≥42 weeks' gestation.
   B. Meconium aspiration syndrome (MAS).
      1. Definition: Respiratory distress in an infant born through MSAF whose clinical findings cannot be otherwise explained.
      2. MAS occurs in 2–6 % of newborns born through MSAF.
      3. Aspiration most commonly occurs in utero. Aspiration with the initial postnatal breaths appears to be decidedly less common.
      4. The thicker the MSAF consistency, the greater the likelihood of MAS.
      5. The more depressed a baby is (as reflected by the need for positive pressure ventilation or low Apgar scores), the greater the likelihood of MAS.
      6. Of those with MAS, 30–60 % require mechanical ventilation, 10–25 % develop pneumothoraces, and 2–7 % die.
      7. 50–70 % of infants with persistent pulmonary hypertension of the newborn (PPHN) have MAS as an underlying disorder.
II. Pathophysiology
   A. Complex mechanisms involved (Fig. 71.1)
   B. At any given moment, several of these mechanisms may be influencing the degree of respiratory distress.
III. Prevention of MAS
   A. Amnioinfusion: a large, international, randomized, controlled trial indicated that this therapy does not reduce the risk of MAS.

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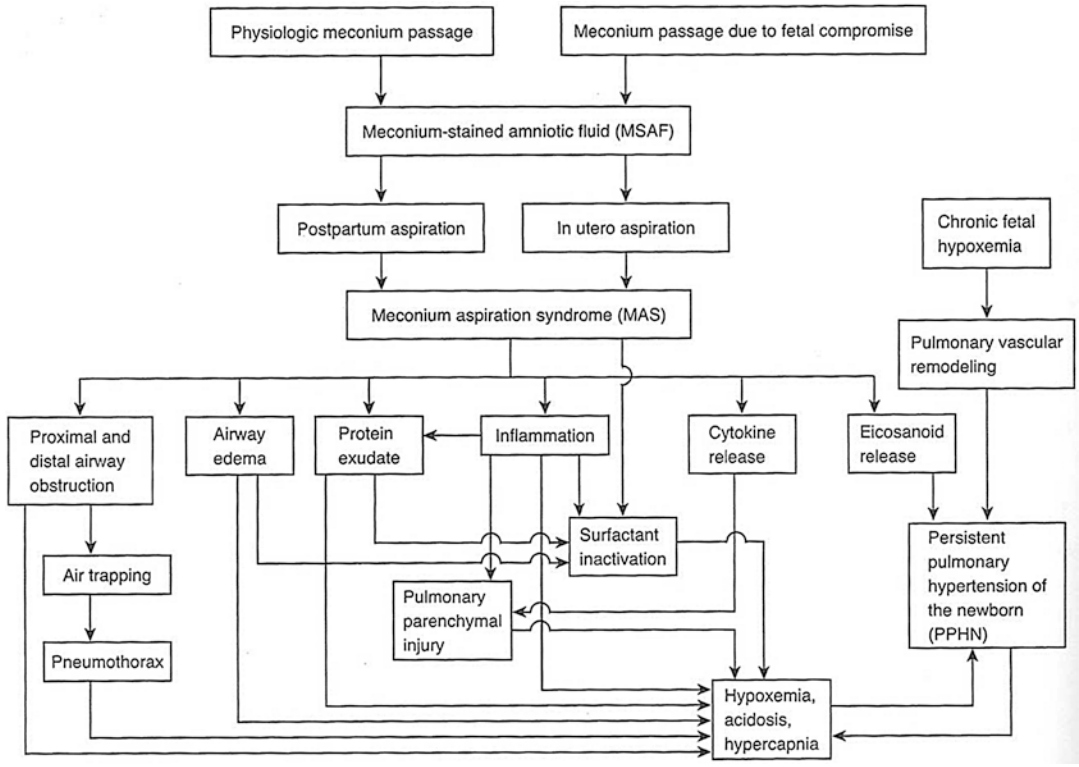

Fig. 71.1 Pathophysiology of the meconium aspiration syndrome (MAS)

B. Oropharyngeal suctioning: a large, international, randomized, controlled trial indicated that intrapartum naso- and oropharyngeal suctioning does not reduce the incidence of MAS.
C. Potentially dangerous maneuvers of no proven benefit:
   1. Cricoid pressure: application of pressure to the infant's airway to prevent intratracheal meconium from descending into the lungs
   2. Epiglottal blockage: insertion of 1–3 fingers into the child's airway to manually "close" the epiglottis over the glottis to prevent aspiration
   3. Thoracic compression: encircling the infant's chest and applying pressure in an attempt to prevent deep inspiration prior to endotracheal cleansing
   4. None of these maneuvers has ever been scientifically validated and all are potentially dangerous (trauma, vagal stimulation, or induction of deep inhalation with chest recoil upon removing encircling hands).
D. Endotracheal intubation and intratracheal suctioning in the delivery room:
   1. A large trial indicated that endotracheal intubation is of no benefit in the apparently vigorous infant born through any consistency MSAF (apparent vigor was defined within the first 10–15 s of life by a heart rate >100 beats/min, spontaneous respirations, and reasonable tone).
   2. The recently published *Neonatal Resuscitation Program (7th edition)* guidelines no longer recommend routine intubation and intratracheal suctioning of depressed or nonvigorous infants. Although this has been a routine intervention for more than 40 years, the NRP Steering Committee now states that there is insufficient evidence to support the practice. Nevertheless, the committee acknowledges that a definitive randomized clinical

trial has not yet been performed to assess the practice in the non-vigorous population. The guidelines state that intubation and intratracheal suctioning may be performed if clinically indicated for individual meconium-stained depressed infants, such as those manifesting airway obstruction.

E. Gastric suctioning
   1. Theoretically, postnatal suctioning of the gastric contents in meconium-stained infants could prevent post-birth reflux or emesis and frank aspiration of MSAF.
   2. No studies to date have assessed this approach.

IV. Radiographic Findings (Chap. 23)
   A. Radiographic findings among infants with MAS are diverse and include:
      1. Diffuse, patchy infiltrates
      2. Consolidation
      3. Atelectasis
      4. Pleural effusions
      5. Air leaks (pneumothorax and pneumomediastinum)
      6. Hyperinflation
      7. "Wet-lung" appearance similar to findings seen with transient tachypnea of the newborn
      8. Hypovascularity
      9. Apparently clear, virtually normal appearance
   B. Correlation of radiographic findings with disease severity:
      1. One early study indicated direct correlation between severity of MAS and the degree of radiographic abnormalities.
      2. Other studies found no such correlation. Patients with minimal signs may have a strikingly abnormal chest radiograph, while the sickest infant may have a virtually normal chest radiograph.
      3. As with other aspiration syndromes, the radiographic appearance usually lags behind the clinical. Inflammation takes time to become radiographically apparent.

V. Conventional Management of MAS
   A. Chest Physiotherapy (CPT)
      1. Objectives of CPT are to prevent accumulation of debris, improve mobilization of airway secretions, and improve oxygenation.
      2. CPT consists of postural drainage, percussion, vibration, saline lavage, and suctioning (nasopharyngeal, oropharyngeal, and intratracheal).
      3. Although commonly performed in both the delivery room (DR) and the newborn intensive care unit (NICU), CPT for MAS has never been studied scientifically and its "benefits" are unproven.
   B. Oxygen
      1. The goal is to maintain acceptable systemic oxygenation. Generally, this consists of sustaining peripheral SpO_2 between 92 and 96 % or arterial partial pressure of oxygen (PaO_2) between 60 and 80 Torr (8 and 10.7 kPa).
      2. Because of the potential for gas trapping and air leaks, some advocate increasing the fraction of inspired oxygen (FiO_2) to 1.0 before implementing more aggressive therapy (mechanical ventilation, etc.). Typically, however, once FiO_2 requirements exceed 0.60, more aggressive support [Continuous Positive Airway Pressure (CPAP) or mechanical ventilation] is indicated.
      3. Oxygen is also a pulmonary vasodilator. Since aberrant pulmonary vasoconstriction frequently accompanies MAS, clinicians often attempt to maintain higher than usual oxygenation early in the course of the disorder [SpO_2 98–100 % or PaO_2 100–120 Torr

(13.3–16 kPa) or even higher]. However, this practice has not been validated in clinical trials. Moreover, high oxygen concentrations have the potential to adversely affect neonates.

4. Supplemental oxygen is used in conjunction with more aggressive therapy.

C. Nasal Cannula
1. This is a noninvasive method of administering oxygen and providing a degree of positive pressure.
2. Both low (1–2 L/min) and high (3–7 L/min) flow rates have been used therapeutically. High flow rates may increase the propensity for gas trapping and air leaks.
3. No clinical trials have been performed to assess the use of nasal cannula flow for MAS.

D. Continuous Positive Airway Pressure
1. CPAP is often begun once FiO_2 requirements exceed 0.50–0.60 or if the patient exhibits substantial respiratory distress. Some clinicians, however, prefer to move directly to mechanical ventilation without a trial of CPAP.
2. CPAP is provided most commonly in newborns intranasally via prongs inserted into the nostrils. CPAP may also be administered via a facemask or via an endotracheal tube.
3. Major potential complications of CPAP are gas trapping, hyperinflation, and excessive functional residual capacity. These factors could contribute to air leaks or to decreased venous return to the heart, further compromising the infant.
4. There is limited published information concerning the use of CPAP in MAS.

E. Conventional mechanical ventilation (CMV)
1. Typically provided with time-cycled, pressure-limited mechanical ventilators. Some clinicians avoid volume-targeted ventilators because of an unsubstantiated fear of air leaks. Others avoid pressure-control because of high flow rates and the potential for gas trapping.
2. Multiple strategies have been advocated.
   a. Use of any settings (pressure, rate, *I*:*E* ratio, FiO_2, etc.) that will maintain arterial blood gases within normal ranges
   b. Hyperventilation to achieve respiratory alkalosis in an attempt to achieve pulmonary vasodilation
   c. "Gentle" ventilation allows for higher $PaCO_2$ and lower pH and PaO_2 in an attempt to prevent lung injury (from barotrauma or volutrauma) and potential side effects from hypocapnia and alkalosis
   d. A recent retrospective report suggests that infants with MAS require higher tidal volumes and greater minute ventilation to achieve "acceptable" $PaCO_2$ levels.
3. To date, there have been no prospective, randomized trials comparing any of the various mechanical ventilator strategies in the management of MAS. Hence, no single approach can be considered optimal.

F. Other commonly used conventional therapies:
1. Sedation
2. Paralysis
3. Systemic alkalosis using parenteral administration of sodium bicarbonate
4. Use of pressors (dopamine and dobutamine) or fluid boluses to maintain high systemic blood pressure to overcome high pulmonary pressures
5. None of these therapies has been rigorously investigated in infants with MAS; some are potentially harmful

VI. Non-Conventional Management
  A. High-frequency ventilation
    1. Includes both high-frequency jet ventilation and high-frequency oscillatory ventilation
    2. Trials in animal models of MAS have generally indicated no additional benefit.
    3. Limited human anecdotal experience has been touted as indicating efficacy.
    4. To date, there are no published prospective human trials that have documented either form of high-frequency ventilation to be more efficacious than conventional ventilation in the management of MAS.
  B. Bolus exogenous surfactant
    1. Rationale
      a. Meconium produces a concentration-dependent direct inactivation of a newborn's endogenous surfactant.
      b. Meconium has a direct cytotoxic effect on the type II pneumocyte.
      c. Meconium causes decreased levels of surfactant proteins A and B.
    2. In the largest randomized, controlled trial assessing bolus surfactant use in term-gestation infants with respiratory failure (51 % of whom had MAS), surfactant-treated infants with MAS had a decreased need for extracorporeal membrane oxygenation (ECMO). However, there were no differences in mortality, duration of mechanical ventilation or oxygen therapy, or total hospital days.
    3. An alternative approach is the use of dilute surfactant to *lavage* the lungs of infants with MAS.
      a. Different techniques have been used, as have several different surfactants.
      b. Several small trials have assessed lung lavage with dilute surfactant. Infants receiving this therapy had more favorable outcomes, such as more rapid and sustained improvement in oxygenation, a shorter ventilator course, and decreased need for ECMO.
    4. Currently no commercially available surfactant is specifically FDA-approved for either bolus or lavage use in MAS in the USA.
    5. Further trials are necessary to assess this therapy.
  C. Inhaled Nitric Oxide (iNO) (Chap. 63)
    1. Results of several trials in newborns with hypoxemic respiratory failure have been published. Approximately half of the babies in these trials had MAS.
    2. Among MAS babies in the various nitric oxide trials, there has been a slight decrease in the need for ECMO. However, there have been no significant differences in mortality, length of hospitalization, or duration of mechanical ventilation.
    3. Currently, iNO should be considered in infants with concomitant persistent pulmonary hypertension who are not responding to conventional therapy.
  D. Steroid therapy
    1. Rationale is to counter the profound inflammation occurring within hours of aspiration.
    2. Steroids could be administered either systemically or via the inhalation route.
    3. Animal data are intriguing; limited human data show some benefit.
    4. Additional clinical trials are warranted involving infants with substantial MAS who require mechanical ventilation.
  E. Extracorporeal Membrane Oxygenation
    1. ECMO is the therapy of last resort and is used when mortality is estimated to be very high, 50–80 %.
    2. Of more than 21,000 newborns treated with ECMO since the mid-1980s, 25–30 % had MAS as their underlying respiratory disorder.

3. Compared to ECMO-treated infants with other disorders, those with MAS have the shortest duration of cardiopulmonary bypass and the highest survival rates, approaching 95 %.
4. V-A bypass is still the most commonly used form of ECMO in infants with MAS. In most centers, this requires permanent ligation of the right common carotid artery and the right internal jugular vein.
5. ECMO survivors have morbidity rates of 20–40 %. It is unknown how much of this morbidity is from pre-existing conditions versus how much is from ECMO.

VII. Summary
   A. MAS remains a common cause of respiratory distress among newborns.
   B. Of the various therapies used in the management of MAS, few have been adequately investigated.
   C. Further work is needed to elucidate optimal management of MAS.

Suggested Reading

Dargaville PA. Respiratory support in meconium aspiration syndrome: a practical guide. Int J Pediatr. 2012;2012:965159. doi:10.1155/2012/965159. Epub 2012 Feb 23.

Dargaville PA, Copnell B, Australian and New Zealand Neonatal Network. The epidemiology of meconium aspiration syndrome: incidence, risk factors, therapies and outcome. Pediatrics. 2006;117:1712–21.

El Shahed AI, Dargaville PA, Ohlsson A, Soll R. Surfactant for meconium aspiration syndrome in term and late preterm infants. Cochrane Database Syst Rev. 2014;12:CD002054.

Fraser W, Hofmeyr J, Lede R, et al. Amnioinfusion for prevention of the meconium aspiration syndrome. N Engl J Med. 2005;353:909–17.

Kääpä PO. Meconium aspiration syndrome (MAS): where do we go? Research perspectives. Early Hum Dev. 2009;85:627–9.

Mirza HS, Wiswell TE. Meconium aspiration syndrome. In: The 5 minute pediatric consult. 7th edn. Philadelphia, Wolters Kluwer, 2015, pp 570–571.

Sharma S, Clark S, Aubakar K, Keszler M. Tidal volume requirement in mechanically ventilated infants with meconium aspiration syndrome. Am J Perinatol. 2015; 32:916–9.

Swarnam K, Soraisham AS, Sivanandan S. Advances in the management of meconium aspiration syndrome. Int J Pediatr. 2012;2012:359571. doi:10.1155/2012/359571. Epub 2011 Nov 22.

The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med. 1997;336:597–604.

Vain N, Szyld E, Prudent L, Wiswell TE, et al. Oro- and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: results of the international, multicenter, randomized, controlled trial. Lancet. 2004;364:597–602.

Wiswell TE. Delivery room management of the meconium-stained newborn. J Perinatol. 2008;28 Suppl 3:S19–26.

Wiswell TE, Gannon M, Jacob JJ, et al. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. Pediatrics. 2000;105:1–7.

Wiswell TE, Knight GR, Finer NN, Donn SM, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. Pediatrics. 2002; 109:1081–7.

Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, Simon WM, Weiner GM, Zaichkin JG. Part 13: Neonatal Resuscitation. 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132 Suppl 2:S543–60.

Persistent Pulmonary Hypertension of the Newborn

72

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I. Description
   A. Persistent Pulmonary Hypertension of the Newborn (PPHN) is a condition in which pulmonary vascular resistance (PVR) is elevated, usually from a failure of its normal post-birth decline. This leads to a variable degree of right-to-left shunting through persistent fetal channels, the foramen ovale and ductus arteriosus, and hypoxemia. A similar clinical picture can arise from decreased systemic vascular resistance (SVR), or any condition where the PVR:SVR ratio is >1. Originally called persistent fetal circulation (PFC), it was a diagnosis for term babies with "clear" lung fields on radiography, profound cyanosis, and a structurally normal heart, secondary PPHN also occurs in babies with primary pulmonary parenchymal disease or with left ventricular dysfunction.
   B. PVR may be elevated as a result of an "appropriate" response to an underlying acute pathologic state (e.g., alveolar hypoxia), where decreased perfusion matches decreased ventilation (an appropriate response for a functioning lung). In addition, increases in PVR can occur with pneumothorax or as a result of structural abnormalities of the pulmonary vascular bed.
   C. PFC is a misnomer, since the fetal organ of respiration, the placenta, has been removed, and the infant is dependent upon the lungs for gas exchange.

II. Pulmonary Vascular Development
   A. Alveolar development is primarily a post-birth event. Intra-acinar vascular development is thus also a post-birth phenomenon. As a consequence, at birth, at the acinar level, there is a decreased cross-sectional area available for pulmonary blood flow and obligate high vascular resistance.
   B. In the newborn, complete vascular smooth muscle development does not extend to the level of the acinus, theoretically making increases in PVR more difficult. Abnormally large amounts of in utero pulmonary blood flow (such as in premature closure of the ductus arteriosus) may contribute to structural/muscular changes in the pulmonary vascular system and increased PVR. (Muscular hypertrophy may be the most long-term energy efficient way to deal with pathologic increases in pulmonary blood flow.)

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C. Some increase in pulmonary vascular muscle mass occurs at the end of gestation, and thus true structurally based PPHN is uncommon in the preterm infant.
D. A number of non-structural (and hence more reversible) factors may significantly impact pulmonary vascular reactivity and pressure, including arterial oxygen and carbon dioxide tensions, and pH. Hypoxia, hypercapnia, and acidosis cause vasoconstriction and elevate pulmonary arterial pressure, and their presence may lead to maladaptation from fetal-to-neonatal (adult-type) circulation.

III. Pathogenesis
A. Normal pulmonary vascular morphology with myocardial dysfunction or increased vascular reactivity from vasoconstrictive stimuli
1. Associated with asphyxia
a. Vasoconstrictive effects of hypoxia, hypercapnia, and acidosis
b. Myocardial dysfunction (especially left ventricular) leading to pulmonary venous hypertension and subsequent PPHN with right-to-left shunting through the ductus arteriosus
2. Associated with meconium aspiration syndrome
a. Alveolar hypoxia results in vasoconstriction.
b. Gas trapping and lung over-distention contribute to increased PVR at the acinar level.
c. Concomitant effects of severe parenchymal lung disease.
d. Some infants will also have morphologic changes in pulmonary vasculature (see below).
3. Sepsis/Pneumonia
a. Infection initiates an inflammatory response.
b. Release of cytokines and other vascular mediators increases PVR.
c. Severe parenchymal lung disease aggravates hypoxemia and hypercapnia.
4. Thrombus or microthrombus formation with release of vasoactive mediators
5. Hyperviscosity syndrome (although in some newborn models using fetal hemoglobin one *cannot* easily elevate PVR/SVR > 1)
6. Air leak syndrome with increased intrathoracic pressure
B. Morphologically or "functionally" abnormal pulmonary vasculature
1. Abnormal extension of vascular smooth muscle, with thickening and increased resistance deeper into the pulmonary vascular tree. May be related to chronic intrauterine hypoxia.
a. Some cases of meconium aspiration syndrome
b. In utero closure of the ductus arteriosus
c. Alveolar capillary dysplasia
d. Idiopathic PPHN
2. Abnormally small lungs with decreased cross-sectional area of the pulmonary vascular bed *and* muscular thickening and distal extension
a. Pulmonary hypoplasia (either primary or secondary)
b. Congenital diaphragmatic hernia
c. Congenital pulmonary adenomatoid malformation
3. Hypoxia-induced functional abnormalities of the pulmonary vasculature
a. Hypoxia down-regulates endothelial NO resulting in reduced NO production (causing pulmonary vasoconstriction).
b. Hypoxia affects upregulation of NO synthase, impairing NO release.
c. Hypoxia also induces vascular myocyte dysfunction.
C. Structurally abnormal heart disease
1. Left ventricular outflow tract obstruction
2. Total anomalous pulmonary venous return

3. Ebstein's anomaly
4. Left ventricular cardiomyopathy
5. Any structural abnormality which results in an obligatory right-to-left shunt

IV. Diagnosis
  A. Differential diagnoses of hypoxemia in the term or late preterm infant
    1. Primary pulmonary disease
    2. Cyanotic congenital heart disease
    3. PPHN, with or without lung disease
  B. Initial work-up
    1. History
      a. Evidence of infection
      b. Meconium-stained amniotic fluid
      c. IUGR/uteroplacental insufficiency (e.g., postmaturity and dysmaturity)
      d. Maternal aspirin use (premature ductal closure)
    2. Physical examination (findings are non-specific, but may help to suggest etiologic considerations)
      a. Murmur
      b. Abnormal breath sounds
      c. Inequality of pulses
      d. Scaphoid abdomen
      e. Potter's facies
    3. Chest radiograph (again, non-specific, but may suggest or exclude associated conditions).
    4. *Arterial* blood gas determination. Attempt to correct ventilation and acid–base abnormalities before attributing hypoxemia to PPHN.
  C. The hyperoxia test (for primary PPHN)
    1. Expose infant to 1.0 FiO_2 for 10–15 min.
    2. Expected responses:
      a. Parenchymal lung disease: PaO_2 should rise.
      b. Cyanotic congenital heart disease: no change in PaO_2
      c. PPHN: PaO_2 may rise slightly, but usually does not.
  D. Simultaneous evaluation of pre- and post-ductal oxygenation
    1. Obtain simultaneous arterial blood gas samples from pre- (right radial artery) and post-ductal (umbilical or posterior tibial artery) sites.
    2. A gradient (20 Torr or 2.7 kPa higher in the pre-ductal PaO_2) suggests a right-to-left ductal shunt. Low values from both sites do not rule-out PPHN; shunting may still be occurring at the level of the foramen ovale. If both values are high and essentially equal, PPHN is unlikely to be present. S_pO_2 may also be used.
  E. The hyperoxia-hyperventilation test
    1. Hypoxemia and acidosis augment pulmonary vasoconstriction.
    2. Alkalosis and hyperoxia decrease PVR.
    3. Method
      a. Hyperventilate the infant (either mechanically or manually) using 1.0 FiO_2 for 10–15 min.
      b. Attempt to decrease $PaCO_2$ (usually to the range of 25–30 Torr or 3.3–4.0 kPa), and increase pH to 7.5 range.
      c. Obtain arterial blood gas.
      d. *Profound prolonged and rapid changes in $PaCO_2$ may alter cerebral blood flow. Use this test with caution.*

4. Result
   a. A *dramatic* response (increase in PaO_2) along with marked lability suggests PPHN.
   b. Must differentiate whether increase in PaO_2 came from induced alkalosis and hyperoxia vs. increased mean airway pressure.

F. Echocardiography (Chap. 25)
1. The "gold standard" of diagnosis
2. Will rule-out congenital heart disease
3. Evaluates myocardial function
4. May enable direct visualization of shunting (Doppler blood flow)
5. Estimates pulmonary artery pressure from regurgitant tricuspid jet

V. Treatment

A. Prenatal
1. Pregnancies found to be complicated by conditions associated with PPHN (e.g., congenital diaphragmatic hernia and prolonged oligohydramnios) should be referred to a high-risk center capable of caring for the infant following delivery.
2. Identification and appropriate obstetrical management of other at-risk pregnancies (e.g., meconium-staining, chorioamnionitis, and postdatism).

B. Neonatal
1. Adequate resuscitation
2. Avoidance of acidosis, hypoxia, and hypercarbia
3. Avoidance of hypothermia, hypovolemia, and hypoglycemia
4. Prompt treatment of suspected sepsis, hypotension, or other problems

C. Establish the diagnosis.

D. General supportive measures
1. Use an appropriate ventilatory strategy, mode, and modality.
2. Assure adequate systemic blood pressure.
3. Maintain adequate oxygen carrying capacity (hemoglobin >15 mg/dL).
4. *Treat the underlying disorder.* Examples:
   a. Surfactant replacement for RDS
   b. Antibiotics, if indicated
   c. Correct mechanical problems (e.g., ascites, pleural effusions, and air leaks)

E. Mechanical ventilation
1. Initial approach should be to establish adequate ventilation while addressing the underlying pulmonary disease, if present. Both conventional mechanical ventilation and high-frequency ventilation may be utilized.
2. There is a paucity of the literature to define an optimal approach to the ventilatory management of PPHN. Two diametrically opposite approaches have been suggested, but have not been compared by adequate clinical investigation.
   a. Conservative ventilation uses the least amount of support possible to achieve gas exchange and pH which are marginally acceptable (by conventional standards). The philosophy is to decrease the level of ventilatory support to the lowest possible, so that lung hyperexpansion (which contributes to PVR) and barotrauma are avoided. PaO_2 levels of 40–45 Torr (5.7–6.0 kPa), $PaCO_2$ levels of 55–60 Torr (7.7–8.0 kPa), and pH levels of 7.25 are tolerated. In usual clinical practice, oxygen saturation values better reflect blood oxygen content; hence, many clinicians opt to follow these values rather than PaO_2 values. Additionally, while PVR is responsive to alveolar oxygen concentration, there is a paucity of human evidence to suggest that it is PaO_2 responsive. From this perspective "keep PaO_2 greater than X" seems an unhelpful approach.

b. Modest hyperventilation and alkalosis. This approach attempts to take advantage of the vasodilatory effects of alkalosis and hypocapnia on the pulmonary vasculature. Decrease the $PaCO_2$ to the "critical" value, below which there is a sharp rise in PaO_2. Alkalosis can be augmented by infusion of sodium bicarbonate (although recent evidence suggests that this increases morbidity, and is thus no longer recommended). If used, pH is usually kept above 7.5. However cerebral blood flow also responds to $PaCO_2$ (decreased flow at low $PaCO_2$) and there is epidemiologic evidence associating low $PaCO_2$ with long-term motor disability in children. This approach has fallen out of favor.

c. Prudence dictates that many clinicians favor a "middle of the road" or an "avoid acidosis and hypercapnia approach," where physiologically normal to near normal blood gases and pH are targeted by using ventilator support which is somewhere in between the philosophies described above.

3. Maintain adequate lung volume. In normal lungs, study of basic mechanics/physiology suggests PVR is lowest at functional residual capacity (FRC). In diseased lungs, there will be a volume where PVR is lowest (probably near FRC) but the exact volume is unknown. Following pulmonary mechanics may be a useful technique in this regard.
4. No matter which approach is chosen, remember that some infants with PPHN demonstrate extreme lability. It is usually better to attempt several small ventilator/FiO_2 changes than one large one.
5. A transitional phase of PPHN occurs at 3–5 days of age. Vascular reactivity diminishes and support can be decreased at a faster rate.

F. Pharmacotherapy (Chaps. 59 and 63)

1. Maintain adequate cardiac output and systemic blood pressure. The degree of right-to-left shunting depends upon the pulmonary-to-systemic gradient. Avoidance of systemic hypotension is critical. CVP monitoring may be of benefit.
   a. Correct hypovolemia if present by administering volume expanders.
   b. Cardiotonic/vascular agents: Dopamine, dobutamine, epinephrine, norepinephrine, and milrinone. All have differing effects on PVR, SVR, and contractility. There is a paucity of evidence guiding one to "the" correct medicine and dose.
   c. Small case series have suggested that milrinone may improve oxygenation in neonates with a poor response to inhaled nitric oxide (iNO). This is likely from milrinone's action as a PDE-3 inhibitor.
2. Correct acidosis
   a. Sodium bicarbonate may be given as a bolus (1–3 mEq/kg) or as a continuous infusion ($\leq$1.0 mEq/h). *Avoid hypernatremia; assure adequate ventilation.*
   b. Tris-hydroxyaminomethane (THAM, 0.3 M) can be given even if $PaCO_2$ is elevated. Dose: 4–8 mL/kg. Observe for hypokalemia, hypoglycemia, and respiratory depression.
3. Pulmonary vasodilating agents
   a. iNO (Chap. 63). iNO has successfully treated PPHN in term infants. Potential toxicities include methemoglobinemia and lung injury from metabolites formed during the oxidation of NO.
      (1) Prematurity and NO. Randomized controlled trials and meta-analyses have shown no improvement in survival when using NO routinely or in a rescue setting.
      (2) Use in this setting is not recommended.
   b. Sildenafil is a PDE-5 inhibitor that may be beneficial as an acute adjuvant to iNO or as a primary treatment in centers without access to iNO. Typically available only in oral form. Not approved by the FDA for use in neonates. Further investigation with large randomized trials is needed.

c. Bosentan is an endothelin-1 (ET-1) antagonist. Evidence is limited to case reports and small randomized controlled trials. One study showed improved short-term oxygenation. Only available in oral form. Primary adverse effect is transaminitis and liver failure. Liver function studies should be checked prior to and during bosentan administration. Further study is needed.
d. Epoprostenol (Flolan) is a prostacyclin (PGI-2 analog) that small case series and case reports have shown may be beneficial in neonates with PPHN. May be given by endotracheal instillation or intravenously in a continuous fashion given its short half-life. Major side effect is systemic hypotension, which may be mitigated in the inhaled form, but the pH of the latter is extremely alkalotic and long-term safety data are lacking. Further study is needed.

G. Extracorporeal Membrane Oxygenation (Chap. 64)
1. Rescue modality generally used when predicted mortality from PPHN is high (generally 80–85 %).
2. Overall survival approximates 70–80 % and is dependent upon underlying disease; lower rates are noted for congenital diaphragmatic hernia and pulmonary hypoplasia.
3. Long-term sequelae in about 20 %, which is equivalent to that reported in infants surviving PPHN treated by conventional means.

Suggested Reading

Kinsella JP, Shaffer E, Neish SR, et al. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. 1992;340:818–22.
Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatr Clin N Am. 2009;56:579–600.
Lapointe A, Barrington KJ. Pulmonary hypertension and the asphyxiated newborn. J Pediatr. 2011;158(2 Suppl):e19–24.
Peckham GJ, Fox WW. Physiological factors affecting pulmonary artery pressures in infants with persistent pulmonary hypertension. J Pediatr. 1978;93:1005–110.
Roberts JD, Polaner DM, Lang P, et al. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. 1992;340:818–21.
Wung JT, James LS, Kilchevsky E, et al. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. Pediatrics. 1985;76:488–93.

Congenital Diaphragmatic Hernia

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Nitesh Singh and David Field

I. Background—congenital diaphragmatic hernia (CDH) has a reported incidence of 1 in 2500 to 1 in 4000 live births with an estimated 30 % spontaneous abortion rate.
   A. Embryology—failure of normal development of the diaphragm during first trimester. Types:
      1. Posterolateral defect or Bochdalek CDH: most common, is most often observed on the left side (85 %) but can also occur on the right side (13 %) or bilaterally (2 %). Classical picture, a hernia of Bochdalek consists of a posterolateral defect of approximately 3 cm in diameter.
      2. Anterior or central portion defects account for less than 5 % of cases.
      3. Complete absence of diaphragm; rare, most severe, worst prognosis.
      4. Eventration. Not a true hernia, results from a failure of muscle development in the primitive diaphragm.
   B. In approximately 60 % of cases, CDH is isolated (non-syndromic). The remainder of cases is variously termed complex, non-isolated, or syndromic CDH. The most common syndrome incorporating CDH is Fryns' syndrome. CDH is also a feature of chromosomal anomalies (e.g., Trisomy 13 or 18). Prognosis is worse in those cases in which CDH is not an isolated finding.
   C. Pathophysiology
      1. Compression of both lungs during pregnancy results in hypoplasia, especially in the ipsilateral lung.
      2. In most severe cases, cardiac function can also be compromised in utero.
      3. After delivery, gaseous distension of gut within the chest can result in further cardiorespiratory compromise.
      4. Pulmonary hypoplasia (including abnormalities of the pulmonary vasculature) and poor oxygenation following delivery commonly result in severe persistent pulmonary hypertension of the newborn (PPHN).
      5. In mild cases, cardiopulmonary development and function may be sufficient to enable normal extrauterine adaptation with presentation at a later age.

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II. Presentation and Diagnosis
   A. Antenatal
      1. Can normally be detected on routine maternal sonographic scan during second or third trimester in about 70 % of cases; herniated abdominal viscera and mediastinal shift should be identifiable. However, a scan reported as "normal" does not conclusively exclude the diagnosis. Cases not detected on antenatal scan tend to have a better prognosis.
      2. Right-sided lesions are more difficult to detect because of the similar echogenicity of lung and liver.
      3. Polyhydramnios is commonly seen.
      4. Various other anomalies have been noted in association with diaphragmatic hernia; hence, all aspects of fetal anatomy should be reviewed once CDH has been detected.
   B. Postnatal (where not suspected antenatally) presentations
      1. At delivery, with failure to respond to normal resuscitative measures. In such cases a barrel chest and scaphoid abdomen may be noted.
      2. Within the first 48 h of life with respiratory distress
      3. In later childhood (up to 10 %), where signs can be variable and may be respiratory and/or gastrointestinal in nature, with a mean age at diagnosis of 1 year (32 days–15 years)
   C. Differential diagnosis
      Cystic lesions of the lung (most commonly congenital pulmonary airway malformation) and growths or effusions, which render one hemithorax opaque, can cause confusion.
   D. Investigations
      Antenatal ultrasound findings or clinical presentation alone may strongly suggest the diagnosis. Useful additional investigations:
      1. Chest radiograph is essential (Chap. 23).
      2. Contrast studies—used to confirm presence of stomach/gut in the chest—rarely necessary.
      3. Ultrasound or (rarely) isotope study to document position of the liver.
      4. Echocardiography can be helpful in assessing the degree of pulmonary hypertension.
      5. CT or magnetic resonance imaging (MRI) scan is rarely necessary.
      6. Pleural endoscopy again is rarely necessary.

III. Predicting Outcome
   Rationale—diaphragmatic hernia produces a spectrum of pathology from very mild pulmonary hypoplasia (causing minimal compromise) to severe (incompatible with life). Significant numbers fall into this latter category. Can they be identified in order that pointless exposure to surgery and intensive care can be avoided?
   A. Antenatal period
      Features including early diagnosis (<25 weeks), polyhydramnios, and presence of the stomach or liver in the chest have all been suggested to equate with poor prognosis. None has been found to be consistently reliable. The ratio of lung diameter to head circumference (LHR) can provide some guide to fetal lung growth particularly with values at the extreme. An LHR of <0.6 is correlated with high mortality, whereas an LHR >1.4 is associated with virtually no mortality. For the CDH fetus with an LHR in the midrange, it has proved less useful. Fetal MRI has been suggested as a tool to give a three-dimensional estimation of lung growth. Currently, a combination of LHR and presence or absence of liver in the thoracic cavity is used by surgical centers considering antenatal intervention.
   B. Postnatal chest radiograph (intrathoracic stomach, estimated degree of pulmonary hypoplasia) is of limited help in predicting outcome.
   C. Postnatal lung function (lung volumes, pulmonary compliance—limited help acutely in predicting outcome)

D. Echocardiography (ventricular thickness—limited help in predicting outcome)
E. Defect size noted at surgery is related to survival in infants with CDH; however, the association is crude.

IV. Management
A. Antenatal. Once a diagnosis is made, families should be counselled by the obstetrician, neonatologist, and pediatric surgeon regarding available options.
1. Termination criteria and regulations vary markedly between countries.
2. Continuing the pregnancy and performing postnatal repair
3. Prenatal fetal surgery—practiced in only a few centers around the world. In utero anatomical repair using hysterotomy and direct fetal surgery is no longer performed in view of poor results. Fetal endoscopic tracheal occlusion (FETO) is the current treatment under assessment as a means of promoting lung growth and restricting the severity of pulmonary hypoplasia. Using fetal tracheoscopy, a balloon is inserted (ideally at 26–28 weeks) and the occlusion is reversed in utero at 34 weeks. This is much less invasive than earlier techniques using tracheal clips and/or larger access cannulas. Harrison et al. concluded that fetal tracheal occlusion did not improve survival and morbidity. Further randomized trials are awaited.

B. At delivery in cases diagnosed antenatally:
1. Avoid distending the gastrointestinal tract with face mask ventilation.
a. In most centers the approach is to intubate and ventilate as soon as possible (i.e., in the delivery room). Consider elective paralysis.
b. Pass a nasogastric tube in the delivery room, ensure it is left to free drainage, and aspirate it every 30 min. Alternatively, insert a Replogle tube and use continuous suction.
2. Minimize factors that could precipitate PPHN and also lung injury.
a. Use adequate sedation.
b. Try to ensure adequate ventilation. The main goal of ventilation is adequate gas exchange. Gentle ventilation techniques, which tolerate a $PaCO_2$ of 60–65 mmHg with adequate oxygenation (defined as preductal $SpO_2 > 85\%$ and ideally >90 %) allowing minimal peak inspiratory pressure, have produced a marked improvement in survival in selected centers.
c. High frequency ventilation may permit adequate gas exchange at lower pressure, avoiding some lung injury.

C. In the NICU, pre-operatively
1. Infants who are not diagnosed antenatally but present soon after delivery with respiratory distress should have efforts made to minimize PPHN and avoid gaseous distension of the bowel.
2. In all affected babies, establish continuous monitoring. Invasive blood pressure/arterial access is essential (remember that samples obtained from sites other than the right arm will be affected by right-to-left shunting). Central venous pressure monitoring, if available via the umbilical vein, is of great help in fluid management.
3. Ensure adequate systemic blood pressure (maintains tissue perfusion and minimizes right-to-left shunting). May require infusion of both volume and inotropes. Take care not to induce fluid overload. A post-ductal pH > 7.25 is acceptable as long as there is evidence of good tissue perfusion, such as good capillary refill, adequate urine output, and normal serum lactic acid levels.
4. Provide adequate ventilatory support. Local policy usually governs the first choice. Both conventional and high frequency ventilation can be used with success. Aim to provide stability as a minimum (i.e., sufficient oxygenation to prevent metabolic acidosis, sufficient

control of carbon dioxide elimination to prevent respiratory acidosis). If this cannot be achieved despite maximum support (including ECMO), the child should be considered non-viable. In those babies who stabilize, their clinical condition should be optimized prior to surgery. Again, local practice often governs the timing of operation; however, evidence to support specific criteria is weak.

5. Introduce pulmonary vasodilators as indicated. PPHN is a common and major complication of diaphragmatic hernia. Nitric oxide empirically would appear to be the agent of choice, but data in relation to CDH suggest its use is unhelpful and potentially harmful.
6. Surfactant. There is no evidence to support the recommendation of surfactant use in CDH. Its use may be indicated in premature babies with chest radiographic findings of alveolar atelectasis suggestive of surfactant deficiency.
7. The use of prostaglandin to maintain ductal patency is employed in some centers to prevent overdistension of the right side of the heart.

D. Surgical repair is clearly essential, but should occur only when the baby is stable. Open repair may be performed through the abdomen (allows correction of associated malrotation at the same time) or chest. A large defect may require use of a patch. Minimally invasive CDH repair using endoscopy is currently under assessment.

E. Post-operative care
   1. Essentially the same pattern of management is recommended.
   2. Failure to be able to wean respiratory support in the days following operation may indicate lethal pulmonary hypoplasia.

F. Extracorporeal Membrane Oxygenation (ECMO) is clearly able to provide stability and control PPHN; however, no evidence of benefit over other forms of care in terms of long-term outcome has been demonstrated. The most recent Cochrane review concluded that the benefit of ECMO for babies with CDH is unclear. Survivors of severe CDH who have been supported on ECMO have significant late mortality and morbidity. There is a growing use of ECMO in some centers to manage CDH patients both pre- and post-operatively.

G. Postnatal management of infants with CDH varies markedly between centers. The CDH EURO Consortium has published consensus document/guidelines providing neonatologists and intensivists with a protocol driven European treatment strategy (the document sets out the findings of a consensus meeting between high volume centers with expertise in the treatment of CDH in Europe).

V. Outcomes

A. Short-term. Approximately two-thirds of live born infants with CDH will survive to hospital discharge. Almost all published results are difficult to interpret, since they are hospital-based and as a result may:
   1. Contain referral bias
   2. Not make clear the effect of antenatal counselling and selective termination
   3. Exclude high risk groups, such as those with associated anomalies

B. Medium term. A proportion of infants who survive the neonatal period will die in the first 2 years of life as a result of pulmonary hypertension/hypoplasia.

C. Long-term morbidity

Infants with CDH often require intensive treatment after birth, have prolonged hospitalizations, and have other congenital anomalies. After discharge from the hospital, they may have long-term sequelae such as respiratory insufficiency, gastro-esophageal reflux (up to 50 %), poor growth, neurodevelopmental delay, behavioral problems, hearing loss, hernia recurrence, and orthopedic deformities.

1. Pulmonary morbidity—Survivors with CDH may require treatment for chronic lung disease (incidence varies from 25 to 2 %), bronchospasm, aspiration, pneumonia, pulmonary hypertension, and pulmonary hypoplasia. Respiratory syncytial virus prophylaxis is also suggested for infants with CDH who have BPD in addition to routine childhood vaccinations.
2. Gastro-esophageal reflux is common and the need for fundoplication for severe reflux has been reported in as many as 19–31 % of CDH survivors.
3. The American Academy of Pediatrics has published post-discharge follow-up guidelines for healthcare providers involved in the care of infants with CDH.

VI. New approaches under development
   A. Further attempts at in utero intervention. It is hoped that with the advancement of imaging techniques it will become possible to define more precisely the degree of pulmonary hypoplasia present in utero, and that through well conducted randomized controlled trials clear indications and guidelines for prenatal intervention will emerge.
   B. Minimally invasive repair techniques have been developed but are currently not of proven benefit over more conventional approaches.

Suggested Reading

American Academy of Pediatrics Committee on Fetus and Newborn, Lally KP, Engle W. Post discharge follow-up of infants with congenital diaphragmatic hernia. Pediatrics. 2008;121(3):627–32.

Deprest J, Brady P, Nicolaides K, et al. Prenatal management of the fetus with isolated congenital diaphragmatic hernia in the era of the TOTAL trial. Semin Fetal Neonatal Med. 2014;19(6):338–48. doi:10.1016/j.siny.2014.09.006. Epub 2014 Nov 11.

Field D, Hyman-Taylor P, Bacon C, et al on behalf of MBRRACE-UK. Perinatal confidential enquiry—congenital diaphragmatic hernia. Leicester: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester. 2014. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/Perinatal%20CDH%20Report%202014%20Full.pdf

Harrison MR, Keller RL, Hawgood SB, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. N Engl J Med. 2003;349(20):1916–24.

Hedrick HL. Management of prenatally diagnosed congenital diaphragmatic hernia. Semin Fetal Neonatal Med. 2010;15(1):21–7.

Jani J, Gratacos E, Greenough A, et al. Percutaneous fetal endoscopic tracheal occlusion (FETO) for severe left-sided congenital diaphragmatic hernia. Clin Obstet Gynecol. 2005;48(4):910–22.

Keijzer R, Puri P. Congenital diaphragmatic hernia. Semin Pediatr Surg. 2010;19(3):180–5.

Lally KP, Lally PA, Lasky RE, et al. CDH study group. Defect size determines survival in infants with congenital diaphragmatic hernia. Pediatrics. 2007;120(3):e651–7.

Lansdale N, Alam S, Losty PD, Jesudason EC. Neonatal endosurgical congenital diaphragmatic hernia repair: a systematic review and meta-analysis. Ann Surg. 2010;252(1):20–6.

Logan JW, Rice HE, Goldberg RN, Cotton CM. Congenital diaphragmatic hernia; a systematic review and summary of best-evidence practice strategies. J Perinatol. 2007;27(9):535–49.

Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory distress in newborn infants. Cochrane Database Syst Rev. 2008;3:CD001340.

Pober BR. Genetic aspects of human congenital diaphragmatic hernia. Clin Genet. 2008;74(1):1–15.

Reiss I, Schaible T, Van den Hout L, et al. Standardised postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. Neonatology. 2010;98:354–64.

Robinson PD, Fitzgerald DA. Congenital diaphragmatic hernia. Paediatr Respir Rev. 2007;8:323–35.

Rossi AC. Indications and outcomes of intrauterine surgery for fetal malformations. Curr Opin Obstet Gynaecol. 2010;22(2):159–65.

Smith NP, Jesudason EC, Losty PD. Congenital diaphragmatic hernia. Paediatr Respir Rev. 2002;3(4):339–48.

Zalla JM, Stoddard GJ, Yoder BA. Improved mortality rate for congenital diaphragmatic hernia in the modern era of management: 15 year experience in a single institution. J Pediatr Surg. 2015;50(4):524–7. doi:10.1016/j.jpedsurg.2014.11.002. Epub 2014 Nov 6.

Pulmonary Hypoplasia/Agenesis

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I. Classification
   A. Pulmonary
      1. Agenesis. Can be isolated or part of a syndrome. Failure of one or both lung buds to develop at the very beginning of lung development (Chaps. 1 and 3). Bilateral agenesis is always fatal. Unilateral defect may be asymptomatic.
      2. Hypoplasia (structural)
         a. Primary. Rare defect, may be associated with other congenital anomalies.
         b. Secondary. Consequence of any lesion which impairs normal development (Table 74.1).
      3. Hypoplasia (biochemical), primary. A small number of cases have been identified which present with features of pulmonary hypoplasia but structurally normal lungs. Abnormalities of surfactant have been identified, in particular absence of surfactant protein B.
   B. Vascular
      1. Macroscopic. Atresia of the main pulmonary trunk can disrupt normal pulmonary vascular development; however, pulmonary function is normally satisfactory. Presentation is with severe cyanosis, which can be remedied by improving pulmonary blood flow.
      2. Microscopic. Pulmonary vasculature can be disrupted at the alveolar level and result in severely reduced gas exchange. Dysplasia is rare, but a small number of patterns have been recognized (e.g., alveolar capillary dysplasia), and these are now being linked to specific genetic abnormalities.

II. Pathophysiology
   A. The exact pathophysiology varies with the underlying mechanism.
      1. Reduced lung size (e.g., secondary to thoracic dystrophy)
      2. Structural immaturity (e.g., secondary to oligohydramnios)
      3. Diffusion deficit (e.g., secondary to alveolar capillary dysplasia)
   B. The main functional problem that results in all the above is pulmonary insufficiency. The main clinical problem tends to be oxygen transfer (lack of adequate pulmonary surface area).

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Table 74.1 Factors which can impair lung growth in utero

1. Compression of chest (e.g., oligohydramnios—all causes)
2. Compression of lung (e.g., effusion and diaphragmatic hernia)
3. Reduction in fetal breathing (e.g., neuromuscular disorder)

III. Diagnosis
   A. Antenatal. Diagnosis may be anticipated on the basis of maternal antenatal ultrasound scan suggesting compression (e.g., severe oligohydramnios and small fetal chest cavity). Magnetic resonance imaging is also being used to clarify this situation.
   B. Postnatal. Diagnosis may be apparent immediately after birth if hypoplasia is severe (i.e., cannot be resuscitated, or severe respiratory distress from birth), or is part of recognizable syndrome (e.g., oligohydramnios sequence). When the infant presents later with apparently isolated mild to moderate respiratory distress, the diagnosis may be delayed. Syndromes either primarily or secondarily associated with pulmonary hypoplasia should be considered. Similarly, conditions that can mimic these signs (e.g., infection) should be excluded. In all cases where hypoplasia is the possible diagnosis, the following should be considered:
      1. Genetics consult
      2. Measurement of lung volumes
      3. Measurement of pulmonary compliance
      4. Examination of surfactant genotype
      5. Lung biopsy
   C. The choice of investigation will vary with the severity of the baby's problem. In severe respiratory failure, lung biopsy may be performed as a terminal event to permit diagnosis and counselling for future pregnancies (see below). If more minor respiratory problems (e.g., unexplained persistent tachypnea), assessment of pulmonary mechanics is appropriate.

IV. Management
   A. Antenatal. If a diagnosis of pulmonary hypoplasia is made in utero, families should be counselled by the obstetrician, neonatologist, clinical geneticist, and surgeon (if appropriate). Potential options will vary according to:
      1. Primary diagnosis and its prognosis
      2. Degree of diagnostic certainty resulting from the evaluation. Essentially parents must decide between
         a. Termination of pregnancy (criteria and regulations vary markedly among and within countries).
         b. Continuing the pregnancy with postnatal intervention and "treatment."
         c. Antenatal intervention, practiced only in relation to certain conditions (e.g., bilateral pleural effusions). Results vary with both the nature and severity of underlying problem. Evidence of benefit for such interventions is not established.
   B. At delivery, standard resuscitation should take place. Where antenatal scans indicate, special measures (e.g., draining pleural effusions) should be performed. Vigorous resuscitation of infants with small volume lungs often results in pneumothorax. If dysmorphic features indicate a lethal syndrome, or if oxygenation proves impossible, intensive care may be withdrawn.
   C. In the NICU
      1. Establish routine monitoring. Invasive blood pressure/arterial access is essential in the severest cases; central venous pressure monitoring, if available via the umbilical vein, is of great help in fluid management.
      2. Ensure adequate systemic blood pressure (maintain tissue perfusion and minimize right-to-left shunting). This may require both infusion of fluids and inotropes. Take care not to induce fluid overload.

3. Provide adequate respiratory support. Infants with mild hypoplasia may not require ventilation. For those requiring invasive support, local practice usually governs the first choice; both conventional and high-frequency devices can be used with success. Aim to provide stability of blood gases (i.e., sufficient oxygenation to prevent metabolic acidosis). More aggressive ventilation may induce pulmonary damage and further impair lung function. If blood gas control proves impossible despite maximum support, the child should be considered non-viable.
4. Attempts to "treat" pulmonary hypoplasia using a combination of continuous positive airway pressure (CPAP) with inhaled nitric oxide (iNO) over a prolonged period have shown some promise during in vitro testing but clinical evidence of benefit is equivocal at best. The use of Sildenafil in this situation should also be considered experimental.
5. Introduce pulmonary vasodilators as indicated; pulmonary hypertension is often a complication. Echocardiography may help confirm the diagnosis. iNO (used as a pulmonary vasodilator) is the agent of choice.
6. Surfactant. There is no clear role for surfactant use in this situation (other than treatment of RDS if the baby has it), but it is frequently tried in an attempt to rescue a deteriorating baby.
7. Extracorporeal Membrane Oxygenation (ECMO) is clearly able to provide stability, but there is no evidence of long-term benefit over other forms of care in pulmonary hypoplasia.
8. A role for the use of partial liquid ventilation is not established.
9. Investigate to establish the diagnosis. Where there are no clear features to support a diagnosis of pulmonary hypoplasia, routine tests should exclude all other causes of respiratory distress.

V. Prognosis
   A. Pulmonary hypoplasia results from a large number of different conditions. The prognosis is governed mainly by the etiology and any associated anomalies.
   B. Mild cases often become asymptomatic with growth. Abnormalities of function can still be measured in later childhood.
   C. Infants with moderate hypoplasia can survive with intensive care but often need long-term respiratory support. The effect of growth is uncertain and death in later childhood can occur.
   D. Severely affected babies die despite full support. No current intervention is known to help in such cases.

VI. Counselling About Future Pregnancies
   A. Some infants will be affected by conditions that can recur in future pregnancies.
   B. A proportion of severely affected cases cannot be diagnosed without examination of lung tissue. Lung biopsy may be impossible to perform safely while the child is alive.
   C. Postmortem study should be obtained whenever possible. If permission for postmortem examination is not obtained, an open or needle biopsy of the lung obtained soon after death may still allow a tissue diagnosis (in many areas, consent to do so is required).

Suggested Reading

Aiton NR, Fox GF, Hannam S, et al. Pulmonary hypoplasia presenting as persistent tachypnea in the first few months of life. Br Med J. 1996;312:1149–50.

Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. Am J Respir Crit Care Med. 2011;11 [Epub ahead of print].

Correia-Pinto J, Gonzaga S, Huang Y, Rottier R. Congenital lung lesions—underlying molecular mechanisms. Semin Pediatr Surg. 2010;19(3):171–9. Review.

DeMello D. Pulmonary pathology. Semin Neonatol. 2004;9:311–29.

Geddes GC, Dimmock DP, Hehir DA, et al. A novel FOXF1 mutation associated with alveolar capillary dysplasia and coexisting colobomas and hemihyperplasia. J Perinatol. 2015;35(2):155–7. doi:10.1038/jp.2014.187.

Kallapur SG, Ikegami M. Physiological consequences of intrauterine insults. Paediatr Respir Rev. 2006;7(2): 110–6. Epub 2006 May 30.

Kilbride HW, Yeast J, Thibeault DW. Defining limits of survival: lethal pulmonary hypoplasia after midtrimester premature rupture of membranes. Am J Obstet Gynecol. 1996;175:675–81.

Major D, Cadenas M, Cloutier R, et al. Morphometrics of normal and hypoplastic lungs in preterm lambs with gas and partial liquid ventilation. Pediatr Surg Int. 1997;12:121–5.

Nogee LM, de Mello DE, Dehner LP, Colten HR. Deficiency of pulmonary surfactant protein B in congenital pulmonary alveolar proteinosis. N Engl J Med. 1993;328:404–10.

Swenson AW, Donn SM. Alveolar capillary dysplasia: a lethal developmental lung malformation. Curr Respir Med Rev. 2009;5:110–4.

Swenson AW, Becker MA, Donn SM, Attar MA. The use of high frequency jet ventilation to treat suspected pulmonary hypoplasia. J Neonatal Perinatal Med. 2011;4:33–7.

Welzing L, Bagci S, Abramian A, Bartmann P, Berg C, Mueller A. CPAP combined with inhaled nitric oxide for treatment of lung hypoplasia and persistent foetal circulation due to prolonged PPROM. Early Hum Dev. 2011;87(1):17–20.

Chylothorax

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I. Anatomy and physiology of the lymphatic system
   A. Lymph is generated in the interstitium and carried in lymph vessels with a unidirectional flow from the intestines to the venous system near the junction of the left internal jugular and the left subclavian veins.
   B. There is variation in the thoracic lymphatic duct anatomy; most (about 60 %) have a single right lymphatic duct along the right posterior mediastinum between the aorta and azygos vein that crosses to the left mediastinum to the esophagus and behind the aortic arch at the fourth to sixth thoracic vertebrae level. This anatomic position of the thoracic duct makes it vulnerable to injury in association with multiple types of surgical interventions in the thoracic cavity.
   C. Lymph contents include cells (mainly lymphocytes), proteins, coagulation factors, and chylomicrons. Lymph flow increases after enteral feeding and decreases at fasting.
   D. Conditions associated with impaired lymphatic flow or increased central venous pressure/SVC pressure lead to lymphatic leakage to spaces along the route of the lymphatic vessels (the pleural and pericardial spaces in the chest cavity).

II. Timing of chylothorax
   A. Congenital chylothorax
      1. Occurs in 1:15,000 pregnancies, male-to-female ratio is 2:1, and more frequently on the right side
      2. Chylothorax is the most frequent cause of congenital hydrothorax (about 65 %).
      3. Prognosis of a fetus with chylothorax depends on the etiology and the presence of other anomalies, prematurit, and on the degree of chylothorax interference with lung development (degree of pulmonary hypoplasia) with overall survival 30–70 %.
   B. Chylothorax following injury to intrathoracic vessels
      1. Occurs at a rate of 4 % following cardiothoracic surgeries in neonates. Patients with genetic syndromes, more complex procedures, and those with vein thrombosis have a higher risk to develop chylothorax.

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2. Chylothorax is reported in association with other surgical procedures involving the thoracic cavity and the diaphragm.
3. Patients who develop chylothorax have a higher mortality and a longer hospital course.

III. Lymphatic developmental anomalies associated with chylothorax can be limited to the lungs or involve other organ systems. Chylothorax is usually caused by sluggish lymphatic drainage and/or by mass formation that impedes lymphatic drainage.
   A. The main types of lymph anomalies are lymphangiomatosis (dilation and increase in the number of lymphatic capillaries) and lymphangiectases (dilation along the course of the lymphatic vessels that is primary or secondary to obstruction to lymphatic flow).
   B. Congenital lymphatic dysplasia syndrome is an inherited form of lymph vessel anomaly associated with congenital chylothorax attributed to valvular incompetence causing chylous reflux from the thoracic duct.
   C. Lymphatic disorders can be associated with some syndromes like Turner, Noonan, trisomy 21, and Ehlers–Danlos.

IV. Diagnostic measures
   A. Identifying chylous fluid
      1. Chylous fluid is clear if the baby has not been fed and appears creamy if fed.
      2. Contains more than 1000 white blood cells per microliter with more than 70–80 % of them lymphocytes
      3. Has similar protein content to plasma, and triglyceride concentration more than 1000 mg/dL (in feeding patients)
   B. Identifying the etiology of the chylothorax
      1. Prenatal evaluation to determine etiology, plan, and prognosis.
         a. Fetal evaluation for chromosomal, cardiac, and thoracic structural anomalies
         b. Maternal evaluations for immunologic and infectious etiologies of hydrothorax
      2. Neonatal studies to identify anatomy of lymphatic vessels and source of lymph leakage include:
         a. Lymphangiography (requires cannulation of lymphatic vessels and can identify leaks from thoracic duct)
         b. MRI lymphangiography (not good for evaluating lymph channels)
         c. Lymphoscintigraphy (a radioisotope injected between digits, can identify thoracic duct injury)

V. Treatment options
   A. Prenatal treatment
      1. The goals are to allow more lung growth and development and to decrease the interference of the accumulating fluid with venous return and cardiac function.
      2. Prenatal treatments mainly include thoracocentesis, pleuroperitoneal shunting, and pleurodesis (creation of adhesions).
      3. Prenatal interventions are considered for large bilateral chylothorax and when chylothorax is associated with hydrops fetalis to improve the survival of these patients.
      4. Attempts are made to prolong pregnancy to avoid prematurity-related morbidities.
   B. Postnatal treatment
      1. The goals are to decrease lymphatic leakage and to allow time for injured lymphatic vessels to heal or to develop enough collateral connections.
      2. A stepwise treatment strategy is used. Progression in the risk and invasiveness of the treatment options are determined by response to the treatment (measured by volume of drained chylothorax). Drainage of more than 10 mL/kg/day is considered high volume.

3. Drainage of chylous fluids interfering with pulmonary function. Try to keep the pleural spaces clear.
4. Drained lymphatic fluid is associated with losses in cells (especially lymphocytes), proteins (including nutritious elements), electrolytes, and immune and coagulation factors.
   a. Drained fluids are partially replaced (usually with 5 % albumin solution).
   b. Both pro- and anticoagulation factors are lost in the drained lymphatic fluid and a shift towards increased risk of thrombosis may occur.
   c. Some centers use periodic intravenous immunoglobulin (IVIG) administration.
5. Other treatment options to decrease lymphatic flow include:
   a. Using a formula high in medium chain triglyceride (MCT) like Enfaport and Portagen (Mead Johnson Nutrition) for enteral feeding
   b. Stopping enteral feeding and supplementing with parenteral nutrition
   c. Using a somatostatin analog (Octreotide, Novartis Pharmaceuticals, East Hanover, NJ) to reduce lymphatic flow presumably by inducing splanchnic vasoconstriction, decreasing hepatic venous flow, and decreasing pancreatic and gastric secretions. Side effects/complications include hyperglycemia, necrotizing enterocolitis (in preterm infants), biliary sludge, hypothyroidism, and pulmonary hypertension.
6. Surgical interventions include
   a. Thoracic duct repair or ligation/embolization
   b. Pleurodesis
   c. Pleuroperitoneal shunts
   d. Surgical excision of localized lymphangiomatosis or other masses contributing to increased central venous pressure
7. Other adjuvant therapies include medications to improve diastolic function for patients with elevated central venous pressure and anticoagulation if a central venous thrombus is present.

Suggested Reading

Bellini C, Ergaz Z, et al. Congenital fetal and neonatal visceral chylous effusions: neonatal chylothorax and chylous ascites revisited. A multicenter retrospective study. Lymphology. 2012;45:91–102.

Bengtsson BS. Neonatal lymphatic (chylous) disorders. NeoReviews. 2013;14:e600–12.

Farmer DL, Albanese CT. Fetal hydrothorax. In: Harrison MR, editor. The unborn patient: the art and science of fetal therapy. 3rd ed. Orlando: W B Saunders; 2001. p. 373–8.

Mery CM, Moffett BS, et al. Incidence and treatment of chylothorax after cardiac surgery in children: analysis of a large multi-institution database. J Thorac Cardiovasc Surg. 2014;147:678–85.

Tutor JD. Chylothorax in infants and children. Pediatrics. 2014;133:722–33.

Apnea, Bradycardia, and Desaturation

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I. Introduction
   A. Neonatal apnea is widely accepted as the cessation of breathing or absence of airflow for >15–20 s. Shorter events may also be classified as apnea if accompanied by bradycardia or hypoxemia.
   B. Apnea of prematurity is largely a developmental condition that resolves with time. The incidence is inversely proportional to gestational age with a 90 % occurrence at <29 weeks' gestation.
   C. Apnea may be central (absent respiratory effort), obstructive (absent airflow), or mixed (central and obstructive). Mixed apnea is the most common type of apnea in premature infants.
   D. Periodic breathing defined as recurring 10–15 s cycles of breathing alternating with pauses of 5–10 s is a pattern reflecting immature respiratory control. Periodic breathing is often associated with intermittent hypoxemia.
   E. The physiologic basis for apnea is complex and not entirely understood; however, immature respiratory control superimposed on the immature lung may contribute to long-term respiratory morbidity.
   F. Bedside impedance monitoring in the neonatal intensive care unit does not detect obstructive apnea; therefore, oxygen saturation and heart rate monitoring are invaluable adjuncts to detect cardiorespiratory events.
   G. Intermittent hypoxemia and/or bradycardia, often associated with apnea, are likely of greater consequence to the preterm infant than apnea alone. The triad of apnea, bradycardia, and desaturation is one of the most troublesome problems in neonatal intensive care.
   H. Apnea of prematurity typically resolves by term gestation; however, it may take longer (44 weeks' postmenstrual age) in the most premature infants.

II. Physiologic Basis for Apnea of Prematurity
   A. The transition from fetal to neonatal life requires an abrupt change in respiratory activity from intermittent (not associated with gas exchange) to largely continuous where survival is dependent on pulmonary gas exchange.

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B. Hypoxia (possibly via adenosine release) and prostaglandins (likely of placental origin) inhibit fetal breathing. Despite the elimination of these mediators at birth, apnea is prominent in the first weeks to months in preterm infants.
C. The integration of chemo- and mechanosensitive input to the brainstem neuro-regulation by neurotransmitters adenosine, gamma aminobutyric acid (GABA), serotonin, and their corresponding receptors provides the basis for the autonomic control of breathing.
   1. The reflexes contributing to apnea in premature infants include a diminished hypercapnic response, failure of a sustained hypoxic ventilatory response, and enhanced inhibition from stimulation of airway mechanoreceptors.
   2. CO_2 chemosensitivity occurs at the ventral medullary surface as well as the carotid bodies. Baseline CO_2 in neonates may be only 1.5 mmHg above the apneic threshold, predisposing them to apnea.
   3. O_2 (hypoxic) chemosensitivity is located primarily in the carotid bodies and is responsible for the hypoxic ventilatory response seen after birth. Sustained hypoxia leads to respiratory depression (as occurs in the fetus).
   4. Activation of the laryngeal chemoreflex results in apnea, bradycardia, hypotension, closure of the upper airways, and encourages swallowing.
D. Obstructive apnea occurs when an infant tries to breathe against an obstructed upper airway resulting in chest wall and diaphragm motion in the absence of airflow.
   1. The site of obstruction is primarily the pharynx, but could also occur at the larynx, or both.
   2. Central apnea often precedes obstructive apnea when the apnea is mixed possibly from a delay in activation of upper airway muscles.
   3. Purely obstructive apnea in the absence of head and neck position is uncommon.
E. In addition to problems with respiratory control, preterm infants are further compromised by immature poorly defined sleep states, a compliant chest wall, underdeveloped diaphragm, small caliber airways, and unfavorable lung mechanics. Paradoxical chest wall movement and retractions associated with partial airway obstruction often occur in response to negative pressure generated by the diaphragm during inspiration.

III. Hypoxemia
A. Hypoxemia in neonates is typically defined by oxygen saturation values (as determined by pulse oximetry, SpO_2) of <85 % or <90 % for a duration that is undefined. An optimal SpO_2 range for an individual infant has yet to be determined, but is dependent upon several variables including postnatal age, gestational age, maturity of the retinal vasculature, severity of retinopathy, presence or absence of pulmonary hypertension, and intrauterine growth restriction.
B. Although there is conflicting evidence regarding the safety of lower saturation ranges, e.g., 85–90 %, from three large randomized controlled trials, it is suggested that functional SpO_2 should be targeted at 90–95 % in infants <28 weeks' gestation.
C. PaO_2 values may be estimated reasonably well at $SpO_2 < 95$ %, but PaO_2 may vary greatly at levels >95 %. Targeting $SpO_2 > 95$ % could lead to extreme hyperoxia.
D. There is evidence that cerebral tissue oxygenation measured in preterm infants by near infrared spectroscopy is better preserved during episodes of isolated bradycardia when compared to hypoxemia or combined bradycardia and hypoxemia.
E. Intermittent hypoxemia or "desaturation events"
   1. Commonly defined as a fall in SpO_2 to <85 % of varying duration
   2. Causes include:
      a. Central or obstructive apnea
      b. Respiratory pauses

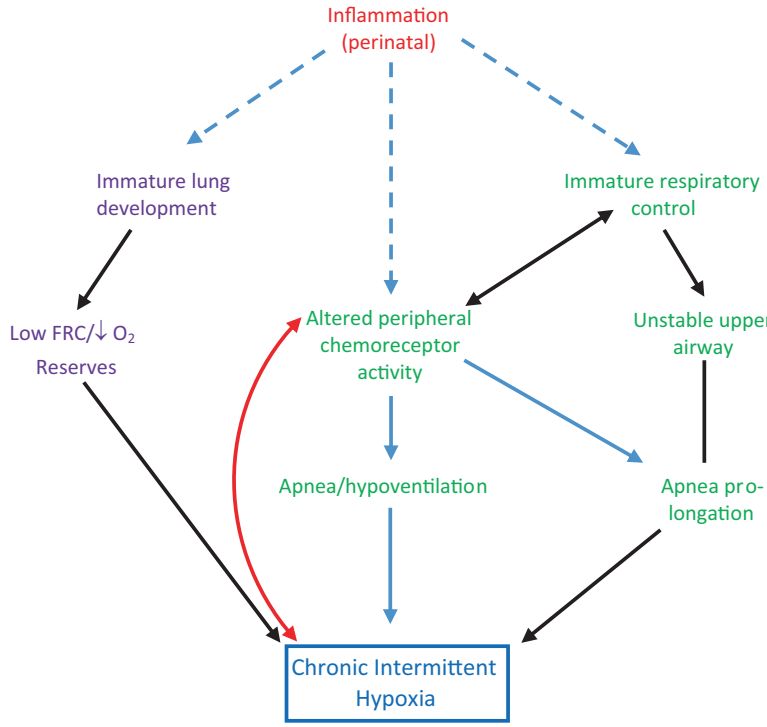

Fig. 76.1 Schematic depicting the perfect storm: the consequences of the adverse effects of perinatal inflammation on the developing lung and respiratory network leading to chronic intermittent hypoxia. Modified from Di Fiore JM, Respiratory Physiology and Neurobiology 2013;189

c. Hypoventilation
d. Low lung volumes (FRC) with diminished oxygen reserves
e. A reactive or poorly developed pulmonary vascular bed

3. Allowing lower baseline oxygen saturation levels predisposes to more frequent or profound intermittent hypoxemia.

F. Inflammation and intermittent hypoxemia (Fig. 76.1)

1. Exposure to higher oxygen tensions after birth increases the production of free radicals that can initiate an inflammatory cascade leading to lung injury and disruption of normal lung and pulmonary vascular maturation.
2. Intrauterine and/or postnatal infection also leads to inflammation.
3. Inflammation is temporally related to chronic intermittent hypoxemia observed during the first several weeks of postnatal life.
4. Systemic infection has been shown to up-regulate inflammatory cytokines in the brain that inhibit respiration.
5. The adverse effects of inflammation on the developing respiratory network (central and peripheral chemoreceptors, mechanoreceptors) and lung create the perfect storm for chronic intermittent hypoxia and potentially associated short- and long-term morbidities in premature infants.

IV. Bradycardia

A. Is defined as a drop in heart rate to <70–100 beats per minute depending on gestational and postnatal age.
B. The mechanism linking apnea and bradycardia is unclear.

C. Bradycardia during hypoxemia might be related to stimulation of the carotid body chemoreceptors, especially in the absence of lung inflation.
D. Bradycardia may occur without hypoxemia and simultaneously with apnea during stimulation of laryngeal receptors causing an increase in vagal tone.
E. At this time, there appears to be no association between bradycardia events and adverse neurodevelopmental outcomes.

V. Monitoring
A. Respiration
1. Flow sensors, including the pneumotachometer and hotwire anemometer, provide volume measurements during mechanical ventilation. The pneumotachometer is limited in the clinical setting by leaks around the endotracheal tube, thereby making it impractical for measuring airflow and volume in neonates.
2. End-tidal CO_2 and thermistor/thermocouple sensors have a limited role at the bedside and correlate poorly with measurements of tidal volume. Their use is limited to detecting the presence or absence of airflow.
3. Impedance monitoring is the most popular method of measuring respiration in the hospital setting. It can provide an accurate measure of ventilation, but is limited by its susceptibility to motion artifact and does not distinguish obstructed breaths from normal ventilation.
4. Respiratory inductance plethysmography (RIP) uses two bands wrapped around the chest and abdomen and can detect both central and obstructive apnea when combined with a proven software algorithm that calibrates the rib cage and abdominal waveforms to create a semi-quantitative volume. RIP is currently limited to the sleep lab setting.

B. Oxygen (Chaps. 6, 7, 18, and 19)
1. Pulse oximetry is the most widely used method for continuous non-invasive monitoring of oxygenation.
2. Factors impacting its accuracy include poor peripheral perfusion (low cardiac output or low intravascular volume), hypothermia, ambient light, and motion artifact.
3. Optimal accuracy of pulse oximetry is limited to saturation ranges between 89 and 95 %.
4. Signal processing can also be modified by alterations in the signal averaging time to reduce false alarms. Alterations in the averaging time will affect the way in which desaturation episodes are detected. For example, a short averaging time of 2 s will increase the number of short episodes identified while a longer averaging time of 16 s may give the appearance of an increase in long desaturation episodes by merging short episodes.
5. The introduction of automated adjustments in the fraction of inspired oxygen (Chap. 60) has decreased the incidence of both hyperoxic and severe hypoxic episodes while increasing the time spent in the intended target range.

C. Heart Rate

EKG signals in the preterm infant can be challenging to obtain because of EKG artifact or poor waveform resolution. Common logistical problems include inadequate electrode adhesiveness and improper electrode positioning. The translucent and fragile skin of the most immature preterm infant, especially within the first week of life, can pose additional challenges. The novel technique of heart rate characteristic monitoring, which combines heart rate decelerations with variability, shows promise for early identification of neonatal morbidity.

VI. Treatment
A. Methylxanthine therapy (primarily caffeine, in the USA) remains the mainstay of pharmacologic treatment for apnea since its introduction in 1975. The primary mechanism of action is to block respiratory depression through inhibition of adenosine receptors in the brain-

stem. Caffeine also enhances diaphragmatic function and increases central nervous system chemoreceptor sensitivity to CO_2. The Caffeine for Apnea of Prematurity (CAP) trial solidified caffeine as the drug of choice to promote weaning from mechanical ventilation and to prevent and treat apnea of prematurity. In this large randomized controlled trial using standard dosing, caffeine was not only determined to be safe, but effective in reducing the incidence of BPD and neurodevelopmental impairment at 18 months and more subtle motor disabilities at 5 years of age. The standard loading dose of caffeine citrate is 20–25 mg/kg and maintenance dose is 5–10 mg/kg per dose given every 24 h IV or orally. Although higher doses of caffeine appear to demonstrate greater efficacy, they should be used with caution and close attention to growth, tachycardia, jitteriness, fluid balance, and feeding intolerance. Current practice has moved toward early prophylactic administration of caffeine in extremely low birth weight infants, and it has been suggested that more prolonged use, beyond approximately 34 weeks' corrected age, decreases episodes of intermittent hypoxia.

B. Non-invasive respiratory support strategies have been implemented as an adjunct to caffeine therapy to avoid extubation failure in infants <32 weeks' gestation for many years. The rationale for implementing these techniques is to avoid prolonged support with mechanical ventilation and its consequences, bronchopulmonary dysplasia and neurodevelopmental delay. Continuous positive airway pressure (CPAP) at 5–8 cm H_2O; heated, humidified, high flow nasal cannula (HHHFNC) at 3–8 LPM flow rates (depending on the size of the infant and nasal cannula prongs); and nasal intermittent positive pressure ventilation (NIPPV) have all demonstrated similar efficacy without one modality consistently demonstrating superiority over another. The benefits of CPAP (the underlying mechanism for all non-invasive strategies) are support of upper airway structures, avoidance of airway obstruction, and improvement in FRC and oxygenation. Synchronized NIPPV in older trials was found to be superior to CPAP and NIPPV although synchronized NIPPV still has limited availability. The benefits of HHHFNC over nasal CPAP (NCPAP) are reduced nasal trauma, simplicity and ease of use, and avoidance of head (especially posterior fossa) compression that may occur with fixation of NCPAP prongs. Although HHHFNC appears to be as effective as NCPAP, precise distending pressures cannot be determined.

C. Red blood cell transfusion is often used as another adjunctive therapy for the treatment of apnea of prematurity with little supportive evidence until recently. PRBC transfusion appears to be associated with a transient and statistically significant reduction in intermittent hypoxic episodes and apnea in extremely low birth weight infants. Improved tissue oxygenation, monitoring techniques, and waveform analysis are likely responsible for these findings.

D. Oxygen supplementation does stabilize respiratory patterns in preterm infants; however, the known toxicities of oxygen must be considered. Keeping infants in the higher range of their SpO_2 target values may be acceptable.

VII. Gastro-esophageal Reflux and Apnea of Prematurity

A. Antacids and metoclopramide are among the most frequently prescribed medications in the NICU. The reason for the prevalence of these drugs appears to be the assumption that gastro-esophageal reflux (GER) is responsible for apnea in preterm infants.

B. It is true that apnea and reflux are common in preterm infants; however, GER is rarely associated with cardiorespiratory events.

C. Although there are some data to the contrary in older former preterm infants, acid reflux has not been demonstrated to cause apnea in infants <29 weeks' gestation.

D. When apnea and GER are temporally related, apnea may be the initiating event by precipitating transient lower esophageal relaxation. Suspected GER is not a reason to withhold caffeine therapy.
E. Pharmacologic treatment of GER has been associated with significant morbidity and little, if any, benefit.

VIII. Outcome
A. The frequency and severity of apnea as determined clinically at the bedside and as documented by home cardiorespiratory monitoring have been associated with abnormal neurodevelopmental outcomes. The challenge with these studies is the question of causation. Infants who have suffered brain injury in the perinatal period are at increased risk for frequent and prolonged apnea and neurodevelopmental delay.
B. Intermittent hypoxemia has been associated with severe ROP requiring laser therapy. In this study, hypoxemia was defined as $SpO_2 < 80\,\%$ for ≥10 s and ≤3 min duration.
C. In a *post hoc* analysis of data from the Canadian oxygen trial (COT), prolonged hypoxemic events <80 % and lasting at least 1 min during the first 2–3 months of life in infants <28 weeks' gestation were associated with developmental disability at 18 months. Bradycardia (heart rate <80) did not impact outcomes. As in previous studies, causation could not be established.

Suggested Reading

Abu Jawdeh EG, Martin RJ, Dick TE, et al. The effect of red blood cell transfusion on intermittent hypoxemia in ELBW infants. J Perinatol. 2014;34(12):921–5.
Collins CL, Holberton JR, Barfield C, et al. A randomized controlled trial to compare heated humidified high flow nasal cannula with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr. 2013;162:949–54.
Corvaglia V, Zama D, Spizzichino M, et al. The frequency of apneas in very preterm infants is increased after non-acid gastro-esophageal reflux. Neurogastroenterol Motil. 2011;23:303–7. e152.
Darlow BA, Marschner SL, Donoghoe M, et al. Randomized controlled trial of oxygen saturation target in very preterm infants: two year outcomes. J Pediatr. 2014;165:30–5.
Di Fiore J, Arko M, Herynk B, et al. Characterization of cardiorespiratory events following gastroesophageal reflux (GER) in preterm infants. J Perinatol. 2010a;30(10):683–7.
Di Fiore J, Bloom JN, Orge F, et al. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. J Pediatr. 2010b;157(1):69–73.
Di Fiore JM, Walsh M, Wrage L, et al. Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia. J Pediatr. 2012;161:1047–52.
Di Fiore JM, Martin RJ, Gauda EB. Apnea of prematurity—perfect storm. Respir Physiol Neurobiol. 2013;189:213–22.
Gizzi C, Montecchia F, Panetta V, et al. Is synchronized NIPPV more effective than NIPPV and NCPAP in treating apnoea of prematurity (AOP)? A randomized cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2015;100:F17–23.
Hillman N, Jobe AH. Noninvasive strategies for management of respiratory problems in neonates. NeoReviews. 2013;14(5):c227–36.
Hunt CE, Corwin MJ, Baird T, et al. Cardiorespiratory events detected by home memory monitoring and one-year neurodevelopmental outcome. J Pediatr. 2004;145:465–71.
Hunt CE, Corwin MJ, Weese-Mayer DE, et al. Longitudinal assessment of hemoglobin oxygen saturation in preterm and term infants in the first six months of life. J Pediatr. 2011;159(3):377–83.
Janvier A, Khairy M, Kokkotis A, et al. Apnea is associated with neurodevelopmental impairment in very low birth weight infants. J Perinatol. 2004;24:763–8.
Kirpalani H, Millar D, Lemyre B, et al. A trial comparing noninvasive ventilation strategies in preterm infants. N Engl J Med. 2013;369:611–20.

Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2014;4:9.

Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannula in very preterm infants after extubation. N Engl J Med. 2013;369:1425–33.

Moorman JR, et al. Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. J Pediatr. 2011;159(6): 900–6.

Nunez J, Cristofalo E, McGinley B, et al. Temporal association of polysomnographic cardiorespiratory events with GER detected by MII-pH probe in the premature infant at term. J Pediatr Gastroenterol Nutr. 2011;52:523–31.

Pillekamp F, Hermann C, Keller T, et al. Factors influencing apnea and bradycardia of prematurity—implications for neurodevelopment. Neonatology. 2007;91(3): 155–61.

Poets CF. Interventions for apnoea of prematurity: a personal view. Acta Paediatr. 2010;99:172–7.

Poets CF, Roberts RS, Schmidt B, et al. Association between intermittent hypoxia or bradycardia and late death or disability in extremely preterm infants. JAMA. 2015;314(6):595–603.

Polin RA, Bateman DA, Sahni R. Pulse oximetry in very low birth weight infants. Clin Perinatol. 2014;41: 1017–32.

Rhein LM, Dobson NR, Darnall RA, et al. Effects of caffeine on intermittent hypoxia in infants born prematurely. JAMA Pediatr. 2014;168(3):250–7.

Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology. 2014;105:55–63.

Schmid MB, Hopfner RJ, Lenhof S, et al. Cerebral oxygenation during intermittent hypoxemia and bradycardia in preterm infants. Neonatology. 2015;107:137–46.

Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354:2112–21.

Schmidt B, Anderson P, Doyle L, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA. 2012;307(3):275–82.

Schmidt B, Whyte RK, Asztalos EV, et al. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA. 2013;309(20): 2111–20.

Support Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362(21):1959–69.

The BOOST II UK, Australia and New Zealand Collaborative Groups. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368:2094–104.

Waitz W, et al. Effects of automated adjustment of the inspired oxygen on fluctuations of arterial and regional cerebral tissue oxygenation in preterm infants with frequent desaturations. J Pediatr. 2015;166(2):240–4.

Yoder BA, Stoddard RA, Li M, et al. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics. 2013;131: e1482–90.

Zagol K, Lake DE, Vergales B, et al. Anemia, apnea of prematurity, and blood transfusions. J Pediatr. 2012;161:417–21.

Optimizing Lung Volume

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Gianluca Lista and Francesca Castoldi

I. The ventilatory management of the premature infant with severe respiratory failure needs to follow some essential rules:
   A. Open partially collapsed lungs by reaching the opening pressure.
   B. Obtain adequate gas exchange with an appropriate and safe tidal volume and efficient minute ventilation.
   C. Keep the alveoli open with adequate PEEP.

II. Lung volume optimization starts from the first breath in the delivery room with:
   A. The facilitation of fetal-to-neonatal transition (liquid needs to be cleared from the lung and air has to enter) and the creation of functional residual capacity (FRC).
   B. The reduction of the risk of ventilator induced lung injury (VILI), respecting lung mechanics, and setting adequate ventilator parameters.

III. The most recent European RDS guidelines recommend:
   A. Stabilize the preterm infant in the delivery room (DR), facilitating the fetal-to-neonatal transition.
   B. Early CPAP and caffeine for extremely preterm infants as soon as possible and to consider tracheal intubation plus mechanical ventilation (MV) for depressed infants or when other methods of respiratory support fail.
   C. To use targeted tidal volume ventilation for infants who require MV as this modality shortens length of MV and reduces BPD.
   D. To consider use of natural surfactant as early as possible in the course of RDS (early is better than delayed administration).

IV. During DR stabilization, Sustained Inflation (SI) (Chap. 30), a peak pressure applied by face mask or nasopharyngeal tube, maintained for a prolonged time and usually followed by CPAP, seems to be a new promising approach:
   A. SI and PEEP allow early establishment or FRC and uniformity of lung aeration.
   B. SI improves the respiratory and cardiovascular transition at birth in preterm lambs.
   C. SI improves circulation and lung compliance in late preterm asphyxiated lambs.

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D. A recruitment maneuver by SI allowed ventilation with an increased end-expiratory lung volume at moderate PEEP levels in an experimental lung model of respiratory failure.
E. SI (e.g., peak pressure of 20–25 cm H_2O maintained for 10–15 s followed by a CPAP of 5 cm H_2O) reduced the need of MV within the first 72 h of life.
F. Short-and long-term safety and the most appropriate duration and pressure of SI have not yet been adequately studied.

V. Surfactant Therapy and Lung Recruitment
A. Tracheal instillation of surfactant (especially when used early in the first 3 h of life) is a useful treatment for severe RDS, allowing the creation of FRC and improving lung compliance.
B. Surfactant therapy and continuous distending pressure (CDP) can improve both clinical and radiologic findings of moderate to severe RDS.
C. A preliminary lung recruitment maneuver (e.g., with PEEP or SI) may allow a better distribution following administration of surfactant. It has been demonstrated that the amount of surfactant is greater in aerated lungs than in atelectatic or partially aerated lungs.
D. The spatial distribution of ventilation in an injured lung is significantly modified by a recruitment maneuver performed after surfactant administration.
E. There is a rationale for a second lung recruitment maneuver after surfactant replacement therapy to optimize lung volume in preterm infants with moderate to severe RDS.

VI. Lung Recruitment Maneuver for Lung Volume Optimization
A. To optimize the lung volume and to reduce the risk of VILI, it is necessary to set the lung volume on the deflation limb of the Pressure/Volume curve, where at the same level of pressure as the inflation limb, a greater lung volume is obtained.
B. Lung recruitment maneuver for lung volume optimization can also be performed during high frequency oscillatory ventilation (HFOV).
1. Lung recruitment maneuver for lung volume optimization during HFOV
a. Four recruitment methods were tested in animals:
(1) Escalating-step-wise pressure (this method produced the greatest increase in lung gas volume and resolution of atelectasis and it is recommended for lung volume recruitment upon initiation of HFOV)
(2) A single sustained dynamic inflation
(3) Repeated dynamic inflation
(4) Standard set Pāw
b. In clinical settings a similar lung recruitment strategy (LRS) (escalating-step-wise pressure) called "incremental–decremental CDP trial" has been used with HFOV in preterm infants with RDS. It consists of two phases:
First recruitment maneuver:
(1) Initial Pāw (e.g., with a SensorMedics 3100A) is set at 6–8 cm H_2O and the FiO_2 resulting in a targeted SpO_2 (current European guidelines suggest an SpO_2 target 90–95 %).
(2) Increase the Pāw (CDP) 1–2 cm H_2O every 2–3 min and stepwise reduce the FiO_2 (0.05–0.10) as SpO_2 improves.
(3) Stop the recruitment when the SpO_2 no longer improves and the FiO_2 is ≤0.25. This point is called "pre-surfactant opening pressure" (CDPo).
(4) Decrease the CDP 1–2 cm H_2O every 2–3 min until SpO_2 deteriorates ("pre-surfactant closing pressure," CDPc).
(5) Recruit the lung once more with the known CDPo for 2–3 min and set the CDP 2 cm H_2O above the CDPc. This is defined the "pre-surfactant optimal pressure" (CDPopt).

(6) At this moment obtain a chest radiograph and administer surfactant.
Second recruitment maneuver:
(1) 5–10 min after surfactant administration decrease the Pāw of 1–2 cm H_2O every 5 min until SpO_2 deteriorates ("post-surfactant closing pressure," CDPc).
(2) Increase the Pāw with steps of 1–2 cm H_2O every 2–3 min until oxygenation is restored ("post-surfactant opening pressure," CDPo).
(3) Set the Pāw 2 cm H_2O above the post-surfactant CDPc. This is defined the "post-surfactant optimal pressure" (CDPopt).

2. Lung Volume Optimization During Conventional Mechanical Ventilation
a. "Mechanical ventilation: should we target pressure or volume?" is a topical dilemma. Experimental and clinical studies showed that during pressure-targeted ventilation a decrease in lung compliance results in a loss of lung volume (in some cases real "atelectrauma"), despite a constant Peak Inspiratory Pressure (PIP). Conversely, during volume-targeted ventilation, a decrease of lung compliance results in an automatic increase of PIP to maintain the desired tidal volume (Vt). On the other hand, sudden improvements of lung compliance (e.g., after surfactant administration) during pressure-targeted ventilation can lead to hyperinflation ("volutrauma"). During volume-targeted ventilation, if lung compliance improves, the ventilator uses the minimal PIP to maintain the Vt close to the set Vt. Volume-targeted ventilation reduces the risk of hypoventilation and hyperinflation. A recent meta-analysis concluded that volume-targeting significantly reduced the length of mechanical ventilation, the risk of hypocarbia, the occurrence of air leak, death, or BPD, and the risk of severe IVH or PVL.
b. Lung recruitment strategy
(1) Using a standardized LRS in spontaneously breathing animals, volume-targeting produced equivalent pathophysiologic outcomes without an increase of pro-inflammatory cytokines (in bronchoalveolar lavage) compared to HFOV.
(2) In a lung protective strategy, the "optimal PEEP" (Best PEEP) seems to play a critical role. A significant percentage of collapsed alveoli is found when the PEEP is 0 ("ZEEP"); but when the PEEP is too high a significant change in FRC can result in overinflation of the more distensible areas with worsening of lung edema even with constant Vt. In animal studies a lung protective strategy with more homogeneous lung volumes during CMV was reached using low Vt and adequate PEEP.
(3) During CMV it is possible to mimic the "incremental–decremental CDP trial" used in HFOV by using low Vt and searching for the best PEEP ("incremental–decremental PEEP trial"), setting the lung volume on the deflation limb of the P/V curve just above the critical closing pressure. In the animal model it has been demonstrated that this strategy can be guided by the SpO_2 and pCO_2 levels.
(a) In preterm infants with severe RDS, after a first LRM performed in the DR by sustained inflation (peak pressure of 25 cm H_2O delivered by a T-piece, maintained for 15 s, followed by an initial PEEP of 5 cm H_2O), a need for MV and persistent high level of FiO_2 can be treated with an "incremental–decremental PEEP trial."
(b) After surfactant administration, the Vt was set at 6 mL/kg (Draeger Babylog 8000 Plus) and the initial PEEP was set at 5 cm H_2O. While monitoring SpO_2, noninvasive Blood Pressure (BP), heart rate (HR), and $TcPCO_2$, a stepwise increment of PEEP (0.2 cm H_2O every 5 min) was applied until the FiO_2 fell to 0.3. In order to avoid lung hyperinflation, the PEEP level was then reduced (stepwise decrements of 0.2 cm H_2O every 5 min) until a drop of SpO_2 and an increase in $TcPCO_2$ suggesting that the critical closing pressure has been reached.

(c) The PEEP level was progressively raised 0.2 cm H_2O every 3–5 min) until stable oxygenation at the lowest FiO_2 was reached (Best PEEP).
(d) Preterm infants so managed showed a significantly reduced oxygen dependency compared to a control group not treated with the LRM.

c. In the course of LRM always consider
(1) It is demanding and time consuming.
(2) CDP used to reach the opening of the lung could be high.
(3) There are risks of air leaks.
(4) Lung stretching may induce inflammatory signals.
(5) Hemodynamic side effects need to be monitored
(a) In a systematic review (31 studies with 985 adult patients), adverse events occurring during LRM were analyzed. Serious adverse events such as barotrauma (1 %) and arrhythmias (1 %) were infrequent, whereas the most common were hypotension (12 %) and desaturation (8 %).
(b) In preterm lambs a significant reduction of pulmonary blood flow and an increase of pulmonary vascular resistance from acute lung overdistension were noted.
(c) In preterm infants, on the other hand, a short-term increase in PEEP from 5 to 8 cm H_2O and then back to 5 again seems to improve dynamic lung function without inducing significant changes in systemic blood flow.

C. Advanced Monitoring Systems
1. To reduce the potential adverse effects of lung volume optimization, traditional clinical control (HR, BP, SpO_2, and $TcPO_2$/$TcPCO_2$) may not be sufficient and more accurate monitoring may be needed.
2. Bioelectric characteristics of lung tissues are modified by the air content. Changes in lung volume from ventilation (e.g., LRMs) result in changes in thoracic impedance. Electric Impedance tomography (EIT) with electrodes applied around the chest wall is used in adult patients to define the optimal PEEP. This technique has been investigated in preterm infants on HFOV for RDS. EIT confirmed that lung hysteresis is present in preterm infants with RDS; during inflation it was possible to identify the lower and upper inflection points in the majority of these infants. EIT it is not available for routine clinical use at present.
3. The optoelectronic plethysmography (OEP) is a new noninvasive method recently used for clinical research to study lung volume and ventilation. A variable number of reflective markers are placed on the thoraco-abdominal surface, and a set of specially designed video cameras register the chest wall and abdominal motion (infrared imaging). Dedicated software analyzes lung volume and its variation during spontaneous breathing or during respiratory support. The OEP could be very useful to validate an LRM (e.g., optimal CDP during HFOV or best PEEP during CMV).

VI. Lung volume optimization should start from the first breaths in the DR and should continue in the NICU in all mechanically ventilated infants (both on CMV and HFOV) to improve short-term respiratory outcomes and to reduce both lung injury and the occurrence of BPD.

Suggested Reading

Aliverti A, Dellacá R, Pelosi P, Chiumello D, Pedotti A, Gattinoni L. Optoelectronic plethysmography in intensive care patients. Am J Respir Crit Care Med. 2000;161(5):1546–52.

Berry D, Jobe A, Jacobs H, Ikegami M. Distribution of pulmonary blood flow in relation to atelectasis in premature ventilated lambs. Am Rev Respir Dis. 1985;132:500–3.

Castoldi F, Daniele I, Fontana P, Cavigioli F, Lupo E, Lista G. Lung recruitment maneuver during volume guarantee ventilation of preterm infants with acute respiratory distress syndrome. Am J Perinatol. 2011;28(7):521–8.

De Jaegere AP, van Veenendaal MB, Michiels A, et al. Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. Am J Respir Crit Care Med. 2006;174:639–45.

de Waal KA, Evans N, Osborn DA, Kluckow M. Cardiorespiratory effects of changes in end-expiratory pressure in ventilated newborns. Arch Dis Child Fetal Neonatal Ed. 2007;92(6):F444–8.

Dellaca RL, Aliverti A, Lo Mauro A, Lutchen KR, Pedotti A, Suki B. Correlated variability in the breathing pattern and end-expiratory lung volumes in conscious humans. PLoS One. 2015;10(3):e0116317.

Donn SM, Boon W. Mechanical ventilation of the neonate: should we target volume or pressure? Respir Care. 2009;54(9):1236–43.

Fan E, Wilcox ME, Brower RG, Stewart TE, Mehta S, Lapinsky SE, Meade MO, Ferguson ND. Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med. 2008;178(11): 1156–63.

Frerichs I, Dargaville PA, van Genderingen H, et al. Lung volume recruitment after surfactant administration modifies spatial distribution of ventilation. Am J Respir Crit Care Med. 2006;174:772–9.

Fujiwara T, Maeta H, Chida S, et al. Artificial-surfactant therapy in hyaline membrane disease. Lancet. 1980;8159:55.

Jobe AJ. Lung recruitment for ventilation: does it work, and is it safe? Pediatrics. 2009;154(5):635–6.

Lachman B. Open up the lung and keep the lung open. Intensive Care Med. 1992;18:319–21.

Miedema M, de Jongh FH, Freichs I, van Veenendaal MB, van Kaam AH. Changes in lung volume and ventilation during lung recruitment in high-frequency ventilated preterm infants with respiratory distress syndrome. J Pediatr. 2011;159(2):199–205.

Monkman S, Kirpalani H. PEEP—a "cheap" and effective lung protection. Paediatr Respir Rev. 2003;4(1):15–20.

Pellicano A, Tingay DG, Mills JF, Fasulakis S, Morley CJ, et al. Comparison of four methods of lung volume recruitment during high frequency oscillatory ventilation. Intensive Care Med. 2009;35:1990–8.

Polglase GR, Hooper SB, Gill AW, Allison BJ, McLean CJ, Nitsos I, Pillow JJ, Kluckow M. Cardiovascular and pulmonary consequences of airway recruitment in preterm lambs. J Appl Physiol. 2009;106(4): 1347–55.

Rimensberger PC, Pache JC, McKerlie C, Frndova H, Cox PN. Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation and high-frequency oscillation. Intensive Care Med. 2000;26(6):745–55.

Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Halliday HL. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants. 2013-update. Neonatology. 2013;103:353–68.

Wheeler KI, Klingenberg C, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Neonatology. 2011;100(3):219–27.

Wyckoff MH, Aziz K, Escobedo MB, et al. Copublishing of the Pediatric and Neonatal Portions of the 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations and the 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics. 2015; 136(Suppl 2).

Weaning and Extubation

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Steven M. Donn and Sunil K. Sinha

I. General Concepts
   A. Weaning
      1. Process of shifting work of breathing from ventilator to patient by decreasing level of support
      2. Generally heralded by:
         a. Improvement in gas exchange
         b. Improving spontaneous drive
         c. Greater assumption of work of breathing by patient
   B. Imposed work of breathing
      1. Endotracheal tube resistance
      2. Ventilator circuit
      3. Demand valve
      4. Estimated to require V_T of 4 mL/kg to overcome imposed work of breathing
   C. Physiologic essentials for weaning
      1. Respiratory drive
         a. Must be adequate to sustain alveolar ventilation
         b. Pre-extubation assessments
            (1) Observation
            (2) Measurement of V_T
            (3) Trial
               (a) Low IMV rate
               (b) ETCPAP
               (c) Minute ventilation test
      2. Reduced respiratory system load
         a. Respiratory system load—forces required to overcome the elastic and resistive properties of lung and airways

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b. Part of total pressure generated by respiratory muscles must overcome elasticity to change lung volume while remainder must overcome resistive properties in order to generate gas flow.
c. Time constant (Chap. 9)
(1) Product of compliance and resistance
(2) Describes how quickly gas moves in and out of lung
(3) Determines whether there is adequate time to empty lung and avoid gas trapping and inadvertent PEEP

3. Maintenance of Minute Ventilation
a. Product of V_T and rate
b. Normal range 240–360 mL/kg/min
c. Inadequate alveolar ventilation can result from inadequate V_T, rate, or both

D. Elements of Weaning
1. Tidal volume (V_T) determinants
a. Amplitude (ΔP)—the difference between PIP and PEEP
b. Inspiratory time (T_I)
c. Gas flow rate
d. Compliance
2. Frequency (rate)
a. Impacts carbon dioxide removal
b. If too rapid, may lead to hypocapnia and decreased spontaneous drive
3. Minute ventilation
a. Measure V_T and rate
b. Assess spontaneous vs. mechanical components
4. Work of breathing
a. Force or pressure necessary to overcome forces which oppose volume expansion and gas flow during respiration
b. Product of pressure and volume, or the integral of the pressure–volume loop
c. Proportional to compliance
d. Additional components
(1) Imposed work
(2) Elevated resistance
e. Indirect measure is energy expenditure (oxygen consumption)
5. Nutritional aspects
a. Inadequate calories may preclude successful weaning by not providing sufficient energy.
b. Prevent catabolism.
c. Avoid excess non-nitrogen calories, which increase CO_2 production.

II. Weaning Strategies
A. General Principles
1. Decrease the most potentially harmful parameter first.
2. Limit changes to one parameter at a time.
3. Avoid changes of a large magnitude.
4. Document the patient's response to all changes.
5. *The most common reason for failing to wean is failing to wean.*

B. Gas Exchange
1. *A normal blood gas is an invitation to decrease support, not stand pat.*
2. Always interpret blood gases in light of the pulmonary status. For example, normocapnia in a baby with severe BPD represents over-ventilation.
3. Capillary blood gases become less reliable as a baby gets older.

C. Oxygenation
   1. Primary determinants
      a. FiO_2
      b. Mean airway pressure
         (1) Peak inspiratory pressure (PIP)
         (2) PEEP
         (3) Inspiratory time
   2. Sequence
      a. Try to decrease $FiO_2 \leq 0.4$
      b. If PaO_2 is high, $PaCO_2$ normal, decrease PIP (or V_T), PIP (or V_T) and PEEP, or T_I
      c. If PaO_2 is high, $PaCO_2$ low, decrease PIP (of V_T), rate (if IMV)
      d. If PaO_2 is high, $PaCO_2$ high, decrease PEEP or T_I, and/or increase rate
   3. Practical hints
      a. If $FiO_2 > 0.4$, consider maintaining Hgb >15 g/dL.
      b. Weaning is facilitated by continuous pulse oximetry.
      c. Avoid "flip-flop" by making small F_iO_2 changes early in disease course.
      d. Avoid a mean airway pressure which is too low to maintain adequate alveolar volume.

D. Ventilation
   1. Primary determinants
      a. Amplitude (ΔP) = PIP − PEEP
      b. Rate (frequency, f)
      c. Minute ventilation = $V_T \times f$
      d. T_E (or I:E ratio)
   2. Sequence
      a. If $PaCO_2$ is low, PaO_2 high, decrease PIP (or V_T) or rate (if IMV)
      b. If $PaCO_2$ is low, PaO_2 normal, decrease rate (if IMV), or T_E
      c. If $PaCO_2$ is low, PaO_2 low, increase PEEP or decrease T_E (longer I:E ratio), or decrease rate (if IMV)
   3. Practical Hints
      a. Try to maintain normal minute ventilation.
      b. Keep V_T in 4–8 mL/kg range.
      c. Avoid overdistention but maintain adequate lung volumes.
      d. Low $PaCO_2$ diminishes spontaneous respiratory drive.
      e. Avoid pre-extubation fatigue. Weaning below an adequate level of support to overcome the imposed work or breathing may doom the baby to fail extubation.

E. Weaning Specific Modes of Ventilation
   1. Assist/Control
      a. Decrease PIP (decreases in rate have no effect if spontaneous rate is above control rate).
      b. Maintain sufficient ΔP to achieve adequate ventilation.
      c. Provide adequate V_T to avoid tachypnea.
      d. Alternative strategy: slowly increase assist sensitivity to increase patient effort and condition respiratory musculature.
      e. Extubate from assist/control or consider switching to SIMV/PSV.
   2. SIMV
      a. Decrease SIMV rate.
      b. Decrease PIP.
      c. Maintain minute ventilation.
      d. Alternative: increase assist sensitivity.
      e. Add PSV.

3. IMV
   a. Decrease PIP (lower Pāw) for O_2.
   b. Decrease rate for CO_2.
   c. Maintain minute ventilation and adequate V_T.
4. SIMV/Pressure support
   a. Decrease SIMV rate.
   b. Decrease pressure support level.
   c. Extubate when $V_T \leq 4$ mL/kg.
5. High-frequency ventilation (Chaps. 41–43)

III. Adjunctive Treatments for Weaning
A. Methylxanthines (theophylline, aminophylline, and caffeine)
1. Mechanisms of action
   a. Increase diaphragmatic contractility and decrease fatigability
   b. Direct stimulant of respiratory center
   c. Reset CO_2 responsiveness
   d. Diuretic effect
2. Indications
   a. Ventilatory support. A secondary outcome of the CAP trial was a reduction in BPD with caffeine use.
   b. Peri-extubation support
   c. Apnea or periodic breathing
3. Complications
   a. Gastric irritation and vomiting
   b. Tachycardia
   c. CNS irritation and seizures
4. Comments
   a. Follow serum concentrations (aminophylline and theophylline).
   b. Peri-extubation support usually discontinued 48–72 h post-extubation

B. Diuretics
1. Mechanism of action—treat pulmonary edema
2. Indications
   a. Pulmonary edema
   b. PDA
   c. Chronic lung disease
3. Complications
   a. Electrolyte disturbances
   b. Contraction alkalosis
   c. Nephrolithiasis/nephrocalcinosis (chronic furosemide therapy)
4. Comments
   a. Follow serum electrolytes.
   b. May need supplemental Na, K, Cl, and Ca.
   c. Long-term furosemide therapy not advised; spironolactone and chlorothiazide preferred.
   d. *There is no evidence to support the routine use of diuretics to facilitate weaning*. They may create fluid and electrolyte disturbances, which actually impede weaning.

C. Bronchodilators
1. Mechanism of action—relaxation of bronchial smooth muscle
2. Indication—bronchospasm or reactive airways leading to increased airway resistance
3. Complications

a. Tachyphylaxis
b. Tachycardia
c. Hypertension

4. Comments
a. Document efficacy before continuing.
b. May be given systemically or by inhalation.
c. If inhalational route, use a spacer.
d. *There is no evidence to support the routine use of bronchodilators to facilitate weaning*.

D. Corticosteroids
1. Mechanisms of action
a. Anti-inflammatory
b. Decrease edema
2. Indications
a. Upper airway edema
b. Pulmonary edema
c. BPD
3. Complications
a. Hypertension
b. Hyperglycemia
c. Increased risk of infection
d. Gastric bleeding
e. Myocardial hypertrophy (long-term use)
f. Decreased growth velocity (long-term use)
4. Comments
a. Highly controversial. Several dosing regimens have been suggested (Chap. 59).
b. Use for short duration.
c. Be aware of need for stress doses for infection, surgery, etc.
d. Inhalational route *may* be effective.
e. Some administer concomitant histamine-2 blocker such as ranitidine. These have been associated with increased risk for NEC.

IV. Impediments to Weaning
A. Infection (especially pulmonary)
B. Neurologic dysfunction or neuromuscular disease
1. Decreased respiratory drive
2. Neuromuscular incompetence
3. Alveolar hypoventilation
C. Electrolyte disturbances
1. Chronic diuretic therapy
2. Renal tubular dysfunction
3. Excess free water intake
4. TPN
D. Metabolic alkalosis
1. Infant may hyperventilate.
2. Correct underlying abnormality.
E. Congestive heart failure
1. Pulmonary edema
2. Impaired gas exchange
3. Organ hypoperfusion
4. May require high PEEP

F. Anemia
   1. Decreased oxygen carrying capacity
   2. High circulatory demands and excessive energy expenditure
   3. Apnea

G. Pharmacologic agents
   1. Sedatives may depress respiratory drive.
   2. Prolonged use of paralytics may lead to atrophy of respiratory musculature.

H. Nutritional
   1. Inadequate caloric intake
   2. Too many non-nitrogen calories, resulting in excess carbon dioxide production

V. Extubation and Post-Extubation Care

A. Extubation
   1. Assessment
      a. Reliable respiratory drive and ability to maintain adequate alveolar ventilation
      b. Low ventilatory support
      c. No contraindications
   2. Extubation
      a. The stomach should be empty. If infant recently fed, aspirate stomach contents, in the event reintubation becomes necessary.
      b. Suction endotracheal tube and nasopharynx.
      c. When heart rate and SaO_2 are normal, quickly remove endotracheal tube.
      d. Provide F_iO_2 as needed.

B. Post-Extubation Care
   1. Nasal CPAP (Chap. 29)
      a. Clinical trials show mixed results. Some clinicians prefer to extubate directly to NCAP to maintain continuous distending pressure and decrease work of breathing.
      b. Use 4–6 cm H_2O.
      c. May also be useful to maintain upper airway patency in infants with stridor.
   2. Nasal cannula (Chap. 28)
      a. Can provide necessary FiO_2
      b. Can provide gas flow to help overcome nasal resistance
      c. Allows most patient freedom
   3. Oxygen hood
      a. Can provide necessary FiO_2
      b. More confining than nasal cannula but easier to regulate specific FiO_2
   4. Prone positioning
      a. Stabilizes chest wall
      b. Improves diaphragmatic excursion by allowing abdominal viscera to fall away from diaphragm and thus decreases work of breathing
      c. Umbilical catheters should be removed
   5. Stridor
      a. May result from subglottic edema or laryngo-tracheomalacia
      b. Treatment options
         (1) FiO_2/humidity
         (2) CPAP
         (3) Inhalational sympathomimetics (e.g., racemic epinephrine)
         (4) Corticosteroids
      c. If persistent, consider reintubation or airway evaluation (Chap. 26).
      d. Subglottic stenosis may require tracheostomy (Chap. 2).

6. Methylxanthines
   a. Some studies have suggested efficacy in the peri-extubation setting.
   b. Duration of treatment 24–96 h (longer if respiratory control irregularities occur).
7. Ongoing assessments
   a. Blood gas assessment. Assure adequate gas exchange.
   b. Chest radiograph. Not routinely necessary unless clinical evidence of respiratory distress.
   c. Weight gain. If inadequate, may indicate excessive caloric expenditure for respiratory work.

Suggested Reading

Balsan MJ, Jones JG, Watchko JF, Guthrie RD. Measurements of pulmonary mechanics prior to the elective extubation of neonates. Pediatr Pulmonol. 1990;9:238–43.

Barrington KJ, Finer NN. A randomized, controlled trial of aminophylline in ventilatory weaning of premature infants. Crit Care Med. 1993;21:846–50.

Baumeister BL, El-Khatib M, Smith PG, Blumer JL. Evaluation of predictors of weaning from mechanical ventilation in pediatric patients. Pediatr Pulmonol. 1997;24:344–52.

Bernstein G, Mannino FL, Heldt GP, et al. Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. J Pediatr. 1996;128:453–63.

Chan V, Greenough A. Comparison of weaning by patient triggered ventilation or synchronous intermittent mandatory ventilation in preterm infants. Acta Paediatr. 1994;83:335–7.

Davis P, Jankow R, Doyle L, Henschke P. Randomised, controlled trial of nasal continuous positive pressure in the extubation of infants weighing 600 to 1250 g. Arch Dis Child. 1998;79:F54–7.

Dimitriou G, Greenough A, Laubscher B. Lung volume measurements immediately after extubation by prediction of "extubation failure" in premature infants. Pediatr Pulmonol. 1996;21:250–4.

Donn SM, Sinha SK. Controversies in patient-triggered ventilation. Clin Perinatol. 1998;25:49–61.

El-Khatib MF, Baumeister B, Smith PG, et al. Inspiratory pressure/maximal inspiratory pressure: does it predict successful extubation in critically ill infants and children? Intensive Care Med. 1996;22:264–8.

Fiastro JF, Habib MP, Quan SF. Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest. 1988;93:499–505.

Gillespie LM, White SD, Sinha SK, Donn SM. Usefulness of the minute ventilation test in predicting successful extubation in newborn infants: a randomized clinical trial. J Perinatol. 2003;23:205–7.

Gupta S, Sinha S, Tin W, Donn SM. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus infant flow driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. J Pediatr. 2009;154:645–50.

McIntyre NR, Leatherman NE. Mechanical loads on the ventilatory muscles. Am Rev Respir Dis. 1989;139:968–72.

Robertson NJ, Hamilton PA. Randomised trial of elective continuous positive airway pressure (CPAP) compared with rescue CPAP after extubation. Arch Dis Child. 1998;79:F58–60.

Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W, Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354(20):2112–21.

Sheth RD, Pryse-Phillips WEM, Riggs JE, Bodensteiner JB. Critical illness neuromuscular disease in children manifested as ventilator dependence. J Pediatr. 1995;126:259–61.

Sillos EM, Veber M, Schulman M, et al. Characteristics associated with successful weaning in ventilator-dependent preterm infants. Am J Perinatol. 1992;9:374–7.

Sinha SK, Donn SM. Weaning newborns from mechanical ventilation. Semin Neonatol. 2002;7:421–8.

Sinha SK, Donn SM. Difficult extubation in babies receiving assisted mechanical ventilation. Arch Dis Child Educ Pract Ed. 2006;91:ep42–6.

Sinha SK, Donn SM, Gavey J, McCarty M. A randomised trial of volume-controlled versus time-cycled, pressure-limited ventilation in preterm infants with respiratory distress syndrome. Arch Dis Child. 1997;77:F202–5.

Tapia JL, Cancalari A, Gonzales A, Mercado ME. Does continuous positive airway pressure (CPAP) during weaning from intermittent mandatory ventilation in very low birth weight infants have risks or benefits? A controlled trial. Pediatr Pulmonol. 1995;19:269–74.

Veness-Meehan KA, Richter S, Davis JM. Pulmonary function testing prior to extubation in infants with respiratory distress syndrome. Pediatr Pulmonol. 1990;9:2–6.

Wilson Jr BJ, Becker MA, Linton ME, Donn SM. Spontaneous minute ventilation predict readiness for extubation in mechanically ventilated preterm infants? J Perinatol. 1998;18:436–9.

Section XI

Bronchopulmonary Dysplasia

Etiology and Pathogenesis

79

Alexandra M. Smith and Jonathan M. Davis

I. Introduction
   A. Bronchopulmonary Dysplasia (BPD) is a form of chronic lung disease that develops in newborns treated with oxygen and mechanical ventilation for a primary lung disorder, most often respiratory distress syndrome (RDS). BPD remains the most prevalent and one of the most serious long-term sequalae of prematurity, affecting approximately 14,000 preterm infants born in the USA each year.
   B. There are many health consequences of BPD, including asthma, pulmonary hypertension, failure to thrive, cognitive impairment, and neurodevelopmental deficits. There is a higher incidence of postnatal mortality and frequent re-hospitalizations in infants with BPD.

II. Definition
   A. BPD has generally been defined using a combination of characteristics such as the presence of chronic respiratory signs, a persistent oxygen requirement, and/or an abnormal chest radiograph at either 28 days of life or 36 weeks' postmenstrual age (PMA). As clinical management of these infants improves and younger and smaller infants survive, the characteristics of BPD have also changed. These definitions of BPD unfortunately lack specificity and fail to account for important clinical distinctions related to extremes of prematurity. They also lack standardization, given the wide variability in criteria for the use of prolonged oxygen therapy.
   B. A consensus conference of the National Institutes of Health in 2000 suggested a definition of BPD that incorporates many elements of previous definitions and attempts to categorize the severity of the disease process (Table 79.1). This severity-based definition correlates weakly (but better) with adverse long-term pulmonary and neurodevelopmental outcomes compared to prior definitions, which showed no significant correlation.
   C. To further standardize the definition of BPD, a physiologic assessment of the need for oxygen at 36 weeks' PMA has been proposed; this definition utilizes an oxygen reduction test. BPD is then defined as the inability to maintain $SpO_2 > 90\%$ when challenged with 21 % oxygen.

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Table 79.1 NIH consensus conference: diagnostic criteria for establishing BPD

Gestational age	<32 weeks	>32 weeks
Time point of assessment	36 weeks' PMA or discharge to home, whichever comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
Treatment with oxygen >21 % for at least 28 days		
Mild BPD	Breathing room air at 36 weeks' PMA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need for <30 % O_2 at 36 weeks PMA or discharge, whichever comes first	Need for <30 % O_2 to 56 days postnatal or discharge, whichever comes first
Severe BPD	Need for >30 % O_2 +/− PPV or NCPAP at 36 weeks PMA or discharge, whichever comes first	Need for >30 % O_2 +/− PPV or CPAP at 56 days postnatal age or discharge, whichever comes first

PMA postmenstrual age, *PPV* positive pressure ventilation, *NCPAP* nasal continuous positive airway pressure

Despite these approaches, there is increasing evidence that a diagnosis of BPD may not accurately predict which infants will develop chronic respiratory morbidity (asthma, repeated respiratory infections, need for medication use, and hospital readmissions) later in life.

III. Incidence
   A. Incidence depends on the definition used and the gestational age of the population studied. While surfactant treatment has improved overall survival for premature infants, the incidence of BPD remains approximately 30–40 % (inversely proportional to gestational age at birth). With the use of standardized oxygen saturation monitoring involved in the physiologic definition, the incidence might be further decreased by about 10 %.
   B. Using the NICHD severity-based definition of BPD, the incidence of severe BPD is 39 % for babies born at 23 weeks' gestation, 26 % for those born at 25 weeks' gestation, 17 % for those born at 26 weeks' gestation, and 8 % for those born at 28 weeks' gestation. The incidence of mild BPD shows a similar decrease from 26 % to 16 % as gestational age increases.
   C. Demographic factors linked to BPD include: gestational age, lower birth weight, male sex, white race, a family history of asthma, and impaired growth for gestational age.

IV. Pathogenesis (Fig. 79.1)
   A. Ventilator Induced Lung Injury (VILI)
      1. Use of mechanical ventilation to establish functional residual capacity (FRC) in a surfactant deficient lung can alter fluid balance and increase endothelial and epithelial cell permeability, causing lung injury.
      2. "Low-volume injury zone" predisposes an atelectatic lung to shear stress, while the use of high tidal volumes (>6 mL/kg) may cause volutrauma in the "high-volume injury zone." Preterm infants are more prone to volutrauma because their compliant chest wall allows uncontrolled expansion. Shear stress, in combination with other pro-inflammatory mediators, can lead to an increase in lung elastase and protease activity that is released from cellular and matrix stores. This leads to remodeling of the extracellular matrix which contributes to disrupted alveolar and capillary development.
      3. VILI contributes to a cascade of inflammation and cytokine release, further amplifying the lung injury process. Elevated levels of cytokines and chemokines such as IL-8, IL-1β, IL-6, and TNF-α, monocyte chemo-attractant proteins, and macrophage inflammatory proteins are seen in serum and tracheal aspirates of infants with BPD, as well as decreased expression of the anti-inflammatory IL-10. These factors cause the recruitment and migration of inflammatory cells and the release of enzymes that cause tissue damage, apoptosis, and cell signaling dysregulation which ultimately leads to the final common pathway of disrupted alveolar and vascular development.

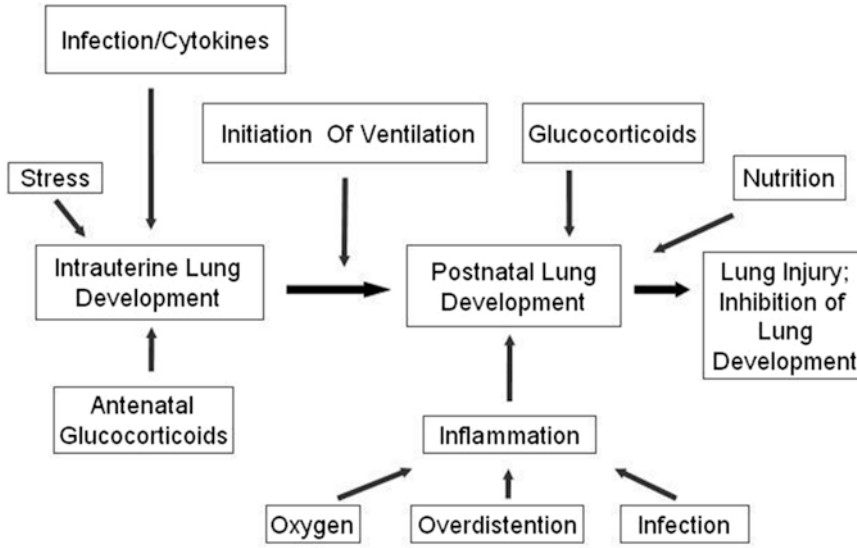

Fig. 79.1 Pathogenesis of BPD

4. Non-invasive ventilation, especially in the form of CPAP started immediately after birth, may be an optimal approach to establishing and maintaining FRC while avoiding some of the risks associated with invasive mechanical ventilation. Infants in the SUPPORT (Surfactant Positive Pressure and Oximetry Randomized Trial) study who were randomized to the CPAP arm had decreased respiratory morbidities at 18–22 months compared to the intubation/surfactant arm. Centers that use more mechanical ventilation for longer periods of time often have higher rates of BPD.

B. Oxygen/Antioxidants (Chap. 7)
1. Oxidative lung injury has been increasingly recognized as an important causative factor in the development of BPD. Many animal studies have suggested that hyperoxia may be the most important trigger for the pathologic changes seen in BPD, resulting in an increased release of reactive oxygen species (ROS), inflammatory mediators, and proteolytic enzymes that are thought to lead to the pathophysiologic changes characteristic of BPD. Hyperoxia, in combination with mechanical ventilation, can also lead to a disruption of growth factors which results in disrupted alveolarization and vascular growth.
2. Under normal conditions, a delicate balance exists between the production of ROS and the antioxidant defenses that protect cells in vivo. Increased generation of ROS can occur secondary to hyperoxia, reperfusion, or inflammation. In addition, ROS can increase injury because of inadequate antioxidant defenses.
3. The premature newborn may be more susceptible to ROS-induced injury since antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase (which develop at a rate similar to pulmonary surfactant), may be relatively deficient at birth and are not induced secondary to an ROS challenge.
4. ROS also have potent pro-inflammatory effects in the lung and facilitate bacterial adherence to epithelial cells while impairing mononuclear cell function.

C. Inflammation

1. There is controversy whether antenatal infection and inflammation (chorioamnionitis/funisitis) are risk factors for BPD. The majority of studies suggest that the presence of inflammation in the chorionic plate or the umbilical cord is not associated with the development of BPD. Some animal studies suggest that prenatal exposure to chorioamnionitis may protect against BPD triggered by postnatal infection/inflammation. However, there is some evidence that levels of IL-6, IL-1β, and IL-8 in amniotic fluid are greater in those who develop BPD than in those who do not. When cord blood is analyzed in infants exposed to chorioamnionitis compared to those who develop BPD, there is an increased circulating pro-inflammatory CD4+ T cell population seen in those exposed to chorioamnionitis, while those who go on to develop BPD have decreased CD4+ cells and a trend towards a decrease in the number of regulatory T cells. Although this provides evidence that there may be a distinct immune profile between the two groups, it does not support a direct causal relationship.
2. Mechanism: Early elevations of ROS and cytokines (IL-6 and IL-8), followed by neutrophil/mononuclear cell influx and increased protease/anti-protease imbalance, leading to decreased endothelial cell integrity, pulmonary edema, and exudate.
    a. The consequence of exaggerated neutrophil recruitment to the neonatal lung can be severe. Proteases and ROS generated by these cells can indiscriminately damage healthy local tissue, leading to simplification and enlargement of alveolar structures, which is a notable feature of the "new BPD." Altered vascular endothelial growth factor (VEGF) expression is also thought to contribute to the process of alveolar simplification through vascular remodeling.
    b. The process of programmed apoptotic cell death is dysregulated. This leads to a prolonged survival of neonatal neutrophils and exacerbation of the pro-inflammatory process. It also leads to abnormal growth of the lung that is characteristic of BPD.

D. Infection
1. A large body of evidence suggests that intrauterine infection and the resulting fetal inflammatory response primes the lung for further injury upon exposure to postnatal infection, mechanical ventilation, oxygen (even room air is supraphysiologic), and abnormal blood flow through a patent ductus arteriosus (PDA).
2. *Ureaplasma urealyticum* has been implicated in the pathogenesis of preterm birth as well as higher cord levels of IL-6, IL-1α, and IL-1β. These pro-inflammatory mediators cause lung microvascular injury, decreased VEGF production, reduced nitric oxide synthase activity, smooth muscle proliferation, and an arrest in alveolar septation, predisposing these infants to BPD. A recent systematic review and meta-analysis suggests that prophylactic administration of macrolides or treatment with macrolides in *Ureaplasma*-positive patients does not significantly reduce the rates of BPD. However, prophylactic azithromycin was associated with a significant reduction in BPD. Further research is needed before this therapy is introduced into routine clinical practice.

E. Nutrition
1. Poor caloric intake during a respiratory illness may result in respiratory muscle fatigue and a longer duration of mechanical ventilation. In one case-controlled study, infants who developed BPD had lower mean energy intakes than matched controls.
2. Vitamin A derivatives are critical in regulation of growth and differentiation of lung epithelial cells. In animals, deficiency of vitamin A results in abnormal lung growth following prolonged exposure to hyperoxia. Preterm infants have lower levels of vitamin A, which has been associated with the development of BPD. Although trials of vitamin A supple-

mentation appear to reduce BPD to a small degree, longer term studies show no benefit in decreasing respiratory morbidity at 1 year corrected gestational age.

3. Trace elements such as copper, zinc, and selenium are vital to the functioning of antioxidant enzymes that may play a role in lung protection from inflammatory insults. Infants deficient in these trace elements may be at a higher risk for developing BPD.

F. Fluids/Patent Ductus Arteriosus
   1. Pulmonary edema, both alveolar and interstitial, has been associated with the development of BPD. A large retrospective study showed that the incidence of BPD and/or death was significantly lower in extremely preterm infants if they lost weight in the first 10 days of life. In contrast, the longer a hemodynamically significant PDA remains (especially after 4 weeks of age), the higher the incidence of BPD.
   2. Meta-analyses of trials using diuretics have demonstrated improvements in short-term pulmonary mechanics, but failed to demonstrate a reduction in the overall incidence of BPD.
   3. Adverse effects of a PDA on respiratory status have been reported, including the need for prolonged respiratory support. The mechanism is thought to be similar to that of fluid overload, as well as histopathologic changes in the vascular network, resulting in hypertrophy of the medial smooth muscle layer leading to increased pulmonary arterial pressure.
   4. Infection can reopen the ductus arteriosus and prolong PDA closure, likely through the actions of prostaglandins and pro-inflammatory cytokines. Infection in the presence of a PDA can significantly increase the incidence and severity of BPD.
   5. It is important to note that despite the evidence of a PDA playing an important role in the development of BPD, early and aggressive closure has not impacted the incidence of BPD at all.

G. Genetics
   1. Given the broad phenotypic range of BPD within the population of premature infants, it is likely that there is a genetic component to the susceptibility to disease.
   2. A recent study from northern Finland and Canada showed no relationship between genes encoding IL-6 and its receptors, IL-10, TNF, or the glucocorticoid receptor and the development of moderate to severe BPD.
   3. A recent study suggests that variants of nuclear factor erythroid-2 related factor-2 dependent antioxidant response elements, which regulate the protective responsive to oxidative stress, may contribute to the development of BPD in high risk preterm infants.
   4. Exome sequencing of neonatal blood spots has revealed candidate genes that appear to be associated with BPD. As these techniques become less expensive, further analyses may provide important new information on the role of genetic susceptibility in BPD.
   5. There is much further work to be done to investigate the role of genetics in the development and phenotype of BPD.

IV. Pathophysiologic Changes

A. Radiographic aspects: the radiographic appearance of BPD has changed with time, and cystic changes in particular are less common. A computerized tomography (CT) scoring system exists, with three key elements being hyper-expansion, emphysema (only as bullae and blebs), and fibrous interstitial changes (including sub-pleural triangular densities). A significant relationship has been found between the CT score and duration of oxygen therapy and mechanical ventilation.

B. Pulmonary mechanics

1. Tachypnea and shallow breathing increase dead space ventilation. Non-uniform damage to the lungs results in worsening ventilation–perfusion (V/Q) mismatch.
2. Lung compliance is markedly decreased, even in those infants who no longer need oxygen therapy. The reduction in compliance results from a variety of factors, including interstitial fibrosis, airway narrowing, edema, and atelectasis.
3. Increased airway resistance is seen, with significant flow limitations especially at low lung volumes.
4. FRC is often reduced in the early stages of BPD because of atelectasis. However, during later stages of BPD, gas trapping and hyperinflation can result in increased FRC.
5. Pulmonary circulation changes include smooth muscle cell proliferation of the pulmonary arteries and incorporation of fibroblasts into the vessel walls, both contributing to high pulmonary vascular resistance. Abnormal vasoreactivity and early injury to the pulmonary circulation lead to pulmonary hypertension, which contributes significantly to the mortality and morbidity of BPD.
6. Airway pathologic changes include patchy loss of cilia from columnar epithelial cells, mucosal edema and/or necrosis (focal or diffuse), infiltration of inflammatory cells, and granulation tissue at the area of the endotracheal tube.
7. Alveolar pathologic changes include early interstitial and alveolar edema, followed by atelectasis, inflammation, exudates, and fibroblast proliferation. Alveolar simplification and failure of secondary alveolar crests to form alveoli reduce surface area for gas exchange.

Suggested Reading

Bry K, Hogmalm A, Backstrom E. Mechanisms of inflammatory lung injury in the neonate: lessons from a transgenic mouse model of bronchopulmonary dysplasia. Semin Perinatol. 2010;34:211–21.

Chakrabarty M, McGreal EP, Kotecha S. Acute lung injury in preterm newborn infants: mechanism and management. Pediatr Respir Rev. 2010;11:162–70.

Choi CW, Lee J, Oh JY, et al. Protective effect of chorioamnionitis on the development of bronchopulmonary dysplasia triggered by postnatal systemic inflammation in neonatal rats. Pediatr Res. 2016;79(2):287–94. doi:10.1038/pr.2015.224.

Davis JM, Auten RL. Maturation of the antioxidant system and the effects on preterm birth. Semin Fetal Neonatal Med. 2010;15:191–5.

Davis JM, Rosenfeld W. Bronchopulmonary dysplasia. In: Avery GB, Fletcher MA, MacDonald MG, editors. Textbook of neonatology. 7th ed. Philadelphia: JB Lippincott; 2015.

Davis JM, Rosenfeld WN, Sanders RJ, Gonenne A. The prophylactic effects of human recombinant superoxide dismutase in neonatal lung injury. J Appl Physiol. 1993;74:22–34.

Davis JM, Parad RB, Michele T, et al. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant CuZn superoxide dismutase. Pediatrics. 2003;111:469–76.

Ehrenkranz RA, Walsch MC, Vohr BR, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005;116: 1353–60.

Huusko JM, Karjalainen MK, Mahlman M. A study of genes encoding cytokines (IL6, IL10, TNF), cytokine receptors (IL6R, IL6ST), and glucocorticoid receptor (NR3C1) and susceptibility to bronchopulmonary dysplasia. BMC Med Genet. 2014;15:120.

Jobe AH. The new BPD: an arrest of lung development. Pediatr Res. 1999;46:641–3.

Kinsella JP, Greenough A, Abman SA. Bronchopulmonary dysplasia. Lancet. 2006;367:1421–31.

Li J, Yu KH, Oehlert J, et al. Exome sequencing of neonatal blood spots and the identification of genes implicated in bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2015;192:589–96.

Merritt TA, Demming DD, Boyton BR. The 'new' bronchopulmonary dysplasia: challenges and commentary. Semin Fetal Neonatal Med. 2009;14:345–57.

Misra RS, Shah S, Fowell DJ, et al. Preterm cord blood CD4+ T cells exhibit increased IL-6 production in chorioamnionitis and decreased CD4+ T cells in bronchopulmonary dysplasia. Hum Immunol. 2015;76:329–38.

Munshi UK, Niu JO, Siddiq MM, Parton LA. Elevation of interleukin-8 and interleukin-6 precedes the influx of neutrophils in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. Pediatr Pulmonol. 1997;24:331–6.

Nair V, Loganathan P, Soraisham AS. Azithromycin and other macrolides for prevention of bronchopulmonary dysplasia: a systematic review and meta-analysis. Neonatology. 2014;106:337–47.

Niedermaier S, Hilgendorff A. Bronchopulmonary dysplasia—an overview about pathophysiologic concepts. Mol Cell Pediatr. 2015;2:2.

Parad RB, Davis JM, Lo J, et al. Prediction of respiratory outcome in extremely low gestational age infants. Neonatology. 2015;107:241–8.

Poindexter BB, Feng R, Schmidt B, et al. Comparisons and limitations of current definitions of bronchopulmonary dysplasia for the prematurity and respiratory outcomes program. Ann Am Thorac Soc. 2015;12(12):1822–30.

Speer CP. Inflammation and bronchopulmonary dysplasia: a continuing story. Semin Fetal Neonatal Med. 2006;11:354–62.

Stampath V, Garland JS, Helbling D, et al. Antioxidant response genes sequence variants and BPD susceptibility in VLBW infants. Pediatr Res. 2015;77: 477–83.

Stevens TP, Finer NN, Waldemar AC, et al. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). J Pediatr. 2014;165: 240–9.

Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. Pediatrics. 2010;126:443–56.

Van Marter LJ. Epidemiology of bronchopulmonary dysplasia. Semin Fetal Neonatal Med. 2009;14:358–66.

Walsh MC, Yao Q, Gettner P, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004;114:1305–11.

Wilson AC. What does imaging the chest tells us about bronchopulmonary dysplasia? Pediatr Respir Rev. 2010;11: 158–61.

Bronchopulmonary Dysplasia: Clinical Management

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I. The management of the infant with BPD is aimed at maintaining adequate gas exchange while at the same time limiting the progression of the lung damage. The challenge is that the supplemental oxygen and mechanical ventilation needed to maintain gas exchange are some of the key factors implicated in the pathogenesis of the lung damage (Chap. 79).
II. Oxygen Therapy
   A. Reduce the FiO_2 as quickly as possible to avoid oxygen toxicity, while maintaining the arterial SpO_2 or PaO_2 at a level sufficient to ensure adequate tissue oxygenation and avoid pulmonary hypertension and cor pulmonale.
   B. There is no sufficient information to recommend a specific range of oxygen saturation, but there is sufficient evidence that SpO_2 values above 95 % and PaO_2 above 70 Torr are associated with a higher incidence of ROP and worse respiratory outcome, while $SpO_2 < 89$ % may be associated with increased NEC and morality. Because of this, it is advisable to maintain oxygen saturation between 90 and 95 % or the PaO_2 between 50 and 70 Torr to minimize the detrimental effects of hypo- and hyperoxemia. After extubation, oxygen can be administered through nasal CPAP, a hood, or a nasal cannula. Patients with severe BPD are commonly discharged home with oxygen therapy.
   C. Adequacy of gas exchange is monitored by blood gas levels.
      1. Blood gas determinations obtained by arterial puncture or capillary sampling may not be reliable because the infant responds to pain with crying or apnea.
      2. Transcutaneous PO_2 measurements may also be inaccurate in these infants and they frequently underestimate the true PaO_2.
   D. Pulse oximeters offer the most reliable estimate of arterial oxygenation in these infants and are simple to use and provide continuous information during different behavioral states.
   E. It is important to maintain a relatively normal blood hemoglobin concentration. This can be accomplished with blood transfusions or by the administration of recombinant erythropoietin. However, limiting the amount of blood taken for laboratory tests is the most effective and safest measure to prevent anemia.

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III. Mechanical Ventilation
   A. Use the lowest settings necessary to maintain satisfactory gas exchange, and limit the duration of mechanical respiratory support to a minimum.
   B. Use the lowest peak airway pressure to deliver adequate tidal volumes. Infants with BPD may require slightly higher tidal volumes (5–8 mL/kg) to achieve adequate alveolar ventilation.
   C. Use inspiratory times between 0.4 and 0.6 s.
      1. Shorter inspiratory times and high flow rates may exaggerate maldistribution of the inspired gas.
      2. Longer inspiratory times may increase the risk of alveolar rupture and of negative cardiovascular side effects.
      3. Pay attention to the time constant (Chap. 9) and watch closely for evidence of gas trapping (Chap. 22).
   D. Adjust end-expiratory pressure between 4 and 8 cm H_2O so that the lowest oxygen concentration necessary to keep SpO_2 above 90% (PaO_2 above 50 Torr) is used. Higher PEEP levels (6–8 cm H_2O) may help reduce expiratory airway resistance and can improve alveolar ventilation in infants with unstable airways and severe obstruction.
   E. Limit the duration of mechanical ventilation as much as possible to reduce the progression of ventilator-induced lung injury and infection.
   F. Weaning from mechanical ventilation must be accomplished gradually, by reducing peak inspiratory pressures below 15–18 cm H_2O and FiO_2 to less than 0.3–0.5.
   G. Reduce ventilator rate gradually to 10–15 breaths per minute to allow the infant to perform an increasing proportion of the work of breathing.
   H. The use of patient triggered ventilation, volume targeted ventilation, and pressure support of the spontaneous breaths can accelerate weaning and reduce the total duration of mechanical ventilation.
   I. During weaning from CMV it may be necessary to increase the FiO_2 to maintain adequate oxygen saturation levels.
   J. Concurrently, the $PaCO_2$ may rise above baseline values during weaning. As long as the pH is within acceptable range, hypercapnia should be tolerated to wean these patients from the ventilator.
   K. Aminophylline or caffeine can be used as respiratory stimulants during the weaning phase. Caffeine administration prior to extubation can reduce the duration of CMV and the incidence of BPD.
   L. When the patient is able to maintain acceptable blood gas levels for several hours on low ventilator settings (RR 10–15 breaths/min, PIP 12–15 cm H_2O, $FiO_2 < 0.3–0.4$), extubation should be attempted.
   M. After extubation, it may be necessary to provide chest physiotherapy to facilitate clearance of secretions and prevent airway obstruction and lung collapse.
   N. In smaller infants, nasal CPAP 6–8 cm H_2O or nasal IPPV (Chap. 32) can stabilize respiratory function and reduce the need for re-intubation and mechanical ventilation.

IV. Fluid Management
   A. Infants with BPD tolerate excessive fluid intake poorly and tend to accumulate water in their lungs, and this excess fluid contributes to their poor lung function.
   B. Water and salt intake must be limited to the minimum required to provide the necessary fluid intake and calories to cover for their metabolic needs and growth.
   C. If pulmonary edema persists despite fluid restriction, short-term diuretic therapy can be used successfully to clear excessive water. The use of diuretics can produce a rapid

improvement in lung compliance and decrease in resistance, but blood gases do not always show improvement. There is, however, no evidence at present to support the chronic use of diuretics in these patients.

D. Chronic use of loop diuretics is frequently associated with hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hypercalciuria with nephrocalcinosis and nephrolithiasis, and hearing loss. Some of these side effects may be reduced by using furosemide on alternate-days.

E. Because of the side effects and the lack of evidence that prolonged use of diuretics changes the incidence or severity of BPD, this therapy is not recommended for routine use and is only indicated for acute episodes of deterioration associated with pulmonary edema.

F. Distal tubular diuretics such as thiazides and spironolactone are also used in infants with BPD, but the improvement in lung function with these diuretics is less consistent than with proximal loop diuretics. Side effects such as nephrocalcinosis and hearing loss may be less frequent than with furosemide, and for this reason these diuretics can be used in infants with established BPD who require more prolonged diuretic therapy. However, evidence of long-term efficacy is lacking.

V. Bronchodilators

A. Infants with severe BPD frequently have airway smooth muscle hypertrophy and airway hyper-reactivity.

B. Because hypoxia can increase airway resistance in these patients, maintenance of adequate oxygenation is important to avoid bronchoconstriction.

C. Inhaled bronchodilators including β-agonists such as isoproterenol, salbutamol, metaproterenol, and isoetharine, and anticholinergic agents such as atropine and ipratropium bromide can reduce airway resistance in some infants with BPD. Their effect is short lived, and their use can be associated with cardiovascular side effects such as tachycardia, hypertension, and arrhythmias. Chronic use is not supported by evidence.

D. Methylxanthines also have been shown to reduce airway resistance in these infants.

1. These drugs have other potential beneficial effects, such as respiratory stimulation and mild diuretic effect, and aminophylline may also improve respiratory muscle contractility.
2. These drugs must also be used with caution because of their multiple side effects.

E. There is no evidence that prolonged use of bronchodilators changes the course of infants with BPD and for this reason their use should be limited to episodes of acute exacerbation of airway obstruction. When indicated, ß agonists are given by inhalation using a nebulizer or a space inhaler connected to a mask or head chamber or inserted in the inspiratory side of the ventilator circuit.

VI. Corticosteroids

A. Many studies have shown rapid improvement in lung function after systemic administration of steroids, facilitating weaning from the ventilator, and a reduction in BPD. Steroids can enhance production of surfactant and antioxidant enzymes, decrease bronchospasm, decrease pulmonary and bronchial edema and fibrosis, and improve vitamin A status. The main effect is from their anti-inflammatory properties, decreasing the response of inflammatory cells and mediators in the injured lung.

B. Potential complications of prolonged steroid therapy include masking the signs of infection, arterial hypertension, hyperglycemia, increased proteolysis, adrenocortical suppression, intestinal perforation, somatic and lung growth suppression, and hypertrophic cardiomyopathy. Of more concern is the fact that long-term follow-up studies showed that infants who received prolonged steroid therapy have worse neurologic outcome, including an increased incidence of cerebral palsy.

C. Because of the seriousness of the neurologic side effects, specifically when systemic steroids are used early after birth, the use of systemic steroids should only be considered after the first 2 weeks of life in infants who show clear evidence of severe and progressive pulmonary damage and who remain oxygen and ventilator dependent.
D. The duration of steroid therapy must be limited to the minimum necessary to achieve the desired effects, usually 5–7 days, and following the recommendation of the American Academy of Pediatrics, the benefits and potential side effects should be discussed with the family before initiating this therapy.
E. Steroids can also be administered by nebulization to ventilator-dependent infants. Inhaled steroids may reduce the need for systemic steroids, reducing the side effects associated with prolonged systemic therapy, but data on effectiveness of topical steroids are not conclusive enough to recommend their routine use.

VII. Nutrition (Chap. 57)

VIII. Pulmonary Vasodilators
A. Because pulmonary vascular resistance is extremely sensitive to changes in alveolar PO_2 in infants with BPD, it is important to assure normal oxygenation at all times.
B. In infants with severe pulmonary hypertension and cor pulmonale, the calcium channel blocker nifedipine has been shown to decrease pulmonary vascular resistance.
1. This drug is also a systemic vasodilator and can produce a depression of myocardial contractility.
2. Its safety and long-term efficacy in these infants have not been established.
C. Inhaled nitric oxide has been administered to infants with BPD in an attempt to improve outcome.
1. Nitric oxide can improve V/Q matching, reduce pulmonary vascular resistance, and reduce inflammation.
2. Although iNO has been shown to improve oxygenation in some infants with BPD, there is no clear evidence that this therapy improves long-term outcome, and it is used mainly during periods of acute exacerbation of the pulmonary hypertension. This use is off label.
D. Phosphodiesterase inhibitors (Sildenafil), Prostacyclin (Epoprostenol), and ET-1 antagonists are also potent pulmonary vasodilators that have been used successfully to treat pulmonary hypertension. There are case series of infants with BPD and pulmonary hypertension treated with sildenafil alone or in combination with other pulmonary vasodilators that have shown improvement of the pulmonary hypertension. However, there is limited information on the safety and effectiveness of these agents in infants with BPD and therefore ***they should be used with caution and close monitoring for potential side effects***.

Suggested Reading

AAP. Postnatal Corticosteroids to treat or prevent chronic lung disease in preterm infants. Pediatrics. 2002;109:330–8.
Aschner JL. New therapies for pulmonary hypertension in neonates and children. Pediatr Pulmonol Suppl. 2004;26:132–5.
Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med. 2003;349: 959–67.
Atkinson SA. Special nutritional needs of infants for prevention of and recovery from bronchopulmonary dysplasia. J Nutr. 2001;131:942S–6.
Bancalari E. Bronchopulmonary dysplasia. Semin Perinatol. 2003;8:1–92.
Brunton JA, Saigal S, Atkinson S. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. J Pediatr. 1998;133:340–5.

Buzzella B, Claure N, D'Ugard C, Bancalari E. A randomized controlled trial of two nasal continuous positive airway pressure levels after extubation in preterm infants. J Pediatr. 2014;164:46–51.
Cole CH, Colton T, Shah BL, et al. Early inhaled glucocorticoid therapy to prevent bronchopulmonary dysplasia. N Engl J Med. 1999;340:1005–10.
D'Angio CT, Maniscalco WM. Bronchopulmonary dysplasia in preterm infants: pathophysiology and management strategies. Paediatr Drugs. 2004;6:303–30.
Doyle LW, Ehrenkranz RA, Halliday HL. Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology. 2010;98:111–7.
Greenough A. Update on patient-triggered ventilation. Clin Perinatol. 2001;28:533–46.
Grier DG, Halliday HL. Corticosteroids in the prevention and management of BPD. Semin Neonatol. 2003;8:83–91.
Kao LC, Durand DJ, McCrea RC, et al. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. J Pediatr. 1994;124:772–81.
Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr. 2009;154(3):379–84.
O'Shea TM, Kothadia JM, Klinepeter KL, et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. Pediatrics. 1999;104:15–21.
Onland W, Offringa M, De Jaegere AP, van Kaam AH. Finding the optimal postnatal dexamethasone regimen for preterm infants at risk of bronchopulmonary dysplasia: a systematic review of placebo-controlled trials. Pediatrics. 2009;123:367–77.
Reyes Z, Tauscher M, Claure N. Randomized, controlled trial comparing pressure support (PS) + synchronized intermittent mandatory ventilation (SIMV) with SIMV in preterm infants. Pediatr Res. 2004;55:466A.
Schmidt B, Roberts R, Millar D, Kirpalani H. Evidence-based neonatal drug therapy for prevention of bronchopulmonary dysplasia in very-low-birth-weight infants. Neonatology. 2008;93:284–7.
Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010;126:443–56.
SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362(21):1970–9.
Tin W. Optimal oxygen saturation for preterm babies. Do we really know? Biol Neonate. 2004;85:319–25.
Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. N Engl J Med. 1999;340:1962–8.
Wardle AJ, Wardle R, Luyt K, et al. The utility of sildenafil in pulmonary hypertension: a focus on bronchopulmonary dysplasia. Arch Dis Child. 2013;98:613–7.
Watterberg KL, Committee on Fetus and Newborn. Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. Pediatrics. 2010;126:800–8.
Yeh TF, Lin YJ, Huang CC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics. 1998;101:e1–8.
Yeh TF, Lin YJ, Lin HC, et al. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. N Engl J Med. 2004;350: 1304–13.

Long-Term Outcomes of Newborns with Bronchopulmonary Dysplasia

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I. Introduction
   A. Bronchopulmonary dysplasia (BPD) is a complex disorder of the respiratory system affecting mostly preterm babies with an incidence of 30–40 % in Extremely Low Birth Weight (ELBW, <1000 g) and 50–70 % in babies <500 g. This complex disorder represents histological distortion of normal lung architecture by factors that cause lung injury and disruption of lung development as a consequence of mechanical ventilation and the underlying disease process.
   B. "*Old BPD*" as described by Northway et al. in 1967 was characterized by extensive inflammatory and fibrotic changes in airways and lung parenchyma. With improved survival of more immature infants, in part from the use of antenatal steroids, gentler ventilatory strategies, and surfactant therapy, a different pattern of this disorder, "*new BPD*" has evolved. This condition represents a developmental disorder of immature lungs unable to reach full structural complexity. This is characterized by alveolar arrest and disordered pulmonary vasculature and a smaller effective surface area resulting in diffusion abnormalities.

II. Neonatal Morbidity
   A. Very preterm infants are more prone to complications of prematurity such as nosocomial blood stream infections, ventilator-associated pneumonia, necrotizing enterocolitis (NEC), and growth failure. These comorbid factors trigger a systemic inflammatory response, adversely impacting the postnatal development of immature lungs contributing to the pathogenesis of BPD.
   B. Survivors with BPD are also more prone to other comorbidities such as IVH, PVL, and ROP; however, there is no direct causal relationship.

III. Long-term Outcomes
   A. Growth and development
      1. Nutrition (Chap. 57)
         a. Sicker neonates are less likely to be fed. Recent studies suggest that VLBW infants with poor enteral nutrition within the first 2 weeks of life were more likely to develop

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BPD. Infants with BPD have greater protein and energy requirements from increased work of breathing, poor lung compliance, hypoxic episodes, and infections. Chronic and episodic hypoxia are described in infants with BPD during feeding and sleep, contributing to growth failure. VLBW infants with all forms of BPD have been shown to have lower weight, length, and head circumference compared to VLBW infants without BPD. Infants with severe BPD appear to be more vulnerable to a negative growth outcome even when corrected for perinatal and demographic variables. Postnatal growth appears to be linked to improvement in respiratory function in childhood. Close monitoring of nutritional intake and supplemental oxygen therapy to avoid hypoxia post discharge is therefore recommended.

b. Recurrent illnesses, hospitalization, and increased metabolic demands associated with BPD also result in poor growth. However, after controlling for confounding factors, studies during childhood have not demonstrated significant differences in the growth of VLBW children with and without BPD.

c. Outcome in adult survivors with BPD (albeit a different population than today's NICU patients) is intricately linked to issues relating to low gestational age and weight with higher rates of many adverse health outcomes in early adulthood; however, the majority lead productive and healthy lives. Longer term studies are essential in evaluating the lifetime consequences of BPD and LBW on survivors.

2. Neurocognitive Development

a. Along with white matter abnormalities on cranial ultrasound scans in the neonatal period, BPD independently predicts adverse developmental outcome in early infancy.

(1) A volumetric magnetic resonance imaging study of preterm infants with BPD showed a uniform reduction in cerebral volume compared to a regional reduction in brain volume seen in preterm infants without BPD. The exact mechanism for this reduction in brain volume is unclear; however, it is likely that episodic hypoxemia, inflammatory stress, nutritional deprivation and drugs, notably postnatal steroids, may be contributory. This reduction in brain volume may correlate with functional deficits more frequently seen in survivors with BPD.

(2) Studies have also shown that patients with severe BPD have an increased incidence of neurodevelopmental disability at 6 and 12 months, which is less notable in mild to moderate BPD.

b. Motor development

(1) Abnormality of tone and movement affecting the limbs, neck, trunk, mouth, and tongue are seen in some infants with BPD. Significant improvement is expected by 2 years of age; however, some postural and balance differences persist into early childhood.

(2) The most common types of cerebral palsy phenotypes associated with BPD are quadriparesis and diparesis. These forms reflect diffuse, bilateral cerebral hemispheric disease in these infants. Recent studies have shown a greater incidence at 24 months of quadriplegia and diplegia in infants who require mechanical ventilation at 36 months' corrected gestational age but not hemiplegia.

(3) Cognitive and motor delay is more prevalent in preschoolers with BPD compared to VLBW peers without BPD.

(4) Cerebral palsy with impaired fine and gross motor function and poorer coordination is reported to be higher in VLBW children with BPD compared to non-BPD VLBW children.

(5) Visual–spatial perceptual deficits are noted in about 30 % of VLBW children with BPD on Visual Motor Integration testing. This deficit persists into adolescence and correlates with duration of oxygen therapy. A higher proportion of these children require occupational and physiotherapy support.

c. Neurosensory impairments
   (1) BPD independently predicts neurosensory impairment at 6 months of age. Beyond this age, PVL, severe ROP, and length of hospital stay are predictive of adverse neurosensory outcome.
   (2) Survivors with BPD who were treated with postnatal dexamethasone have shown a higher incidence of cerebral palsy and cognitive impairment compared to untreated BPD survivors.

d. Cognitive and academic consequences
   (1) Studies have demonstrated one-quarter to two-thirds of an SD lower IQ scores in VLBW infants with BPD compared to non-BPD-VLBW children at school age. Memory and learning difficulties are also more prevalent in these infants.
   (2) Attention deficit hyperactivity disorders (ADHD) are reportedly as high as 15 % in VLBW infants with BPD, twice as high compared to non-BPD VLBW children at school age. One study showed that 50 % of school age VLBW infants with BPD enrolled for speech and language therapy for difficulty with both expressive and receptive language skills, a similar percentage of preschool VLBW infants with BPD have needed special educational support with reading, spelling, and mathematics.
   (3) A recent study demonstrated that there was persistence of impaired cognitive functions in adult survivors with BPD. This study showed that this population displayed deficits in executive functioning even at a mean age of 24.2 years suggesting important implications for healthcare, social well-being, and cognitive rehabilitation.

B. Other systems
   1. Respiratory system
      a. Early childhood (0–5 years) hospital readmission rates, mainly from reactive airway disease, pneumonia, and RSV infections are higher in BPD infants in the first 2 years of life in comparison to term controls. Respiratory function testing shows substantial expiratory flow impairment with modest reduction in Total Lung Capacity (TLC), increase in Functional Residual Capacity (FRC), and increased Residual Volume (RV) to TLC ratio consistent with gas trapping. Studies have shown improvement in expiratory flow abnormalities in the first 2 years; however, chronic coughing, wheezing, and other asthma-like symptoms requiring use of inhaled bronchodilators is more common in comparison to term controls.
      b. At school age (6–18 years), children with BPD had poorer lung function and reduced exercise tolerance in comparison to non-BPD survivors of similar weight. Spirometry shows persisting reduction in Forced Expiratory Flow (FEV1); however, TLC and FRC were normal or only modestly reduced. RV/TLC ratio remained elevated suggestive of air trapping. High-resolution computed tomography (CT) of the chest of children with BPD showed areas of multifocal emphysema, atelectasis extending to the pleura, bronchial wall thickening, bullae, and air trapping. These finding suggest that children diagnosed with BPD are potentially at risk for developing COPD later in life from to the widespread involvement of the peripheral airways. Healthy lifestyle choices and avoidance of smoking should be advocated. A recent study from Norway

has however shown that 11 year olds born between 1999 and 2000 demonstrated improved pulmonary function compared to a 10-year older cohort. This suggests that improved neonatal care has not only increased survival, it has improved long-term pulmonary outcomes.

c. Adulthood: Restriction in FEV1 persists into adulthood and adult survivors with BPD are twice as likely to report wheezing and three times as likely to use asthma medications as full-term control subjects. Uncertainty remains about the respiratory consequences of BPD in later adult life (>40 years) with the potential for further decline in respiratory function, pulmonary hypertension, and development of COPD.

2. Cardiovascular system
   a. Pulmonary hypertension is reported in 18–37 % infants with moderate to severe BPD. Pulmonary hypertension contributes to both increased morbidity and mortality with a 2-year mortality rate of 33–48 %. Screening for pulmonary hypertension is recommended in infants with BPD
   b. Systemic hypertension is reported in about 12 % of infants with moderate to severe BPD. Approximately 50 % of cases require medical treatment.
3. Renal
   a. Nephrocalcinosis is reported in as many as 40 % of VLBW infants, more prevalent in babies with severe respiratory disease, acidosis, parenteral nutrition, and treatment (loop diuretics, methlyxanthines, and glucocorticoids) in the neonatal period.
   b. While up to 80 % resolve spontaneously in the first 2 years, the long-term consequence of this condition, previously thought to be benign, is unknown with presumed risk of long-term systemic hypertension. Long-term follow-up and predischarge renal ultrasound surveillance is advised.

IV. Summary
   A. BPD is a multisystem disorder with consequences beyond the neonatal period. Close attention to growth and development following discharge from neonatal units is essential in optimizing outcome.
   B. Long-term follow-up is recommended while longitudinal studies continue to fully evaluate the lifelong implications of this respiratory disease with multisystem involvement.

Suggested Reading

Baraldi E, Carraro S, Filippone M. Bronchopulmonary dysplasia: definitions and long-term respiratory outcome. Early Hum Dev. 2009;85(10 Suppl):S1–3.

Bhandari A, McGrath-Morrow S. Long-term pulmonary outcomes of patients with bronchopulmonary dysplasia. Semin Perinatol. 2013;37:132–7.

Doyle LW, Anderson PJ. Pulmonary and neurological follow-up of extremely preterm infants. Neonatology. 2010; 97:388–94.

El Mazloum D, Moschino L, Bozzetto S, Baraldi E. Chronic lung disease of prematurity: long-term respiratory outcome. Neonatology. 2014;105:352–6.

Gough A, Linden MA, Spence D, et al. Executive functioning deficits in young adult survivors of bronchopulmonary dysplasia. Disabil Rehabil. 2015;37(21):1940–5.

Islam JY, Keller RL, Aschner JL, et al. Understanding the short- and long-term respiratory outcomes of prematurity and bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2015;192:134–56.

Kobaly K, Schluchter M, Minich N, et al. Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. Pediatrics. 2008;121:73–81.

Northway Jr WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967;276:357–68.

Short EJ, Kirchner HL, Asaad GR, et al. Developmental sequelae in preterm infants having a diagnosis of bronchopulmonary dysplasia: analysis using a severity-based classification system. Arch Pediatr Adolesc Med. 2007;161:1082–7.

Van Marter LJ, Kuban KC, Allred E, et al. Does bronchopulmonary dysplasia contribute to the occurrence of cerebral palsy among infants born before 28 weeks of gestation? Arch Dis Child Fetal Neonatal Ed. 2011; 96(1):F20–9.

Vollsæter M, Skromme K, Satrell E, et al. Children born preterm at the turn of the millennium had better lung function than children born similarly preterm in the early 1990s. 2015; 10(12):e0144243. doi:10.1371/journal.pone.7.

Section XII

Complications Associated with Mechanical Ventilation

Thoracic Air Leaks

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Jennifer R. Bermick and Steven M. Donn

I. Description: Thoracic air leak refers to a collection of gas outside the pulmonary space. A variety of disorders are included in this category including pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema, pneumoperitoneum, and subcutaneous emphysema.
II. Incidence and Risk Factors: Estimates for the overall incidence of air leak in normal term infants range from 0.07 to 2 %. The incidence increases to 5–9 % in very low birth weight infants.
   A. The incidence of air leak varies depending on:
      1. Gestational age
      2. Degree of hypoxemia
      3. Resuscitation technique
      4. Concomitant respiratory disease
      5. Type and style of assisted ventilation
      6. Quality of radiographs and their interpretation
   B. The likelihood of pneumothorax being symptomatic without underlying lung disease is small and many go undetected.
   C. Several disease states increase the risk of pulmonary air leaks:
      1. Respiratory distress syndrome, incidence 5–30 % (reduced with intratracheal surfactant administration)
      2. Meconium aspiration syndrome, incidence 10–50 %
      3. Pneumonia
      4. Transient tachypnea of the newborn
      5. Pulmonary hypoplasia
      6. Congenital diaphragmatic hernia
III. Pathophysiology: Air leak syndromes arise by a common pathway that involves damage of the respiratory epithelium, usually by high transpulmonary pressures. Damaged epithelium allows air to enter the interstitium, causing pulmonary interstitial emphysema. With continued high

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transpulmonary pressures, air dissects toward the visceral pleura and/or hilum via peribronchial or perivascular spaces.

A. Pneumothorax results when the pleural surface is ruptured with air leaking into the pleural space.
B. Pneumomediastinum results when air, following the path of least resistance, dissects toward the hilum and enters the mediastinum.
C. Pneumopericardium results when air dissects into the pericardial space.
D. Subcutaneous emphysema occurs when air from the mediastinum egresses into the fascial planes of the neck and skin.
E. Pneumoperitoneum results from the dissection of retroperitoneal air, from pneumomediastinal decompression, into the peritoneum. (It can also occur from a ruptured abdominal viscus.)

IV. Air Leak Syndromes
  A. Pneumothorax often results from high inspiratory pressures, long inspiratory duration, and uneven ventilation.
    1. Etiology
      a. Spontaneous pneumothoraces are seen in up to 2 % of normal term infants around the time of birth, with only 10 % of these being symptomatic.
      b. Lung diseases including meconium aspiration syndrome, congenital bullae, pneumonia, and pulmonary hypoplasia result in uneven lung compliance and alveolar overdistention.
      c. Direct injury by suctioning through the endotracheal tube is a rare cause.
      d. Ventilatory support
        (1) Prolonged inspiratory time (*I*:*E* ratio greater than or equal to 1).
        (2) High mean airway pressure (>12 cm H_2O).
        (3) Low inspired gas temperature (<36.5 °C). This is especially true for infants weighing <1500 g and is thought to result from decreased mucociliary clearance precipitating airway obstruction at lower temperatures and lower humidity.
        (4) Poor patient–ventilator interaction resulting in dyssynchrony (i.e., infants who actively expire during part or all of the positive pressure plateau).
    2. Diagnosis is made using the combination of clinical signs, physical examination findings, arterial blood gases, transillumination, and radiography.
      a. Clinical signs of pneumothorax include those of respiratory distress, such as tachypnea, grunting, nasal flaring, and retractions. Cyanosis, decreased breath sounds over the affected side, chest asymmetry, episodes of apnea and bradycardia, shift in cardiac point of maximal impulse, and hypotension may also occur.
      b. Arterial blood gases may show respiratory or mixed acidosis and hypoxemia.
      c. Transillumination generally reveals increased transmission of light on the involved side.
      d. Chest radiography remains the gold standard for diagnosis of pneumothorax.
    3. Prevention
      a. Rapid rate ventilation (>60 bpm) may reduce active expiration, a precursor of pneumothorax. This is done in an attempt to provoke more synchronous respiration. High frequency ventilation may also provide better ventilation and oxygenation while decreasing the incidence of pneumothorax.
      b. Patient triggered ventilation reduces the incidence of air leak by synchronizing respiration. Using this mode of ventilation, the infant's respiratory efforts trigger the delivery of the positive pressure inflation. Flow-cycling enables complete synchronization, even in expiration.

c. Suppression of respiratory activity by patient sedation and/or paralysis may be an important means of preventing pneumothoraces in patients who are actively exhaling or "fighting" the ventilator.

4. Management
   a. Nitrogen washout is controversial, but can sometimes be an effective way of eliminating small pneumothoraces and alleviating respiratory distress.
      (1) Technique
         (a) Infant is placed in a 1.0 FiO_2 oxygen hood for 12–24 h.
         (b) Vital signs including oxygen saturation, heart rate, and blood pressure are continuously monitored.
      (2) Precautions
         (a) Should not be used in preterm infants.
         (b) Do not use if pneumothorax is under tension.
         (c) Exposure to high FiO_2 is not without risk.
   b. Needle aspiration can be used to treat a symptomatic pneumothorax. It is frequently curative in infants who are not mechanically ventilated and may be a temporizing treatment in infants who are mechanically ventilated.
      (1) Technique
         (a) Attach a 23-gauge butterfly needle to a 50 mL sterile syringe by a 3-way stopcock.
         (b) Locate the second or third intercostal space in the mid-clavicular line on the affected side.
         (c) Prepare the area with antiseptic solution.
         (d) Under sterile conditions, if possible, locate the intercostal space *above* the rib (to avoid lacerating intercostal vessels located on the inferior surface of the rib). Insert the needle through the skin and into the pleural space applying continuous suction with the syringe as the needle is inserted. A rush of air is usually experienced when the pleural space has been entered.
         (e) Once the pleural space has been entered, stop advancing needle to avoid the risk of puncturing the lung.
         (f) Apply slow, steady suction to the syringe until resistance is felt, indicating that no more air remains in the area surrounding the needle.
         (g) Air is evacuated from the syringe by turning the stopcock off to the infant and evacuating air from the side port.
         (h) Once all possible air is evacuated, the needle is removed and the site is dressed if necessary.
      (2) Potential complications
         (a) Infection
         (b) Laceration of intercostal vessels
         (c) Incomplete evacuation of air leak
         (d) Lung puncture
         (e) Damage to other intrathoracic structures (e.g., phrenic nerve, thoracic duct)
         (f) Recurrence of air leak
   c. Chest tube (thoracostomy) drainage is needed for continuous drainage of pneumothoraces that develop in infants receiving positive pressure ventilation as the air leak may be persistent under these conditions.
      (1) Straight chest tube technique; Fig. 82.1
         (a) Select a chest tube of appropriate size for the infant. For very small infants, 10 French chest tubes are adequate while for larger infants, 12 French chest tubes function better. Be sure the trocar is freely mobile inside the chest tube.

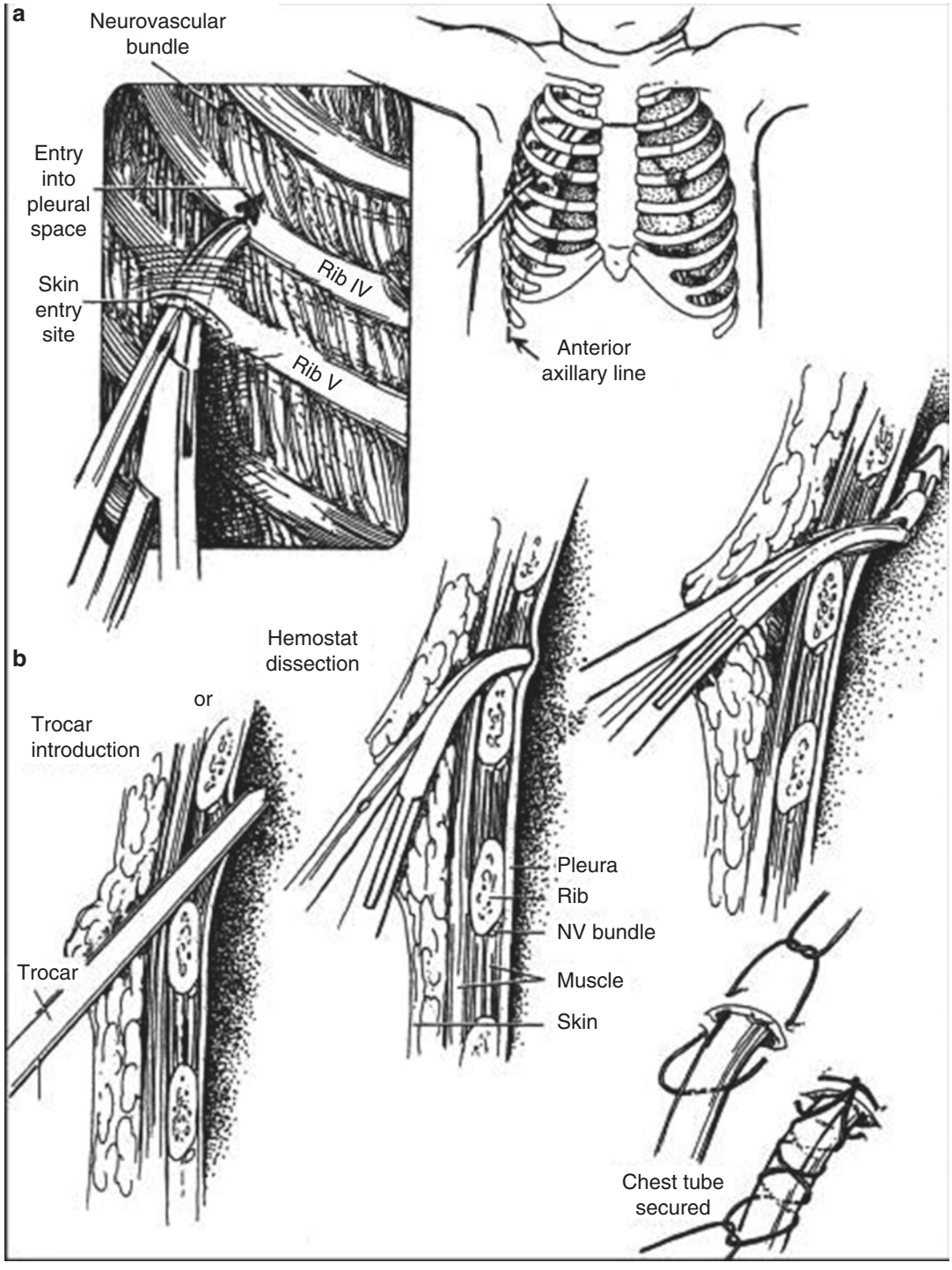

Fig. 82.1 Chest tube insertion in the newborn for pneumothorax. (**a**) Preferably, a small hemostat is inserted through a small incision in the anterior or midaxillary line and is tunneled upward, entering the chest above the next rib. The chest tube is inserted and secured with a suture ligature. Several knots should be placed after each circumferential pass of the thread to avoid any slippage. (**b**) A trocar can be used as an alternative method of tube insertion, as long as the trocar is withdrawn by a few millimeters within the tube; this technique allows easier guidance of the tube, for example, if it has to be placed posteriorly and inferiorly to drain an effusion

(b) Locate the fifth intercostal space in the anterior axillary line on the affected side.
(c) Prepare the site with antibacterial solution.
(d) Administer an analgesic to the patient.
(e) Cover the site with sterile drapes.
(f) Inject the area with a small amount of 1 % Lidocaine solution. Do not exceed 4 mg/kg.
(g) Make a small incision (approximately 1 cm) directly over the sixth rib. Avoid breast tissue and the nipple.
(h) With a curved hemostat, dissect the subcutaneous tissue above the rib. Make a subcutaneous track to the third or fourth intercostal spaces.
(i) Applying continuous, firm pressure, enter the pleural space with the closed hemostat. Widen the opening by spreading the tips of the hemostat.
(j) Carefully insert the chest tube. If a trocar is used, insert it to only 1.0–1.5 cm to avoid puncturing the lung. Advance the chest tube a few centimeters to desired location while withdrawing the trocar. The anterior pleural space is usually most effective for infants in a supine position. Be certain the side ports of the chest tube are within the pleural space. Vapor is usually observed in the chest tube if it is in the pleural space.
(k) Attach the chest tube to an underwater drainage system under low (−10 to −20 cm H_2O) continuous suction.
(l) Suture the chest tube in place and close the skin incision using 3-0 or 4-0 silk. The chest tube is best held in place with a "purse string" stitch encircling it. Taping to secure the tube is also recommended.
(m) Cover the area with sterile petrolatum gauze and a sterile, clear plastic surgical dressing.
(n) Confirm proper chest tube placement radiographically. If residual air remains, the chest tube may need to be readjusted, or a second tube placed until air is evacuated or no longer causing hemodynamic compromise.

(2) Pigtail Catheter Technique
(a) Less dissection required compared to straight chest tube placement.
(b) 8.5 French pre-assembled kits are available.
(c) Prepare site with antibacterial solution.
(d) Administer analgesia to the patient.
(e) Drape the patient using sterile procedure.
(f) Identify the fifth intercostal space in the midaxillary line on the affected side.
(g) Inject this site with a small amount of 1 % lidocaine. Do not exceed 4 mg/kg.
(h) Using the needle introducer attached to a syringe, enter the skin at a 30°–45° angle distal to the fourth intercostal space avoiding breast tissue and nipple. Guide the needle superficially above the fifth rib, avoiding the inferior structures, and into the intercostal space.
(i) Gently apply negative pressure on the syringe while entering the pleural space. As air or fluid is aspirated, watch for improvement in vital signs. Avoid evacuating the entire amount of air or fluid to avoid lung injury.
(j) Remove the syringe and insert the guide wire into the needle introducer. In some kits, the guide wire is contained in a plastic bag to detect the presence of air. Advance the guide wire through the introducer until the guide wire marker enters the hub.

(k) Keeping the position of the guide wire, remove the needle introducer over the distal end of the guide wire.
(l) Advance the dilator over the guide wire and gently dilate the site.
(m) Remove the dilator, keeping the guide wire in place.
(n) Advance the pigtail catheter over the guide wire and into the pleural space. Advance until each of the side ports is intrathoracic in location. Leave 13 cm (measured from the chest wall to the hub of the catheter) of tubing extra-thoracic.
(o) Attach the chest tube to an underwater drainage system as detailed above.
(p) Adequately secure the chest tube.
(q) Confirm placement radiographically.
(r) Complications are the same as those seen in needle aspiration.

B. Pulmonary interstitial emphysema (PIE) occurs most often in ventilated, preterm infants with RDS. Interstitial air can be localized or widespread throughout one or both lungs. PIE alters pulmonary mechanics by decreasing compliance, increasing residual volume and dead space, and increasing *V/Q* mismatch. It also impedes pulmonary blood flow.
1. Diagnosis is made using a combination of clinical signs, transillumination, and chest radiography.
   a. Clinical signs of PIE include profound respiratory acidosis, hypercarbia, and hypoxemia. Because air is interstitial instead of intra-alveolar, proper gas exchange does not occur and effective ventilation is decreased. The interstitial gas reduces pulmonary perfusion by compression of blood vessels, resulting in hypoxemia.
   b. Transillumination of a chest with diffuse and widespread PIE will result in increased transmission of light, similar to that seen in a pneumothorax.
   c. Chest radiography may reveal a characteristic cystic appearance or may be more subtle with rounded, nonconfluent linear microradiolucencies in earlier stages. In later stages of PIE, there may be large bullae formation with hyperinflation in the involved portions of lung.
2. Management
   a. Generalized PIE management is focused on reducing or preventing further barotrauma to the lung.
      (1) Decreasing PIP to the minimum required to attain acceptable arterial blood gases (PaO_2 45–50 Torr or 6–6.7 kPa and PCO_2 <60 Torr or 8 kPa).
      (2) Adjust PEEP to maintain sufficient FRC and to stent airways.
      (3) High frequency jet ventilation (HFJV) is a successful means of ventilation for infants with PIE. This mode results in improved ventilation at lower peak and mean airway pressures with more rapid resolution of PIE.
   b. Localized PIE may resolve spontaneously or persist for several weeks with a sudden enlargement and deterioration in the infant's condition. Progressive overdistension of the affected area can cause compression of the adjacent normal lung parenchyma.
      (1) Supportive management includes positioning the infant with the affected side down to minimize aeration of the affected lung and promote aeration of the unaffected lung.
      (2) Severe cases of unilateral PIE may respond to collapse of the affected lung by selective bronchial intubation of the unaffected lung.

C. Pneumomediastinum is often of little clinical importance and usually does not need to be drained. Cardiovascular compromise is rare, but can occur if the air accumulation is under tension and does not decompress spontaneously.

1. Diagnosis
   a. Clinical findings include tachypnea, cyanosis and distant heart sounds on chest auscultation.
   b. Chest radiography is the gold standard.
2. Management
   a. Nitrogen washout, as described above.
   b. Needle aspiration (using technique described above for pneumothorax). Insert the needle midline immediately subxiphoid and apply negative pressure as the needle is advanced in a cephalad direction.
   c. A mediastinal tube is rarely needed, but if necessary, should be placed by a qualified surgeon.

D. Pneumopericardium occurs when air from the pleural space or mediastinum enters the pericardial sac through a defect that is often located at the reflection near the ostia of the pulmonary veins. The majority of cases occur in infants ventilated with high PIP (>32 cm H_2O), high mean Paw (>17 cm H_2O), and/or long inspiratory time (>0.7 s).
   1. The typical presentation is the abrupt onset of cardiovascular compromise from cardiac tamponade, which is a life-threatening complication that results from air entering the pericardial sac. A symptomatic pneumopericardium should be drained immediately.
   2. Management
      a. Needle aspiration via the subxiphoid route may be used as a temporizing measure or to treat symptomatic pneumopericardium.
         (1) Prepare the subxiphoid area with an antiseptic solution.
         (2) Attach a 20- or 22-gauge intravenous catheter to a short piece of IV tubing that is then attached via a stopcock to a syringe.
         (3) Locate the subxiphoid space and insert the catheter with the needle at a 30°–45° angle pointed toward the infant's left shoulder.
         (4) Aspirate with the syringe as the catheter is advanced.
         (5) Stop advancing the catheter once air is aspirated. Remove the needle, sliding the plastic catheter into the pericardial space. Reattach the syringe and remove the remaining air. Once the air is removed, either remove the catheter, or place it to water seal if the leak is continuous.
         (6) The procedure can be facilitated by transillumination guidance.
         (7) Complications of pericardiocentesis include hemopericardium and laceration of the right ventricle or left anterior descending coronary artery.
      b. Pericardial tube placement and drainage may be necessary if the pericardial air reaccumulates. The pericardial tube can be managed like a chest tube with less negative pressure used for suction (−5 to −10 cm H_2O).
      c. Prevention of further pericardial air leak by appropriate ventilator management is very important.

E. Subcutaneous emphysema usually has no clinical significance although large air collections in the neck can result in tracheal compromise.
   1. Typically presents as crepitus upon palpation of the affected area, but can also be seen on radiography.
   2. Management
      a. Supportive measures.
      b. Surgical decompression may be necessary if tracheal compromise is present.

F. Pneumoperitoneum often will not adversely affect the patient's clinical status, but treatment is warranted when respiratory status is compromised. Upward pressure on the diaphragm may

compromise ventilation from decreased lung volumes and may reduce blood return to the heart by exerting pressure on the inferior vena cava.

1. Distinguishing the cause of a pneumoperitoneum is very important and will drastically change patient management. Pneumoperitoneum caused by a trans-thoracic air leak can be differentiated from pneumoperitoneum caused by bowel perforation by measuring the oxygen from a gas sample obtained from the peritoneum. A baseline gas concentration is obtained and compared to a gas concentration obtained from a peritoneal sample when ventilator F_iO_2 is set at 1.0. If the PaO_2 from the latter sample is high, the source of the air leak is likely thoracic.
2. Management
   a. Needle aspiration can be used as a temporizing measure or as treatment. Following the general procedure for needle aspiration of pneumothorax, the needle is inserted in the midline approximately 1 cm below the umbilicus. Negative pressure is applied while the needle is advanced through the peritoneum and air is evacuated.
   b. Peritoneal drain placement may relieve a continuous peritoneal air leak.

Suggested Reading

Bhatia R, Davis PG, Doyle LW, et al. Identification of pneumothorax in very preterm infants. J Pediatr. 2011;159:115–20.

Cabatu EE, Brown EG. Thoracic transillumination: aid in the diagnosis and treatment of pneumopericardium. Pediatrics. 1979;64:958–60.

Crowley MA. Chapter 74: Neonatal respiratory disorders. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine. 10th ed. Philadelphia: Elsevier Saunders; 2015. p. 1113–36.

Donn SM, Engmann C. Neonatal resuscitation: special procedures. In: Donn SM, editor. The Michigan manual of neonatal intensive care. 3rd ed. Philadelphia: Hanley & Belfus; 2003. p. 33–41.

Donn SM, Faix RG. Delivery room resuscitation. In: Spitzer AR, editor. Intensive care of the fetus and neonate. St. Louis: Mosby-Year Book; 1996. p. 326–36.

Donn SM, Kuhns LR. Pediatric transillumination. Chicago: Year Book Medical; 1983.

Donn SM, Sinha SK. Chapter 73: Assisted ventilation and its complications. In: Martin RJ, Fanaroff AA, Walsh MC, editors. Fanaroff and Martin's neonatal-perinatal medicine. 10th ed. Philadelphia: Elsevier Saunders; 2015. p. 1087–112.

Jeng MJ, Lee YS, Tsao PC, Soong WJ. Neonatal air leak syndrome and the role of high-frequency ventilation in its prevention. J Chin Med Assoc. 2012;75:551–9.

Keszler M, Donn SM, Bucciarelli RL, et al. Controlled multicenter trial of high frequency jet ventilation vs. conventional ventilation in newborns with pulmonary interstitial emphysema. J Pediatr. 1991;119:85–93.

Korones SB. Chapter 23: Complications. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. St. Louis: Elsevier Saunders; 2011. p. 389–425.

MacDonald MG. Thoracostomy in the neonate: a blunt discussion. NeoReviews. 2004;5:301–6.

Smith J, Schumacher RE, Donn SM, Sarkar S. Clinical course of symptomatic spontaneous pneumothorax in term and late preterm infants: report from a large cohort. Am J Perinatol. 2011;28:163–8.

Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2001;2:CD000510.

Zak LK, Donn SM. Thoracic air leaks. In: Donn SM, Faix RG, editors. Neonatal emergencies. Mount Kisco: Futura; 1991. p. 311–25.

Patent Ductus Arteriosus

83

Jonathan P. Wyllie

I. Incidence
   A. Most common cardiac problem in newborns
   B. Varies inversely with gestational age
      1. Up to 20 % at GA > 32 weeks
      2. 20–40 % between 28 and 32 weeks
      3. 60 % below 28 weeks

II. Ductus Ateriosus in Fetal Circulation
   A. Derived from sixth aortic arch
   B. May be absent in association with congenital heart disease involving severe right outflow tract obstruction (rare)
   C. Carries most of RV output (50–60 % of total cardiac output) from sixth to seventh week on; caliber equal to descending aorta.
   D. Patency both passive (from high blood flow) and active (locally derived Prostaglandin E_2 [PGE_2])

III. Postnatal Closure
   A. Mechanisms mature after 35 weeks.
   B. Initiated by spiral medial muscle layer starting at pulmonary end
   C. Duct shortens and thickens with functional closure or 12–72 h.
   D. Factors promoting closure
      1. Low ductal flow (↑ systemic + ↓ pulmonary resistance = ↑pulmonary flow)
      2. Reduced sensitivity to PGE_2
      3. Decreased production of PGE_2
      4. Increased arterial oxygen tension

IV. Persistent Ductal Patency
   A. Isolated PDA accounts for 3.5 % of congenital heart disease presenting in infancy. It occurs despite ductal constriction and has a different pathogenesis from that in the preterm infant.
   B. Preterm PDA is related to:
      1. Immature closure mechanism
      2. Decreased sensitivity to constrictors such as oxygen tension

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3. Increased sensitivity to PGE_2
4. Other associated factors
   a. Acidosis
   b. Severe lung disease
   c. Exogenous surfactant use
   d. Phototherapy
   e. Furosemide use, especially in first few days of life
   f. Excessive fluid administration
   g. Lack of antenatal steroid therapy

V. Physiologic Effects of the PDA
   A. Left-to-right shunt
      1. Exacerbation of respiratory disease
      2. Altered pulmonary mechanics
      3. Increased cardiac work load
   B. Diastolic steal
      1. Altered perfusion of brain, systemic organs
      2. Risk of necrotizing enterocolitis

VI. Clinical Effects of PDA from Left-to-Right Shunt
   A. Increased oxygen requirement
   B. Increased ventilatory requirement
   C. Apnea
   D. Bronchopulmonary dysplasia
   E. Impaired weight gain
   F. Congestive heart failure

VII. Clinical Features
   A. Usually occurs after fall in pulmonary resistance
   B. Onset related to severity of lung disease and size of baby
   C. In VLBW infant, most common manifestation is after 4 days of age, earlier in LBW.
   D. Signs
      1. Early hypotension and reduced systemic perfusion
      2. Failure of RDS to improve (or deterioration) at 2–7 days
      3. Increase FiO_2/ventilator settings
      4. Pulmonary hemorrhage
      5. Acidosis
      6. Apnea
      7. Hyperdynamic precordium (95 %)
      8. Bounding pulses (85 %)
      9. Murmur (80 %)
         a. Normally silent until day 4
         b. Systolic murmur
         c. Upper left sternal border
         d. Variable

VIII. Clinical outcomes *associated* with PDA (causality unproven)
   A. Mortality
   B. Inotropic resistant hypotension
   C. Intraventriculat hemorrhage
   D. Pulmonary hemorrhage
   E. Necrotizing enterolcolitis

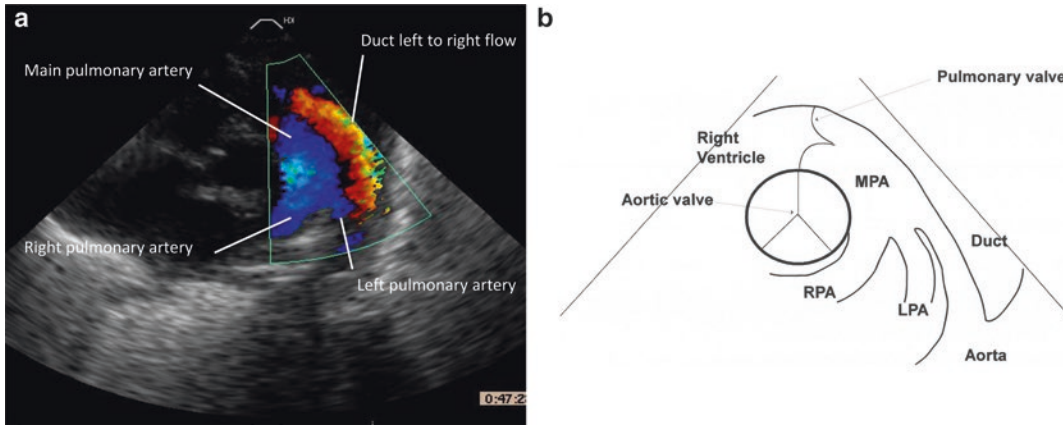

Fig. 83.1 (**a**) Short axis view of main pulmonary artery (MPA) with color Doppler demonstrating ductal flow into MPA (*red/yellow*). (**b**) Diagrammatic representation of same short axis view without color Doppler

F. Bronchopulmonary dysplasia
G. Periventricular leukomalacia

IX. Diagnosis
A. Chest radiograph (poor specificity)
1. Cardiac enlargement
2. Pulmonary engorgement (hyperemia)
3. Absence of pulmonary explanation for deterioration
B. Electrocardiogram not usually helpful unless attempting to rule-out another condition
C. Biomarkers
1. B-type natriuretic peptide (BNP)
2. Aminoterminal B-type natriuretic peptide (NT-proBNP)
3. Cardiac troponin T (cTnT)
4. Urinary NT-proBNP/creatinine ratios
D. Echocardiogram (Fig. 83.1a, b)
1. Ductal patency
2. Flow velocity/pattern
3. Ductal diameter (>1.5 mm in first 30 h)
4. LA volume load (LA:Ao ratio > 1.5)
5. LVEDD:Aortic ratio > 2.0
6. LV output
7. LV function
8. Diastolic flow in descending aorta
9. Diastolic flow in mesenteric or coeliac vessels

X. Treatment
A. Fluid restriction
1. Fluid regimen <169 mL/kg/day at day 3 have less symptomatic PDA
2. No evidence for fluid restriction closing PDA
3. Fluid restriction may be justified if PDA causing congestive cardiac failure
B. Diuretics
1. Furosemide
a. Little evidence except in congestive cardiac failure.
b. Improvement of pulmonary dynamics for 24 h.

2. Chlorothiazide
   a. Little evidence except in congestive cardiac failure
   b. Temporizing measure

C. Ventilation
1. Increase mean Pāw (PIP)
2. Increase PEEP

D. Indomethacin
1. Less than 2–3 weeks old
2. Now difficult to source
3. Reasonable renal function (serum creatinine <1.3 mg/dL)
4. No thrombocytopenia (platelets >50,000/mm^3)
5. No significant hyperbilirubinemia
6. Closure in up to 79 % but relapse in up to 33 % of these.
7. Prophylactic treatment treats up to 64 % unnecessarily
8. Early treatment more likely to be effective
9. Dosage regimens:
   a. 0.2 mg/kg × 2–3 doses
   b. 0.1 mg/kg/day × 6 doses

E. Ibuprofen
1. Fewer short-term side effects than indomethacin
2. No longer term advantage over indomethacin
3. 5 % incidence of severe pulmonary hypertension if used prophylactically
4. Early treatment more likely to be effective
5. Dosage regimen:
   a. 10 mg/kg loading dose and 5 mg/kg at 24 and 48 h.
   b. Oral or intravenous

F. Paracetamol (Acetaminophen)
1. Fewer short-term side effects than indomethacin or ibuprofen
2. As yet unproven but appears promising
3. Dosage regimen
   a. 15 mg/kg per dose. 12 doses every 6 h for 3 days
   b. Oral or intravenous

G. Surgical ligation

XI When to treat

A. Prophylactic: insufficient evidence to justify
1. Nonbeneficial short-term effects
2. No long-term advantage demonstrated

B. Pre-symptomatic: insufficient evidence at present
1. Reduces
   a. PDA
   b. Duration of oxygen therapy
2. No effect upon:
   a. Mortality
   b. BPD
   c. IVH
   d. ROP
   e. Duration of ventilation

C. Symptomatic: Further studies are needed to evaluate the validity of expectant symptomatic therapy compared to conservative treatment.

Suggested Reading

Bose CL, Laughon M. Treatment to prevent patency of the ductus arteriosus: beneficial or harmful? J Pediatr. 2006;148:713–4.

Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics. 2007;119:1165–74.

Clyman RI, Couto J, Murphy G. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? Semin Perinatol. 2012;36:123–9. doi:10.1053/j.semperi.2011.09.022.

Meyer S. PDA in neonates—please doctor act individually! Acta Paediatr. 2012;101:e145–6.

Negegme RA, O'Connor TZ, Lister G, Bracken MB. Patent ductus arteriosus. In: Sinclair JC, Bracken MB, editors. Effective care of the newborn infant. Oxford: Oxford University Press; 1992. p. 281–324.

Oncel MY, Yurttutan S, Erdeve O, et al. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Pediatr 2014; 164:510–4.e1.

Neonatal Pulmonary Hemorrhage

84

Tonse N.K. Raju

I. Description: A rare, but severe condition characterized by massive bleeding into the lungs and airways. The clinical status deteriorates rapidly with the associated mortality ranging from 50 to 80 %. The incidence of long-term pulmonary morbidity, such as chronic lung disease (CLD) among the survivors exceeds 80 %.

II. Incidence: The reported incidence figures vary depending upon the definitions used, the diligence of monitoring for pulmonary hemorrhage, and the source of the data used in the study (e.g., autopsy versus clinical).

A. General and NICU populations: In a retrospective case-control study from Brazil, Ferreira et al. reported pulmonary hemorrhage incidence to be 6.7 cases per 1000 live births, 8 % and 11 % among those <1500 g and <1000 g, respectively. About 1.4 % of all infants admitted to the NICU have been reported to develop pulmonary hemorrhage, more than 80 % of whom are diagnosed as having respiratory distress syndrome (RDS). Such infants are also likely to have been treated with exogenous surfactant and were receiving mechanical ventilatory support at the time of the bleeding.

B. Gestational Age: As noted above in the Brazilian study, the incidence is inversely proportional to gestational age (or birth weight as its proxy), especially between 23 and 32 weeks' gestation.

1. Exogenous Surfactant: Even since exogenous surfactant therapy became the standard of care for RDS, there has been a slight, but noticeable increase in the incidence of pulmonary hemorrhage. In a cohort of 14,464 VLBW infants, among the infants born at 25–26 weeks' gestation, pulmonary hemorrhage incidence was 10 % in 1991, which increased to 16 % in 2001. Among those born at 27–28 weeks' gestation, the incidence was 6.5 % in 1991 and 8 % in 2001.
2. In a post-marketing surveillance study of an animal-derived natural surfactant, the incidence of pulmonary hemorrhage was 6.4 % among the 903 infants treated with surfactant for RDS. This represents a slight increase from 3 to 4 % reported in the pre-surfactant era.

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C. A meta-analysis concluded that exogenous surfactants increased the risk for pulmonary hemorrhage by 47 %. The risk was slightly higher with animal-derived surfactants than with synthetic preparations. In autopsy series, about 80 % of VLBW infants were found have pulmonary hemorrhage.
D. Other Conditions: Among the infants requiring extracorporeal membrane oxygen (ECMO) therapy, about 6 % (range 5–10 %) have been reported to develop pulmonary hemorrhage either during or after ECMO.

III. Other Antecedent Factors and Infants at Risk
A. Prematurity, RDS, and exogenous surfactant therapy: In combination, these three are the most consistent risk factors for pulmonary hemorrhage, especially in infants <28 weeks' gestation (or birth weight <1000 g). The complication rate is not influenced by the type of natural surfactant used or its time of administration (prophylactic, early, or rescue).
B. Intrauterine growth restriction: (IUGR) The association between IUGR and pulmonary hemorrhage has been noted in some reviews; however, the association is inconsistent.
C. Lung complications: Pulmonary interstitial emphysema (PIE) and/or pneumothorax
D. Infections: bacterial, viral, or fungal infections, such as *Listeria monocytogenes*, *Hemophilus influenza*, *and* congenital cytomegalovirus have been reported to be associated with pulmonary hemorrhage.
E. General clinical status: Metabolic acidosis, especially in infants with RDS; hypothermia, hypoglycemia, and shock, and disseminated intravascular coagulation (DIC).
F. Meconium aspiration syndrome: Infants requiring extracorporeal membrane oxygenation (ECMO) therapy.
G. Inherited coagulation disorders: Although rare, one must consider familial bleeding disorders, such as von Willebrand disease, especially with a family history. A report by the Centers for Disease Control and Prevention found that von Willebrand disease was an underlying condition in 2 of 5 infants dying from idiopathic pulmonary hemorrhage.
H. Trauma: Mechanical injury to the vocal cords, trachea, or other laryngeal and oropharyngeal structures, especially from endotracheal intubation.

IV. Pathophysiology: The pulmonary effluate has a very high protein content, as well as a large number of cellular elements from the blood. Thus, the hemorrhage may be a consequence of increased trans-capillary pore size. A series of interrelated factors may lead to an eventual bleeding episode.
A. Hemodynamic factors: Some experts consider pulmonary hemorrhage as a manifestation of an exaggerated hemorrhagic pulmonary edema brought about by an acute increase in pulmonary blood flow. The latter can occur from multiple, interrelated causes: the normal postnatal drop in the pulmonary vascular resistance; improved pulmonary compliance from surfactant therapy; and normal postnatal absorption of lung fluid. These changes may lead to an acute increase in pulmonary blood flow and hemorrhagic pulmonary edema.
B. In six infants with severe and refractory pulmonary hypertension, Steiner et al. from Austria used sildenafil as a "last resort" as a pulmonary vasodilator. A loading dose of 0.1 mg/kg over 45 min was followed by a continuous infusion of 0.5–1 g/kg/day. Two of six infants developed severe pulmonary hemorrhage at 19 and 66 h after sildenafil start. The authors ascribed this complication to a severe and precipitous drop in pulmonary vascular resistance, leading to reversal of ductal shunting (from right-to-left to left-to-right) and pulmonary vascular hyperperfusion.
C. The relation to PDA and pulmonary hemorrhage is shown indirectly in the EPIPHAGE2 study led by Roze et al. from France. A large cohort of infants underwent an earlier diagnosis of PDA through screening echocardiography, thus were treated early compared to those

not receiving screening. Among the 1484 infants in their overall cohort, the incidence of pulmonary hemorrhage was 8.4 % in 656 infants not receiving early screening for PDA, compared to 5.7 % in the 827 infants so screened (an odds ratio of 0.6, with 95 % confidence interval, 0.4—0.89). Hematologic factors: Disseminated intravascular coagulation (DIC) secondary to sepsis can lead to abnormal coagulation and hemorrhage. Bleeding may be found at other sites, such as the gastrointestinal and renal mucous membranes, and in the brain. The underlying sepsis or shock could further compromise local vascular integrity, leading to an acute episode of bleeding.

V. Pathology: A wide range of pathologic appearances has been reported. In mild forms, scattered red blood cells in the intra-alveolar and intra-parenchymal spaces may be the only findings, with little or no blood in the airways. In infants who die from pulmonary hemorrhage, massive amounts of frank blood may be found in the parenchyma, small and large airways, trachea and the oral cavity (Fig. 84.1).
   A. Macroscopic features: The lung weight is increased, its lobar borders obliterated, and frank blood is seen in the airways, trachea, and the pleural space.
   B. Microscopic features: Large islands of blood in the alveolar and parenchymal spaces may be seen. Blood may occupy the lumen of larger bronchi and the trachea. Pulmonary hemorrhage is reported to be predominantly alveolar in infants treated with exogenous surfactants, while it is predominantly interstitial in those not treated with surfactants. Thus, surfactant

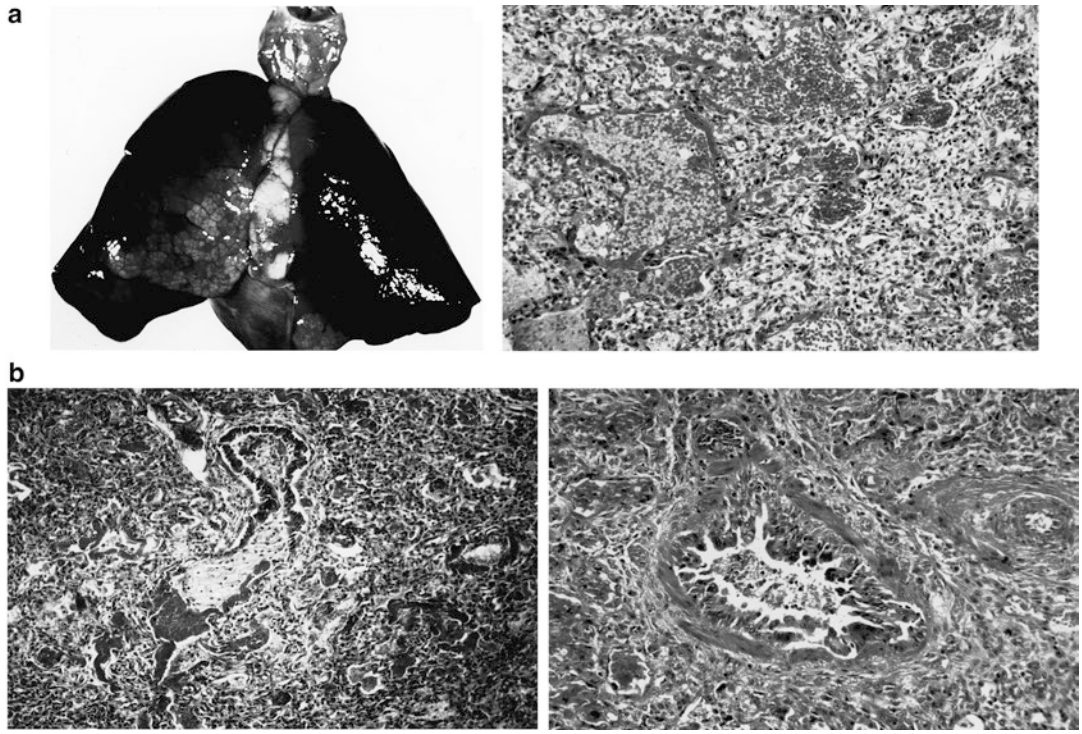

Fig. 84.1 Gross appearance of the lungs in an infant who died of massive pulmonary hemorrhage (*top left*). Microscopic findings of lung section in the same infant shows large quantities of blood in the alveolar spaces and scattered bleeding sites in the interstitial spaces. Generalized features of hyaline membrane formation and widespread inflammatory reaction are seen (*top right*). Two other cases are shown. (*Bottom left*) Massive pulmonary hemorrhage occurred 2 weeks prior to death. (*Bottom right*) Infant died at 4 weeks of age from respiratory failure secondary to bronchopulmonary dysplasia; there was no clinical evidence of pulmonary hemorrhage. Scattered areas of bleeding can be identified. Both infants show varying degrees of chronic changes in the lungs

therapy may alter the distribution of bleeding sites rather than causing an increase in the incidence of pulmonary hemorrhage.

C. Other changes: Reactive leucocytosis, changes of RDS and BPD may be found, along with that of pneumonia and bleeding in other organs, especially the intestine, kidneys, and the brain.

VI. Clinical Features: The severity and magnitude of clinical signs depend upon the magnitude of hemorrhage and the severity of the underlying condition leading to the episode. The clinical manifestations result from several interrelated pathophysiologic consequences of blood loss, hemorrhage into the lung parenchyma, and the airways.

A. A rapidly deteriorating pulmonary condition is the hallmark of massive pulmonary hemorrhage.
   1. Hypoxia, hypercarbia, and increasing requirements for ventilatory support are seen secondary to worsening of pulmonary compliance from blood in the lung tissue.
   2. Frank blood can be seen pouring out of the mouth, or in milder cases, blood-tinged tracheal and oropharyngeal effluent may be seen.
   3. The blood obstructs the airways, increasing resistance, and further causes worsening of the already deteriorating blood gas and acid-base status.

B. Extraneous blood in the lung parenchyma increases the consumption of the administered surfactant and inhibits its function. Plasma proteins and blood also inhibit endogenous surfactant production.

C. The pulmonary deterioration almost invariably accompanied by an acute deterioration in the systemic status; a rapid drop in blood pressure and cardiac output leads to classic signs of shock, along with severe pallor and anemia.

D. In infants who survive the acute episode, widespread pulmonary inflammation from blood in the lung tissues can lead to later complications, such as pneumonia and a prolonged need for assisted ventilation and subsequent BPD.

E. Because the clinical findings are interrelated and depend upon the severity of hemorrhage, in some cases, several hours may elapse before the signs of shock and collapse appear.
   1. Always suspect pulmonary hemorrhage in infants receiving assisted ventilation who, appear otherwise "stable," but gradually manifest worsening hypoxia, hypercapnia, and acidosis, requiring higher than the original ventilator settings.
   2. Localized, small, pulmonary hemorrhage may cause the signs to evolve over 6–8 h; in such cases, pulmonary hemorrhage should always be high on the list of differential diagnosis.

F. In the presence of systemic shock and sudden deterioration, consider pulmonary hemorrhage even in the absence of blood or blood-tinged oro-tracheal effluent, since the bleeding may be interstitial.
   1. A reduction in hematocrit and platelet counts may occur hours later.
   2. Cardiac murmur and/or other signs of a PDA may be found.

G. Other causes of left-to-right shunting and of pulmonary edema must be evaluated, such as congestive cardiac failure (VSD, ASD, or cerebral arteriovenous malformations).

VII. Investigations

A. Chest radiograph. There are no specific diagnostic features in chest radiographs.
   1. Diffuse, scattered haziness, consolidation, fluffy radio-densities, and features of the underlying disease (RDS, BPD, or PIE) should suggest pulmonary hemorrhage.
   2. Cardiomegaly. may or may not be present, depending upon the underlying cause of pulmonary hemorrhage (Figs. 84.2 and 84.3).

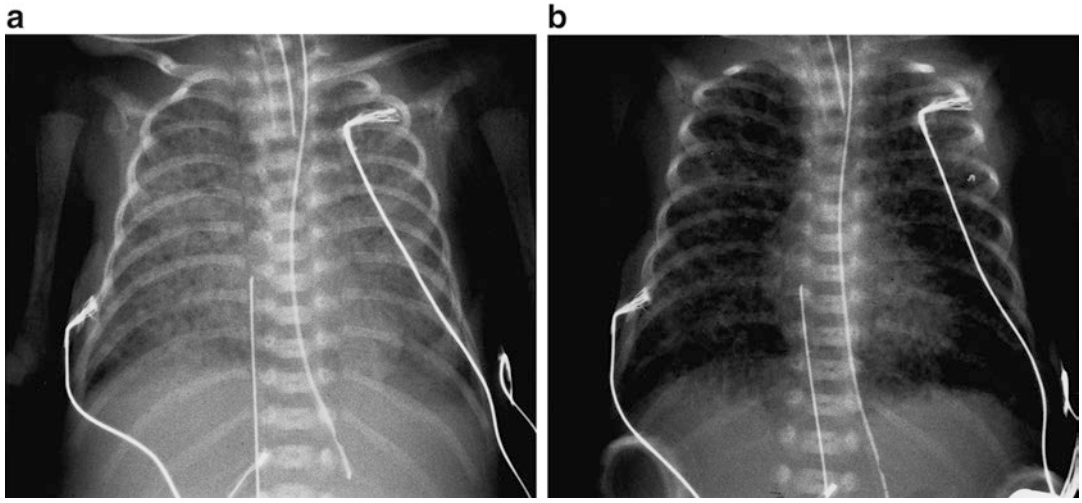

Fig. 84.2 Evolution of pulmonary hemorrhage in an infant with RDS. Chest radiographs show typical features of severe PIE on the fifth day (**a**) and severe pulmonary hemorrhage on the seventh day (**b**). Heart size is normal

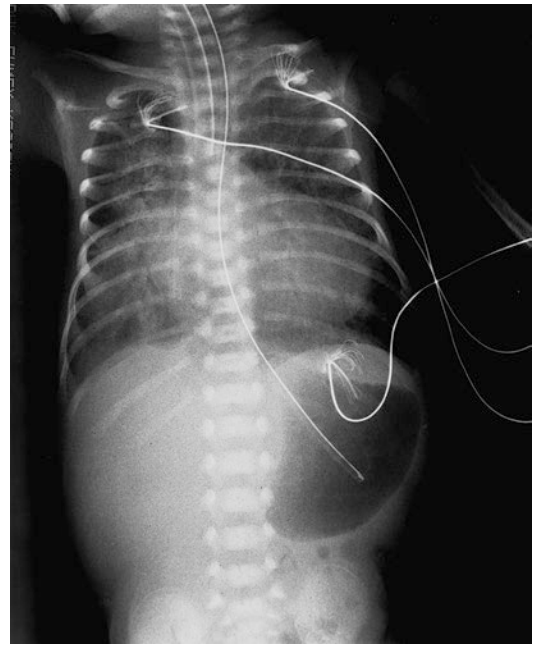

Fig. 84.3 Chest radiograph of a preterm infant developing severe pulmonary hemorrhage on the sixth day secondary to a large, florid patent ductus arteriosus and signs of congestive heart failure. Pulmonary hemorrhage was accompanied by respiratory deterioration. Scattered radio-opaque densities, mostly in both lower lobes can be seen, and there is moderate cardiomegaly

B. Evaluating the PDA.
   1. Suspect a significant PDA in infants with pulmonary hemorrhage, even in the absence of a typical "PDA murmur," or a wide pulse pressure, or heaving precordium.
   2. An echocardiogram is recommended.
C. Blood tests and work-up for sepsis
   1. Blood gas and acid-base status
   2. Hemoglobin and hematocrit
   3. Platelet count

4. Total and differential white blood cell count
5. Bacterial culture from blood and urine should be considered.
6. Viral and fungal cultures may be indicated.
7. Consider tests for DIC (PT, PTT, fibrin degradation products, etc.).

D. Search for inherited disorders of coagulation (e.g., hemophilia, von Willebrand Disease). For bleeding in other organs: Urinalysis to rule-out major bleeding in the kidney and a cranial ultrasound examination to rule-out intracranial hemorrhage is recommended depending upon other findings.

VIII. Treatment

A. General Supportive Care

1. Intensive care and anti-shock measures
   a. Transfuse with blood, plasma, or platelets as indicated.
   b. Correct metabolic acidosis.
   c. Administer inotropic agents to improve systemic blood pressure.
2. Ventilatory Support. With a few exceptions, most recommendations for ventilatory support have evolved based on empirical observations.
   a. Conventional ventilatory support: Increase ventilatory settings to provide a higher rate, higher positive end expiratory pressure (PEEP) and higher mean airway pressure (Pāw).
   b. High-frequency oscillatory ventilation (HFO) support: In a prospective observational study, it was found that 10/17 infants with massive pulmonary hemorrhage responded to early treatment with HFO. All of them survived. By contrast, only 1/3 offered conventional ventilatory support survived.
3. Treat the PDA. Unless there is severe thrombocytopenia, indomethacin/ibuprofen therapy can be used in proven or suspected pulmonary hemorrhage to treat the PDA, even if had been given earlier.
4. Treatment of infections. Antibiotics most likely to be effective against common bacterial pathogens are to be used: ampicillin (or vancomycin), along with a drug for Gram-negative coverage may be given until a specific etiologic agent, if any, is identified.

B. Specific Treatment Strategies

1. Recombinant Factor VIIa (rFVIIa). rFVIIa, a vitamin K-dependent glycoprotein, structurally similar to the plasma-derived natural factor VII, is considered a universal hemostatic agent. It acts by triggering the extrinsic coagulation cascade and forming a hemostatic seal at the site of capillary leak, providing a plug and stopping the bleeding. A dose of 80 μg/kg rFVIIa can normalize a prolonged prothrombin time. This drug has also been used with success in two isolated cases of neonatal pulmonary hemorrhage at doses of 50 μg/kg/dose, repeated every 3 h for 2–3 days. In other studies, rFVIIa was used in infants developing pulmonary hemorrhage at much higher doses, also resulting in cessation of pulmonary hemorrhage. More work is needed to establish the dosage and the frequency of its administration, as well as to assess the consistency of response in neonatal pulmonary hemorrhage patients.
2. Exogenous surfactant. Exogenous surfactant improves the respiratory status in infants with pulmonary hemorrhage. The administered surfactant replenishes the endogenous surfactant pool depleted from inhibition or inactivation from blood and plasma in the alveoli.
3. Other measures to stop pulmonary hemorrhage. Nebulized epinephrine with or without 4% cocaine has been found to temporize massive bleeding. Experience using these drugs is limited in the newborn.

4. Yeh et al. from Taiwan reported treating 18 infants who developed pulmonary hemorrhage with a combination of supportive care, surfactant instillation, and rapid and repeated injections/instillations of 0.5 mL of epinephrine (1:10,000 dilution) in the form of irrigation until pulmonary hemorrhage was resolved. They reported that 17/18 infants recovered.

IX. Outcome
   A. Mortality: average 50 %; range 30–90 %
   B. Morbidity: 50–75 % of survivors develop BPD of varying severity.

X. Prevention
   A. Antenatal corticosteroids. Enhancing lung maturity may reduce pulmonary hemorrhage through its indirect effect on the lungs and pulmonary vascular bed.
   B. Preventing PDA. Although early indomethacin and ibuprofen have shown a strong effect in reducing the incidence of significant PDA, whether such a strategy will affect pulmonary hemorrhage is unclear.
   C. Monitoring for PDA and its prompt therapy. Vigilant monitoring for the signs of PDA in preterm infants treated with exogenous surfactants for RDS should be the mainstay for preventing pulmonary hemorrhage. In infants with rapid improvement in pulmonary compliance, even a minimally patent ductus arteriosus can cause a sudden worsening of pulmonary compliance, and lead to pulmonary hemorrhage.
   D. High-Frequency Oscillatory Ventilation (HFOV). In a large trial, the incidence of pulmonary hemorrhage was 5/244 (2 %) in a group of small preterm infants treated with HFOV compared to 17/254 (7 %) in the conventionally ventilated group ($p < 0.02$).

Suggested Reading

Alkharfy TM. High-frequency ventilation in the management of very-low-birth-weight infants with pulmonary hemorrhage. Am J Perinatol. 2004;1:19–26.

Amizuka T, Shimizu H, Niida Y, Ogawa Y. Surfactant therapy in neonates with respiratory failure due to hemorrhagic pulmonary oedema. Eur J Pediatr. 2003;162:69.

Baroutis G, Kaleyias J, Liarou T, et al. Comparison of three treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Eur J Pediatr. 2003;62:476–80.

Centers for Disease Control and Prevention. Investigation of acute idiopathic pulmonary hemorrhage among infants—Massachusetts, December 2002-June 2003. MMRW Morb Mortl Wkly Rep. 2004;3:817.

Clyman RI. The role of patent ductus arteriosus and its treatments in the development of bronchopulmonary dysplasia. Semin Perinatol. 2013;37(2):102–7.

Courtney SE, Durand DJ, Asselin M, et al. High-frequency oscillatory ventilation versus conventional ventilation for very-low-birth-weight infants. N Engl J Med. 2002;347:643–52.

Dufourq N, Thomson M, Adhikari M, Moodley J. Massive pulmonary hemorrhage as a cause of death in the neonate—a retrospective review. S Afr Med J. 2004;94:299–302.

Findlay RD, Taeusch HW, David WR, Walther FJ. Lysis of blood cells and alveolar epithelial toxicity by therapeutic pulmonary surfactants. Pediatr Res. 1995;37:26–30.

Goretksy MJ, Martinasek D, Warner BW. Pulmonary hemorrhage: a novel complication after extracorporeal life support. J Pediatr Surg. 1996;1:1276–81.

Greisen G, Andreasen RB. Recombinant factor VIIa in preterm neonates with prolonged prothrombin time. Blood Coagul Fibrinolysis. 2003;14:117–20.

Kluckow M, Evans N. Ductal shunting, high pulmonary flow, and pulmonary hemorrhage. J Pediatr. 2000;137:68–72.

Lamboley-Gilmer G, Lacaze-Masmonteil T, Neonatologists of the Curosurf® Study Group. The short-term outcome of a large cohort of very preterm infants treated with Poractant Alfa (Curosurf®) for respiratory distress syndrome. A postmaketing phase IV study. Pediatr Drugs. 2003;5:639.

Leibovitch L, Kenet G, Mazor K. Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. Pediatr Crit Care Med. 2003;4:444–6.

Lin TW, Su BH, Lin HC, et al. Risk factors of pulmonary hemorrhage in very-low-birthweight infants: a two-year retrospective study. Acta Pediatr Taiwan. 2004;45:255–8.
Long W, Corbet A, Allen A, et al. Retrospective search for bleeding diathesis among premature newborn infants with pulmonary hemorrhage after synthetic surfactant treatment. J Pediatr. 1992;120:545–8.
Olomu N, Kulkarni R, Manco-Johnson M. Treatment of severe pulmonary hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight infants. J Perinatol. 2002;22:672–4.
Pandit PB, Dunn MS, Colucci EA. Surfactant therapy in neonates with respiratory deterioration due to pulmonary hemorrhage. Pediatrics. 1995;95:32–6.
Pappin A, Shenker N, Jack M, Redline RW. Extensive intraalveolar pulmonary hemorrhage in infants dying after surfactant therapy. J Pediatr. 1994;124:621–6.
Raju TNK, Langenberg P. Pulmonary hemorrhage and exogenous surfactant therapy: a meta-analysis. J Pediatr. 1993;123:603–10.
Rao KVS, Michalski L. Intrauterine pulmonary hemorrhage secondary to antenatal Coxsackie B-2 infection. Pediatr Res. 1997;1:265A.
Rozé JC, Cambonie G, Marchand-Martin L, Gournay V, Durrmeyer X, Durox M, Storme L, Porcher R, Ancel PY, Hemodynamic EPIPAGE 2 Study Group. Association between early screening for patent ductus arteriosus and in-hospital mortality among extremely preterm infants. JAMA. 2015;313(24):2441–8.
St. John EB, Carlo WA. Respiratory distress syndrome in VLBW infants: changes in management and outcomes observed by the NICHD neonatal research network. Semin Perinatol. 2003;27:288–92.
Steiner M, Salzer U, Baumgartner S, et al. Intravenous sildenafil i.v. as rescue treatment for refractory pulmonary hypertension in extremely preterm infants. Klin Padiatr. 2014;226(4):211–5.
Suresh GK, Soll RF. Exogenous surfactant therapy in newborn infants. Ann Acad Med Singapore. 2003;32:335–45.
Tobias J, Berkenbosch JW, Russo P. Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. Pediatr Crit Care Med. 2003;41:49–51.
van Houten J, Long W, Mullett M, et al. Pulmonary hemorrhage in premature infants after treatment with synthetic surfactant: an autopsy evaluation. J Pediatr. 1992;120:540–4.
Yeh TA, Wang CC, Hsieh WS, Chou HC, Chen CY, Tsao PN. Short-term outcome of pulmonary hemorrhage in very-low-birth-weight preterm infants. Pediatr Neonatol. 2013;54(5):330–4.

Retinopathy of Prematurity

85

Alistair Fielder

I. Introduction
   A. Retinopathy of prematurity (ROP) is a major cause of childhood blindness, but is particularly important because visual disability can very largely be prevented by timely intervention.
   B. The therapeutic window is very short and treatment needs to be performed, depending on ROP severity, within a maximum of 72 h.
   C. Such a short period of opportunity for successful ROP treatment requires precise guidelines for screening and treatment, which is possible in countries with a high standard of neonatal care where the population at risk has been defined by audit and research (e.g., the USA, Sweden, the UK). However, this presents a major challenge in countries in which neonatal care can be more variable and larger babies can be at risk of sight-threatening ROP.
   D. Acute phase ROP has 5 stages, or 6 with aggressive posterior ROP (Table 85.1).
      1. Severe disease is referred to as Pre-threshold Type 1 ROP (Table 85.2) or worse, and thus includes stages 4 and 5 (associated with retinal detachment).
      2. The indication for treatment is Type I disease.
      3. Mild disease, which is defined as ROP less than Pre-threshold ROP Type 1, resolves fully without visually disabling sequelae.

II. Prophylaxis
   A. Standard of care remains critical in keeping severe disease to a minimum although it is recognized that despite meticulous neonatal care ROP is not entirely preventable.
   B. The major ROP risk factor is the degree of prematurity, but many associations and complications of preterm birth have also been implicated including:
      1. Oxygen
         a. Hyperoxia, hypoxia, and fluctuations of arterial oxygen even within the normal range
         b. It is therefore important to target arterial oxygen saturation between 90 and 95 %. Try to avoid fluctuations whenever possible.
      2. Steroids administered postnatally may be associated with more severe ROP, but it is not established whether this is a causal relation.
      3. Surfactant treatment does not affect ROP incidence.

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Table 85.1 International classification of retinopathy of prematurity revisited

A. Severity by Stage
1. Demarcation line
Thin white line, lying within the plane of the retina and separating avascular from vascular retinal regions
2. Ridge
The line of stage 1 has increased in volume to extend out of the plane of the retina. Isolated vascular tufts may be seen posterior to the ridge at this stage
3. Ridge with extraretinal fibrovascular proliferation
This may:
(i) Be continuous with the posterior edge of the ridge
(ii) Be posterior, but disconnected, from the ridge
(iii) Extend into the vitreous
4. Retinal detachment—subtotal
Extrafoveal (4 A), or involving the fovea (4 B)
5. Retinal detachment—total
The detached retina is funnel shaped which may be open or closed along all or part of its extent.
***Aggressive Posterior ROP* (*AP-ROP*)**
Commences with posterior pole vessel dilatation and tortuosity in all four quadrants. Deceptively featureless (which is why it has only recently been defined), it does not progress from stage 1–3, but appears as a flat network of vessels at the junction between vascularized and nonvascularized retina. Typically, AP-ROP is circumferential and may located in zone I or posterior zone II
B. Location by Zone
Retinal blood vessels grow out from the optic disc in zone I towards the periphery (zone III); thus, the retinal zone vascularized reflects maturity. ROP in zone I affects the most immature baby and is very likely to become severe with a poor outcome, whereas ROP located in zone III carries a very low risk to become severe and for an adverse outcome
C. Extent
ROP extent around the retinal circumference is recorded in "clock hours" 1–12
D. Plus Disease
Plus disease is an indicator of ROP activity—in order of increasing severity: venous dilatation and arteriolar tortuosity of the posterior pole retinal vessels, iris vessel engorgement, pupil rigidity and vitreous haze. *Plus involves vessels in two or more quadrants. Pre-plus describes abnormalities that are insufficient for the diagnosis of plus. Plus and preplus are critical indicators that ROP is, or will become, severe*

Table 85.2 Age at first screening examination in weeks

GA	PMA	PNA
22*	30	8
23*	30	7
24	30	6
25	30	5
26	30	4
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4
33**	36	3
34**	36	2

Data for babies 24–32 weeks GA provided by clinical studies (Reynolds et al. 2002). * & ** are estimates based on limited clinical data

4. Light reduction by lowering the ambient illumination of the NICU does not reduce the incidence or severity of ROP.
5. Many other risk factors have been suggested including vitamin E deficiency, hyperglycemia, exchange transfusions, necrotizing enterocolitis, treatment for patent ductus arteriosus, and other complications of prematurity.

III. Screening
   A. Purpose: to identify severe ROP which might require treatment, and which even if it does not, is associated with a high incidence of visually severe sequelae.
   B. Which babies should be examined?
      1. UK guideline:
         a. All babies under 1251 g BW or less than 31 weeks' GA MUST be screened.
         b. All babies between 1251 and 1501 g BW or between 31 and 32 weeks' GA *should* be screened, regardless of clinical condition.
      2. UK guideline has no "sickness" criteria.
         USA guidelines: Infants with a birth weight less than 1500 g or gestational age of 30 weeks or less to be screened. In addition, selected infants with a birth weight between 1500 and 2000 g or gestational age of more than 30 weeks with an unstable clinical course, and who are believed by their attending pediatrician or neonatologist to be at high risk may also be screened.
      3. Countries with more variable standards of neonatal care:
         a. The UK and US guidelines are applicable for babies less than 32 weeks.
         b. The UK and US guidelines are not applicable to babies 32 weeks and over who occasionally develop blinding ROP very rapidly.
         c. The variations in these countries emphasize the need for locally derived protocols.

IV. Examination protocol (Table 85.2)
   A. Principles
      1. ROP develops to a defined temporal trajectory which ends when the retina is fully vascularized at about 40 weeks' GA.
      2. Age at ROP onset and its rate of progression are both governed mainly by postmenstrual age (PMA). Thus, its onset is later in the very immature compared to the more mature baby.
      3. Neonatal events influence the risk of developing ROP but not its timing. Sight-threatening ROP most unlikely to be present before 31 weeks' PMA.
      4. The screening program needs to be designed so that ROP requiring treatment is identified timely.
         a. The mean age for treatment at pre-threshold is 35 weeks' PMA.
         b. The time available for treatment is short, but the degree of urgency is not identical for all cases.
            (1) Aggressive posterior ROP should be treated as soon as possible and within 48 h.
            (2) Other eyes, considered less urgent, requiring treatment should normally be treated within 48–72 h.
      5. The initial examination should be scheduled as in Table 85.2 (Reynolds et al. 2002). In those countries in which babies more than 32 weeks' GA are at risk, screening will need to commence earlier than in smaller babies.
      6. Subsequent examinations
         a. Every 1–2 weeks. This frequency minimizes loss to follow-up, and ensures that almost all screening is completed while the baby is hospitalized.

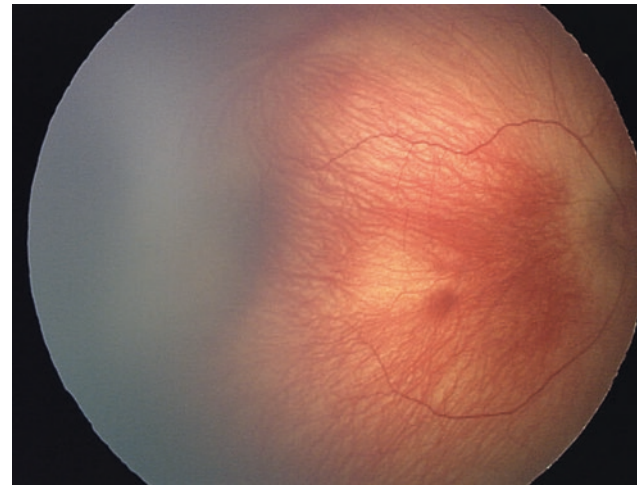

Fig. 85.1 Normal retina of preterm baby. The retinal vessels extend up to the *grey area*, to the left of the image, but do not reach the retinal periphery. The *grey region* is the normal, yet to be vascularized, retina. ROP develops at the junction of the vascularized and yet to be vascularized retina

b. Eyes with progressing ROP and certainly those eyes with Type 2 pre-threshold ROP should be examined at least once a week to assure that treatment, if necessary, is optimally timed.
c. Babies for transfer to another hospital prior to completion of the screening program. Ensure that the receiving hospital is alerted to screening requirements of the baby and when the next examination needs to be scheduled.
d. Babies for discharge to home. Ensure a follow-up appointment until screening is completed.

7. Completion of screening
   a. Premature cessation of screening is a major cause for litigation.
   b. For the eye without ROP, it is critical to continue screening until the risk for sight-threatening ROP has passed—vascularization has entered zone III (peripheral most portion of the temporal retina). Because assessing whether the retinal vessels are in zone III is prone to misinterpretation, it is recommended that screening continue into 37 weeks' PMA.
   c. For the eye with ROP, the need for examinations is dictated by clinical criteria.
8. Screening examination
   a. To be carried out by an experienced ophthalmologist following pupillary dilation.
   b. ROP is recorded (Figs. 85.1, 85.2, and 85.3) according to the following criteria:
      (1) Severity by stages: 1–5 and *aggressive posterior ROP* (*AP-ROP*)
      (2) Location by zone I–III. This is critical because the closer to zone I (i.e., posterior) the greater the propensity to become severe, whereas ROP in zone III almost never causes visual disability. (Fig. 85.4)
      (3) Extent by clock hour involvement
      (4) Presence of "*pre-plus*" *and* "plus" disease
      (5) It is critical to record each of these criteria on every occasion and to record the absence or presence of plus disease even if no ROP is observed. A sample form is downloadable from www.rcpch.ac.uk/ROP.

V. Treatment (Table 85.3)
   A. Principles
      1. Most ROP is mild and will have no major visually disabling sequelae. Severe ROP is defined as pre-threshold ROP, types 1 and 2.

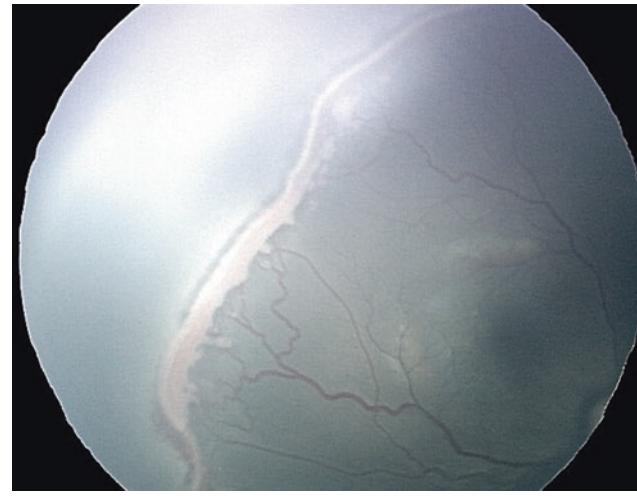

Fig. 85.2 Stage 2 and 3 ROP in the peripheral retina. The *grey line* towards to *top* and *bottom* of the image are stage 2 while in the middle section are fronds of neovascularization, stage 3. The *grey* appearance is because the image comes from a black baby

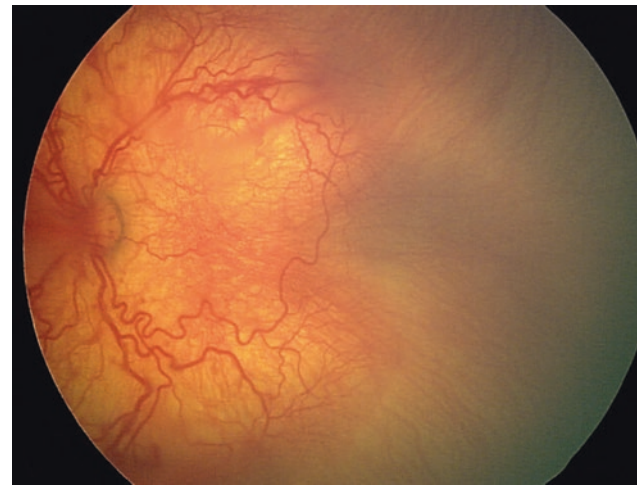

Fig. 85.3 Aggressive posterior ROP. Note extreme vascular congestion and tortuosity but subtle if any peripheral ROP lesion. This eye needs treatment within 48 h. Because of the absence of an obvious ROP lesion—compare with stage 3 above—in the last the severity of the situation was not appreciated and these eyes were likely to become blind. Permission confirmed from Arch Ophthalmol 2005;123:991-9, Fig. 12a, p 996

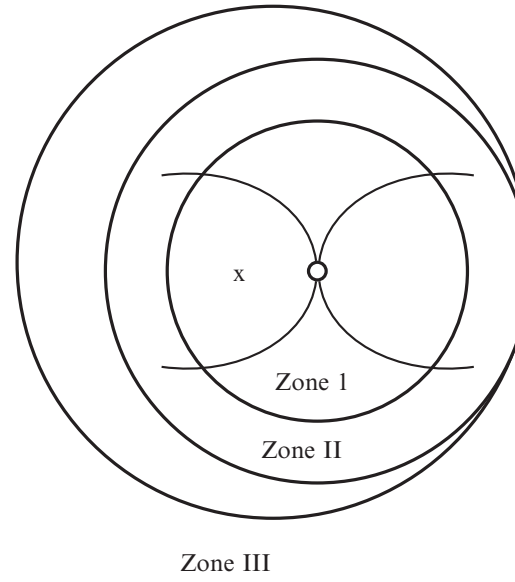

Fig. 85.4 Diagram showing the retinal zones. *X* marks the macula

Table 85.3 ROP—indications for treatment

Type 1 Pre-threshold ROP
Zone I, any stage of ROP with plus disease and stage 3 without plus disease
Zone II, stage 2 or 3 with plus disease
Type 1 ROP which is particularly active such as aggressive posterior ROP should be treated as soon as possible, within 24–48 h, but if less aggressive but still requiring treatment the eyes should be treated within 72 h
Type 2 Pre-threshold ROP
Zone I, stage 1 or 2 ROP without plus disease
Zone II, stage 3 ROP without plus disease
Type 2 pre-threshold ROP is an indication that ROP may progress to Type 1 and therefore should be observed closely
Note that "Plus" disease is a feature or Type 1 ROP with one rare exception (zone I, stage 3 without "plus"). In effect the presence of "plus" is the major driver for treatment

a. Type 1 Pre-threshold ROP (should be treated):
   (1) Zone 1, any ROP with "plus" disease
   (2) Zone 1, stage 3 ROP without "plus" disease
   (3) Zone 2, stages 2 or 3 with "plus" disease
b. Type 2 Pre-threshold ROP (should be observed):
   (1) Zone 1, stages 1 or 2 without "plus"
   (2) Zone 2, stage 3 without "plus"

2. Type 2 ROP alerts the ophthalmologist that ROP is severe and may, if it progresses to Type 1 ROP required treatment, as this is now the indication for treatment.
3. "Plus" disease is now the key criterion for treatment and is the critical difference between Type I that requires treatment and Type 2 ROP that does not.
4. Unfortunately, diagnosing "plus" disease is not always simple, nor robust, so it is recommended that all other ROP features are included in evaluating if treatment is needed.
5. It is recognized that the window of opportunity for treatment is not precisely defined and some eyes require intervention more urgently than others.

B. Treatment practicalities

Once pre-threshold Type 1 has been diagnosed, treatment by laser (cryotherapy is used very infrequently) should be performed:

1. Within 48 for eyes with AP-ROP and
2. Within 48 and 72 h for eyes which with less aggressive ROP but still requiring treatment.
3. Bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) agent, has very recently been used as a first line treatment. It has been reported to be beneficial for zone I, but not zone II, ROP. Caution is advised as concerns about possible systemic effects on the developing baby have yet to be determined.

VI. Long-term follow-up

A. All severe ROP requires ophthalmic follow-up, at least to 5 years of age because of the risk of reduced vision, refractive errors (especially myopia), and strabismus.
B. The follow-up of very low birthweight babies who did not develop severe ROP is less well defined and is influenced by local protocols, but the likelihood of developing refractive errors and strabismus in childhood is much higher than in their term counterparts.

VII. Responsibilities and Organization

A. Effective and efficient screening for ROP and its subsequent management requires multiprofessional teamwork.

B. National guidelines form the basis of protocols, which should be developed locally and jointly by the neonatal and ophthalmic teams.
C. Identification of babies requiring screening is the responsibility of the neonatal team.
D. Arrangement for follow-up needs to be made for the baby who is transferred to another hospital and for any post-examination follow-up.

VIII. Information for Parents
A. Mild ROP is very common, but most babies do not develop severe ROP, so conversations and literature for parents need to convey this sense. A sample is downloadable from www.rcpch.ac.uk/ROP.
B. For babies with, or close to, severe ROP that might require treatment, a personal discussion between the ophthalmologist and parents is important, and this should involve also a member of the neonatal team. A sample is downloadable from www.rcpch.ac.uk/ROP.

IX. Future Directions
A. Data of babies at risk for severe ROP need to be collected from all countries so that guidelines applicable to all countries can be developed.
B. The retinovascular changes associated with ROP are not well defined. Methods of automated vessel analysis from digital images to quantify precisely these changes are at an advanced stage of development. This will (hopefully) open opportunities for non-physician ROP screening in those countries with a high screening requirement, but where currently access to services is low.
C. Postnatal growth-based models show considerable promise in predicting severe ROP and have the potential to reduce the number of screening examinations.
D. A telemedical approach to screening by non-physicians taking and evaluating the images shows promise for the future in NICUs, where there is a dearth of ophthalmic expertise.
E. The use of insulin-like growth factor-1 and anti-VEGF agents for prevention and treatment of ROP, respectively, is being explored at preclinical and clinical levels. It is essential that their ophthalmic and systemic effects are understood before being used in routine clinical practice.

Suggested Reading

American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131:189–95.

An International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol. 2005;123:991–9.

Au SCL, Tang S-M, Rang S-S, Chen L-J, et al. Association between hyperglycaemia and retinopathy of prematurity: a systematic review and meta-analysis. Sci Rep. 2015;5:9091.

Binenbaum G. Algorithms for the prediction of retinopathy of prematurity based on postnatal weight gain. Clin Perinatol. 2013;40:261–70.

Boost II Australia and United Kingdom Collaborative Groups. Outcomes of two trials of oxygen saturation targets in preterm infants. N Engl J Med. 2016;2016(374):749–60.

Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity. Arch Ophthalmol. 2003;121:1684–96.

Eriksson L, Haglund B, Ewald U, Odlind V, Kieler H. Short and long-term effects of antenatal corticosteroids assessed in a cohort of 7,827 children born preterm. Acta Obstet Gynecol Scand. 2009;88:933–8.

Fielder A, Blencowe H, O'Connor A, Gilbert C. Impact of retinopathy of prematurity on ocular structures and visual functions. Arch Dis Child Fetal Neonatal Ed. 2015;100:F179–84.

Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008;84:77–82.

Holmström G, Hellström A, Jakobsson P, Lundgren P, et al. Evaluation of new guidelines for ROP screening in Sweden using SWEDROP—a national quality register. Acta Ophthalmol. 2015;93:265–8.
Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603–15.
Quinn GE, Fielder AR. Retinopathy of prematurity. In: Taylor DSI, Hoyt CS, editors. Pediatric ophthalmology and strabismus. 4th ed. New York: Elsevier; 2013. p. 432–48.
Quinn GE, Ying G-S, Daniel E, Hildebrand PL, e-ROP Cooperative Group. Validity of a telemedicine system for the early evaluation of acute-phase retinopathy of prematurity. JAMA Ophthalmol. 2014;132:1178–84.
Reynolds JD, Dobson V, Quinn GE, Fielder AR, et al, CRYO-ROP and LIGHT-ROP Cooperative Groups. Evidence-based screening for retinopathy of prematurity: natural history data from CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol. 2002; 120: 1470–6.
Stahl A, Hellstrom A, Smith LE. Insulin-like growth factor-1 and antivascular endothelial growth factor in retinopathy of prematurity: has the time come? Neonatology. 2014;106:254–60.
Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al, The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013; 368: 2094–104.
Tin W, Wariyar U. Giving small babies oxygen: 50 years of uncertainty. Semin Neonatol. 2002;7:361–7.
Wilkinson AR, Haines L, Head K, Fielder AR. UK retinopathy of prematurity guideline. Early Hum Dev. 2008;84:71–4. Full guideline and sample downloadable forms available www.rcpch.ac.uk/ROP.
Wu C, Löfqvist C, Smith LE, VanderVeen DK, WINROP Consortium, et al. Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants: a multicenter study analyzing weight velocity deviations for the prediction of retinopathy of prematurity. Arch Ophthalmol. 2012;130(8):992–9.

Neurologic Complications of Mechanical Ventilation

86

Vivien Yap and Jeffrey M. Perlman

I. Background
   A. The developing brain of the newborn, and in particular the premature infant, is at increased risk for hemorrhagic and/or ischemic injury (Table 86.1).
   B. The most frequent lesions noted are periventricular intraventricular hemorrhage (PV-IVH) and injury to white matter, often referred to as periventricular leukomalacia (PVL).
   C. These lesions are most likely to occur in the premature infant with respiratory distress syndrome (RDS) requiring mechanical ventilation.
   D. The etiology of both lesions is likely multifactorial including:
      1. Perturbations in cerebral blood flow (CBF), which are considered to be of paramount importance.
      2. The cerebral circulation in the sick preterm newborn appears to be pressure-passive, i.e., changes in CBF directly reflect similar changes in systemic blood pressure.
      3. The periventricular white matter at greatest risk for injury resides within arterial border and end zones of the long penetrating vessels. The terminations of these long penetrators result in distal arterial fields that are most sensitive to a reduction in cerebral blood flow. Since active development of this periventricular vasculature occurs predominantly in the last 16 weeks of human gestation, in the more immature the infant, even a lesser degree of hypoperfusion may cause cerebral ischemia.
      4. Resting cerebral blood flow to white matter is low.
      5. The cerebral circulation is also exquisitely sensitive to changes in $PaCO_2$ and, to a lesser extent, pH.
      6. These factors increase the potential for cerebral injury during periods of systemic hypotension or hypertension.
      7. Mechanical ventilation of the sick newborn infant can directly or indirectly affect CBF via systemic vascular or acid-base changes and increase the risk for cerebral injury (see below).

II. Mechanical Ventilation and Potential Brain Injury
   A. Direct Effects

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Table 86.1 Risk factors for cerebral injury in sick premature infants requiring mechanical ventilation

A.	Cerebral
	(1) Vulnerable capillary beds, e.g., germinal matrix, periventricular white matter
	(2) Pressure passive cerebral circulation
B.	Respiratory
	(1) Respiratory distress syndrome
	(2) Pneumothorax/pulmonary interstitial emphysema
C.	Vascular
	Perturbations in systemic hemodynamics: e.g., hypotension, hypertension, fluctuations in systemic blood pressure
D.	Perinatal factors
	Chorioamnionitis
E.	Consequences of mechanical ventilation
	(1) High mean airway pressure
	(2) Hypocarbia, hypercarbia

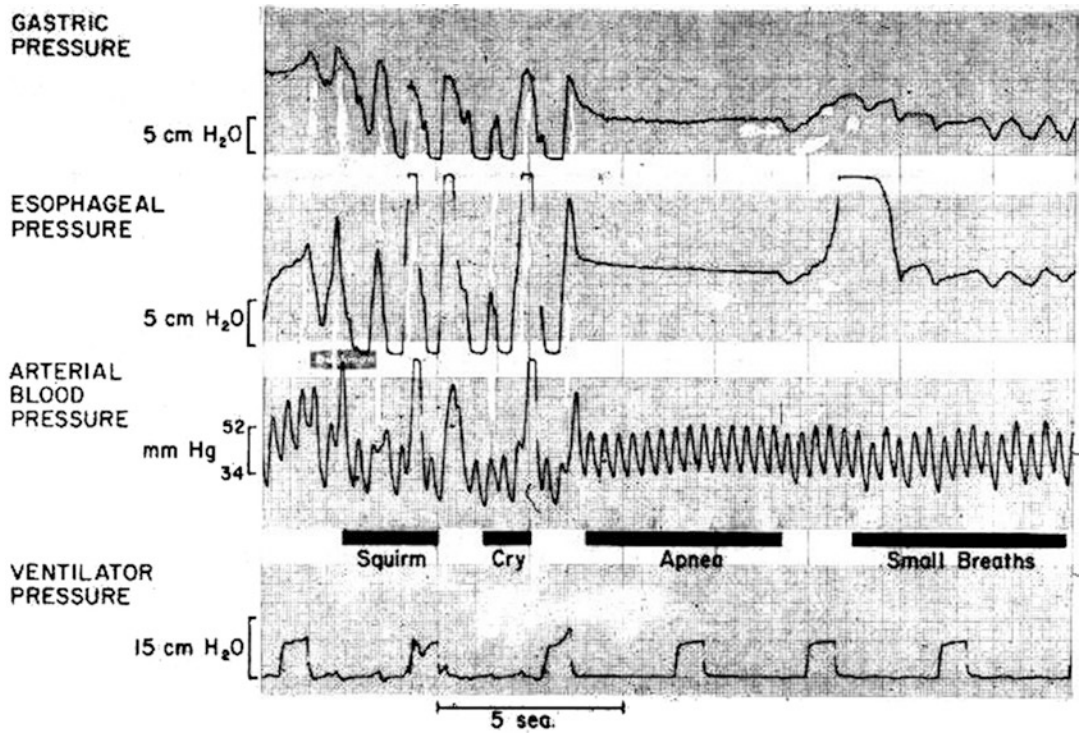

Fig. 86.1 Relationship of arterial blood pressure to asynchronous breathing (squirm, cry) compared to apnea of shallow breathing

1. Infants breathing out of synchrony with the ventilator.
   a. The sick preterm infant with RDS may exhibit beat-to-beat fluctuations in arterial blood pressure. The arterial fluctuations that affect both the systolic and diastolic components of the waveform appear to be related to the infant's own respiratory effort, which invariably is out of synchrony with the ventilator breaths.
   b. The fluctuations are increased with increasing respiratory effort and are minimized when respiratory effort is absent (Fig. 86.1).

c. The arterial blood pressure fluctuations are associated with similar beat-to-beat fluctuations in the cerebral circulation consistent with a pressure-passive state. The cerebral fluctuations, if persistent, have been associated with subsequent PV-IVH. Minimizing the fluctuation is associated with a reduction in hemorrhage.
d. Minimize fluctuations by:
   (1) Increasing ventilator support
   (2) Use of patient-triggered mechanical ventilation (e.g., assist/control or pressure support ventilation)
   (3) Use of sedatives
   (4) Skeletal muscle paralysis (This has become less frequent in recent years with synchronized ventilation).

2. Impedance of venous return
   a. Increase in mean airway pressure (Pāw) may impede venous return to the heart with two consequences:
      (1) An increase in central venous pressure and, as a result, an increase in intracranial venous pressure;
      (2) Decreased cardiac output (and thus decreased cerebral perfusion).
   b. A combination of an elevated venous pressure and a concomitant decrease in cardiac output markedly increases the risk for cerebral hypoperfusion within vulnerable regions of the brain (i.e., periventricular white matter).
   c. High Pāw is often utilized with either conventional or high-frequency ventilation in the sick infant with respiratory failure. Cardiac output (CO) is affected by changes in Pāw during HFOV in a similar manner to conventional ventilation with increases in Pāw associated with decreases in CO.
   d. An *association* between the use of high-frequency ventilation and PVL has been observed.
   e. Close hemodynamic monitoring is critical in the sick infant requiring high Pāw to support respiratory function.
   f. Some of the primary determinants of Pāw with conventional ventilation include inspiratory time (T_I), PIP, PEEP, and gas flow rates. A long T_I has been associated with a significant increase in air leak.
3. Volume-targeted versus pressure-targeted ventilation.
   There is evidence that volume-targeted ventilation (Chap. 38) as opposed to pressure-targeted ventilation in the premature infant leads to decreased occurrence of pneumothorax, hypocarbia, and the combined outcome of PVL and severe IVH. (*Wheeler*)
4. Effects of $PaCO_2$
   a. The cerebral circulation is exquisitely sensitive to changes in $PaCO_2$, (i.e., hypocarbia decreases CBF, and hypercarbia increases CBF). This relationship appears to be intact in the sick newborn infant.
   b. Hyperventilation with a reduction in $PaCO_2$ has been utilized as a strategy to augment pulmonary blood flow. The resultant hypocarbia may significantly reduce CBF.
   c. Hypocarbia in mechanically ventilated preterm infants, particularly during the first days of life has been shown to be to be an independent predictor of PVL, predisposing these infants to subsequent neurodevelopmental delay.
   d. Conversely, hypercarbia, with an increase in CBF, has been associated with an increased risk for PV-IVH.
   e. Devise a ventilation strategy to achieve normocapnia.

B. Indirect Effects: Complications of RDS
   1. Ventilated infants with RDS are at increased risk for air leak, (i.e., pneumothorax and/or pulmonary interstitial emphysema).
   2. There is a strong association between pneumothorax and subsequent PV-IVH.
   3. At the time of pneumothorax, there appears to be a marked increase in flow velocity within the anterior cerebral arteries, especially during diastole. This increase in flow velocity resolves some hours after resolution of the pneumothorax. These alterations on flow velocity within the anterior cerebral arteries likely result from:
      a. Increase in mean systemic pressure, especially diastolic pressure
      b. Decreased cardiac output
      c. Impeded venous return
      d. Increased $PaCO_2$
      e. Hemodynamic changes that accompany evacuation of pleural air.

C. Other Associations: Sensorineural hearing loss. Term infants with pulmonary hypertension subjected to hyperventilation are at increased risk for sensorineural hearing loss. The mechanism of such injury remains unclear.

D. Potential Therapeutic Strategies
   1. Reduce fluctuations in systemic hemodynamics.
      a. Synchronized ventilation
      b. Sedation
      c. Paralysis (rarely)
   2. Avoid systemic hypotension and/or hypertension (Chap. 56)
      a. Consider inotropic support
      b. Consider volume expansion
   3. Avoid impedance of venous return by using lower Pāw (if feasible)
   4. Avoid hypocapnia
   5. Avoid hypercapnia
   6. Avoid pneumothorax
      a. Surfactant administration for RDS
      b. Synchronized ventilation
      c. Wean as rapidly as tolerated
   7. All these risks are reduced with a complete course of antenatal steroids administered within 48 h of delivery

Suggested Reading

Altman DI, Powers WJ, Perlman JM, et al. Cerebral blood flow requirement for brain viability in newborn infants is lower than in adults. Ann Neurol. 1988;24:218–26.

Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2013;8:CD006764. doi:10.1002/14651858.CD006764.

Fabres J, Carlo WA, Phillips V, Howard G, Ambalavanan N. Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. Pediatrics. 2007;119:299–305.

Fujimoto S, Togari H, Yamaguchi N, et al. Hypocarbia and cystic periventricular leukomalacia in premature infants. Arch Dis Child. 1994;71:F107–10.

Greisen G, Munck H, Lou H. Severe hypocarbia in preterm infants and neurodevelopmental deficit. Acta Pediatr Scand. 1987;76:401–4.

Gullberg N, Winberg P, Selldén H. Changes in stroke volume cause change in cardiac output in neonates and infants when mean airway pressure is altered. Acta Anesthesiol Scand. 1999;43:999–1003.

Gullberg N, et al. Changes in mean airway pressure during HFOV influences cardiac output in neonates and infants. Acta Anaesthesiol Scand. 2004;48(2):218–23.
Hendricks-Munoz KD, Walter JP. Hearing loss in infants with persistent fetal circulation. Pediatrics. 1988; 81:650–6.
Hill A, Perlman JM, Volpe J. Relationship of pneumothorax to the occurrence of intraventricular hemorrhage in the premature newborn. Pediatrics. 1982;69:144–9.
Kaiser JR, Gauss CH, Pont MM, Williams DK. Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol. 2006;26:279–85.
Kamlin CO, et al. Long versus short inspiratory times in neonates receiving mechanical ventilation. Cochrane Database Syst Rev. 2004;18(4):CD004503.
Mirro R, Busija D, Green R, Leffler CB. Relationship between mean airway pressure, cardiac output and organ blood flow with normal and decreased respiratory compliance. J Pediatr. 1987;111:101–6.
Pape KE, Armstrong DL, Fitzhardinge PM. Central venous system pathology associated with mask ventilation in the very low birth weight infant. A new etiology for intracerebellar hemorrhage. Pediatrics. 1976;58:473–83.
Perlman JM, Volpe JJ. Are venous circulatory changes important in the pathogenesis of hemorrhagic and/or ischemic cerebral injury? Pediatrics. 1987;80:705–11.
Perlman JM, McMenanim JB, Volpe JJ. Fluctuating cerebral blood flow velocity in respiratory distress syndrome: relationship to subsequent development of intraventricular hemorrhage. N Engl J Med. 1983;309:204–9.
Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood flow velocity in preterm infants with respiratory distress syndrome. N Engl J Med. 1985;312:1353–7.
Pryds O. Control of cerebral circulation in the high-risk neonate. Ann Neurol. 1991;30(3):321–9.
Pryds O, Greisen G, Lou H, Friis-Hansen B. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation. J Pediatr. 1989;115:638–45.
Shankaran S, Langer JC, Kazzi SN, Laptook AR, Walsh M. Cumulative index of exposure to hypocarbia and hyperoxia as risk factors for periventricular leukomalacia in low birth weight infants. Pediatrics. 2006;118:1654–9.
Takenouchi T, Perlman JM. Intraventricular hemorrhage and white matter injury in the preterm infant. In: Neurology: neonatology questions and answers. 2nd ed. 2012.
Wheeler KI, Klingenberg C, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. Neonatology. 2011;100(3):219–27.
Wiswell TE, Graziani LJ, Kornhauser MS. Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high frequency jet ventilation. Pediatrics. 1996;98:918–24.

Section XIII

Other Considerations

Nursing Care of the Ventilated Neonate

87

Kimberly LaMar

As a provider of care for neonates in transport, progressive care or intensive care settings, nurses are essential to the health of this vulnerable population and their families. The following points should be considered:

I. History taking assists in focusing on an area while keeping the mind open to other possibilities. Complete history should include maternal for obstetric and past or existing medical conditions, family, social, delivery room, and neonatal information. It is also important to know environmental and community/epidemiologic impacts, such as the peak in Respiratory Syncytial Virus infections in fall and winter months.
II. Normal physiology, pathophysiology, and embryology are key to understanding the concepts of respiratory disease in the neonate
III. Assessment/Clinical examination is the frame for delivering nursing care to the neonate and his family. Details of the four approaches (observation, auscultation, percussion, and palpation) for assessment are available in publication. Considerations for the delivery of nursing care include:
    A. Use of pain scales and stress scales for use with neonates including preterm and ventilated neonates. (Chap. 62)
    B. Coordination of assessment with other care activities to avoid undue disturbance of required rest period for neonate
    C. Focused assessments through the ongoing care of the neonate rather than a full assessment frequently through the nursing shift to support rest and developmental care
IV. Monitoring in addition to cardiac, blood pressure, and temperature monitoring may include:
    A. Transcutaneous electrodes
        1. May measure oxygen or carbon dioxide levels through skin tension rather than arterial monitoring. Correlation is dependent upon the perfusion of skin.
        2. Complications include ineffective readings from technique, thermal burns, requiring frequent changes with subsequent increase in nursing time for care. This is especially true of prematures with very friable skin.

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B. Pulse oximetry
   1. Emits wavelengths to a receptor that measures oxygen saturation of Hgb
   2. Accuracy depends on perfusion, body temperature, Hgb level
C. End tidal CO_2 (capnometry)
   1. Device that attaches to end of endotracheal tube adaptor to assure position of endotracheal tube in the airway.
   2. It has a filter paper sensitive to carbon dioxide, changes color from purple to yellow if exposed to carbon dioxide exhaled in the trachea.

V. Radiology (Chap. 23)
A. Radiology is a specialty of medicine. This is intended as a few general guidelines for nurses. It is important that nurses understand basic principles for assisting in a quality radiographic examination and to assist in the identification of emergency conditions.
B. Anything placed on the neonate's skin should be carefully considered for absolute necessity in order to provide for the protection of skin integrity and avoid interference of imaging. Items to consider include heat probe patches, any monitoring electrodes and wires, warming pads that can cause a "waffle" appearance on film. All lines and tubes must be kept from crossing the field being examined.
C. Assure patient is positioned correctly in as symmetrical alignment as possible with head midline. Must assist the radiography technician in accomplishing this successfully to avoid negative outcomes such as dislodging tubes or lines.
D. Evidence suggests the post-extubation x-ray does not offer value and should not be done routinely without a specific purpose or pathophysiology being evaluated
E. Assess the reason for the examination using a systematic approach to avoid missing key findings
   1. Soft tissue, bony structures, mediastinum, thymus
   2. Trachea, pulmonary vasculature
   3. Chest-lungs, heart, diaphragm
   4. Abdomen-stomach, bowel gas pattern, visible masses
   5. Lines/tubes-endotracheal, umbilical catheters, peripherally inserted central catheters, chest drainage devices, naso/orogastric

VI. Pharmacotherapy
A. Neonatal nurses should be well versed in the drug therapies that have impact on the neonate's respiratory system. There are many drugs in development continuously with new drugs constantly being approved for use for neonates.
B. Drugs may be delivered a number of ways including orally, intramuscularly, subcutaneously, intervenously, inhaled, lingually, or by a dermal application.
C. Some of the more common types of medications may include sedatives, analgesics, antibiotics, muscle relaxants, nitric oxide, exogenous surfactants, diuretics, steroids, and bronchodilators.

VII. Anticipatory Guidance
A. Should be aware of normal course of disease or treatments
B. Anticipate the care required. Examples of these include:
   1. Normal physiology of transition from intrauterine life to extrauterine life including judicious use of inhaled oxygen
   2. Respiratory distress syndrome—has a diuretic phase 48–72 h after birth that will generally coincide with increased compliance and improvement in condition.
   3. Surfactant—immediate increase in compliance after dosing, requires less ventilatory support. An inability to recognize this may result in pneumothorax

4. Chronic Lung Disease—As lungs develop dependency on ventilation or oxygen, may have an increase in frequency and severity of desaturation spells.

VIII. Documentation
   A. Electronic medical record systems must be used appropriately to achieve expected results of decrease in errors from poor documentation
   B. Should be timely and accurate
   C. American Nurses Association has set standards for nurses that they must document in the medical record to communicate with other healthcare providers any information concerning their patient, whether in flowsheets, care plans, patient teaching, incident reports, etc.
   D. The Standards for Nursing Practice in British Columbia has set the purpose of documentation as improving communication to other nurses and care providers, promoting good nursing care in determining the effectiveness of treatments and necessary changes to the plan of care, and assisting in decision-making about funding for nursing research and resource management. Finally, it meets professional and legal standards for nursing measured against a standard of a reasonable and prudent nurse with similar education and experience.
   E. Should include:
      1. Assessment of the neonate
      2. Objective data, such as monitoring results, vital signs, evidence of pain and response to treatment of pain, ventilator, and/or oxygen therapies.
      3. Need for any nursing procedure, outcome, tolerance, complications of procedure, if any
      4. Amount, type, color, consistency of secretions
      5. Any apneic, desaturation, or bradycardia episodes not iatrogenically caused, such as associated with suctioning, positioning, tube placement
   F. Abbreviations
      1. Use as infrequently as possible
      2. Only use approved abbreviations
      3. Medication documentation with set standards, such as dosage documentation
      4. Print, not cursive writing for all abbreviations
      5. Use appropriate symbols
      6. Do not invent new ones
      7. Clarify unknown abbreviations with the writer

Nursing Procedures for Respiratory Care of the Neonate

Nursing procedures have an impact on the outcomes of neonates in the intensive care. Listed below are some more common procedures and concepts specifics to nursing.

I. Transport of neonates (Chap. 88)
   A. May be from one unit to another unit such as transport from delivery room to NICU or to operating suite, or to radiology. May be from one facility to another facility, city to city, country to country
   B. Regionalization of neonatal care has assisted in the establishment of facilities for levels of care and setting expectation for transport teams with expertise in this type of care.

II. Developmental care
   A. Nurses must collaborate with other healthcare providers, including therapists, in developmental care, speech, physical, and play therapies.
   B. Nurses are involved in developmental care in inpatient settings and outpatient clinics.

C. Pain management and developmentally appropriate care should gain particular attention during any nursing procedure related to respiratory care for neonates.
D. Alternative therapies, such as touch or massage therapy, may be considered, but in context of other care and needs of neonate and family.

III. Families
A. The American Nurses Association defines family as whomever the patient [parents] designate as family.
B. Principles of family centered care include the concept that parents are not visitors with restrictions in access to their child but are active participants in the healthcare decisions of their child.
C. Visitation should support the developmental and care needs of the neonate and family.
D. Nurses play a pivotal role in the dissemination and interpretation of communications to the family including education in the ongoing inpatient and future home care of the neonate.
E. Nurses must collaborate with other healthcare providers including social workers, case managers, and quality/peer review workers for the care and education of families. Multidisciplinary rounds at the bedside with families present are one technique to assure all aspects of care are being coordinated appropriately.
F. Nurses providing neonatal care must be well versed in cultural competence, patient safety, and ethics as these principles are continuously evident in neonatal nursing.
G. The role of nutrition in support of the respiratory system is gaining greater recognition. Neonatal nurses play a significant role in supporting adequate nutrition of neonates from education and support of breastfeeding or provision of breast milk to techniques for enteral and parenteral nutritional support.
H. Neonatal nurses must be educated in the provision of end-of-life care for neonates and their families. (Chaps. 93 and 94)

IV. Chest physiotherapy (CPT)/postural drainage (PD)
A. No benefit in the delivery room.
B. PD rarely used secondary to concerns on neonate's lack of cerebral autoregulation, especially in prematures.
C. CPT may include vibration although no evidence to support its use.
D. No evidence that routine CPT assists in clearing secretions or weaning from ventilator. Has been associated with an increase in intracranial hemorrhage in the first 24 h.
E. Must monitor neonate's tolerance during CPT.
F. Complications include hypoxia, bradycardia, rib fractures, subperiosteal hemorrhage.

V. Suctioning
A. Suctioning should never be performed on a schedule but rather according to need per an assessment with an understanding of the disease process.
B. Indicators for suctioning may include visible secretions, coarse or decreased breath sounds, decrease in saturations or acute change in blood gas results, agitation, change in vital sounds related to respiratory system, or "noisy" signal on pulmonary graphic monitor.
C. Upper airways should be suctioned gently.
D. Tracheal suctioning in the delivery room has been reserved for non-vigorous neonates or those requiring resuscitation in the immediate period after delivery regardless of the consistency of secretions or meconium.
E. Endotracheal tube suctioning is performed only to maintain the patency of the endotracheal tube and never for attempts to clear actual airways beyond the endotracheal tube. In addition:

1. Complications include hypoxemia, bradycardia, tachycardia, atelectasis, pneumonia, lability in blood pressure and intracranial pressure, trauma to airway, sepsis, tube blockage and dislodgement, and pneumothorax.
2. Pre-oxygenation has been shown to result in higher PaO_2 after suctioning with decreased recovery time although it has been unable to assess other outcomes such as retinopathy of prematurity, intracranial hemorrhage, and chronic lung disease.
3. Endotracheal tube suctioning has theoretical concerns about deep suctioning although there is no evidence to refute deep suctioning according to a recent Cochrane review. Such research may be unethical related to the known potential for harm associated with deep suctioning.
4. No clear evidence on how many passes should be made when suctioning but needs to be established each time suctioning is performed. One small study found no increase in secretion removal in two passes versus one pass.
5. Saline should only be used as a lubricant for the catheter and never instilled in the endotracheal tube. Research has shown it does not thin secretions nor does it mobilize secretions.
6. Head turning does not improve secretion removal and may be associated with intracranial pressure fluctuations and hemorrhage.
7. A Cochrane review found utilization of a closed system that allows for suctioning without disconnection from the ventilator may have short-term benefits such as decreased variability in oxygenation and heart rate. It was unable to assess the clinical relevance of these benefits or to assess other outcomes, and therefore, is unable to make any implications for practice.
8. Neonate should be contained during suctioning to improve tolerance.
9. Nurse must stay at bedside and assure recovery from suctioning.

VI. Artificial respirations through the use of assistive devices
   A. Neonatal Resuscitation Program (NRP) certification is essential for any caregiver applying respirations through the use of assistive devices;
      1. Anesthesia bags that require an oxygen or air source to inflate
      2. Self inflating bags that do not require an oxygen or air source to inflate
      3. T Piece devices or bubble CPAP to maintain continuous distending pressure
      4. May see use of these devices in the delivery room as well as the intensive care nursery, operating suites, or areas delivering care to neonates
   B. Nurse has the responsibility to collaborate with respiratory therapy, physicians, Extracorporeal Membrane Oxygenation (ECMO) technicians for the use of assistive devices
   C. Nurse should check equipment at least once a shift or upon entry to delivery or operating suite to assure equipment is in proper working condition, has safety features such as pop-off valves that are functional, and that equipment is easily accessible.

VII. Transillumination
   A. As an adjunct to clinical assessment and radiographs
   B. May see a diameter larger than 1 cm around the light when placed on anterior chest or in midaxillae line with air leaks in chest
   C. Edema, tape, equipment may decrease its usefulness
   D. Assists in locating vessels for cannulation

VIII. Chest drainage devices
   A. Should be familiar with the set up and function of the drainage devices before they are needed as these are emergent procedures.
   B. Connections should be secured with tape.

C. Tubing is typically very heavy and should be firmly secured to bed alleviating any tension which could dislodge drain.
D. Drainage device should be assessed for air bubbling in water seal chamber in most devices.
E. Chest tubes should be assessed for secretions, movement in tube of air or secretions.
F. No benefit to milking chest tubes and may cause harm.
G. Fluid removed should be assessed and documented at least once per 8 h shift unless clinical condition calls for increased monitoring.
H. Dressing should be assessed for occlusiveness, drainage under dressing, condition of skin, and any foul odor or change in color of secretions.
I. Should use a separate wall suction for clearing airway.
J. Must have an alternate set up for emergent need of second set up or replacement of current set up ready at bedside. Should also have an emergent means available at the bedside for a qualified healthcare professional to remove air quickly as a life-saving measure while setting up for chest tubes.

IX. Stabilization of respiratory devices
A. Nurse must pay careful attention to the securing and maintenance of respiratory devices such as the endotracheal tube; continuous positive airway pressure (CPAP) devices (whether prongs or masks); chest tubes; monitoring devices; ECMO catheters and supportive lines, such as venous and arterial access; environmental control, such as probes for temperature.
B. There are a number of devices on the market to secure ET tubes and CPAP devices. Nurse must meet the goal of skin integrity and avoid accidental dislodging of tubes by neonate, caregivers, or family members.
C. Babies requiring mechanical ventilation require complex monitoring. Nurses should keep themselves familiar with the newer developments and know how to handle troubleshooting.

X. Weighing
A. Need to establish frequency of weighing as part of daily plan of care.
B. Need at least two personnel to weigh labile neonate, one person may weigh stable neonate.
C. Preferable to disconnect respiratory devices while transferring to and from scale and reconnecting to ventilatory device while on scale and when returned to bed, if using a free standing scale. If in-bed scale, usually may leave on the ventilator during weighing process.
D. Perform a focused assessment of neonate before and after weighing.

XI. Positioning
A. Published data support prone positioning for monitored neonates requiring respiratory support to optimize respiratory performance.
B. May be additional benefit in raising head of bed slightly to allow gravity to contribute to expansion of lungs although position should be changed periodically to avoid pooling of secretions at base of lungs.
C. Must reinforce American Academy of Pediatrics “Back to Sleep” position that supine positioning during sleep is preferred for care at home where there is no benefit of monitoring and 24 h bedside care.
D. Massage therapy, touch therapy, and stroke therapy have empirical reports of benefits but must be considered in coordination of all care for tolerance by neonate.
E. Kangaroo care may be beneficial as an adjunct for respiratory care.
1. May kangaroo neonate receiving ventilation
2. Preferable to assist mother to transfer neonate to chest before mother sits in chair rather than handing neonate to mother who is sitting

F. Co-bedding of multiples
   1. Gaining support in research but lack of clear evidence for best methodology to implement its use
   2. Some limited anecdotal use in ventilated infants with improvement in respiratory status, weaning from ventilator without increase in spontaneous extubation or infectious risk, but as a newer modality should still be approached in context of total care and tolerance by neonate.

Suggested Reading

Catlin A, Brandon D, Wool C, Mendes J. Palliative and end of life care for newborns and infants: from the National Association of Neonatal Nurses. Adv Neonatal Care. 2015;15(4):239–40.

Galbusera V, Battan AM, Mandelli N. The assistance of the ventilated infant: role of the nurse in the management of the endotracheal tube. Pediatrics. 2010;62(3 Suppl 1):169–71.

Hemmat F, Atashzadeh-Shoorideh F, Mehrabi T, Zayeri F. A survey of nurses' awareness of patient safety culture in neonatal intensive care units. Iran J Nurs Midwifery Res. 2015;20(4):490–5.

Miedaner F, Allendorf A, Kuntz L, Woopen C, Roth B. The role of nursing team continuity in the treatment of very low birth weight infants: findings from a pilot study. J Nurs Manag. 2016;24(4):458–64.

Rogowski JA, Staiger DO, Patrick TE, Horbar JD, Kenny MJ, Lake ET. Nurse staffing in neonatal intensive care units in the United States. Res Nurs Health. 2015;38(5):333–41.

Shaw RR. Late preterm birth: a new nursing issue. Am J Matern Child Nurs. 2008;33(5):287–93.

Smith JR, Donze A, Wolf M, Smyser CD, Mathur A, Proctor EK. Ensuring quality in the NICU: translating research into appropriate clinical care. J Perinatal Neonatal Nurs. 2015;29(3):255–61.

Transport of Ventilated Babies

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Steven M. Donn and Molly R. Gates

I. Equipment
  A. Goals of Neonatal Transport
    1. Optimally, all infants requiring neonatal intensive care should be delivered at a facility capable of providing such services. Unfortunately, numerous circumstances arise which prevent this, including geographical and economic constraints, and unexpected complications of labor, delivery, or the neonatal period.
    2. The next best option is maternal transport when time and circumstances permit the transfer of a mother with an identified high-risk pregnancy to a facility able to care for the infant.
    3. When neither of these options is possible, transport of a critically ill newborn must be accomplished in a manner that maximizes safety and minimizes complications to the infant. Neonatal transport must be considered an extension of the Neonatal Intensive Care Unit, and the same philosophy of care delivered in the NICU should be delivered in the transport vehicle.
  B. Transport Vehicles
    1. Ground ambulance
      a. The most frequently used vehicle
      b. Provides the most access to the patient during transport
      c. Enables the largest number of transport team members
      d. Easy to stop vehicle in the event of patient deterioration and need for medical intervention
      e. Subject to traffic delays, road conditions, and weather (though to a lesser extent than airborne vehicles)
      f. Should be adaptable to special needs of neonatal transport

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2. Helicopter
   a. Provides a rapid means of transport
   b. Not subject to traffic or road conditions, but weather conditions may preclude use
   c. Size of vehicle may limit number of team members
   d. Landing pad may not be adjacent to hospital, requiring extra time and possible ambulance use
   e. Virtually no access to patient en route
   f. Must land in event of patient deterioration
   g. Requires special training of crew
   h. Expensive
3. Fixed Wing Aircraft
   a. Enables long distance transport
   b. Subject to weather conditions
   c. Size of vehicle may limit number of team members
   d. Rapid, although travel time to/from airport and hospitals must be considered.
   e. Intermediate (though limited) access to patient en route; deterioration may be problematic
   f. Special problems at higher altitudes
   g. Expensive
4. Combination

   At times, it may be advantageous to combine modes of transport, such as the "fly-drive" method. Transport team and only essential emergency equipment is flown to referring hospital, helicopter returns to tertiary facility immediately, while ambulance is dispatched with the remainder of transport equipment and possibly additional team members. This eliminates helicopter "down time" while infant is stabilized, and allows creation of a more stable environment for transport of infant.

C. Transport Incubator and Related Equipment
1. Several commercial types are available.
   a. Self-contained types include virtually all necessary components as "built-ins," which may offer a better price, although repairs may be costlier and may take the device out of service for a longer period of time.
   b. More basic models are available, to which specific components can be added according to the specific needs of an institution.
2. Basic necessities
   a. The incubator must be able to maintain the infant in a thermo-neutral environment, and for small infants, infant servo-controlled heaters are recommended. This is especially important for winter climates that have a significantly low ambient temperature. Additional heat-conserving or heat-generating devices are necessary in colder climates.
      (1) Heat shield or thermal blanket
      (2) Exothermic chemical mattress
   b. An electronic cardiorespiratory monitor, which should work well despite vehicle vibration or electrical interference
   c. A pulse oximeter with motion artifact correction
   d. A means of recording the temperature of the incubator and the baby
   e. A source of air and oxygen, including a blender and an analyzer, and the means to deliver increased FiO_2 to the infant
   f. A self-contained power source (battery) and the ability to be run by an external power source (e.g., wall electricity, vehicle generator, or inverter)

g. Easy accessibility to the infant (e.g., portholes, front and side doors)
h. A means of securely anchoring the incubator within the transport vehicle
i. All necessary resuscitative equipment, including
   (1) Bag and masks (assorted sizes)
   (2) Laryngoscope and endotracheal tubes (assorted sizes)
   (3) Vascular access devices
   (4) Emergency medications and the means to deliver them
j. Adequate lighting, including a back-up flashlight

3. Recommended options
   a. Transport ventilator, especially if transporting critically ill infants or transporting long distance
   b. Communications device
      (1) Vehicle radio system
      (2) Cellular telephone
   c. Vascular infusion pump(s)
   d. Blood pressure monitoring device, either invasive or noninvasive
   e. Transcutaneous $TcPO_2/PCO_2$ device or portable blood gas analyzer for long-distance transport of a critically ill infant

D. Transport Equipment (Tables 88.1 and 88.2)

Table 88.1 Typical transport equipment

Adapters
Adhesive tape ½″ and 1″
Alcohol wipes
Antiseptic ointment
Antiseptic swabs
Blood culture bottle
Blood supplies
BP transducer
Bulb syringe
Butterflies: 23 g, 25 g
Camera with film
Catheters: 22 g, 24 g
Chest tubes #10
Connectors
Cotton balls
DeLee suction tube
$D_{10}W$: 250 mL bag
Dressings, 4×4
Dressings 2×2
Forceps, sterile
Gauze squares: see dressings
Gloves, sterile
Glucose screening strips
Heimlich valves
Hemostats, sterile
Labels

(continued)

Table 88.1 (continued)

Lancets
Large bore tubing
Lubricating gel
Microbore tubing
Needles: 18 g, 21 g, 25 g
NG tubes: 5 and 8 Fr.
Occlusive dressing
Paperwork (extra)
Platelet infusion set
Pneumothorax aspiration set
Replogle tubes: 6 and 8 Fr.
Saline Squirts
Scalpel
Scissors, sterile
Stopcocks
Stopcock plugs
Suction catheters: 6 and 8 Fr.
Suture: 4-0 silk
Syringes: TB
Syringes: 3 mL
Syringes: 5 mL
Syringes: 10 mL
Syringes: 20 mL
Syringes: 30 mL
Syringes: 60 mL
T-connectors
Tape, plastic: ½″ and 1″
Tape measure, sterile
Thermometer
Toumey syringe: 60 mL
Umbilical catheters
Umbilical double lumen
Umbilical catheter insertion tray
Umbilical tape
Waterproof adhesive tape

Equipment should be readily available to treat any emergency that might occur at either the referring hospital or en route.

E. Transport Medications (Table 88.3)
Medications should also be readily available, as well as the means to deliver them (e.g., syringes, diluents, catheter connectors). Medications must be secured and checked regularly for condition and expiration date.

F. Miscellaneous Issues
1. A digital camera is useful, both to give the parents a picture of the infant and to document any unusual physical findings.
2. All necessary documents for the medical record as well as printed information given to the parents should be prepared in advance. Keeping them together by means of a clipboard works well.

Table 88.2 Respiratory care transport equipment

Hood and aerosol tubing (include extra tubing)
Venturi mask
Stethoscope
Infant restraints
Chemical exothermic mattress
Resuscitation bag
Flashlight
Cargo netting
Wrench for medical gas “E” tanks
Surfactant administration devices
Electronic cardiorespiratory monitor
ECG electrode patches and leads
Blood pressure cable
Neonatal mask
Infant mask
Manometer
PEEP valve
22 mm connectors (2)
15 mm connectors (2)
Rubber connector
Endotracheal tubes
2.5 mm (2)
3.0 mm (2)
3.5 mm (2)
4.0 mm (2)
Endotracheal tube adapters
Endotracheal tube stylets (2)
Pulse oximeter
Pulse oximetry probes with elasticized wrap (2)
Laryngoscope handle with spare batteries and bulb
Laryngoscope blades
Miller #0
Miller #1
Magill forceps
Hemostats and scissors
Adhesive tape
Adhesive solution
Cotton swabs
Adhesive remover
Nasal CPAP prongs, assorted sizes
Sterile water soluble lubricant
Oxygen tubing (2)
Oxygen tubing connectors (2)
Flowmeter nipples (2)
Suction catheters, 6 French (2)
Air and oxygen connectors
Nasal cannula, newborn
Nasal cannula, premature
Aluminum oxygen tank
Aluminum air tank
Inhaled nitric oxide and delivery system

Table 88.3 Typical transport medications

Adenosine 3 mg/mL
Ampicillin 250 mg
Aquamephyton 10 mg/mL
Atropine 0.1 mg/mL
Calcium Gluconate 10 %
Dexamethasone 4 mg/mL
Dextrose in water, 25 %
Diazepam 5 mg/mL
Digoxin 25 μg/mL
Dobutamine
Dopamine 40 mg/mL
Epinephrine 1:10,000
Furosemide 10 mg/mL
Gentamicin 10 mg/mL
Glucagon and diluent
Heparin
Isoproterenol 1 mg/5 mL
Lidocaine 1 %
Lidocaine 2 %
Lorazepam 2 mg/mL
Midazolam 1 mg/mL
Narcan 0.4 mg/mL
Pancuronium 1 mg/mL
Potassium chloride
Prostaglandin E (PGE)
Sodium bicarbonate, 4.2 % (0.5 mEq/mL)
Sodium chloride
Sterile water
THAM
5 % Albumin
Morphine 0.5 mg/0.5 mL
Phenobarbital 30 mg
Phenobarbital 60 mg
Surfactant

3. Team members must protect themselves at all times.
   a. Dress appropriately for the weather.
   b. Use flame-retardant clothing for air transport.
   c. Use approved helmets for air transport.
   d. Have provisions (e.g., snacks and drinks) for long-distance transports, especially if there is a likelihood of missing meals.
   e. Always use seat belts.
   f. Maintain current knowledge of transport supplies and procedures.
4. Packs or containers for miscellaneous transport gear should be lightweight, sturdy, well-labeled, and secure. Housing all supplies needed for a given procedure in one compartment is useful.

II. Stabilization of the Transported Newborn
   A. Basic Stabilization Upon Arrival

1. Respiratory
   a. Assess the adequacy of gas exchange
      (1) Clinical assessment
         (a) Breath sounds
         (b) Chest excursions
         (c) Skin color
         (d) Presence of distress
      (2) Laboratory assessment
         (a) Blood gas analysis
         (b) Chest radiograph
   b. Airway management
      (1) Patency (suction if necessary)
      (2) If already intubated and tube position is satisfactory, secure tube adequately.
      (3) If not intubated, consider elective intubation if there is any chance that this might become necessary en route. It is safer (and easier) to do this under controlled conditions at the referring hospital than in the back of an ambulance or while in flight.
   c. Place an orogastric tube (especially important for air transport).
2. Cardiac
   a. Assess tissue perfusion, treat if inadequate.
      (1) Blood pressure
      (2) Capillary refill time
      (3) Urine output
   b. Auscultation
      (1) Murmur
      (2) Abnormal heart sounds
      (3) Abnormal rhythm
   c. Chest radiograph
   d. If cyanotic congenital heart disease suspected, consider starting infusion of Prostaglandin E (consult with neonatologist or cardiologist before doing so)
3. Hematologic
   a. Check for sites of active bleeding.
   b. Assure all vascular connections are secure.
   c. Check hematocrit if not already done. Consider transfusion if low and infant is critical, and transport is anticipated to be long.
4. Metabolic
   a. Perform glucose screen. If low, check serum glucose and treat.
   b. Assure adequate glucose load during transport. Stress may increase consumption.
   c. Check baby's temperature and maintain thermoneutrality. Pre-warm transport incubator before transferring baby to it.
5. Vascular access
   a. It is generally best to achieve vascular access prior to departing the referring hospital in the event that an emergency arises en route.
   b. A well-placed peripheral venous line is usually sufficient.
   c. If difficulty in securing peripheral venous access, consider placing an umbilical venous catheter. Confirm position radiographically before infusing medications through it (Chap. 16).
   d. An umbilical artery catheter (Chap. 16) is generally not needed for transport unless no other vascular access can be achieved. It is an elective procedure, which can be

time-consuming and can significantly delay the departure and prolong the transport. Many community hospitals are ill equipped to handle a complication. As a rule, this procedure is best left until the infant is admitted to the NICU.

6. Miscellaneous issues
   a. Make sure the infant is secured within the transport incubator. Retaining straps should be used but must not be too tight to impair thoracic excursions.
   b. Tighten all connections (e.g., endotracheal tube adapter, ventilator circuit, vascular catheter connections, power lines) before departing. Label all lines.
   c. Consider the use of infant "ear muffs" to decrease noise exposure for air transports.
   d. Always have spare batteries for equipment that requires them.
   e. Give the parents an opportunity to see and touch the infant before departing the referring hospital.
   f. Be sure baby is properly identified.
   g. Collect records from referring hospital to accompany infant.

B. Stabilization During Transport
   1. If the infant was well stabilized in the referring hospital, there should be little else necessary once underway.
   2. Check to be sure all of the vehicle equipment is functioning at the time the switch from incubator to vehicle is made.
      a. Power (generator or inverter)
      b. Gas (air and oxygen) sources
      c. Suction source
   3. Be sure the transport incubator is securely anchored and that there is no loose equipment or tanks, which could cause a hazard en route.
   4. Monitoring of the infant during the transport should be no different than that which is done in the NICU.
   5. Should the infant unexpectedly deteriorate en route, it is generally best to stop the vehicle (this may mean landing if in a helicopter) while attending to the infant. It is extremely difficult to perform resuscitative procedures and draw up and administer medications in a moving vehicle, and to do so places both the patient and the transport team members at risk for injury.

C. After the Transport
   1. A thorough transport note should be written in the medical record to document the events of the transport, as well as any treatments rendered, and how the baby tolerated any procedures.
   2. All supplies should be promptly replenished.
   3. Any mechanical problems (vehicle, equipment, or other) should be reported and corrected immediately.
   4. Give feedback to the referring physician and notify the parents that the baby arrived safely.

III. Special Considerations

A. Intensive Care
   1. Although transport vehicles are an attempt at extending intensive care services to referring hospitals, they are not intensive care units. One of the most difficult decisions during neonatal transport is deciding whether a specific procedure should be performed in the referring hospital/transport vehicle or deferred until admission to the NICU. Some aspects to consider include:
      a. Urgency of the procedure in light of the patient's condition (i.e., elective, semi-elective, or emergent)

   b. Availability of experienced personnel to assist
   c. Suitability of available equipment
   d. Ability to handle a major complication, if it occurs
   e. Adequacy of monitoring the patient during the procedure
2. Some procedures which are of an elective nature should be considered in view of the difficulty with which they are performed in a transport vehicle
   a. Endotracheal intubation. Control of the airway in a baby with respiratory distress is crucial. Do not wait until the baby is in marked distress to intubate.
   b. Vascular access. Placement of a peripheral intravenous catheter prior to departure from the referring hospital is strongly advised. This is an extremely difficult procedure in a dimly lit and moving vehicle, especially if the baby is hypotensive. It also enables prompt treatment of problems such as hypoglycemia.
3. If transport to an ECMO facility is being considered, remember the following:
   a. Not all transport teams can provide inhaled nitric oxide during the transport. Do not delay transfer for PPHN if this is the case.
   b. It is, at present, infeasible in most instances to transport a baby on high frequency ventilation. If a baby cannot be safely managed temporarily by conventional or manual ventilation, transport may be ill advised.

B. Effects of Altitude
1. Impact on respiratory status
   a. The partial pressure of oxygen decreases as altitude increases; thus, the availability of oxygen to the baby decreases and alveolar hypoxia increases. The baby must work harder to achieve satisfactory gas exchange.
   b. The cabins of fixed-wing aircraft are either pressurized or non-pressurized. If non-pressurized, this effect of altitude will occur early. Pressurized cabins generally have a pressure equivalent to that at 8000 ft rather than atmospheric pressure at sea level.
   c. These effects must be appreciated in the management of respiratory insufficiency. They underscore the need for close monitoring (i.e., pulse oximetry) as well as anticipating the need for increasing support as altitude is increased.
2. Impact on contained gases
   a. As altitude increases, and thus barometric pressure decreases, the volume of contained gases also increases.
   b. This effect must be taken into consideration in the management of the infant.
      (1) Gas in the stomach and bowel will expand, potentially aggravating respiratory distress by impinging on the diaphragm. Be sure an orogastric or nasogastric tube is in place to vent the stomach.
      (2) Abnormal accumulations of gas in the chest (e.g., pulmonary interstitial emphysema, pneumomediastinum) can also expand, leading to pneumothorax. Observe closely and be ready to intervene.
   c. The effects of altitude must also be considered in treatments.
      (1) Medications and fluids are packaged at sea level, and thus are at higher pressure at altitude. Take caution when drawing up medications from vials.
      (2) As the aircraft descends, carefully observe gravity drip infusions; external pressure may create a gradient which causes reversal of flow from the baby with subsequent blood loss.

C. Hypothermia for Neuroprotection
1. Occasionally, babies may need to be transferred for hypothermic neuroprotection following intrapartum hypoxic-ischemic encephalopathy.

2. Passive cooling may be initiated in the referring hospital and continued during transport.
   a. Radiant warmer is discontinued.
   b. Attempt to reach a rectal temperature of 33.5–34.5 °C.
   c. In rare instances, use of ice packs may be necessary.
3. Keep careful attention to temperature during transport. Make certain rectal thermometers are able to detect temperatures below this range to avoid over-cooling.

D. Miscellaneous Effects on the Infant
1. Noise and vibration. While not totally avoidable, some measures can be taken to minimize their effects.
   a. Muffle noise by using "ear muffs" or cotton inserts.
   b. Make sure vehicle suspension is in good order.
   c. Avoid excessive speed or poorly maintained roads, if possible.
2. Cold stress
3. Position infant optimally for clinical support and to maximize caregivers' ongoing assessment.

E. Miscellaneous Effects on the Transport Team
1. Motion sickness, aversion to exhaust fumes
2. Stress
3. Safety issues

F. Effects on the Family
1. Separation from the infant (especially for the mother)
2. Economic hardship
3. Psycho-social stress

G. Systems Issues
1. Organized procedures must be in place and communicated to all potential participants for requesting, accepting, dispatching, and conducting neonatal transports.
2. Periodic review of transports enables identification and correction of system problems.
3. Contingency planning and prior consideration of unusual circumstances improves response and lessens stress.

Suggested Reading

Bossley CJ, Cramer D, Mason B, Smyth J, et al. Fitness to fly testing in term and ex-preterm babies without bronchopulmonary dysplasia. Arch Dis Child Fetal Neonatal Ed. 2012;97(3):F199–203.

Donn SM, Gates MR. Neonatal transports. In: Donn SM, editor. Michigan manual of neonatal intensive care. 3rd ed. Philadelphia: Hanley & Belfus; 2003. p. 447–55.

Donn SM, Faix RG, Gates MR. Neonatal transport. Curr Prob Pediatr. 1985;15:1–63.

Donn SM, Faix RG, Gates MR. Emergency transport of the critically ill newborn. In: Donn SM, Faix RG, editors. Neonatal emergencies. Mt. Kisco, NY: Futura; 1991. p. 75–86.

Gates MR, Geller S, Donn SM. Neonatal transport. In: Donn SM, Fisher CW, editors. Risk management techniques in perinatal and neonatal practice. Armonk, NY: Futura; 1996. p. 563–80.

Lilly CD, Stewart M, Morley CJ. Respiratory function monitoring during neonatal emergency transport. Arch Dis Child Fetal Neonatal Ed. 2005;90:F82–3.

Role of the Respiratory Therapist in the NICU

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Timothy Myers

I. As respiratory therapists spend 24 h per day with critically ill newborns in a neonatal intensive care unit, respiratory care is essential to the eventual recovery and discharge of these fragile patients with cardiopulmonary manifestations.
II. History information gathering that assists in focusing on potential etiologies of cardiorespiratory compromise, while keeping the mind open to other possibilities (e.g., sepsis) include:
    A. Maternal, including past and existing medical conditions
    B. Family
    C. Social
    D. Delivery room
    E. Neonatal
III. Embryology, normal physiology, pathophysiology, cardiac and congenital defects, and special conditions of the newborn are key to understanding the concepts of cardiopulmonary disease in the neonate.
    A. Embryology
        1. Five periods of embryonic lung growth
        2. Development and stages of the heart growth
        3. Fetal Circulation: pressures, flow, and shunts
        4. Development and function of placenta and umbilical cord
    B. Normal physiology
        1. Concepts of surface tension
        2. Laplace's Law
        3. Alveolar mechanics
        4. Surfactant function, purpose, and testing
        5. Fetal lung fluid function, purpose, and testing
        6. Location and function of baroreceptors and chemoreceptors
    C. Pathophysiology
        1. Assessment of fetal status (amniocentesis, fetal heart rate, scalp pH)
        2. Meconium presence in amniotic fluid

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3. Identify the most common birth presentations.
4. Impact of multifetal gestation
5. Physiologic changes during labor, delivery, and after birth

D. Cardiac Defects: defects occur in approximately 1 of every 100 deliveries. Depending on defect, newborn may have mild signs that require minimal intervention to severe, life-threatening signs that require immediate intervention. It is important for the respiratory therapist to understand the defects and interventions necessary to stabilize the newborn.
   1. Persistent Pulmonary Hypertension of the Newborn (PPHN)—the ability to quickly determine that fetal circulation has not converted to normal "adult" circulation leads to quick interventions for the management and treatment of this condition.
   2. Ductal-dependent lesions
      a. Patent Ductus Ateriosus
      b. Atrial and ventricular septal defects
   3. Mixing lesions
      a. Tetraology of Fallot
      b. Transposition of the Great Vessels
      c. Total Anomalous Pulmonary Venous Return
      d. Truncius Arteriosus
      e. Hypoplastic Left Heart Syndrome
   4. Non-mixing lesions
      a. Subaortic stenosis
      b. Coarctation of the Aorta
      c. Tricuspid Atresia

E. Congential Defects
   1. Airway
      a. Upper
      b. Lower
      c. Fistulas
   2. Diaphragmatic Hernia (Chap. 75)

F. Pulmonary Conditions
   1. Transient Tachypnea of the Newborn (TTN)—Most commonly found in newborns delivered by Cesaren Section. Inability to properly eliminate fetal fluid leads to interventions based on clinical signs and severity.
   2. Respiratory Distress Syndrome (RDS) (Chap. 69)
      a. Etiology—a primary cause of respiratory disorders of the preterm
      b. Pathophysiology—surfactant deficiency and morphologic immaturity
      c. Clinical signs, diagnosis, and severity
      d. Treatment
   3. Bronchopulmonary Dysplasia (BPD)—typically occurs following of RDS (Chaps. 79–81)
      a. Pathophysiology and diagnosis
      b. Treatment—prevention is the primary treatment methodology in scrutinizing respiratory care interventions at necessary levels for treatment of pulmonary conditions
   4. Pulmonary dysmaturity—understanding the pathophysiology, clinical signs, and treatment of this disorder with no underlying apparent lung disease
   5. Barotrauma/Air leaks (Chap. 82): While relatively rare in today's NICU, the ability to quickly assess and diagnose air leaks and quickly correct the cause while managing the condition are paramount.

G. Apnea (Chap. 76)
   1. Central—most common is Apnea of Prematurity
   2. Obstructive
   3. Mixed

IV. Techniques of Resuscitation and Stabilization
   A. Understand factors and outcomes of fetal asphyxia and apnea
   B. Understand the components of resuscitation as define in AHA and AAP standards outlined in Neonatal Resuscitation Provider program (Chap. 14)
      1. Airway and breathing
      2. Circulation support
      3. Delivery of medications
      4. Environmental conditions and control
      5. Special delivery room procedures (e.g., line insertion)
      6. Equipment of resuscitation
   C. Apgar and gestational age scoring

V. Assessment
   A. Observation
      1. General state
         a. Sleeping, awake, alert, crying or motions of crying, if ventilated
         b. Must be an objective assessment as patient cannot give subjective feedback
      2. Assessment of Respiratory Distress
         a. Color
            (1) Generalized and central color determined by examining the mucous membranes and skin for ruddiness, intense redness, pallor, or cyanosis, and jaundice
            (2) Signs and rationale of cyanosis
            (3) Cyanosis results from the presence of >5 g/dL of unsaturated Hgb.
         b. Mouth and Nose
            (1) Secretions: amount, color, consistency. Usually, clear or white. Excessive secretions may be associated with a tracheo-esophageal fistula.
            (2) Nasal flaring to signify "air hunger" to decrease resistance in upper airways and/or collapse
            (3) Grunting is the infant exhaling against a partially closed glottis in an attempt to slow the respiratory flow and maintain a higher functional residual capacity.
         c. Chest assessment
            (1) Size and shape. normal chest size in a full-term infant is 33 ± 3 cm, or 2 cm less than the head circumference
            (2) Hyperinflation or "barrel chest" in meconium aspiration syndrome or other gas trapping conditions
            (3) Chest symmetry assessed at the nipple line
            (4) Chest ventilation synchrony-chest rises with spontaneous or mechanical breath
            (5) Respiratory rate counted for a full minute. Tachypnea is a rate >60/min, apnea is cessation of respirations for 20 s or longer, and hypopnea is shallow spontaneous respiratory effort.
            (6) High frequency ventilation assessed by amount of chest vibration or "wiggle."
            (7) Retractions (recessions) are caused by infant's soft cartilage and muscle groups that draw in to augment respiration. May be intercostal, subcostal, sternal, suprasternal, and/or subxiphoid.

d. Auscultation
(1) External
(a) Air leak may be heard in very infants on ventilatory support due to uncuffed endotracheal tubes. These may also be identified with flow-volume loops on the ventilator graphics.
(b) Stridor is a high pitched upper airway sounds heard either at inspiration or expiration. May be associated with post-extubation, edema, laryngomalacia, or damage to the vocal cords.
(2) Internal
(a) Assess with warmed neonatal stethoscope, comparing and contrasting both sides of chest, anterior and posterior.
(b) Must assess for symmetry of breath sounds, diminished or absent sounds, and for synchrony in ventilated patients
(c) Neonates on high frequency ventilation should be auscultated on and off the ventilator. Should coordinate this time to coincide with care requiring brief pauses of the ventilator.
(d) Crackles are fine, medium, or coarse and represent air and/or fluid movement in the small or large airways.
(1) Fine originate in the dependent lobes and are heard at the end of inspiration and may be associated with RDS or BPD.
(2) Medium crackles originate in the distant airways and may be associated with air moving through tenacious fluid, such as with pneumonia or TTNB.
(3) Coarse crackles are associated with fluid in the large airways and usually resolve with airway suctioning.
(e) Wheezes, while rare in the neonate, may be heard on end expiration.

VI. Assessment of Oxygenation and Ventilation
A. Transcutaneous (Chap. 18)
1. May measure oxygen or carbon dioxide tensions through skin rather than arterial monitoring or pulse oximetry. Correlation is dependent upon the perfusion of skin.
2. May have a combination of transcutaneous carbon dioxide and pulse oximetry through an electrode sensor placed on the abdomen or thigh.
3. Trending—not an absolute reading as these is a gradient between arterial oxygen and transcutaneous oxygen levels in most patients that require this type of monitoring.
4. Complications include ineffective readings secondary to technique, over or underheating. Skin sensitivity requires frequent electrode site changes, especially for premature babies with very friable skin.

B. Pulse oximetry (Chap. 19)
1. Emits wavelengths to a receptor that measures oxygen saturation of Hgb
2. Monitor intermittently or continuously
3. Accuracy depends on perfusion, body temperature, Hgb
4. Has been used in some instances of closed loop ventilator systems to control inspired oxygen concentration

C. Capnography and end-tidal CO_2 detectors (Chap. 21)
1. Capnography—uses spectrophotometric infrared analysis of exhaled gas to determine end-tidal CO_2. Is available in both sidestream and mainstream analyzers. As these monitors either sample a sizeable portion of the exhaled gas (sidestream) or contribute a significant amount of deadspace (mainstream), they are not normally used as part of the management of newborns, especially premature.

2. One type attaches to endotracheal tube adaptor to assure position of endotracheal tube in the airway. It has a filter paper sensitive to carbon dioxide, changes color from purple to yellow if exposed to carbon dioxide.

VII. Radiology—there are distinct clinical skills required of the respiratory therapist in this specialty area to allow proper assessment, management, and treatment of the newborn. It is important that respiratory therapists understand basic principles for assisting in a quality radiographic exam and to assist in the identification of emergency conditions (Chap. 23).
   A. Anything placed on the neonate's skin should be carefully considered for absolute necessity and potential for interference with imaging. Items to consider include any monitoring probes, electrodes and wires, and warming pads that can cause a "waffle" appearance on image. All lines and tubes must be kept from crossing the field being examined.
   B. Assure patient is positioned correctly in as symmetrical an alignment as possible with head in a neutral position in the midline. Must assist the radiography technician in accomplishing this successfully to avoid negative outcomes such as dislodging of tubes or lines.

VIII. Pharmacotherapy (Chap. 59). Respiratory therapists should be well versed in the drug therapies that have impact on the neonate's respiratory system. Drugs may be delivered a number of ways including orally, intramuscularly, subcutaneously, intravenously, endotracheally, sublingually, or dermally.

IX. Documentation (Chap. 95)
   A. Should be timely and accurate into a medical record that is accessible by NICU team and consultants
   B. American Association for Respiratory Care has set standards for respiratory therapist that they must document in the medical record to communicate with other healthcare providers any information concerning their patient whether in flowsheets, care plans, electronic medical records, patient teaching, incident reports, etc.

X. Transport of Neonates (Chap. 88)
   A. May be from one unit to another unit, such as transport from delivery room to NICU, or NICU to operating suite, or transition nursery to radiology. May be from one facility to another facility, city to city, or even country to country and requires a highly skilled, highly trained team.
   B. Regionalization of neonatal care has assisted in the establishment of facilities for levels of care and setting expectations for transport teams with expertise in this type of care.
   C. The respiratory therapist must understand the nuances of altitude and oxygen.
   D. Properly maintained and assessed equipment is imperative to the safe and efficient transport of newborns. Back-up systems should be in place for all essential equipment.

XI. Respiratory Care of the Newborn
   A. Artificial respirations through the use of assistive devices: manual, t-piece resuscitators or ventilators. Neonatal Resuscitation Program (NRP) certification is essential for any caregivers applying inflations through the use of assistive devices:
      1. Anesthesia bags require an oxygen or air source to inflate.
      2. Self inflating bags do not require an oxygen or air source to inflate.
      3. T-Piece devices maintain PEEP.
      4. May see use of these devices in the delivery room as well as the NICU, operating suites, or any areas delivering care to newborns
   B. Oxygen Therapy. Understandig the indications and potential hazards/complications, as well as, the equipment utilized to manage oxygen in the newborn is a necessary concept for all respiratory therapist in this highly sensitive patient population.

1. Oxygen blenders, analyzers, and neonatal flowmeters are absolutely critical in this patient population to titrate oxygen delivery to this highly sensitive patient population.
2. Humidification—as oxygen is a dry, cool gas, heated humidification is more critically important to the neonate than any other patient population regardless of duration of delivery
3. Low-flow devices—(variable performance)—provide an FDO_2 (fractional concentration of delivered oxygen) that varies with the patient's inspiratory flow and are classified as variable-performance oxygen delivery systems.
4. High-flow devices—(fixed performance)—can provide a specific FDO_2 at flows that meet or exceed the patient's inspiratory flow requirement and are classified as fixed-performance oxygen delivery systems.

C. Inhaled Nitric Oxide (Chap. 63)—Inhaled nitric oxide (INO) is a colorless, odorless gas that is also a potent pulmonary vasodilator. When given via the inhaled route, it is a selective pulmonary vasodilator. INO is approved by the United States Food and Drug Administration (FDA) for the treatment of term and near-term (late preterm) neonates with hypoxemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary arterial hypertension.
   1. Optimal alveolar recruitment should be established prior to initiation of INO.
   2. For newborns with a response to INO therapy, the dose should be weaned to the lowest concentration that maintains that response.
   3. Recommended that FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy; with conventional mechanical ventilation the INO gas injector module should be placed on the dry side of the humidifier.
   4. The lowest effective doses of INO and O_2 should be used to avoid excessive exposure to NO, NO_2, and resultant methemoglobinemia.

D. Surfactant replacement therapy (Chap. 58)
   1. Can be safely given in delivery room or NICU setting
   2. Respiratory therapist needs to be well versed in potential complications (plugged endotracheal tube, regurgitation of surfactant, desaturation, bradycardia, etc.) and clinical interventions to prohibit, minimize, or remediate these issues.
   3. Assessment of need, outcomes, and indications for re-dosing
   4. Understand proper monitoring and infection control practices during administration.
   5. Understand proper delivery techniques of intratracheal delivery via various routes (direct instillation, laryngeal mask airways, bronchoalveolar lavage or aerosolized).

XII. Airway Clearance

A. Routine airway clearance is not recommended or necessarily in the newborn population with the exception of "as needed" suctioning.

B. Suctioning should never be performed on a routine schedule but rather according to need per an assessment with an understanding of the disease process. Studies have shown no increase in secretions or occlusion of endotracheal tubes when suctioning was extended to occur once every 12 h versus every 6 h in neonates ventilated for RDS.
   1. Indicators for suctioning may include visible secretions, coarse or decreased breath sounds, decrease in saturation, or acute change in blood gas results, agitation, or change in vital sounds related to respiratory system. Pulmonary graphics may also show a "noisy" flow signal.
   2. Upper airways should be suctioned gently. Tracheal suctioning in the delivery room has been reserved for non-vigorous neonates or those requiring resuscitation in the immediate period after delivery regardless of the consistency of secretions or meconium.

3. Endotracheal tube suctioning is performed only to maintain the patency of the endotracheal tube and never for attempts to clear actual airways beyond the endotracheal tube.
4. Complications include hypoxemia, bradycardia, tachycardia, atelectasis, pneumonia, lability in blood pressure and intracranial pressure, trauma to airway, sepsis, tube blockage and dislodgement, and pneumothorax.
5. Saline should only be used as a lubricant for the catheter and never instilled in the endotracheal tube. Research has shown it does not thin secretions nor does it mobilize secretions.
6. The use of closed suction catheters should be considered part of a strategy to prevent ventilator-associated pneumonia, and they do not need to be changed daily for infection control purposes. The maximum duration of time that closed suction catheters can be used safely is unknown.

XIII. Endotracheal Intubation and Securing Respiratory Devices (Chap. 15)
- A. Endotracheal Intubation
  1. Full understanding of rationale for endotracheal intubation
     a. Purpose of providing an airway and/or assisted mechanical ventilation and surfactant administration.
     b. Drugs given to assist neonatal intubation provide analgesia and assistance in smooth passage of the tube.
  2. Maintenance and standardization of intubation equipment
  3. Understanding appropriate procedure and techniques of neonatal intubation
     a. Pre-intubation assessment
     b. Intubation technique for oral or nasal intubation
     c. Selection of endotracheal size to newborn weight or gestational age
  4. Post-intubation assessment and documentation
- B. Securing Respiratory Devices
  1. Securing and maintenance of respiratory devices, such as the endotracheal tube, nasal prongs, chest tubes, monitoring devices, ECMO and other vascular catheters (such as venous and arterial access), and environmental control (such as probes for temperature) falls under the responsibility of the RT.
  2. There are a number of devices on the market for the securing of ET tubes and nasal prongs. Skin integrity and prevention of accidental dislodgement of devices by newborn, caregivers, or family members should be paramount.

XIV. Assisted Ventilation of the Newborn
- A. Understanding of the physiologic principles of mechanical ventilation
  1. Mechanics
  2. Mechanisms of Gas Transport
  3. Oxygenation and ventilation
  4. Perfusion
  5. Nuances of neonatal population
     a. Differences in respiratory muscles—higher fatigue
     b. Differences in lung/chest mechanics—stiff lungs, pliable chest wall
     c. Differences in respiratory control—apnea, periodic breathing, and changing response to oxygen and carbon dioxide
     d. Differences in the lung—high dead space to tidal volume ratios, surfactant deficiency, lower compliance, small FRC, higher resistance
- B. Non-Invasive Ventilation (NIV) (Chaps. 27–29, 31–33)
  1. Comprehension and understanding of the various methodologies to provide continuous distending pressure by NIV

2. Comprehension and understanding of the various devices which NIV is provided in the NICU setting
3. Rationale of providing NIV for various clinical abnormalities and disease states of newborns, determining optimal levels of continuous positive airway pressure (CPAP) or positive end expiratory pressure (PEEP)
4. Comprehension and understanding of the potential hazards and complications of NIV
5. Comprehension and understanding of escalation and titration of NIV levels of therapy

C. Invasive Ventilation (Chaps. 34–43)
1. Design principles and classification of mechanical ventilators (Chap. 44)
2. Levels of Support
   a. Full Support
   b. Partial Support
   c. No Support
3. Rationale and role of mean airway pressure, ventilation controls, and oxygenation controls
4. Comprehension and understanding of pulmonary function and graphics associated with mechanical ventilation
5. Understanding and rationale for initiation and titration of mechanical ventilation
6. High-Frequency Ventilation (Chaps. 41–43)

Suggested Reading

AARC. Endotracheal suctioning of mechanically ventilated patients with artificial airways. Respir Care. 2010; 55(6):758–64.

Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63.

DiBlasi RM, Myers TR, Hess DR. Evidenced-based clinical practice guideline: inhaled nitric oxide for neonates with cute hypoxic respiratory failure. Respir Care. 2010;55(12):1717–45.

Eberle P, Trujillo L, Whitaker K. Comprehensive perinatal & pediatric respiratory care. 4th ed. Stamford, CT: Cengage Learning; 2014.

Hess DR, Kallstrom TK, Mottram CD, Myers TR, et al. Care of the ventilator circuit and its relation to ventilator-associated pneumonia. Respir Care. 2003;48(9):869–79.

Hess DR, MacIntyre NR, Galvin WF, Mishoe C. Respiratory care: principles and practice. 3rd ed. Burlington, MA: Jones and Barlett Learning; 2016.

Myers TR. AARC clinical practice guideline: selection of oxygen delivery device for neonatal and pediatric patients—2002 revision and update. Respir Care. 2002;47(6):707–16.

Neonatal eHandbook. Department of Health and Human Services, State Government of Victoria, Australia. http://www.health.vic.gov.au/neonatalhandbook/index.htm. Accessed July 2015.

Perlman J, Kattwinkel J, Wyllie J, Guinsburg R, et al. Neonatal resuscitation: in pursuit of evidence gaps in knowledge. Resuscitation. 2012;83(5):545–50.

Restrepo RD, Walsh BK. Humidifaction during invasive and noninvasive mechanical ventilation: 2012. Respir Care. 2012;57(5):782–8.

Restrepo RD, Hirst KR, Wittenebel L, Wettstein R. AARC clinical practice guideline: transcutaneous monitoring of carbon dioxide and oxygen: 2012. Respir Care. 2012;57(11):1955–62.

Strickland S, Rubin BK, Drescher GS, et al. AARC clinical practice guideline: effectiveness of nonpharmacologic airway clearance therapies in hospitalized patients. Respir Care. 2013;58(12):2187–93.

Walsh BK, editor. Neonatal and pediatric respiratory care. 4th ed. Philadelphia: Elsevier Health Sciences; 2015.

Walsh BK, Crotwell DN, Restrepo RD. Capnography/capnometry during mechanical ventilation: 2011. Respir Care. 2011;56(4):503–9.

Walsh BK, Daigle B, DiBlasi RM, Restrepo RD. AARC clinical practice guideline: surfactant replacement therapy: 2013. Respir Care. 2013;58(2):367–75.

Long-Term Ventilator Dependency in Infants Without Lung Disease

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Stamatia Alexiou and Joseph Piccione

I. Description
   A. Indications for long-term ventilator dependency include respiratory failure from either lung failure or "pump" failure.
   B. Lung failure results from inadequate gas exchange at the alveolar capillary interface so that arterial levels of oxygen, carbon dioxide, or both are unable to be maintained within normal physiologic values.
   C. The pump consists of the chest wall, muscles involved in respiration, and respiratory controllers that connect the central and peripheral nervous system. Pump failure leads to alveolar hypoventilation with subsequent hypercapnia and sometimes hypoxemia.

II. Examples of pump failure
   A. Mechanical problems causing alterations in chest wall mechanics
      1. Hypoplastic thorax syndromes (i.e., Jeune's Syndrome, Jarcho-Levin, Ellis-van Creveld)
      2. Constrictive chest wall syndromes (i.e., fused ribs, VACTERL association)
   B. Disordered central control of breathing
      1. Congenital Central Hypoventilation Syndrome (CCHS)
      2. Chiari malformation
   C. Neuropathies (e.g., spinal muscular atrophy)
   D. Neuromuscular Disorders
      1. Muscular dystrophy
      2. Mitochondrial myopathy
      3. Metabolic myopathies
   E. Diseases affecting neuromuscular junctions
      1. Congenital myasthenia gravis
      2. Botulism

III. Pathophysiology of pump failure
   A. Motor output from the CNS needs to be transferred to respiratory muscles by way of the spinal cord, peripheral nerves, and neuromuscular junction.

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B. Any complication along this pathway will result in inadequate chest wall excursion and failure to generate the subatmospheric pressure needed to create airflow into the lungs.
C. Mechanical defects impose additional work on the muscles of respiration since they need to generate sufficient pressure to displace a less compliant chest wall. If this work cannot be maintained over time, the patient is at risk of respiratory muscle fatigue and alveolar hypoventilation.

IV. Ventilation Strategies
A. Abnormal respiratory drive
1. Since patients with an abnormal respiratory drive do not respond appropriately to hypoxemia or hypercarbia, their mechanical ventilation strategy needs to include a mandatory rate.
2. Assuming their lung parenchyma and chest wall mechanics are normal, targeted tidal volume should be maintained within the normal range (6–10 mL/kg).
3. Patients with Chiari malformations may have a blunted response to hypercarbia and may also have obstructive apnea while asleep. In addition to providing adequate minute ventilation, when noninvasive mechanical ventilation is used, additional distending pressure may be needed to overcome upper airway obstruction.
B. Altered chest wall mechanics
1. Skeletal deformities resulting in constrictive or hypoplastic thoraces decrease the compliance of the chest wall. They can also place the respiratory muscles (including the diaphragm) at a mechanical disadvantage and compromises their force-generating capability (muscle fiber length–tension relationship).
2. In order to maintain minute ventilation while minimizing respiratory muscle expenditure, patients often require a high peak inspiratory pressure (sometimes > 30 cm H_2O), to overcome a low chest wall compliance.
3. In a term infant, initial exhaled volumes of about 6 mL/kg are appropriate and can be titrated depending upon the results of arterial blood gas results.
C. Neuromuscular abnormalities
1. The chest wall of patients with diseases such as spinal muscular atrophy and mitochondrial myopathies is usually highly compliant so inspiratory pressures and tidal volumes should be within the normal range.
2. Mandated breaths that are either pressure or volume targeted can be given in addition to spontaneous breaths that are pressure supported.
3. Because of muscle weakness, clinicians must ensure that the flow trigger sensitivity is set low enough to allow effective triggering of the ventilator.

V. Types of ventilatory support
A. Invasive mechanical ventilation requires the need for a tracheostomy tube
B. Noninvasive positive pressure ventilation (i.e., Bi-level) requires a well-fitting and comfortable interface

VI. Benefits of mechanical ventilation
A. Improved survival
B. Decreased hospitalization
C. Improved neurocognitive outcomes
D. Improved quality of life
E. Preservation of chest wall mechanics
F. Sustained lung growth

Suggested Reading

Annane D, Orlikowski D, Chevret S, et al. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev. 2007;4:CD001941.

Baydur A, Layne E, Aral H, et al. Long term non-invasive ventilation in the community for patients with musculoskeletal disorders: 46 year experience and review. Thorax. 2000;55:4–11.

Castro Codesal ML, Featherstone R, Martinez Carrasco C, et al. Long-term non-invasive ventilation therapies in children: a scoping review protocol. BMJ Open. 2015;5(8):e008697.

Colombo I, Scoto M, Manzur AY, et al. Congenital myopathies: natural history of a large pediatric cohort. Neurology. 2015;84(1):28–35.

Mayer OH. Chest wall hypoplasia—principles and treatment. Paediatr Respir Rev. 2015;16(1):30–4.

McDougall CM, Adderley RJ, Wensley DF, et al. Long-term ventilation in children: longitudinal trends and outcomes. Arch Dis Child. 2013;98:660–5.

Panitch H. Children dependent on respiratory technology. In: Wilmott RW, Boat TF, Bush A, Chernick V, Deterding RR, Ratjen F, editors. Kendig & Chernick's disorders of the respiratory tract in children. 8th ed. Philadelphia: Saunders Elsevier; 2012. p. 261–71.

Roussos C, Koutsoukou A. Respiratory failure. Eur Respir J Suppl. 2003;47:3s–14s. Review.

Simonds AK. Recent advances in respiratory care for neuromuscular disease. Chest. 2006;130:1879–86.

Ward S, Chatwin M, Heather S, et al. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax. 2005;60:1019–24.

Chronic Home Mechanical Ventilation

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Wan Chong Tsai

I. Home Mechanical Ventilation
   A. Assisted ventilation outside the hospital environment in the home
   B. Premature infants are a small but growing population
      1. Preterm infants with birthweight <1000 g have tracheostomy rate of 6.9 % compared to 0.9 % in preterm infants with birthweight >1000 g.
      2. Incidence of home ventilation from chronic respiratory failure increased by almost three-fold from 1.23 per 100,000 live births to 4.77 per 100,000 live births from 1984 compared to 2010.

II. Indications for long-term home mechanical ventilation
   A. Recognition of chronic respiratory failure
      1. Result of a non-correctable imbalance in the respiratory system, in which ventilatory muscle power and central respiratory drive are inadequate to overcome the respiratory load
      2. Leads to ventilator dependency
      3. Ventilator support normalizes gas exchange and alveolar ventilation through the following mechanisms.
         a. Relieves respiratory load
         b. Reduces respiratory muscle work
         c. Improves O_2 and CO_2 sensitivity
   B. Medical assessment for initiation of long-term mechanical ventilation
      1. Clinical characteristics of pediatric ventilator dependency
         a. Child who has recovered from acute respiratory failure but remains incapable of sustaining normal gas exchange without mechanical ventilation support
         b. Absence of spontaneous respiration
         c. Failure to extubate after many attempts by skilled respiratory care team
         d. Multiple hospitalizations for recurrent acute respiratory failure requiring mechanical ventilation
         e. Disease states that benefit from home ventilation

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2. Diseases that are progressive with resultant severe respiratory failure requiring support can be successfully controlled by assisted mechanical ventilation to sustain life.
   a. Restrictive lung diseases
      (1) Thoracic restrictive disorders
      (2) Diffuse pulmonary fibrosis
   b. Chronic obstructive lung diseases
      (1) COPD
      (2) Cystic fibrosis
      (3) Bronchiectasis
   c. Mixed lung diseases
      (1) Bronchopulmonary dysplasia (BPD)
      (2) Tracheobronchomalacia
   d. Central hypoventilation syndromes
      (1) Congenital
         (a) Idiopathic
         (b) Anatomic (Arnold-Chiari malformation, myelo-meningocele)
      (2) Acquired
         (a) Traumatic
         (b) Vascular
         (c) Infectious
         (d) Surgical diseases affecting the respiratory centers
   e. Ventilatory muscle dysfunction
      (1) CNS diseases
      (2) Polyneuropathy, polyradiculopathy
      (3) Myopathy, muscular dystrophy
      (4) Chest wall diseases
3. Adequate physiologic and clinical patient stability for home ventilation
   a. Disease process does not fluctuate greatly for >1 month.
   b. Multi-organ co-existing conditions are well controlled.
4. Alternate means of support considered (failed trial, deemed inadequate or undesirable)
5. Ventilator dependency demonstrated in order to continue living or to improve the quality of life

C. Best candidates for home ventilation
   1. Young, otherwise healthy
   2. Except for isolated disorder of the respiratory tract (BPD)
   3. Stable disorders (spinal cord injury, post-polio)
   4. Slowly progressive disorders (neuromuscular disorders)

III. Goals of long-term mechanical ventilation
   A. Provide medically safe assisted ventilation in the home while optimizing the quality of life without recreating the hospital environment
   B. Extend life
   C. Provide an environment, which will enhance individual potential and quality of life
   D. Reduce morbidity
   E. Improve physical and physiologic function
   F. Be cost-effective

IV. Chronic Ventilation Strategy
   A. Use ventilator to provide enough support to normalize alveolar hypoventilation
   B. Wean as soon as respiratory status stabilizes and can maintain alveolar ventilation without support.

1. SpO_2 normal ± O_2 supplement (<4 LPM for home)
2. End tidal CO_2 ~ normal

C. Work of breathing is minimal.

V. Timing of modifications and weaning is dependent on disease state.
   A. Stable disorders (spinal cord injury)—never weanable
   B. Slowly progressive disorders (neuromuscular disorders)—escalate support over years
   C. Slowly recovering disorders (BPD)—reducing support over 1–3 years but still long-term expectation

VI. Nonmedical assessment for initiation of long-term mechanical ventilation
   A. Available resources in outpatient medical team, home, and community
   B. Physical environment
   C. Attendant care needs

VII. Modes and Types of Portable Home Ventilators
   A. Performance of the ventilator and settings are more important than ventilator mode.
   B. Delivery
      1. Volume
         a. First mode for polio, fixed tidal volume, no leak compensation
         b. Not tolerated in high airway resistance, low compliance, small children
      2. Negative vs. Positive Pressure Ventilation
         a. Positive pressure ventilators are the most commonly used for children.
         b. Better triggering to overcome low flow, or inappropriate spontaneous breath rate
   C. Control, Assist/Control, IMV and weaning modes determined by
      1. Mechanisms of respiratory failure in each child
      2. Machine performance specifications
      3. Size of child, ability to trigger ventilator
      4. Cuffed vs. uncuffed tracheostomy tube and constancy or magnitude of leaks around the tracheostomy tube

VIII. Monitoring systems
   A. Observation of clinical variables
      1. Alleviation of signs
      2. May be more important and more effective than invasive monitoring
   B. Assessment of physiologic variables
      1. Acute: 24 h for arterial blood gas normalization
      2. Chronic:
         a. Polysomnogram-critical for patient-ventilator asynchrony, air leaks
         b. Arterial blood gas while awake
         c. Nocturnal oximetry and capnometry
         d. Respiratory muscle evaluation—work of breathing
         e. Pulmonary function, if able to perform

IX. Complications of home mechanical ventilation
   A. Tracheostomy tube
      1. Obstruction of the tracheostomy tube is the most common early complication.
         a. Mucus plugging
         b. Granulation tissue
      2. Accidental decannulation
      3. Increased respiratory infections (e.g., tracheobronchitis or pneumonia)
      4. Airway injuries
         a. Tracheal stenosis

   b. Tracheal dilatation
   c. Tracheomalacia
5. Stoma injuries
   a. Tracheoinnominate fistula
   b. Poor wound healing

B. Acute respiratory exacerbations
1. Respiratory Exacerbations
   a. Definition is nonspecific
   b. Clinical signs of lower respiratory tract infection include fever, leukocytosis, purulent sputum, change in tracheal secretions, worsening respiratory parameters on baseline ventilator settings (desaturation is common).
   c. Absence of infiltrate on chest radiograph (ventilator-associated tracheobronchitis)
   d. Presence of infiltrate on chest radiograph (ventilator associated pneumonia vs. healthcare-associated pneumonia vs. nosohusial pneumonia)
2. Acute respiratory failure is expected during illnesses above baseline of chronic respiratory failure.
3. Patients have reduced pulmonary reserve to handle acute illness.
4. Management
   a. Escalate support briefly and temporarily until recovery from acute illness.
   b. Escalate pulmonary inhaled regimen and pulmonary hygiene or clearance.

C. Prolonged mechanical ventilation
D. Pulmonary hypertension, cor pulmonale

Suggested Reading

Cristea AI, et al. Outcomes of children with severe bronchopulmonary dysplasia who were ventilator dependent at home. Pediatrics. 2013;132(3):e727–34. doi:10.1542/peds.2012-2990.

Eigen H, et al. Home mechanical ventilation of pediatric patients. American Thoracic Society Position Paper. Am Rev Respir Dis. 1990;141(1):258–9.

Finder JD, et al. Respiratory care of the patient with Duchenne muscular dystrophy: American Thoracic Society consensus statement. Am J Respir Crit Care Med. 2004;170(4):456–65.

Johnston J, et al. Care of the child with a chronic tracheostomy. American Thoracic Society Consensus Statement. Am J Respir Crit Care Med. 2000;161(1): 297–308.

Long-term invasive mechanical ventilation in the home. American Association for Respiratory Care clinical practice guideline. Respir Care. 2007; 52(8): 1056–62.

Overman AE, et al. Tracheostomy for infants requiring prolonged mechanical ventilation: 10 years' experience. Pediatrics. 2013;131(5):e1491–6. doi:10.1542/peds.2012-1943.

Wetmore R, et al. Tracheal suctioning in children with chronic tracheostomies: a pilot study applying suction both while inserting and removing the catheter. Ann Otol Rhinol Laryngol. 1999;108(7 Part 1):695–9.

Discharge Planning and Follow-Up of the NICU Graduate

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Win Tin and Mithilesh Lal

I. Discharge Planning of the NICU Graduate
   A. Introduction
      Hospitalization of an ill newborn is not only one of the most costly of all hospital admissions, but is also a very stressful event for a family. Discharging an NICU patient early has several advantages, including enhancement of family/infant bonding, provision of a better environment for infant development, and reduction in cost. Discharge too early, however, can impose some risk of deterioration of an infant and can lead to hospital re-admissions and further stress on the family. Effective discharge planning is essential for making the discharge a positive and stress-free experience.
   B. Essential Features of Effective Discharge Planning
      1. Ensures a safe and effective transition from hospital to community care and prepares caregivers from the early stages through education
      2. Customized to meet the needs of an individual infant and family
      3. Involves multi-disciplinary agencies as appropriate
      4. Avoids duplication of services and minimizes disruption to the family
      5. Provides good communication between the NICU and community-based primary care providers
      6. Simplifies the care of an infant, but without making major changes immediately prior to discharge
      7. Identifies unresolved medical issues and specifies arrangements for appropriate follow-up
   C. Assessment of Readiness for Discharge
      1. Assessment of infant
         a. Healthy infants can be considered ready for discharge if they:
            (1) Maintain temperature in an open cot
            (2) Feed well orally and maintain appropriate growth
            (3) Do not need any regular cardio-respiratory monitoring

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b. Infants with specific ongoing problems need individualized discharge plans; they should be considered ready for discharge only when the specific needs can be provided at home by the parents, with the support of care providers in the community.
c. Common problems among NICU graduates include bronchopulmonary dysplasia (BPD) requiring home oxygen therapy, and long-term feeding problems requiring nasogastric tube feeding. Community nurse specialists/practitioners play a vital role in these circumstances.

2. Family assessment should start from the time of the admission of an infant to the NICU and include:
a. Parenting skills and the willingness to take responsibility
b. Parents' experience and understanding of routine infant care and their ability to cope with specific problems
c. Family structure and extended family support
d. Parents' medical and psychologic history
e. Home environment
f. Financial concerns
g. Cultural differences and language difficulties

D. Pre-discharge Evaluation and Examination
1. Specific evaluation and screening of NICU graduates
a. Ophthalmologic examination
(1) Routine retinopathy of prematurity (ROP) screening for all infants with risk factors, according to guidelines (Chap. 85).
(2) Specific eye examination should be arranged for those with congenital infections, congenital eye abnormalities, chromosomal abnormalities, and absent red reflex.
b. Hearing screening. Universal screening has become the standard of care; otherwise, a risk-based approach should include infants with a family history of sensorineural hearing loss, neonatal meningitis or encephalitis, severe hyperbilirubinemia, congenital infection, congenital malformation of the ear, prolonged use of oto-toxic drugs such as aminoglycosides, and following hypoxic-ischemic injury. Prematurity per se is also considered a high risk factor.
c. Cranial ultrasound screening for hemorrhagic and/or ischemic brain injuries in high risk infants according to individual NICU guidelines. However, a structurally normal cranial sonogram does not rule out long-term neurodevelopmental problems and parents need to be aware that follow-up of these infants remains the most important part of the ongoing assessment.
d. Immunizations. Preterm infants should receive immunizations based on chronological age, using the same dosage as in term counterparts. Influenza, pneumococcal, and other vaccines need consideration based on local guideline.
e. Candidates for RSV prophylaxis with palivizumab should be identified prior to discharge and should preferably receive the first dose in the NICU in season (Chap. 70).

2. Pre-discharge examination is essential to ensure that good general health and growth is maintained in an infant who is ready for discharge. It also flags problems requiring further evaluation (e.g., heart murmur and unstable hip). However, a normal pre-discharge examination does not give complete reassurance and the parents need to be aware of this.

E. Discharge Information/Letter
1. Written information should be made available to the primary care providers and the parents.
2. All medical terminology contained in the letter should be explained to the parents and should include:

a. Infant's particulars (name, date of birth, address, etc.)
b. Date of admission and discharge
c. List of important medical problems
d. Brief clinical summary
e. Ongoing problem(s) at the time of discharge
f. Medications at discharge
g. Instruction on immunizations
h. Plans for follow-up and further assessments

II. Follow-Up of the NICU Graduate
A. NICU graduates are at high risk of adverse neurodevelopmental outcome; hence, carefully planned follow-up forms an essential part of NICU service provision.
B. Importance of Follow-Up
1. For the child:
a. Early identification of major problems of perinatal origin (e.g., cerebral palsy, developmental delay, and major hearing or visual impairment). This will facilitate any further diagnostic tests, assessment, and involvement of other appropriate professionals and agencies.
b. Screening for other medical problems (e.g., squint, speech delay, and growth failure) so that early remedial measures can be implemented
c. Maintenance of optimum health in order to achieve better potential for growth and development
2. For the parents/caregivers:
a. Support to families of children with special needs. It is important that one "lead" clinician coordinates the infant's care with the help and support of other professional agencies and services to minimize confusion and to provide consistency of care and advice.
b. Counseling to the caregivers regarding the child's problems and its relationship to perinatal events, probable prognosis of the condition, appropriate investigations, and to discuss the results of various assessments
c. Advice on immunization, medications, diet, as well as the need for other specialists/therapists involvement
d. Reassure caregivers and address concerns regarding the child's condition and progress.
3. For the professionals/institutions:
a. Follow-up studies/programs (hospital based or population based) are very useful as an audit process:
(1) To evaluate and improve the standards of neonatal intensive care
(2) To monitor changing patterns of prognosis (mortality and morbidity) with time
(3) To evaluate newer treatment and interventions where the long-term neurodevelopmental outcome is used as primary outcome measure
(4) To provide reliable sources of data/information for counseling
b. Follow-up programs/clinics also provide training opportunities for professionals.
C. Who should be followed-up?
1. This depends to a great extent on the resources available.
2. Commonly used categories of babies for follow-up include:
a. Very preterm and very low birth weight infants (<32 weeks' gestation and/or <1500 g at birth). Accurately assessed gestation is a better predictor than birth weight for long-term morbidity. Outcome at 2 years is already part of National Neonatal Audit Program (NNAP) in the UK. This program requires 2-year outcome data on all infants <30 weeks' gestation currently so that the rates of normal survival can be compared across units.
b. All NICU graduates who required mechanical respiratory support.

c. Small-for-gestational age babies (birth weight or head circumference >2 standard deviations below the mean for gestational age)
d. Babies with perinatal neurologic problems such as hypoxic-ischemic encephalopathy, known ischemic and/or hemorrhagic brain injury, or ventriculomegaly, microcephaly, and those with abnormal neurologic behavior (neonatal convulsion, hypotonia, etc.)
e. Hydropic infants, from any cause
f. Babies who had intrauterine or severe perinatal infections
g. Babies who had metabolic derangements like persistent hypoglycemia, hyperbilirubinemia requiring exchange transfusion, etc.
h. Babies with congenital abnormalities
i. Babies exposed to toxic agents (e.g., drugs) in utero
j. Babies with ongoing problems with respiratory control

D. Who should follow-up NICU graduates?
1. This will vary from one unit to another depending on the structure and resources, but the follow-up team should ideally consist of:
a. The "lead" clinician (usually a developmental pediatrician), whose role is to co-ordinate between the families and other appropriate professionals/agencies
b. Community liaison nurse or nurse practitioner
c. Pediatric physiotherapist
d. Pediatric dietician
2. The NICU follow-up team may often need support and consultation from other specialties such as pediatric pulmonology, ophthalmology, pediatric surgery, orthopedic surgery, neurosurgery, neurology, genetics, audiology, speech and language therapy, psychology, and occupational therapy. However, it is important that the family rely upon one named clinician who will co-ordinate and communicate with other professionals involved in the care of the child.

E. Components of follow-up assessment
1. Listening to the parents/caregivers and addressing their concerns are probably the most important part of follow-up.
2. Anthropometric assessment: weight, length, and head circumference should be regularly monitored.
3. System review, particularly any health problems; feeding and bowel habits
4. Assessment of vision and hearing. Some children may need further referral for detail assessment.
5. Neurologic/neurodevelopmental assessment:
a. Assessment of posture, tone, reflexes, and presence of primitive reflexes. Joint assessment may prove very useful.
b. Assessment of gait and detailed neurological examination in older children
c. Achievement of developmental milestones. It is common practice to report neurodevelopmental outcomes at 18–24 months' corrected age. Unlike serious motor, sensory deficits and developmental delay, it is more difficult to assess cognitive function around 24 months. Also school age problems such as poor attention span, difficult behavior, and coordination problems can only be detected around 5–6 years of age.
d. When defining preterm infants' developmental level, correction of prematurity is usually applied up to 2 years. Such correction can make about a 10 % difference depending on gestational age for up to 3 years. This is not necessary once the child is in the education system, as peer group comparison is the norm.

e. Developmental screening tests such as Schedule of Growing Skills or Denver Developmental Screening Test can be used to identify children for more detailed assessment but the diagnostic and predictive value remains uncertain. These may also overestimate children with developmental problems.
f. Formal developmental assessment is done commonly using the Bayley Scales of Infant and Toddler Development (BSID III) and the Griffiths Scales. Compared to BSID II, the current scale results in a higher score by 7 points on average, making it more difficult to interpret and providing an underestimation of disability. These are of little value in very poorly performing children (>3 SD below mean).
g. Validated parent report questionnaire has been shown to have good correlation and diagnostic utility in comparison to time and resource heavy formal assessments. These have been used in large RCTs evaluating the safety and efficacy of an intervention.

6. Systemic examination
7. Review of medications (including oxygen therapy); some may need to be discontinued, whereas others may need adjustment of dosage.
8. Check whether all the immunizations have been given and all necessary screening tests have been completed.

F. How often and how long should NICU graduates be followed?
1. This depends on the needs of the child and family and also on the resources available. Problems such as minor cognitive and learning problems, clumsiness, or poor attention span are more common among NICU graduates than in normal term counterparts, and ideally NICU graduates should be followed until they are school age or penultimately to adulthood.
2. Most do not need follow-up regularly once their growth and development are satisfactorily progressing.
3. Communication between the follow-up team and the community pediatrician/school is important if the child needs longer term follow-up, mainly because of potential education difficulties.

G. In summary, follow-up of NICU graduates is essential to facilitate better care for the child and family, advancement of perinatal services, and to ensure the provision of appropriate support services for these children.

Appendix: Suggested 2-Year Corrected Age Outcome Assessment Proforma

Answer response for each question: **yes/no/unknown**
Neuromotor
Does the child have difficulty walking?
Is this child's gait non-fluent or abnormal reducing mobility?
Is this child unable to walk without assistance?
Is this child unstable or needs to be supported when sitting?
Is this child unable to sit?
Does this child have any difficulty with the use of one hand?
Does this child have difficulty with the use of both hands?
Is this child unable to use hands (i.e., to feed)?
Neurosensory
Auditory:
Does the child have a hearing impairment?

(continued)

(continued)

Does the child have a hearing impairment corrected by aids?
Does the child have a hearing impairment uncorrected by aids?
Vision:
Does the child have any visual problems including squint?
Does the child have any visual defect not fully correctable?
Is the child blind or sees light only?
Communication:
Does the child have difficulty with communication?
Does the child have any difficulty with speech (<10 words/signs)?
Does the child have <5 meaningful words, vocalizations, or signs?
Is the child unable to understand words or signs out of familiar context?
Is the child unable to understand words or signs?
Neurological Diagnosis
Does the child have a diagnosis of cerebral palsy? If yes please specify the type of cerebral palsy:
• Spastic bilateral: 2/3/4 limb involvement
• Hemiplegia: Right/Left sided
• Dyskinetic/Dystonic/Choreoathetoid/Unclassifiable
Development—at 24 months corrected age
Is development normal (<3 months delay)?
Is there mild delay (3–6 months delay)?
Is there moderate delay (6–12 months delay)?
Is there severe delay (>12 months delay)?
Malformations
Does child have malformations that impair daily activities despite assistance?
Respiratory and CVS System
Does this child have limited exercise tolerance with or without treatment?
Is this child on supplemental oxygen or any respiratory support?
Gastro-intestinal Tract
Does this child require TPN, NG, or PEG feeding?
Renal
Does child have renal impairment and on dietary or drug treatment?
Does child have renal dialysis or awaiting renal transplant?
Neurology
Has the child had a seizure in the last 12 months?
Is the child on anticonvulsants?
Has the child had more than one seizure in a month despite treatment?
Has the child got a VP shunt in situ?

Suggested Reading

AAP policy statement—screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2006; 117(2):572–76.

Johnson S, Fawke J, Hennessy E, Rowell V, Trikic R, Wolke D, Marlow N. Neuro-developmental disability through 11 years of age in children born before 26 weeks of gestation. Pediatrics. 2009;124:e249–57.

Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? Pediatr Res. 2014;75(5):670–4.

Lal M, Tin W. International perspectives: measuring perinatal outcomes—why, when, and how: a British perspective. Neoreviews. 2012;13:e515–26.

Marlow N. Is survival and neurodevelopmental impairment at 2 years of age the gold standard outcome for neonatal studies? Arch Dis Child Fetal Neonatal Ed. 2015;100(1):F82–4.

Marlow N, Wolke D, Bracewell M, Samara M. Neurologic and developmental disability at 6 years of age following extremely preterm birth. N Engl J Med. 2005;352(1):9–19.

Measurement of health status at 2 years. Report of the two working groups convened by the National Perinatal Epidemiology Unit and Oxford Regional Health Authority. Disability and Perinatal Care; 1994.

Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, Marlow N. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ. 2012;345:e7961.

Tin W, Wariyar U, Hey E. Changing prognosis for babies of less than 28 weeks' gestation in the north of England between 1983 and 1994. BMJ. 1997;314:107–11.

Wood NS, Marlow N, Costeloe K, et al. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med. 2003;343:378–84.

Section XIV

Ethical and Legal Considerations

Initiation of Life Support at the Border of Viability

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Naomi Laventhal, Joanne Lagatta, and William Meadow

I. Important Considerations Regarding Resuscitation of Infants at the Borderline of Viability
   A. Guidelines for who should be resuscitated in the delivery room
   B. Considerations regarding withdrawal of resuscitative efforts
II. Considerations in Deciding Whether to Offer Delivery Room Resuscitation to Preterm Infants
   A. International consensus guidelines in industrialized countries are generally based upon gestational age.
      1. Infants born before 22 weeks are uniformly not resuscitated (futility).
      2. Resuscitation is generally recommended for infants born at or after 25 0/7 weeks without complicating co-morbidities (best interest standard).
      3. Infants born before 25 weeks but after 23 0/7 weeks (or in some centers 22 0/7 weeks) are considered to be in the "gray zone" of gestational viability; in this case, local guidelines, caregiver, and family preferences should apply.
         a. Survival of 22 week infants partly depends upon whether they are born in centers offering resuscitation at that gestational age.
         b. Parents, physicians, and other caregivers may differ in their beliefs.
            (1) What constitutes a reasonable chance of survival?
            (2) What constitutes a good/poor outcome?
         c. Available guidelines within this gray zone may not be specific for gestational age thresholds or definitions of "good" or "bad" outcomes.
   B. Besides gestational age, important prognostic factors include estimated weight, gender, administration of prenatal corticosteroids, and singleton status. Many neonatologists use population-based outcomes tools for counseling and decision-making about initiation of resuscitative efforts in the delivery room.

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C. Prenatal counseling at the margin of viability
   1. Prenatal counseling and decision-making can be based on large national datasets or institutional data; both have limitations. In either case, individuals within institutions should consistently select and apply the data source to minimize variation.
   2. Factors such as message framing by the practitioner and low numeracy among some expectant parents support the use of decision aids or provision of written information; pilot studies of decision aids with pictographs for decision-making at the margin of viability have been shown to be helpful.
   3. The value of providing numeric estimates of mortality and morbidity remains controversial.

D. Extremely premature infants appear to represent a unique patient population.
   1. Physicians prioritize parental autonomy.
      a. In a series of international surveys, neonatal care providers do not appear to base decisions to resuscitate consistently for different patient groups with a similar prognosis.
      b. Compared to cases describing older patients, for premature babies physicians were more likely to withhold resuscitation at the parents' request despite stating that resuscitation would be in the infant's best interest.
   2. Practitioners have been shown to be systematically pessimistic about outcomes of extremely preterm infants, even following educational interventions.

III. Considerations Regarding Withdrawal of Resuscitative Efforts at the Borderline of Viability

A. In the delivery room
   1. Discontinuation of resuscitation in the delivery room
      a. Observations of an infant's status and the response to resuscitative efforts are quantified by the Apgar score.
      b. Infants with a 10-min Apgar score of zero despite 10 min of adequate resuscitation are felt to have a minimal chance of intact survival, and discontinuation of resuscitation is considered acceptable.
   2. Limitations of physician assessment in the delivery room
      a. 1- and 5-min Apgar scores have limited correlation with survival or subsequent neurodevelopmental outcome at the margin of gestational viability.
      b. Clinical assessment of gestational age in the delivery room has been shown to be inaccurate.

B. Early in the NICU
   1. Information gathered over the course of treatment in the NICU may alter the prognosis of an individual infant from the original prognosis based on gestational age, birth weight, singleton status, receipt of antenatal steroids, and gender.
   2. Withdrawal of intensive care treatments can occur based on an assessment of an individual infant's prognosis, after discussion of the risks and benefits to continued treatment (ethical equivalence of withdrawing and withholding therapies).
   3. Evidence to guide discussions regarding withdrawal of treatment. Some neonatologists may include:
      a. Severe physiologic instability
      b. High likelihood of severe neurologic impairment based upon known congenital defects or acquired brain injury
      c. Physician assessment of non-survival
      d. Combinations of the above
   4. Limitations to evidence regarding withdrawal of intensive care treatment
      a. Measurements of physiologic instability, such as Score for Neonatal Acute Physiology (SNAP scores), are useful for risk adjustment in a large population but have poor discrimination for predicting individual outcomes.

b. Severely abnormal brain ultrasound findings in the first weeks of life have not been shown to universally predict poor outcomes; conversely, normal brain ultrasounds do not universally predict intact outcomes.
c. Clinician intuitions of infant non-survival tend towards being overly pessimistic; at least half of the time that clinicians predict an infant's non-survival, that infant, in fact, survives to discharge.

5. Possible strategies for use of evidence regarding withdrawal of intensive care treatment
   a. Infants predicted by medical caregivers to die before discharge have a high likelihood of either death or severe neurologic morbidity.
   b. Combinations of clinical intuitions of non-survival and abnormal brain ultrasound predict death or severe neurologic impairment with a positive predictive value >95 %.
   c. Conversely, the sensitivity of all recognized strategies to predict poor outcome in ELBW infants is poor—that is, nearly 40 % of ELBW infants who have *no* recognized risk factors for poor outcome have significant impairments nonetheless.

IV. In determining whether to offer or discontinue (see Chap. 94) intensive care treatments for extremely preterm infants:
   A. Neonatologists should review available prognostic information.
      1. Epidemiologic data (likely outcomes as suggested by large cohort studies) reflect an average of varied practices across institutions.
      2. Local outcomes data reflect smaller numbers but may be more specific to institutional practices in this gestational age group.
      3. Individual prognostic markers (that may be known before birth, or, with increasing accuracy, become available after a trial of intensive care therapy in the NICU)
      4. Early declaration of mortality among the most premature infants results in marked variation between intact survival among resuscitated infants vs. intact survival among NICU graduates.
   B. The degree of confidence in prognostic estimates should be considered; when the prognosis is highly uncertain, physicians should act in accordance with parental values and preferences.
   C. Conversely, when the probability of an adverse outcome (either death or significant neurologic disability) is very high, parents should be fully informed about the likely outcome, and afforded the option of palliative care.

Suggested Reading

Andrews B, Lagatta J, Chu A, et al. The nonimpact of gestational age on neurodevelopmental outcome for ventilated survivors born at 23–28 weeks of gestation. Acta Paediatr. 2012;101(6):574–8.

Blanco F, Suresh G, Howard D, Soll RF. Ensuring accurate knowledge of prematurity outcomes for prenatal counseling. Pediatrics. 2005;115(4):e478–87. April 1, 2005.

Cummings J, et al. Antenatal counseling regarding resuscitation and intensive care before 25 weeks of gestation. Pediatrics. 2015;136(3):588–95. September 1, 2015.

Dupont-Thibodeau A, Barrington KJ, Farlow B, Janvier A. End-of-life decisions for extremely low-gestational-age infants: why simple rules for complicated decisions should be avoided. Semin Perinatol. 2014;38(1):31–7.

Guillén Ú, Suh S, Munson D, et al. Development and pretesting of a decision-aid to use when counseling parents facing imminent extreme premature delivery. J Pediatr. 2012;160(3):382–7.

Haward MF, Murphy RO, Lorenz JM. Message framing and perinatal decisions. Pediatrics. 2008;122(1):109–18. July 1, 2008.

Hawley ST, Zikmund-Fisher B, Ubel P, Jancovic A, Lucas T, Fagerlin A. The impact of the format of graphical presentation on health-related knowledge and treatment choices. Patient Educ Couns. 2008;73(3): 448–55.

Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Pediatrics. 2010;126(5):e1400–13. November 1, 2010.

Lagatta J, Andrews B, Caldarelli L, Schreiber M, Plesha-Troyke S, Meadow W. Early neonatal intensive care unit therapy improves predictive power for the outcomes of ventilated extremely low birth weight infants. J Pediatr 2011;159(3):384–91.e381.

Lagatta J, Yan K, Hoffmann R. The association between 5-min Apgar score and mortality disappears after 24 h at the borderline of viability. Acta Paediatr. 2012; 101(6):e243–7.

Laventhal N, Spelke MB, Andrews B, Larkin LK, Meadow W, Janvier A. Ethics of resuscitation at different stages of life: a survey of perinatal physicians. Pediatrics. 2011;127(5):e1221–9.

Meadow W, Frain L, Ren Y, Lee G, Soneji S, Lantos J. Serial assessment of mortality in the neonatal intensive care unit by algorithm and intuition: certainty, uncertainty, and informed consent. Pediatrics. 2002;109(5):878–86. May 1, 2002.

Meadow W, Lagatta J, Andrews B, et al. Just, in time: ethical implications of serial predictions of death and morbidity for ventilated premature infants. Pediatrics. 2008;121(4):732–40. April 1, 2008.

Meadow W, Lagatta J, Andrews B, Lantos J. The mathematics of morality for neonatal resuscitation. Clin Perinatol. 2012;39(4):941–56.

Muthusamy AD, Leuthner S, Gaebler-Uhing C, Hoffmann RG, Li S-H, Basir MA. Supplemental written information improves prenatal counseling: a randomized trial. Pediatrics. 2012;129(5):e1269–74. May 1, 2012.

Myers NTL, Andrews BL, Lagatta JM, Meadow W. Use and perceived impact of population-based outcomes prediction tools for prenatal counseling at the margin of gestational viability. Platform presentation presented at Pediatric Academic Societies Annual Meeting; April 28, 2015; San Diego, CA.

Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. N Engl J Med. 2015;372(19): 1801–11.

Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity—moving beyond gestational age. N Engl J Med. 2008;358(16): 1672–81.

Zikmund-Fisher BJ, Smith DM, Ubel PA, Fagerlin A. Validation of the subjective numeracy scale: effects of low numeracy on comprehension of risk communications and utility elicitations. Med Decis Making. 2007;27(5): 663–71. September 1, 2007.

Withdrawal of Ventilatory Support: Clinical and Ethical Considerations

94

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I. Introduction
   A. Assisted ventilation should be viewed as a temporary support measure for infants with *potentially reversible* respiratory failure. In effect, it is a *trial of life*, and the desired outcome is survival with a reasonable chance of an independent existence free of profound disability in later childhood.
   B. Physicians who start assisted ventilation have *a duty* to consider with parents the withdrawal of ventilatory support if it seems likely that the desired outcome will not be achieved.
   C. The idea that life support must be continued as long as an infant is alive and that no one has the right to terminate assisted ventilation is an extremist view that few would defend.
   D. The withdrawal of life support and the redirection of care towards a peaceful death that minimalizes pain and discomfort is widely practiced and featured in recommendations of professional pediatric organizations.

II. Withdrawing Ventilatory Support
   A. A robust and coherent code of practice is needed to define the circumstances that justify the withdrawal of assisted ventilation. Otherwise ad hoc standards will be applied to each case and a decision will be justified only *after* it has been made.
   B. The code of practice should be derived from medical, logical, and moral concepts, based on a respect for human life that can be applied consistently across a broad range of individual circumstances. We should not have to change the rules for each infant.
   C. In practice, there are two main circumstances where withdrawal of ventilatory support is a consideration:
      1. When it is considered that the infant has already entered the process of dying and that ventilatory support is prolonging death rather than offering a reasonable hope of survival. This is the concept of futility.
      2. Where the continuation of assisted ventilation might well allow the infant to survive but with a significant risk of profound neurodevelopmental disability.

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III. The Dying Infant and Futility of Treatments
   A. Physicians are not obliged to continue with treatments that serve no purpose, especially when associated with prolonged pain or distress for the infant.
   B. The problem for the physician is to decide when assisted ventilation has ceased to become a trial of life and is simply prolonging the process of dying.
   C. The infant's state is often one of multiple organ impairments, where specific treatments directed towards affected organ systems have been offered without success. In effect, the decision to withdraw ventilatory support is based on *medical indications* that further ventilatory support is futile.
   D. In this way elective withdrawal of assisted ventilation gives some control over the timing and circumstances of the death instead of parents and staff presiding over an infant surrounded by the technological trappings of failed intensive care and who will die from cardiac standstill at an unpredictable time.
   E. Many so-called "lethal" congenital malformations, including those diagnosed in utero and primarily affecting the lungs/chest wall, may not be immediately lethal.
   F. Snap judgments should not be made at birth. Instead adequate time should be allowed to clarify the diagnosis and prognosis with parents so that they can contribute in an informed way to decision-making. This often means starting assisted ventilation with no commitment to continuing it.
   G. Severe and prolonged bronchopulmonary dysplasia (BPD) presents special problems, as the course is often characterized by repeated episodic deterioration, with the infant never quite gaining ground after each episode. The notion of futility may take a long time to dawn because of the difficulty in stepping off the therapeutic roller coaster once it has started. Each therapeutic intervention encourages hope for the parents and so it is important to engage them early and realistically about their infant's future.
   H. When ventilatory support has been withdrawn because of advanced BPD there are ethical challenges because survival for days or even weeks is not uncommon. The redirection of their care includes a firm understanding that re-intubation and ventilation are rarely an option, whereas the infant's comfort certainly is. In particular, parents need to be involved in decisions about pain relief, hydration, nutrition, and the use of supplemental oxygen.

IV. The "Quality of Life" Decision
   A. Here the judgment is that an infant might well survive as a result of continuing ventilatory support, but the quality of life is seriously called into question.
   B. It is ethically acceptable to withdraw assisted ventilation from those infants whose life might be saved only by further prolonged and distressing intensive care and where it is likely that profound neurodevelopmental or physical disability will make them forever dependent on a caregiver for everyday living.
   C. The arguments surrounding quality of life decisions have been well rehearsed and include the following concepts:
      1. "Quality of life" is a subjective notion.
      2. We can rarely be certain about the extent of any predicted handicap.
      3. The infant cannot take part in the decision-making.
      4. No one has the right to "act like God" and to judge whether death or survival with severe handicap is the better of the two.
      5. The concept of acting "in the best interests" of the infant readily rolls off the tongue but is fraught with uncertainty (Section V).
      6. On the other hand, faced with an intolerable existence, responsible adults may exercise their right to end their own lives, and someone has to speak on behalf of the infant.

V. Acting in the Infant's Best Interests
   A. The idea of acting in a patient's best interests is enshrined in medical practice but is rarely of *practical help* in decision-making.
   B. Of course, the infant's interests are paramount compared to the interests of others. However, the infant's interests are intimately linked with those of the parents, who carry a duty of care after the infant is discharged.
   C. The concept of best interests implies that *we know* what those interests are, but faced with complex medical challenges, we often do not.
   D. Perhaps the best "test" in these circumstances is the balance between the burden of treatments and the likely outcome. We may have a reasonable understanding of pain, suffering, and distress, and to some extent, these can be controlled. However, *neurodevelopmental outcomes* for individual infants and their potential *impact* are often impossible to assess in a helpful way.
   E. That is why the "best interests" argument is often used as a *conclusion* after the event, as in "After discussions with the parents I thought it best to continue ventilatory support but with hindsight, given the child's disabilities, the decision was probably not in the infant's best interests." This illustrates an obvious limitation to the best interest argument—if conversely ventilatory support is withdrawn and death ensues, hindsight cannot determine whether the decision was appropriate.

VI. Engaging Parents in Decision-Making
   A. Parents of seriously ill infants need time to make their views known. When it is clear that their infant is seriously ill, parents should be led into the discussion earlier rather than later. It is preferable to hold discussions in a quiet room away from the neonatal unit.
   B. Parents should be given the option of inviting close family members to discussions and staff should be aware that they might have religious needs they are reluctant to broach. If an interpreter is required, it is best not to use family members.
   C. Do not shoulder the burden of decision-making on parents ("*These are the facts*, *what do you want us to do*?"). Instead, make clear your medical view and indicate that you are seeking the parents' support.
   D. Explain that withdrawing ventilatory support is not simply a matter of "turning off a switch." They should be prepared for events and offered a choice of how they would like their infant to be cared for during and after withdrawal. They should be advised that their baby may gasp or show other reflex activities and have color changes to their face and body before death.
   E. They may want to know how long it will be before their baby dies once assisted ventilation is withdrawn and they should be made aware beforehand of the inherent uncertainty. However, in practice most decisions made on the basis of futility of care concern infants in whom it is highly likely that death is imminent. In those cases do not over-burden parents with *detailed* discussions about quality of life predictions. Instead the focus should be on ensuring a dignified and stress-free end of life.
   F. Agree a time and location for withdrawal of ventilatory support and whether the parents wish to be present.

VII. Conflicts between Parents and Staff
   A. A common scenario for withdrawing ventilatory assistance on the basis of a quality of life decision is when an infant has *persisting* abnormal neurologic signs associated with a brain scan that points to irreversible damage. A trusting relationship built up over time between the parents and the senior physician, together with a consensus view among experienced staff caring for the infant, will often avoid conflict.

B. Local practices vary regarding the role of an ethics committee. Probably their most helpful role is to act as a forum for debate and discussion rather than decision-making.
C. It is uncommon for parents to request thoughtfully and consistently that assisted ventilation be withdrawn against medical advice. On those occasions the physician's duty of care is primarily towards the infant.
D. It is more common for parents to request that ventilation be *continued* contrary to medical advice. Here, the physician's duty to the infant is to ensure that the parents understand the facts and arguments, and that they are capable of acting on behalf of the infant. Coercing parents to agree to withdrawing ventilatory support can cause regret and guilt that may remain with them long after their baby dies. Instead, counselling should be continued with an emphasis on the concept of compassionate care with the primary aim being to relieve pain, discomfort, and distress. As part of an informative counselling process, it can be helpful for the parents to meet with an ethics committee.

VIII. Parental Involvement after Withdrawal of Ventilatory Support
A. Parents should be prepared for events and offered a choice of how they would like their infant to be cared for during and after withdrawal.
B. A minority simply want to bid farewell to their infant, depart from the neonatal unit, and leave the details to the staff. Their wishes should be respected.
C. At the other extreme, some wish to remove the endotracheal tube, intravascular lines not being used, and monitoring devices themselves.
D. Facilities should be made available to allow parents to remain with their infant in a secluded room immediately after withdrawal with a choice of whether they want a nurse to be with them. Suckling at the mother's breast may be possible and some will wish to bathe and dress their infant.
E. Parents may wish to have photographs taken of their infant especially if the opportunity did not arise earlier. If the infant is one of a multiple births, it is usually possible to arrange for a family photograph. Ask the parents if they would like footprints and handprints. Retain all images within the medical record if they are not claimed by the parents as they may well ask about them some years later.
F. At an appropriate time clarify whether the parents wish to retain the infant's clothing such as a vest, bodysuit, or hat.

IX. Pain Relief, Sedation, and Comfort
A. The use of drugs in palliative care is based on the principle that the *primary intent* should be to relieve discomfort, distress, or pain. An unintended consequence may be shortening of life ("doctrine of double effect").
B. Laws and practices concerning the use of palliative drugs vary from country to country and state to state. There are some broad principles which should be respected:
    1. Always aim to keep parents fully informed and supportive of your approach to palliative care including the use of drugs.
    2. Make sure you understand the laws that are applicable in your own country or state. If you are uncertain, seek the help of a senior neonatologist, risk manager, or hospital attorney.
    3. The development of modern laws that govern palliative care and end of life practices is extraordinarily complex. Do not be the first to "test the law" in your own area.
C. If an intravenous catheter is already in place and it is predictable that pain relief and sedation will be needed, intravenous access should be maintained.
D. It is treading on a legal tightrope initially to prescribe sedatives or analgesics well in excess of recommended dosages, as the *primary intent* may be readily perceived as one of hastening death, which is tantamount to euthanasia.

E. Normally, the action of muscle relaxants will have been reversed shortly before ventilation is withdrawn in order to assess spontaneous breathing activity. The use of muscle relaxants as part of palliative care probably amounts to falling off that legal tightrope, as it is difficult to see this as anything other than an intention to promote death.

F. However, the management of "agonal gasping" continues to create anxiety for parents and staff, at least in part to the link between "agony" and "agonal." Parental support by an experienced nursing team can help to relieve much of the anxiety. It is important to understand whether the legal authority in your area of practice permits the use of muscle relaxants in this situation.

G. When quality of life has been the main consideration, it may take time before agreement is reached with parents to withdraw ventilatory support. In some cases by then the infant may no longer be dependent upon the ventilator and may well survive without it. In effect, the time taken for a quality of life decision may exceed a narrow window of opportunity to effect withdrawal of ventilation. Parents should be made aware of this in a sensitive way without coercion.

H. It is often argued that withdrawing ventilatory support and withholding fluids and nutrition are morally equivalent. However that is probably not the case because assisted ventilation is an *extraordinary measure* of medical care providing temporary breathing support for infants with *potentially reversible* respiratory failure. In contrast, all babies are *normally dependent* on a caregiver for the provision of fluid, nutrition, and warmth.

I. The priority when considering hydration and nutrition is the infant's comfort and freedom from distress. If the medical condition suggests that death is highly likely to occur within several hours of withdrawing ventilatory support, then fluid and nutrition should be withheld.

J. In other situations oral feeds should be continued if tolerated. Tube or intravenous feeding has the potential to cause unnecessary distress and discomfort. If the infant is intolerant of oral feeds and it is felt that the provision of hydration and nutrition are the sole factors keeping the infant alive, it is reasonable to withhold all feeds while managing any hunger-induced discomfort by sedation.

X. Engaging Staff in Decision-Making

A. Deceptive Signals: We need to guard against "giving up" on sick infants prematurely. There are deceptive signals that might erroneously *tip the balance* to persuade staff that continuing ventilatory support is not justified:

1. Despair
2. Adverse appearance of the infant:
   a. Undernutrition and dehydration
   b. Cholestatic jaundice
   c. Hydrops
3. Biased impression of prognosis based on unthoughtful comparisons with other very sick infants who have passed through the Neonatal Unit.
4. Non-visiting parents

B. Problems arise where there is no proper leadership on the Neonatal Unit, where the staff do not work together as a team, and where there is no proper forum for discussing ethical issues. Staff may feel unable to discuss the possibility of withdrawing assisted ventilation from an infant and instead subtle unspoken signals occur.

1. *Standing off on clinical rounds*: disgruntled staff turn away and show a lack of interest in discussing the infant and contributing to further management.

2. *Exaggeration of clinical signs*: an infant with pallor might be described as appearing "white as a sheet"; skin peeling might be referred to as "peeling off in layers."
3. *Therapeutic nihilism*: all suggested treatments are rejected on the basis of their side effects.
4. *Incongruous search for the expert*: paradoxically, staff may suggest calling in an "expert" such as a nephrologist or cardiologist to advise on organ system failure. This may be a "cry for help" in the hope that the specialist will indicate that nothing further can be done for the infant.
5. G*roup formation among staff*: small groups form among the staff and discuss among themselves the apparent futility of continuing ventilatory support.
6. "*The parents don't realize how sick the infant is*." In spite of the physician discussing the infant's progress with the parents at frequent intervals, the staff may insist that the parents do not understand how ill the infant is.

C. These unspoken signals reflect desperation and despair among staff, who cannot communicate their feelings to the senior physician. They are cries for help. It is essential that this situation is recognized and steps are taken to improve the organization and communication on the Neonatal Unit. Unless this happens, decisions about withdrawing assisted ventilation will generate a crisis each time and provoke additional suffering for parents and indeed for infants.

D. A helpful way of encouraging staff engagement is by enabling a nurse and junior doctor to be present at discussions about withdrawal of ventilatory care.

XI. Requesting a Post-mortem Examination After Withdrawal of Ventilatory Support

A. It is not appropriate to subject parents at the same time to the dual burden of deciding about withdrawing assisted ventilation and consenting to a post-mortem examination.

B. Having withdrawn assisted ventilation to relieve unnecessary pain and suffering, they may be unwilling to subject their infant to what they perceive as further suffering through a post-mortem examination.

C. When requesting post-mortem consent parents should not be given the impression that it is "to establish the cause of death" because it raises doubts that the decision to withdraw ventilatory support was made in ignorance about the infant's problems.

D. Instead, it provides an opportunity to confirm with parents that the disease was so severe that survival was not possible. In some cases it is helpful in supporting a decision made with the quality of life in mind. They can be reassured that having faced a most difficult parenting challenge they acted in a way that protected their baby from further suffering.

Suggested Reading

American Academy of Pediatrics, Committee on Fetus and Newborn. Non- initiation or withdrawal of intensive care for high-risk newborns. Pediatrics. 2007;119: 401–3.

Campbell AGM. Quality of life as a decision making criterion I. In: Goldworth A, Silverman W, Stevenson DK, Young EWD, editors. Ethics and perinatology. Oxford: Oxford University Press; 1995. p. 82–98.

Chiswick ML. Withdrawal of life support in babies: deceptive signals. Arch Dis Child. 1990;65:1096–7.

Chiswick M. End of life decisions in chronic lung disease. Semin Fetal Neonatal Med. 2009;14:396–400.

Delaney-Black V. Delivering bad news. In: Donn SM, Fisher CW, editors. Risk management techniques in perinatal and neonatal practice. Armonk, NY: Futura; 1996. p. 635–49.

Eden LM, Callister LC. Parent involvement in end-of-life care and decision making in the newborn intensive care unit: an integrative review. J Perinat Educ. 2010;19:29–39.

Hawryluck L. Neuromuscular blockers—a means of palliation? J Med Ethics. 2002;28:170–2.

Kuhse H. Quality of life as a decision making criterion II. In: Goldworth A, Silverman W, Stevenson DK, Young EWD, editors. Ethics and perinatology. Oxford: Oxford University Press; 1995. p. 104–20.

Larcher V. Ethical considerations in neonatal end-of-life care. Semin Fetal Neonatal Med. 2013;18:105–10.
Managing death and end of life decisions in perinatal medicine. In: Field D, editor special issue. Semin Fetal Neonatal Med. 2008;13(5).
Perkin RM, Resnik DB. The agony of agonal respiration: is the last gasp necessary? J Med Ethics. 2002;28:164–9.
Royal College of Paediatrics and Child Health. Withholding or withdrawing life sustaining treatment in children. A framework for practice. London: RCPCH; 2004.
Uthaya S, Mancini A, Beardsley C, Wood D, Ranmal R, Modi N. Managing palliation in the neonatal unit. Arch Dis Child Fetal Neonatal Ed. 2014;99:F349–52.
Verhagen AA, Dorscheidt JHHM, Engels B, Hubben JH, Sauer PJ. Analgesics, sedatives and neuromuscular blockers as part of end-of-life decisions in Dutch NICUs. Arch Dis Child Fetal Neonatal Ed. 2009;94: F434–8.
Warrick C, Perera L, Murdoch E, Nicholl RM. Guidance for withdrawal and withholding of intensive care as part of neonatal end-of-life care. Br Med Bull. 2011;98:99–113.
Willems DL, Verhagen AA, van Wijlick E. Committee end-of-life decisions in severely ill newborns of Royal Dutch Medical Association. Infants' best interests in end-of-life care for newborns. Pediatrics. 2014;134: e1163–8.

Medical Liability, Documentation, and Risk Management

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Steven M. Donn and Jonathan M. Fanaroff

I. Medical Liability
   A. Definition: Liability arising from delivery of medical care
   B. Legal bases of medical malpractice
      1. Negligence—most common
      2. Breach of contract
      3. Insufficient informed consent
      4. Failure to prevent foreseeable injury to third parties/Duty to warn
      5. Emotional distress
      6. Loss of chance
      7. Intentional misconduct
      8. Divulgence of confidential information
      9. Defamation
   C. Tort: A civil wrong in which a person has breached a legal duty with harm caused to another
      1. Can be intentional or negligent
      2. Defined roles of plaintiff v. defendant(s)
   D. Medical negligence
      1. Predominant theory of medical malpractice
      2. Plaintiff must establish each of the following four elements by a preponderance of the evidence (more likely than not/>50 % chance):
         a. Duty of defendant to plaintiff. Supervising residents or nurse practitioners may be enough to establish a duty even if a physician has never seen the patient.
         b. Breach—care provided fell below accepted medical standards (the "standard of care"), usually defined as what a reasonable health care provider would do under similar circumstances. Generally established by expert testimony.

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c. Proximate cause (breach directly led to injury).
d. Damages:
(1) Economic—medical expenses and costs of care. Lifetime care costs can be very high in neonatal cases
(2) Non-economic—pain and suffering, emotional distress. Limited in some states.
(3) Punitive—malicious or egregious conduct

E. Areas of malpractice risk in neonatology
1. Delivery room management/resuscitation
2. Medication errors—wrong medicine, wrong dose, and wrong patient
3. Delay in diagnosis/treatment—acidosis, hypotension, sepsis, congenital heart disease, seizures, hypoglycemia, meningitis, jaundice, and others

II. Documentation
A. Importance of the medical record
1. Memorialization of the hospital course—"If it wasn't documented, it wasn't done."
2. Communication among physicians and other health care professionals
3. Key piece of evidence in litigation

B. Legal issues associated with medical records
1. Confidentiality
2. Record retention
3. Patient rights
4. Release of records
5. Electronic medical records
6. Fraud and abuse
7. Spoliation—altering of records. Remember electronic medical records record not only what was documented, but also when, where, and by whom.

C. Communicating via the medical record
D. Effective documentation
1. Meets guidelines for evaluation and management (coding and billing)
2. Employs risk management skills (see below)
3. Complete, factual, and accurate
4. Timely (date and time all notes and orders)
5. Original (be careful with "copy and paste")
6. Must be legible
7. Objective
8. Discussions with parents including evidence of informed consent and refusal
9. Correct the medical record properly. Draw a single line so the record is still legible. Date and time new entries and explain why a correction is necessary.

E. Things to avoid
1. Language that accepts or assigns blame
2. Superlative modifiers (e.g., "profound," "severe," "emergent," etc.)
3. Offensive language
4. Judgmental language
5. Speculation

F. Procedure notes
1. List indication(s)
2. Informed consent and time-out
3. Describe procedure and equipment used

4. Note patient tolerance and complications, if any
5. Document appropriate follow-up study (e.g., chest radiograph) *and response* ("X-ray obtained → UVC pulled back 2 cm")

III. Risk Management: A systematic process to identify, evaluate, and address problems which may injure patients, lead to malpractice claims, and cause financial loss to health care providers
   A. Key elements
      1. Identification of potential risk
         a. External—legal action and patient complaints
         b. Internal (preferred method)—incident reporting and occurrence screening
      2. Calculation of probability of adverse effect from risk
      3. Estimation of impact of adverse leffect
      4. Establish risk prevention.
   B. Risk management success depends upon:
      1. Attitude
         a. Awareness of potential liability
         b. Commitment to effective communication
         c. Appreciation of impact of "other forces" (e.g., business decisions)
      2. Knowledge
         a. Unique neonatology/family relationship
         b. Informed consent
         c. Communication systems and skills
         d. Documentation requirements
         e. Neonatal malpractice claims
      3. Culture
         a. Culture of blame and finger-pointing leads to silence and repeated mistakes.
         b. Culture of safety allows caregivers to openly discuss barriers to safer care.
   C. Root Cause Analysis (RCA)—Evaluating the causative factors after things go wrong
      1. RCA Team Members
         a. Individuals with knowledge of the issues involved in the incident
         b. Risk management members
         c. Quality improvement members
      2. Key Questions
         a. What happened?
         b. Why did it happen?
         c. What are we going to do to prevent it from happening again?
         d. How will we know that the changes we make actually improve the safety of the system?
      3. Potential) actions to decrease the likelihood of an event after an RCA
         a. Train staff
         b. Write new policies
         c. Decrease workload
         d. Checklists
         e. Standardize equipment
         f. Redesign process to improve safety
         g. Simulation

Suggested Reading

Donn SM. Medical liability and the neonatologist. NeoReviews. 2016;17:e3–7. doi:10.1542/neo.17-1-e3.
Donn SM, McDonnell WM. When bad things happen: adverse event reporting and disclosure as patient safety and risk management tools in the neonatal intensive care unit. Am J Perinatol. 2012;29(1):65–70.
Fanaroff JM. Medical malpractice/expert testimony/disclosure of errors. Pediatr Rev. 2010;31:e24.
McAbee GN, Donn SM, editors. Medicolegal issues in pediatrics. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011.

Section XV

Research, Quality, and the Literature

Interpreting Clinical Research

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C. Omar Kamlin and Peter G. Davis

I. Introduction
   A. Clinical research helps improve patient outcomes.
   B. Keeping up to date is difficult because of the rate at which new research is published.
   C. Clinicians need to:
      1. Identify what is worth reading in detail.
      2. Learn and implement a step by step approach to evaluating and interpreting the medical literature.
      3. Determine whether the results should change their practice.
      4. Ask the questions:
         a. Is it *valid*—can we trust the results?
         b. Is it *important*—if true, is it worthwhile?
         c. Is it *applicable*—can the results be used to help my patients?

II. Clinical Research
   A. At the outset, the reader should identify the aims of the study and ask "what is this research about?" Is it:
      1. Evaluating a new therapy (e.g., does nitric oxide reduce mortality and morbidity of ventilated preterm infants?)?
      2. Evaluating a new diagnostic test (e.g., does procalcitonin improve the accuracy of diagnosis of neonatal sepsis?)?
      3. Assessing causality (e.g., do postnatal steroids cause cerebral palsy?)?
      4. Determining the natural history or prognosis of a condition (e.g., what is the respiratory function in adulthood of infants with BPD?)?
   B. Structure of an article and questions you should ask yourself before committing to read the whole article:
      1. Title—is this of interest to you?
      2. Authors—what is their track record?

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3. Journal—is it a reputable pediatric or general medical journal?
4. Abstract—is the background and synopsis of the methodology sufficiently detailed to make you want to continue reading?
5. Methods/Study Design—the most important section of a paper where flaws in design are likely to be picked up. Is there a control group? Have appropriate statistics been applied in the analysis?

C. Therapy
1. Possible study designs, in decreasing order of validity
   a. Randomized controlled trial (RCT)
   b. Cohort study (comparing groups from different places or different periods of time)
   c. Case control study
   d. Case series
2. Check list for evaluation (validity, importance, and applicability) of a study on therapy
   a. Were treated and untreated infants at equal risk for a bad outcome before therapy? Best achieved by random allocation of patients.
   b. Was there a pre-specified primary outcome, and was there an estimate of the sample size required to detect a clinically important difference in this outcome? Was the trial registered?
   c. Were both groups treated equally apart from the therapy being evaluated? Best achieved by masking of caregivers.
   d. Were important outcomes assessed (e.g., death, neurodevelopment in infancy versus short-term physiologic changes?)
   e. Were the groups assessed equally for the outcome of interest? Best achieved by masking of those assessing outcomes.
   f. Were the study infants similar to those you treat?
   g. If a *statistically* significant difference in outcomes was reported, was the difference *clinically* important?
   h. Is the therapy available and affordable in your practice?
   i. Were all the enrolled patients accounted for at the end of the study?

D. Diagnostic Tests: Criteria for evaluation of a study on diagnostic tests
1. Was there a blind comparison with a "gold standard"?
2. Were the patients similar to those in your practice?
3. Was the "normal" range defined?
4. Is the diagnostic test precise (reproducible), free of bias, and applicable in your clinical area?
5. To determine importance of the results, draw up a 2×2 table (Tables 96.1 and 96.2)

Table 96.1 2×2 table for diagnostic tests

	Gold standard result		
	Disease (+)	No disease (−)	
Test positive (+)	a	b	Positive predictive value a/(a+b)
Test negative (−)	c	d	Negative predictive value d/(c+d)
	Sensitivity a/(a+c)	Specificity d/(b+d)	

Sensitivity refers to the proportion of subjects with disease that have a positive test [a/(a+c)]
Specificity refers to the proportion of subjects free of disease that have a negative test [d/(b+d)]
Positive predictive value is the proportion of subjects with a positive result who have the disease [a/(a+b)]
Negative predictive value is the proportion of subjects with a negative result who are disease free [d/(c+d)]
The accuracy of the test can be calculated by examining proportion of true results (true positives and true negatives) of all results [(a+d)/(a+b+c+d)]

Table 96.2 Using a 2×2 table

	Outcome	
	Yes (+)	No (−)
Exposed (+)	a	b
Not exposed (−)	c	d

In an RCT or cohort study the relative risk of the exposure causing the outcome is (a/a + b)/(c/c + d); in a case control study the relative odds are ad/bc

E. Causality
   1. Types of study (in decreasing order of validity)*
      a. RCT
      b. Cohort
      c. Case control
      d. Case series

      *Although an RCT is the most robust test of causality, other designs may be more useful, particularly when looking for rare events.
   2. Check list for evaluation of a study investigating causation
      a. Was an inception cohort (i.e., a group assembled prior to exposure) formed with exposed and non-exposed groups similar in all important baseline characteristics, other than exposure to the factor(s) being investigated?
      b. Were exposures and clinical outcomes measured the same way in both groups?
      c. Was follow-up long enough and complete?
      d. Is the association strong and biologically plausible? Did the exposure precede the outcome?

F. Prognosis. Criteria for evaluation of a study investigating prognosis
   1. Was an inception cohort assembled?
   2. Was follow-up long enough and complete?
   3. Were the outcomes assessed by individuals masked to the subject's history and/or interventions?
   4. Was the assessment objective?
   5. Are the results applicable to your own practice and how will the evidence affect what you tell your patient/parents?

III. Statistical Considerations

A. A good Methods section will describe the statistical tests used in a simple manner.

B. Inappropriate choice of statistical tests may lead to misleading interpretation of results (was the test chosen only because it yielded a "significant *P* value?").

C. A statistical test provides the reader with a probability, a *P* value, of the results (a difference between two groups) resulting from chance alone. The arbitrary but widely accepted cutoff is 0.05 (1 in 20). When the *P* value is <0.05, then the null hypothesis (no difference between two interventions) can be rejected, and we may conclude that one intervention is better than the other.

D. Confidence intervals (CI) are an alternative way of assessing the play of chance. The 95 % CI gives the range of values, within which we can be 95 % certain the true value lies. The advantage of a CI over a *P* value is that it can quantitate the size of the difference, and the width of the interval provides an indication of precision of the estimate of that difference.

IV. Where to Search for the Evidence
   A. Library—physical and online. With ready availability of computers and hand held devices, searching the internet to access primary articles has become much easier using search engines such as PubMed, Ovid, etc.
   B. E Table of Contents (ToC) Alerts—go to the homepage of the journal and sign up for email alerts. A typical service will include a monthly (or weekly) table of contents for the printed version and an email when a newly accepted article is made available online.
   C. Saved Searches—Third party providers (e.g., AMEDEO; www.amedeo.com) can search a wide range of journal ToC and filter the results according to your field of interest (there is a neonatology filter as an option) and send you the results in a weekly email. There are hyperlinks to the abstract of these articles found on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/).
   D. Searching for pre-appraised evidence
      1. Cochrane Database of Systematic Reviews, TRIP database (UK)
      2. Review articles
      3. Clinical Practice Guidelines, including consensus opinion statements

V. Some Recognized Pitfalls
   A. Do not assume statistical significance is the same as clinical significance (important!).
   B. Do not assume results from a published study are applicable to your patients.
   C. Studies without a control group are unreliable and potentially misleading.
   D. Do not forget to consider potential harms and economic effects of an intervention.
   E. Beware of review articles—these are often biased opinions of the author and may not be a systematic appraisal of the literature.
   F. Although systematic reviews represent the pinnacle of the evidence-based pyramid, they may not be reliable, especially if the studies included are small and/or of poor quality.

VI. Conclusion
   A. "Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values."
   B. A sound, structured approach to reading journal articles helps determine the best course of action to take with your own patients in a time effective manner.

Suggested Reading

Barrington KJ. How to find and how to read articles in neonatology. Semin Fetal Neonatal Med. 2015;20: 378–83.
Crombie IK. Pocket guide to critical appraisal. 2nd ed. London: Wiley; 2008.
Davis PG, editor. Clinical research. Semin Fetal Neonatal Med. 2015;20(6):377–441.
Haynes RB, Sackett DL, Guyatt GH, Tugwell P. Clinical epidemiology: how to do clinical practice research. 3rd ed. Philadelphia: Lippincott, Williams and Wilkins; 2005.
The Cochrane Library. http://www.thecochranelibrary.com/view/0/index.html, http://neonatal.cochrane.org/

Data Collection and Assessment of Respiratory Outcomes

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Alan R. Spitzer

I. General Principles of Quality Improvement
   A. There are significant differences between medical research and quality improvement.
      1. Medical research represents the testing of a novel idea, treatment, surgical therapy, or device for the purpose of determining if this new approach represents a better way to provide care to a patient or manage a particular disease.
      2. Quality improvement is the application of a previously established, tested approach to a patient population for the purpose of improving the outcome for either individual patients or groups of patients.
         a. In some instances, there may be more than one accepted approach to a clinical problem. In instances like this, the boundary line between research and quality improvement may become blurred if one tests various approaches to care simultaneously in order to determine if one therapy may be more effective than another.
         b. Such evaluations fall into the category of comparative effectiveness outcomes research, indicating the hazy border between quality outcome evaluation and research in such circumstances.
   B. Nothing is more valuable in improving future outcomes for a patient population than knowing the outcomes of previously treated patients.
      1. If you do not know where you have been, it is impossible to determine where you will be able to go with your patient population. Future patients can potentially benefit significantly from the collection of outcome data on past patients (Fig. 97.1). While stand-alone data can be very valuable, comparisons of local outcomes to established outcomes or national benchmark data in similar NICUs can provide greater insights into the problem being studied.
      2. The collection of accurate, validated outcome data is the most important tool the clinician has for improving care in the NICU. In collecting outcome data, the greater the degree of inclusivity in the patient population, the more correct the assessment of outcome is likely to be. Editing of data through elimination of some patients (late transfers, early mortalities, etc.) can occasionally lead to erroneous conclusions about outcomes.

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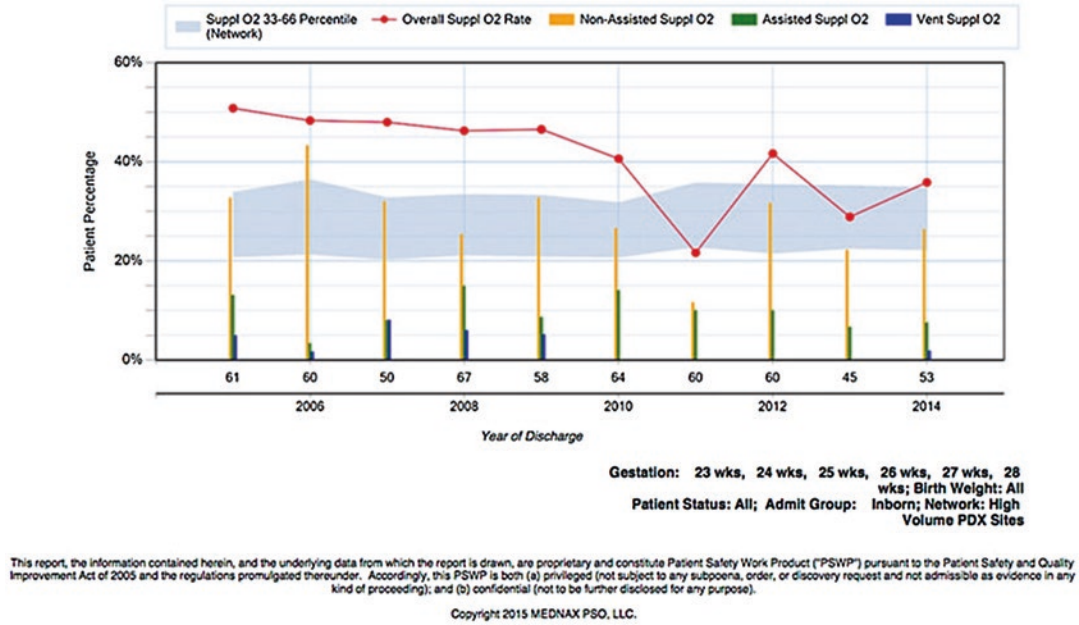


Fig. 97.1 Bronchopulmonary dysplasia (BPD) rates at 36 weeks' gestational age in an individual NICU practice with comparisons. The figure indicates the incidence (patient percentage) of 23–28-week gestational age neonates with BPD over a 10-year time period in an individual NICU. The overall BPD rate is indicated in red and is seen to decline somewhat during this interval. The *background gray bar* is the overall rate of BPD for the 33–66th percentile comparison group, which is relatively flat during the same time period. The figure also indicates a declining use of ventilator assistance in these infants with a concomitant rise in the use of assisted, non-ventilator oxygen administration (nasal CPAP, high-flow nasal cannula). The numbers below the graph on the X-axis indicate the number of patients treated each year

3. The application of previously established principles of care, based upon accurate outcome data, will usually yield far better clinical improvement in the immediate future than the dramatic appearance of a major new technology or therapy. It has been suggested that new innovations in care usually take approximately 10 years before they establish a significant foothold in medical practice, even when initial results are dramatic. The introduction of surfactant replacement therapy provides an excellent example of this statement. Fujiwara's initial publications on the significant effects of surfactant first appeared in 1980–1981. Widespread use of surfactant did not occur in the USA until the early 1990s. The application of already established approaches as employed in a quality improvement project, however, may result in benefits to patients within weeks to months following their application.

C. Collections of data may be comprehensive (all patients treated) or targeted (selected patient groups), but it is essential for understanding outcomes to collect data on *all* the patients in the desired patient population.
   1. Partial, incomplete data collections are highly likely to lead to erroneous conclusions about outcomes.
   2. As is often the case with many research projects, there may be a temptation to collect data that is too detailed and excessive for the purposes of quality improvement. In any data collection set, it is more valuable to collect limited, accurate information that allows specific questions to be addressed than extensive volumes of incomplete data that cannot be easily compiled or accurately interpreted.

3. A targeted planning meeting to determine what data should be collected is a valuable exercise for any group planning a quality improvement project. The time that is expended during this process will be more than made up for in the long run when assessing outcomes for a patient population and knowing how best to proceed with one's patients.
4. With each transcription of a data set for the purpose of statistical assessment, the probability of inaccuracies being transcribed increases. The more that data copied and moved from one storage resource to another, the more likely inaccuracies and outliers (unexpected outcomes that lie significantly beyond anticipated results) will appear within a data set.
5. In general, the use of electronic health records (EHR) that allow automatically extracted, validated, data set collections is likely to provide the most complete information and the fewest errors in assessing outcomes. As with any collection of electronic information, however, the quality of the information that can be extracted is only as good as the reliability of data points entered into the EHR. The flow of data through electronic systems, however, must be reviewed on an ongoing basis to be certain that all data entry flows accurately through each step of the data system into the data repository.
6. It is extremely helpful to assign a member of a practice to serve as the quality improvement coordinator for the group. This individual should assume responsibility that data entry into the EHR (or whatever data collection process is being used) is accurate and complete and should serve as the "champion" of the quality project. In any group of neonatologists, there will tend to be varying degrees of compulsiveness about medical record keeping. It is essential that the project coordinator educates all members of the group to recognize the importance of maintaining accurate and complete data entry so that a high level of confidence in the data results.
7. In most quality systems, de-identification of the data collected is valuable, especially if consideration is given to possible publication of findings in the future. De-identification means the effective removal of all information that could be used to potentially identify an individual patient, including birth date, day of birth, medical record number, etc. Submission of the de-identification process to the local or a national institutional review board (IRB) may be valuable to insure appropriate data collection.

II. Evaluating Neonatal Respiratory Outcomes
   A. Because of their critical and central role in both survival and quality of life, understanding and attempting to improve respiratory outcomes in any neonatal patient population represents an essential undertaking for most neonatology practices.
   B. In general, for quality improvement purposes in the NICU, it is better to focus on the respiratory diseases that affect the majority of patients treated (e.g., respiratory distress syndrome, meconium aspiration, and bronchopulmonary dysplasia), rather than the rare diseases (e.g., congenital diaphragmatic hernia and congenital pulmonary airway malformation) that appear far less frequently. While the care of uncommon problems and diseases represents a hallmark for a high level neonatal practice, the greatest gains will be made in improving the outcomes for more common respiratory diseases. Similarly, the more common therapies utilized in the NICU will be more amenable to quality evaluation and improvement. This statement represents a modification of the Pareto principle, which states that 20 % of problems typically will be responsible for 80 % of important outcomes in any patient population.
   C. There is often a tendency to focus on the more obscure, uncommon issues that appear in every NICU in trying to impact outcomes. While these issues are important to consider, rare diseases and how best to influence their outcomes are more appropriate for research as opposed to quality assessment.

D. In evaluating respiratory outcomes, two overall areas are the most fertile for assessment: process measures and outcome measures. Process measures refer to the approaches used by the clinicians to treat the patient (e.g., frequency of ventilator use in a premature infant population and use of high-flow nasal cannula or CPAP over time), while outcome measures examine the results of changes in process (e.g., mortality rates, rate of bronchopulmonary dysplasia, and incidence of apnea and bradycardia).

E. As noted earlier, the effect of any process measure upon an outcome can be evaluated with a defined, targeted data collection. As an example, if one wished to assess the effect of a particular approach to blood gas management upon duration of ventilation, collection of a specific data set could be created to answer this question. It should be noted, however, that a targeted data set collection is more difficult to maintain for prolonged periods than more general collections of less complete, but more inclusive, data on an overall NICU census that is extracted from an EHR.

F. Data collections over periods of time can be especially helpful in tracking the effects of changes in management upon outcomes and are essential in assessing whether improvement in outcomes has been effected successfully or whether an alternate process strategy is necessary (Fig. 97.1).

III. Planning a Quality Improvement Project for Respiratory Outcomes

A. The first step in defining a quality improvement (QI) project is determining the problem to be studied. The problem can be in either a process or an outcome, but there should be general agreement in the NICU planning group about the problem to be studied.

1. To make the project of the greatest value in the NICU, the problem to be studied should be the one that is thought currently to be of significance in its effects upon patient outcomes.
2. Random selection of an issue to be studied is less likely to achieve buy-in from various stakeholders in the NICU and more likely to result in a failure to achieve the intended goal, since there will be little passion to "fix" the issue.

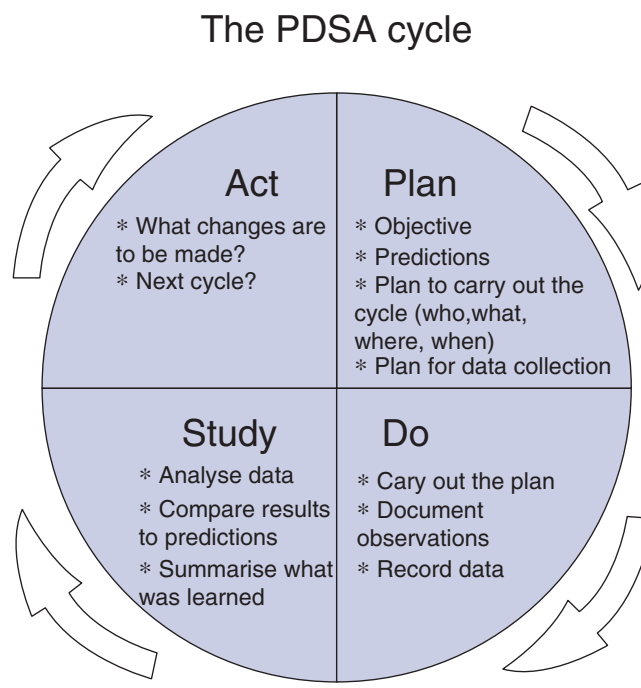
B. The most effective strategy to achieve buy-in from all the stakeholders in creating a QI project is to meet and discuss what issue or issues are of the greatest significance to the most members of the group. If one is interested in attempting to decrease the rate of BPD in the NICU, for example, having only a few physicians engaged in the project will be far less effective than a program that includes all the physicians, NNPs, nurses, respiratory therapists, pharmacists, etc. One must be cautious, however, that while creating a committee to address the issue is essential, care must be exerted not to overpopulate the committee to the point where agreement on an approach is not easily achieved because of the divergence of opinions that may emerge. Far too many CQI projects have failed to materialize because agreement cannot be achieved and the project falls apart before it ever gets underway.

C. As noted previously (Pareto principle), one should attempt to control the few variables that are most likely to achieve a positive outcome effect, as opposed to many variables that are less likely to achieve the desired effect. If reduction in rate of BPD is desired, such well-studied and reported processes as more frequent use of nasal CPAP and reduction in immediate delivery room intubation are more likely to yield benefit than modifying other less impactful processes.

D. The patients to be studied should be all inclusive in the NICU. For BPD reduction, one should attempt to study *all* infants below 1250 g birth weight, or less than 28 weeks' gestation, not just occasional patients in this category.

E. While, as noted, consensus of approach and buy-in of stakeholders is critical for success, a single champion of the project can be extremely helpful in managing a QI project to completion. The absence of such an individual inevitably means that no one "owns" the project and

Fig. 97.2 The PDSA cycle



the opportunity for success will be reduced. Someone needs to keep all various individuals engaged in the program until data can be analyzed and further acted upon.

F. Communication between stakeholders throughout the duration of the project is important so that there is assurance that everyone remains on the same page through the project. An electronic bulletin board, or an old-time physical one, can be very helpful in this respect. Excessively frequent analysis of data should be avoided, however, as improvements are often slow to achieve, especially early, and may discourage people from remaining engaged. It is helpful to set up an agreed timeframe for outcome assessment (e.g., monthly and quarterly) in advance so that staff know what to expect.

G. The simplest approach to most CQI projects is the PDSA cycle (Plan, Do, Study, Act), as seen in Fig. 97.2. The PDSA cycle was first introduced into industry by Deming, but has ideal applicability for medical practices as well. In the PDSA cycle, a problem is identified and an initial approach is devised (Plan). The project is implemented and data are collected (Do). An analysis of the data is made and an assessment of the impact is generated (Study). Lastly, a decision is made about whether adequate success has been achieved or whether some modification needs to be made and another cycle initiated (Act).

1. Part of the initial plan should be a reasonable estimate of the time necessary to achieve the desired goal. For example, one would not necessarily expect the rate of BPD to decline within 3 months, and it would be far too early to determine if any improvement achieved has been sustained. Some projects may require 1 or 2 years before success can be established, whereas other CQI projects may return results far more immediately.
2. It may be helpful to create a run chart that indicates outcomes during the desired time periods so that everyone engaged in the project can see the effects of the quality improvement project (Fig. 97.3).
3. Annotation of the interventions used to enhance a desired outcome on the run chart is helpful in tracking which approaches appear to be most effective.

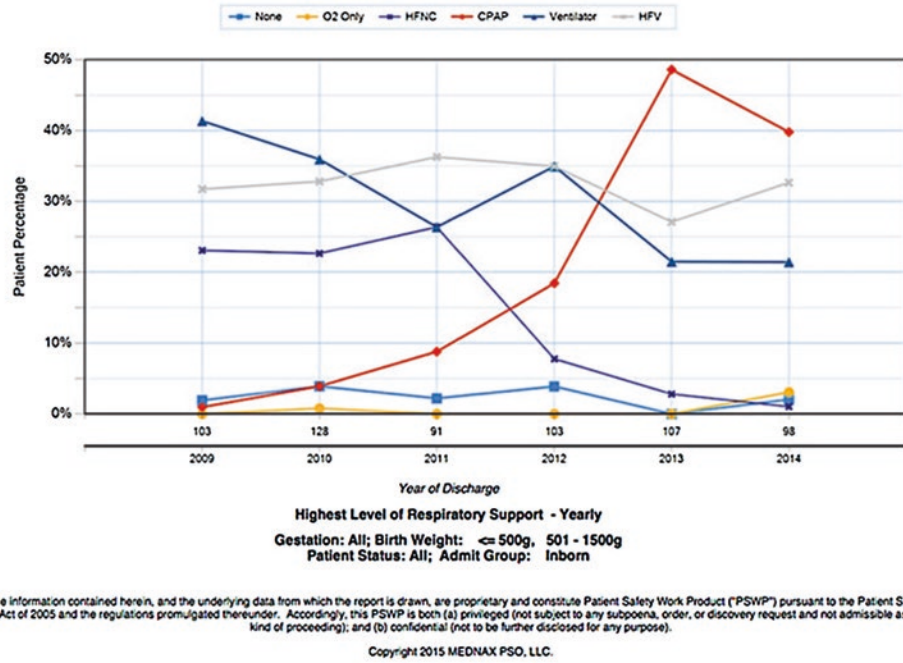


Fig. 97.3 Run chart of changes in the highest level of ventilatory assistance in an NICU. Flow chart of ventilatory assistance strategies. Figure indicating the changes in the highest level of respiratory support in an individual NICU for babies less than 1500 g. There is a marked increase in the use of nasal CPAP (0 % to 40–50 %) as well as a decline in the use of conventional mechanical ventilation (41–22 %) and high-flow nasal cannula (22–2 %). The use of the other modalities of therapy appears relatively consistent. The numbers below the X-axis represent the total number of patients treated each year in this weight class

H. Other data-driven CQI approaches can also yield significant results, such as Six-Sigma. In Six-Sigma, the following concepts are utilized, which are not that dissimilar from PDSA:
   1. Emphasis on a data-driven technology (again, sound data collection is imperative)
   2. Define needs and expectations for the patient population.
   3. Eliminate potential process errors that might affect outcomes.
   4. Structure a clear approach to identify root causes of problems.
   5. Utilize appropriate statistical methodology to analyze results.
   6. Assess outcomes and cost savings that align with the strategic objectives of the institution.

I. The Six-Sigma approach blends well with the Institute for Healthcare Improvement's (IHI) Triple Aim for defining healthcare quality:
   1. Improve the individual patient care experience overall.
   2. Enhance population health.
   3. Provide quality care at the least possible cost.

J. If the IHI goals can be achieved in a substantial number of outcomes for an individual NICU, it is likely that the overall care in the NICU represents a true quality approach. There is, however, never an end to quality improvement. Respiratory outcomes:The outstanding neonatology practice will constantly be seeking better methods to care for its patients.

Suggested Reading

Ellsbury D, Clark RH, Ursprung R, et al. A multi-faceted approach to improving outcomes in the NICU: the Pediatrix 100,000 babies campaign. Pediatrics. 2016; 137(4). pii: e20150389.

Spitzer AR, Ellsbury D. Quality improvement in neonatal/perinatal medicine. Clin Perinatol. 2010; 37: 1–305. Philadelphia, PA: W.B. Saunders.

Spitzer AR, Ellsbury D. Evidence-based neonatal pharmacotherapy. Clin Perinatol. 2012; 39: 1–252. Philadelphia, PA: Elsevier.

Spitzer AR, Ellsbury D, Clark RH. The Pediatrix Clinical Data Warehouse—a unique national resource for improving outcomes for neonates. Indian J Pediatr. 2015;82:71–9.

Practical Quality Improvement in the NICU

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Michelle Nemshak and Rebecca Vartanian

I. Defining Quality Improvement (QI)
   A. Quality improvement has several definitions, including "the combined and unceasing efforts of everyone—healthcare professionals, patients and their families, researchers, payers, planners and educators—to make the changes that will lead to better patient outcomes (health), better system performance (care) and better professional development."
   B. Although QI has strong industry and statistical roots, incorporation of QI methodology in healthcare gained national relevance when two reports released by the Institute of Medicine acknowledged both the system failures resulting in patient harm and the "chasm" that exists between the care we could provide and the care we do provide.

II. QI Basics
   A. Several approaches to QI (e.g., Lean, Six Sigma, and the Model for Improvement) are found in healthcare settings.
      1. Each approach may have different language and tools.
      2. Similarities include a focus on the process one is trying to change, the importance of measurement, and using small tests of change.
      3. Observation of process and going to the "front-line" to see, hear, and learn
      4. Providers should familiarize themselves with the approach used within their health system to facilitate communication with staff and leadership.
      5. The Institute for Healthcare Improvement provides free resources for individuals to understand the basics of QI (www.ihi.org).
   B. Team composition
      1. Team composition is the key for improvement project success, both in the planning and implementation phases.

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2. Attention should be given to include key stakeholders and customers who will be affected by changes, and leadership to ensure alignment with organizational goals and to provide resources.
3. The Vermont Oxford Network has also demonstrated the importance of including the family voice by including parents on the QI team.

C. Selecting what to change in order to achieve the outcome desired
1. Change concepts are large buckets that are filled with specific ideas for change.
2. Change concepts include improving workflow, limiting waste, reducing variation, and reducing error.
3. Specific changes may include standardized feeding guidelines for premature babies or barcoding medications to reduce error.
4. Often changes are small, incremental, and phased. Remember improvement is a process, not a product.

D. The term "potentially better practices"…
1. Best practices are usually conditional.
2. "Potentially" means the intervention may be effective.
3. Context is vital and should be examined with every potentially better practice (e.g., using a snow blower to clear 2 ft of snow is a potentially better practice than a shovel—however, if you live in Miami or Phoenix, that would not be a reasonable purchase. Even if it did snow, the expense of a snow blower for the frequency and amount of snow would not be effective).

E. Measures
1. Selecting process, outcome, and balancing measures a priori allows for baseline data collection.
2. Measuring whether your change occurred (did you actually do what you set out to do?) and what impact it had (did you choose the right process to change?) is one difference between issuing a guideline and performing QI.

F. Data
1. Developing audit tools during the planning phase can facilitate timely data collection and feedback.
2. Using visual data displays like annotated run charts and/or statistical process control charts allows teams to understand the normal variation in their process prior to intervention and assess for improvement during P–D–S–A cycles.

G. Collaboration
1. Opportunities to work with other NICUs exist at the regional, state, and national levels through different organizations.
2. Allows for sharing of tools and experiences to further individual center's improvement journey

III. QI as Scholarly Work
A. There is a growing body of literature regarding the effectiveness of QI efforts within the clinical setting.
B. The SQUIRE 2.0 guidelines provide a framework for abstract and manuscript production.
C. Involvement in QI is now a requirement for maintenance of certification Part 4 for neonatologists in the USA.

Suggested Reading

Batalden PB, Davidoff F. What is "quality improvement" and how can it transform healthcare? Qual Saf Health Care. 2007;16(1):2–3.

Institute of Medicine (IOM). To err is human: building a safer health system. Washington, DC: National Academy Press; 2000.

Institute of Medicine (IOM). Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2001.

Kaplan HC, Provost LP, Froehle CM, Margolis PA. The Model for Understanding Success in Quality (MUSIQ): building a theory of context in healthcare quality improvement. BMJ Qual Saf. 2012;21(1):13–20.

Lachman P, Jayadev A, Rahi M. The case for quality improvement in the Neonatal Intensive Care Unit. Early Hum Dev. 2014;90(11):719–23.

Langley GL, Moen R, Nolan KM, Nolan TW, Norman CL, Provost LP. The improvement guide: a practical approach to enhancing organizational performance. 2nd ed. San Francisco: Jossey-Bass Publishers; 2009.

Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. Am J Med Qual. 2015;30(6):543–9.

Contemporary Classics in Neonatal Respiratory Care

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Rachel L. Chapman

The following articles, listed alphabetically, have been chosen as the top 100 peer-reviewed articles related to neonatal respiratory care and published in the last 10 years:

1. Ahmed SJM, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. Pediatrics. 2010;125:e115–21.
2. Ambalavanan N, Van Meurs KP, Perritt R, et al. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. J Perinatol. 2008;28:420–6.
3. Ambalavanan N, Carlo WA, Wrage LA, et al. $PaCO_2$ in surfactant, positive pressure, and oxygenation randomised trial (SUPPORT). Arch Dis Child Fetal Neonatal Ed. 2015;100:F145–9.
4. Ambalavanan N, Cotten CM, Page GP, et al. Integrated genomic analyses in bronchopulmonary dysplasia. J Pediatr. 2015; 166:531–7.
5. Baird R, MacNab YC, Skarsgard ED, et al. Mortality prediction in congenital diaphragmatic hernia. J Pediatr Surg. 2008;43: 783–7.
6. Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med. 2006;355:343–53. Erratum in: N Engl J Med. 2007;357:1444–5.
7. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2007;1:CD000509.
8. Bassler D, Plavka R, Shinwell ES, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med. 2015;373:1497–506.
9. Beardsmore CS, Westaway J, Killer H, et al. How does the changing profile of infants who are referred for extracorporeal membrane oxygenation affect their overall respiratory outcome? Pediatrics. 2007;120: e762–8.
10. Been JV, Rours IG, Kornelisse RF, et al. Chorioamnionitis alters the response to surfactant in preterm infants. J Pediatr. 2010;156:10–5.
11. Bhandari V, Finer NN, Ehrenkranz RA, et al. Synchronized nasal intermittent positive-pressure ventilation and neonatal outcomes. Pediatrics. 2009;124:517–26.

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DOI 10.1007/978-3-319-39839-6_99

12. The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368: 2094–104.
13. Bose C, Extremely Low Gestational Age Newborn Study Investigators. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. Pediatrics. 2009;124:e450–8.
14. Breatnach C, Conlon NP, Stack M, et al. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med. 2010;11:7–11, 164–6.
15. Checkley W, West KP, Wise RA, et al. Maternal vitamin A supplementation and lung function in offspring. N Engl J Med. 2010;362:1784–94.
16. Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev. 2015;3:CD000104.
17. Consortium on Safe Labor. Respiratory morbidity in late preterm births. JAMA. 2010;304(4):419–25.
18. Crowther CA, Haslam RR, Hiller JE, et al. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. Lancet. 2006;367:1913–9.
19. Dargaville PA, Copnell B, Mills JF, et al. Randomized controlled trial of lung lavage with dilute surfactant for meconium aspiration syndrome. J Pediatr. 2011;158:383–9.
20. Davis PG, Schmidt B, Roberts RS, et al. Caffeine for Apnea of Prematurity trial: benefits may vary in subgroups. J Pediatr. 2010;156:382–7.
21. De Visser YP, Walther FJ, Laghmani EH, et al. Phosphodiesterase-4 inhibition attenuates pulmonary inflammation in neonatal lung injury. Eur Respir J. 2008;31:633–44.
22. Doyle AU, Davis LW, Morley PG, et al. Outcome at 2 years of age of infants from the DART study: a multicenter, international, randomized, controlled trial of low-dose dexamethasone. Pediatrics. 2007;119:716–21.
23. Engel WA, The Committee on Fetus and Newborn. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. Pediatrics. 2008;121:419–32.
24. Farhath S, He Z, Nakhla T, et al. Pepsin, a marker of gastric contents, is increased in tracheal aspirates from preterm infants who develop bronchopulmonary dysplasia. Pediatrics. 2008;121:e253–9.
25. Field D, Elbourne D, Hardy P. Neonatal ventilation with inhaled nitric oxide vs. ventilatory support without inhaled nitric oxide for infants with severe respiratory failure born at or near term: the INNOVO multicentre randomised controlled trial. Neonatology. 2007;91:73–82.
26. Finer NN, Rich W, Wang C, et al. Airway obstruction during mask ventilation of very low birth weight infants during neonatal resuscitation. Pediatrics. 2009;865–9.
27. Friedrich AU, Pitrez L, Stein PMC. Growth rate of lung function in healthy preterm infants. Am J Resp Crit Care Med. 2007;176:1269–73.
28. Gadgua MM, Cutter GR, Abman SH, Kinsella JP. Effects of early inhaled nitric oxide therapy and vitamin A supplementation on the risk for bronchopulmonary dysplasia in premature newborns with respiratory failure. J Pediatr. 2014;164:744–8.
29. Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. Cochrane Database Syst Rev. 2008;(1):CD000456.
30. Gupta S, Sinha SK, Tin W, Donn SM. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus infant flow driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. J Pediatr. 2009;154:645–50.e2.
31. Hansen AU, Wisbork K, Uldbjerg N, Henriksen TB. Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study. BMJ. 2008; 336:85–7.

32. Henderson-Smart DJ, Cools F, Bhuta T, Offringa M. Elective high-frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev. 2007;18:CD000104.
33. Hibbs AM, Walsh MC, Martin RJ, et al. One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to prevent) Chronic Lung Disease trial. J Pediatr. 2008;153:525–9.
34. Higgins RD, Bancalari E, Willinger M, Raju TNK. Executive summary of the workshop on oxygen in neonatal therapies: controversies and opportunities for research. Pediatrics. 2007;119:790–6.
35. Hintz SR, Van Meurs KP, Peritt R, et al. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr. 2007;151:16–22.
36. Hofmeyr GJ, Xu H. Amnioinfusion for meconium-stained liquor in labour. Cochrane Database Syst Rev. 2010;(1):CD000014.
37. Huddy CL, Bennett CC, Hardy P, et al. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4–5 years. Arch Dis Child Fetal Neonatal Ed. 2008;93:F430–5.
38. Hülskamp G, Lum S, Stocks J, et al. Association of prematurity, lung disease and body size with lung volume and ventilation inhomogeneity in unsedated neonates: a multicentre study. Thorax. 2009;64: 240–5.
39. Kattwinkel J, Stewart C, Walsh B, et al. Responding to compliance changes in a lung model during manual ventilation: perhaps volume, rather than pressure, should be displayed. Pediatrics. 2009;123:e465–70.
40. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med. 2006;355:354–64.
41. Kinsella JP, Cutter GR , Steinhorn RH. Noninvasive inhaled nitric oxide does not prevent bronchopulmonary dysplasia in premature newborns. J Pediatr. 2014;165:1104–8.
42. Kirpalani H, Millar D, Lemyre B, et al. A trial comparing noninvasive ventilation strategies in preterm infants. N Engl J Med. 2013;369:611–20.
43. Konduri GG, Vohr B, Robertson C, et al. Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up. J Pediatr. 2007;150:235–40.
44. Kribs A, Roll C, Göpel W, et al. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. JAMA Pediatr. 2015;169:723–30.
45. Kubicka, ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? Pediatrics. 2008;121:82–8.
46. Kugelman A, Feferkorn I, Riskin A, et al. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized, controlled, prospective study. J Pediatr. 2007;150:521–6.
47. Laughon M, Alldred EN, Bose C, et al. Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. Pediatrics. 2009;123:1124–31.
48. Lavoi PM, Pham C, Jang KL. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the National Institutes of Health. Pediatrics. 2008;122:479–85.
49. Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. Cochrane Database Syst Rev. 2014;9:CD003212.
50. Litmanovitz I, Carlo WA. Expectant management of pneumothorax in ventilated neonates. Pediatrics. 2008;122:e975–9.

51. Lista G, Castoldi F, Bianchi S, et al. Volume guarantee versus high-frequency ventilation: lung inflammation in preterm infants. Arch Dis Child. 2008;93:F252–6.
52. Logan JW, Rice HE, Goldberg RN, Cotton CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. J Perinatol. 2007;27:535–49.
53. Mahut B, De Blic J, Emond S, et al. Chest computed tomography findings in bronchopulmonary dysplasia and correlation with lung function. Arch Dis Child. 2007;92: F459–64.
54. Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013;369:1425–33.
55. Marlow N, Greenough A, Peacock JL, et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. Arch Dis Child Fetal Neonatal Ed. 2006;91:F320–6.
56. McEvoy C, Schilling D, Spitale P, et al. Decreased respiratory compliance in infants less than or equal to 32 weeks' gestation, delivered more than 7 days after antenatal steroid therapy. Pediatrics. 2008;121:e1032–8.
57. Mercier JC, Hummler H, Durrmeyer X, et al. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet. 2010;376:346–54.
58. Miller TL, Zhu Y, Altman AR, et al. Sequential alterations of tracheal mechanical properties in the neonatal lamb: effect of mechanical ventilation. Pediatr Pulm. 2007;42:141–9.
59. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358:700–8. Erratum in: N Engl J Med. 2008;358:1529.
60. Murphy KE, Hannah ME, Willan AR, et al. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomized controlled trial. Lancet. 2008;372: 2143–51.
61. Nixon PA, Washburn LK, Schechter MS, O'Shea TM. Follow-up study of a randomized controlled trial of postnatal dexamethasone therapy in very low birth weight infants: effects on pulmonary outcomes at age 8 to 11 years. J Pediatr. 2007;150:345–50.
62. Patel DS, Rafferty GF, Lee S, et al. Work of breathing during SIMV with and without pressure support. Arch Dis Child. 2009;94: 434–6.
63. Patel DS, Sharma A, Prendergast M, et al. Work of breathing and different levels of volume-targeted ventilation. Pediatrics. 2009;123:e679–84.
64. Pfister RH, Soll RF, Wiswell T. Protein containing synthetic surfactant versus animal derived surfactant extract for the prevention and treatment of respiratory distress syndrome. Cochrane Database Syst Rev. 2007;4:CD006069.
65. Rabi Y, Rabi D, Yee W. Room air resuscitation of the depressed newborn: a systematic review and meta-analysis. Resuscitation. 2008;72:353–63.
66. Ramanathan R, Sekar KC, Rasmussen M, et al. Nasal intermittent positive pressure ventilation after surfactant treatment for respiratory distress syndrome in preterm infants <30 weeks' gestation: a randomized, controlled trial. J Perinatol. 2012;32: 336–43.
67. Rojas MA, Lozano JM, Rojas MX, et al. Very early surfactant without mandatory ventilation in premature infants treated with early continuous positive airway pressure: a randomized, controlled trial. Pediatrics. 2009;123:137–42.
68. Sai Sunil Kishore M, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. Acta Paediatr. 2009;98:1412–5.
69. Salvo V, Lista G, Lupo E, et al. Noninvasive ventilation strategies for early treatment of RDS in preterm infants: an RCT. Pediatrics. 2015;135(3):444–51.
70. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354:2112–21.

71. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med. 2007;357:1893–902.
72. Scopesi F, Calevo MG, Rolfe P, et al. Volume targeted ventilation (volume guarantee) in the weaning phase of premature newborn infants. Pediatr Pulm. 2007;42:864–70.
73. Sharma A, Greenhough A. Survey of neonatal respiratory support strategies. Acta Paediatr. 2007;96:1115–7.
74. Sharma A, Milner AD, Greenough A. Performance of neonatal ventilators in volume targeted ventilation mode. Acta Paediatr. 2007;96:176–80.
75. Singh J, Sinha SK, Alsop E, et al. Long term follow-up of very low birthweight infants from a neonatal volume versus pressure mechanical ventilation trial. Arch Dis Child Fetal Neonatal Ed. 2009;94:F360–2.
76. Stenson B, Brocklehurst P, Tarnow-Murdi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. N Engl J Med. 2011;364: 1680–2.
77. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Cochrane Database Syst Rev. 2007;4:CD003063.
78. Stevens TP, Finer NN, Carlo WA, et al. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). J Pediatr. 2014;165:240–9.
79. Straustrup A, Trasande L. Epidemiological characteristics and resource use in neonates with bronchopulmonary dysplasia: 1993–2006. Pediatrics. 2010;126:291–6.
80. Staustrup A, Tresande L, Holzman IR. Randomized controlled trial of restrictive fluid management in transient tachypnea of the newborn. J Pediatr. 2012;160:38–43.
81. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362:1970–9. Erratum in: N Engl J Med. 2010;362:2235.
82. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362:1959–69.
83. Sweet D, Bevilacqua G, Carnielli V, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome. J Perinat Med. 2007;35:175–86.
84. Tingay DG, Mills JF, Morley CJ, et al. Trends in use and outcome of newborn infants treated with high frequency ventilation in Australia and New Zealand, 1996–2003. J Paediatr Child Health. 2007;43: 160–6.
85. Telford K, Waters L, Vyas H, et al. Outcome after neonatal continuous negative-pressure ventilation: follow-up assessment. Lancet. 2006;367:1080–5.
86. Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med. 2009;360:111–20.
87. Trevisanuto D, Cavallin F, Nguyen LN, et al. Supreme laryngeal mask airway versus face mask during neonatal resuscitation: a randomized controlled trial. J Pediatr. 2015;167:286–91.
88. van den Hout L, Reiss I, Felix JF, et al. Risk factors for chronic lung disease and mortality in newborns with congenital diaphragmatic hernia. Neonatology. 2010;98: 370–80.
89. Vargas-Origel A, Gomez-Rodriguez G, Aldana-Valenzuela C, et al. The use of Sildenafil in persistent pulmonary hypertension of the newborn. Am J Perinatol. 2010;27:225–30.
90. Vaucher YE, Peralta-Carcelen M, Finer N, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. J Pediatr. 2014;165:240–9.
91. Vento M, Moro M, Escrig R, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. Pediatrics. 2009;124:e439–49.

92. Ventolini G, Neiger R, Mathews L, et al. Incidence of respiratory disorders in neonates born between 34 and 36 weeks of gestation following exposure to antenatal corticosteroids between 24 and 34 weeks of gestation. Am J Perinatol. 2008;25:79–83.
93. Verlato G, Cogo PE, Balzani M, et al. Surfactant status in preterm neonates recovering from respiratory distress syndrome. Pediatrics. 2008;122:102–8.
94. Walsh MC, Hibbs AM, Martin CR, et al. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr. 2010;156:556–61.
95. Walsh MC, Laptook A, Kazzi SN, et al. A cluster-randomized trial of benchmarking and multimodal quality improvement to improve rates of survival free of bronchopulmonary dysplasia for infants with birth weights of less than 1250 grams. Pediatrics. 2007;119:876–90.
96. Watson RS, Clermont G, Kinsella JP, et al. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics. 2009;124:1333–43.
97. Wintermark P, Tolsa JF, Van Melle G, et al. Long-term outcome of preterm infants treated with nasal continuous positive airway pressure. Eur J Pediatr. 2007;166: 473–83.
98. Wyllie J, Perlman JM, Kattwinkel J, Neonatal Resuscitation Chapter Collaborators, et al. Part 7: neonatal resuscitation: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation. 2015;95:e169–201.
99. Zivanovic S, Peacock J, Alcazar-Paris M, et al. Late outcomes of a randomized trial of high-frequency oscillation in neonates. N Engl J Med. 2013;369:1425–33.
100. Zupancic JAF, Hibbs AM, Palmero L, et al. Economic evaluation of inhaled nitric oxide in preterm infants undergoing mechanical ventilation. Pediatrics. 2009;124:1325–32.

Section XVI

Ventilatory Case Studies

Ventilatory Case Studies

100

Brooke D. Vergales and Jay P. Goldsmith

Case 1

I. Baby A
   A. Prenatal data
      1. Mother: 32-year-old G6 P2 → 3 who presented with Braxton Hicks type contractions and found to have advanced dilation of the cervix at 24 weeks' gestation
      2. No time to give corticosteroids prior to delivery; no clinical evidence of infection
   B. Patient data
      1. 700 g male born by emergent cesarean section secondary to transverse lie. Apgar scores of 7 (1 min) and 7 (5 min)
      2. Intubated at 4 min of life, stiff lungs requiring high ventilatory pressures
      3. Surfactant given at 14 min of age in delivery room
   C. Physical findings
      1. Severe respiratory distress: retractions, poor air exchange, and wet rales bilaterally
      2. Hypotonia appropriate for gestational age
      3. Fused eyelids, poor skin integrity, and visible veins
   D. Clinical course
      1. Conventional mechanical ventilation (CMV—volume guarantee ventilation: increasing ventilatory support up to V_T of 6 mL/kg with peak inspiratory pressures (PIP) of 25–30 cm H_2O, PEEP 6, rate 30 breaths per minute (bpm), FiO_2 0.6–1.0 to maintain acceptable blood gases. Switched to high frequency oscillatory ventilation (HFOV) because of high tidal volumes and PIP.
      2. Decreasing blood pressure. Dopamine initiated.
      3. Increasing CO_2 retention despite increasing delta *P* and mean airway pressure (Pāw)
      4. Repeat surfactant given via endotracheal tube at 12 h of age.

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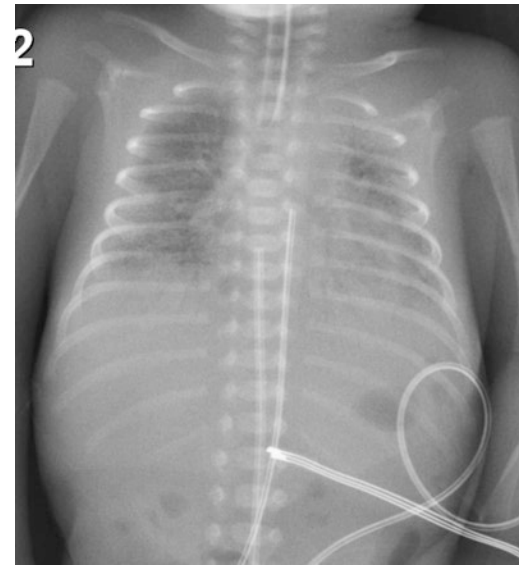

Fig. 100.1 Chest radiograph 1 h after birth showing ground glass appearance, air bronchograms, and decreased lung volume consistent with respiratory distress syndrome (RDS)

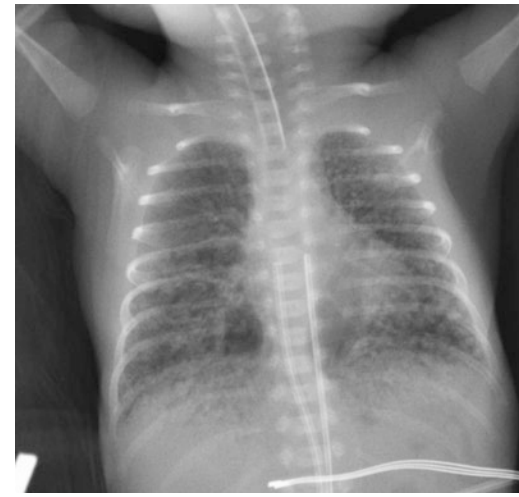

Fig. 100.2 Chest radiographs taken at 15 h of life showing microradiolucencies throughout all lung fields with areas of bullae and hyperinflation

E. Chest radiographs
   1. Figure 100.1. Chest X-ray (CXR) 3 h after birth showing severe respiratory distress syndrome (RDS) with ground glass appearance, air bronchograms, and decreased lung volume
   2. Figure 100.2. CXR taken at 24 h of life showing microradiolucencies throughout all lung fields with areas of large bullae and mild hyperinflation

F. Laboratory values
   1. Normal CBC, CRP<0.3
   2. Increasing hypercapnia and acidosis with increased base deficit over first 15 h of life

G. Differential diagnosis
   1. Severe RDS complicated by pulmonary interstitial emphysema (PIE)
   2. Concern for necrotizing pneumonitis (doubt, too early)

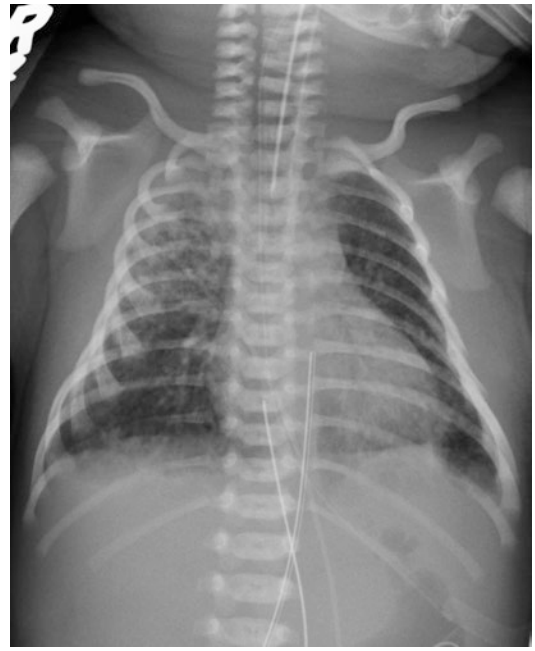

Fig. 100.3 Chest radiograph after a spontaneous left-sided pneumothorax at 28 h was relieved with pigtail chest tube insertion

3. Possible lobar emphysema or congenital pulmonary malformation of the lung (doubt, disease process too generalized)

H. Potential therapies
1. Change to high frequency jet ventilation (HFJV)—low volume strategy.
2. Start inhaled heliox as a strategy to control rising PCO_2 and acidosis (although at present FiO_2 is too high and use in preterm infants is unestablished).
3. Linear pleurotomies or scarification of lungs with creation of pneumothoraces and placement of chest tubes
4. Positional therapy or single lung inflation with selective intubation (works best with unilateral PIE)
5. Ipsilateral bronchial occlusion with Swan–Ganz catheter (few reported cases in unilateral PIE)

I. Denouement
1. Conservative therapy and high frequency oscillation not successful; transitioned to HFJV
2. Patient developed a spontaneous left-sided pneumothorax at 28 h (see Fig. 100.3) which was relieved with pigtail chest tube insertion.
3. Prolonged ventilatory support with the development of bronchopulmonary dysplasia (BPD) and grade 2 intraventricular hemorrhage (IVH)
4. Discharged on home mechanical ventilator with trach in place at 5 months of age

Suggested Reading

Donn SM. Neonatal ventilators: how do they differ? J Perinatol. 2009;29:s73–8.

Greenough A, Dixon AK, Roberton NR. Pulmonary interstitial emphysema. Arch Dis Child. 1984;59:1046.

Kezler M. State of the art in conventional mechanical ventilation. J Perinatol. 2009;1–14.

Keszler M, Donn SM, Bucciarelli RL, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr. 1991;119:85.

Phatek RS, Pairaudeau CF, Smith CJ, Pairaudeau PW, Klonin H. Heliox with inhaled nitric oxide: a novel strategy for severe localized interstitial pulmonary emphysema in preterm neonatal ventilation. Respir Care. 2008;53:12.

Stefanescu BM, Frewan N, Slaughter JC, O'Shea TM. Volume guarantee pressure support ventilation in extremely preterm infants and neurodevelopmental outcome at 18 months. J Perinatol. 2015;35(6):419–23. doi:10.1038/jp.2014.228. Epub 2015 Jan 8.

Verma RP, Chandra S, Niwas R, Komaroff E. Risk factors and clinical outcomes of pulmonary interstitial emphysema in extremely low birth weight infants. J Perinatol. 2006;26:197–200.

Case 2

II. Baby B
- A. Prenatal data
  1. Mother: 18-year-old G2 P1 → 2 at term
  2. Pregnancy reported as uncomplicated.
- B. Patient data
  1. 3510 g female infant born by precipitous vaginal delivery; vertex presentation.
  2. Thick meconium-stained amniotic fluid
  3. Infant was limp and not breathing at delivery and brought to warming table.
  4. Stimulated and dried with warm towels after oropharyngeal suctioning
  5. Apgar scores 4 (1 min) and 9 (5 min)
- C. Initial course
  1. Oxygen by hood ($FiO_2 = 0.4$)
  2. First arterial blood gas at 30 min of age: pH 7.19; $PaCO_2 = 54$ Torr; and $PaO_2 = 29$ Torr
  3. Intubation; placed on CMV: PIP 20 cm H_2O, rate 30 breaths per minute, and PEEP 4 cm H_2O
  4. Sepsis workup → antibiotics started
- D. Initial CXR, before intubation (Fig. 23.9)
  1. Bilateral alveolar filling
  2. Mild cardiomegaly
  3. Hyperinflation—flattened diaphragms
- E. Clinical course
  1. Patient treated for meconium aspiration syndrome, PPHN
  2. Oxygen saturations fell to <60 % when patient agitated → patient started on fentanyl drip at 1 μg/kg/h
  3. Increased respiratory settings on time-cycled, pressure-limited ventilation up to PIP 30 cm H_2O, FiO_2 to 0.6
  4. Arterial blood gases on these settings: pH 7.31, PCO_2 31, PO_2 28, BE—9
- F. Further clinical testing
  1. 2-D Echocardiogram revealed normal structural heart anatomy and no right-to-left shunting
  2. Worsening chest radiograph (Fig. 100.4)

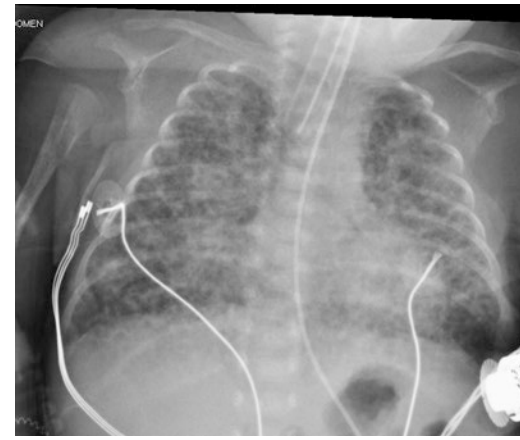

Fig. 100.4 Chest radiograph at 24 h showing hyperinflation, small heart, and no air leaks

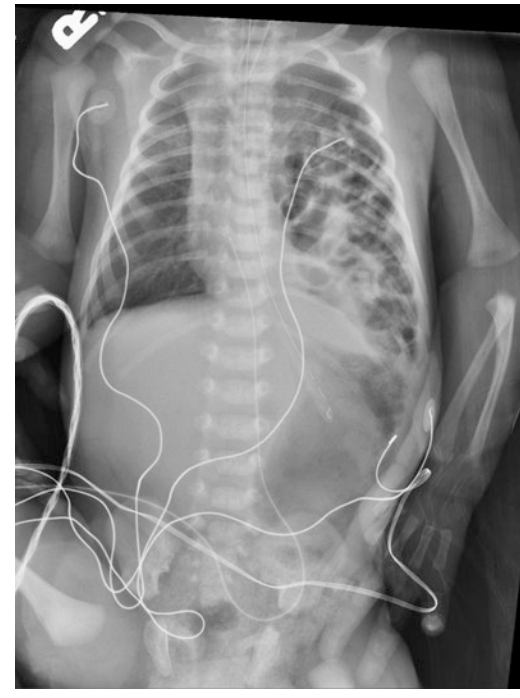

Fig. 100.5 Chest radiograph at 12 h of age demonstrating bowel in left chest and shift of mediastinum to right

3. Pulmonary waveform graphic analysis (Fig. 22.5)

G. Therapeutic options

1. HFOV
2. Surfactant
3. Inhaled nitric oxide (iNO)
4. Intravenous or inhaled epoprostenol
5. Allow patient to wake up, normalize blood gases, and wean ventilator rapidly using pulmonary graphics and blood gases to monitor gas trapping and V/Q matching.

H. Denouement

1. Normal 2-D echocardiogram and pulmonary graphics revealed normal pulmonary arterial pressure.
2. Patient iatrogenically overventilated

3. Patient allowed to wake up and breathe on her own
   a. V/Q normalized
   b. Ventilator settings weaned quickly
4. Patient extubated in next 24 h and discharged home 6 days later

Suggested Reading

Bhutani VK, Benitz WE. Pulmonary function and graphics (Chapter 18). In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: Elsevier; 2010. p. 306–20.

Donn SM. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura; 1997.

Kezler M, Abubakar MK. Physiologic principles (Chapter 2). In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: Elsevier; 2010. p. 19–46.

Case 3

III. Baby C
   A. Prenatal data
      1. Mother: 37-year-old G4 P3 → 4 induced at 41 weeks' gestation
      2. Postdates and decreased fetal movement for 2 days
   B. Patient data
      1. 3810 g female born vaginally, vertex presentation, assisted by vacuum extraction under epidural anesthesia.
      2. Tight nuchal cord
      3. Apgar scores 4 (4 min) and 6 (5 min)
      4. Initial arterial blood gas at 1 h in oxyhood (FiO_2 0.4): pH 7.12, $PaCO_2$ 83 Torr, and PaO_2 44 Torr
      5. Intubated, placed on time-cycled, pressure-limited ventilator. Umbilical artery catheter placed for blood pressure and blood gas monitoring, double lumen umbilical venous catheter placed for access.
   C. Physical findings
      1. Dysmature, peeling skin, decreased subcutaneous tissue, and long nails
      2. Increased anterior/posterior diameter of chest, coarse inspiratory rales, and tachypnea
      3. Acrocyanosis, hypotonia
   D. Chest radiograph/laboratory results
      1. CXR: Fluffy lung fields, diaphragm flat, and no air leaks (Fig. 23.11)
      2. White blood count 27,200 with left shift; platelets 110,000
      3. Glucose and calcium normal
      4. Normal metabolic profile at 12 h of life
   E. Clinical course
      1. Placed on antibiotics, maintenance IV fluids at 80 mL/kg/day
      2. Sedated
      3. Received normal saline bolus × 2, then started dopamine for hypotension
      4. 2-D Echo: increased pulmonary vascular resistance with right-to-left shunt at foramen ovale and ductus arteriosus
      5. Repeat CXR showed flattened diaphragms, interstitial fluid, small heart, and no air leaks.
      6. FiO_2 increased to 0.6, ventilatory settings increased to Pāw = 16 cm H_2O. Unable to adequately oxygenate (PaO_2 less than 50 Torr)

F. Diagnosis
   1. Persistent pulmonary hypertension of the newborn (PPHN)
   2. Suspected total anomalous pulmonary venous return or other congenital heart anomaly (doubt with normal cardiac anatomy seen on 2-D echo)

G. Potential therapies
   1. Switch to HFOV.
   2. Inhaled nitric oxide (use of iNO at lower FiO_2 rather than waiting until baby is on 100% oxygen has been shown to be advantageous)
   3. Surfactant
   4. Inhaled or continuous IV Flolan (epoprostenol)
   5. Bosantan (endothelin receptor antagonist)
   6. Extracorporeal membrane oxygenation (ECMO)

H. Failure of mechanical ventilation
   1. Inability to adequately oxygenate (unacceptably low PaO_2 and high oxygenation index)
   2. Inability to adequately ventilate (unacceptably high $PaCO_2$)
   3. Toxic ventilatory settings (will cause unacceptable pulmonary sequelae) or ventilator parameters predictive of poor outcome
   4. Inadequate pulmonary blood flow

I. Predictive indices of poor outcome (term or late preterm babies): indications for ECMO
   1. Alveolar/arterial oxygen gradient ($AaDO_2$)
      a. $(AaDO_2) = (760 - 47) - PaCO_2 - PaO_2$
         760 mmHg = atmospheric pressure
         47 mmHg = water vapor
      b. $AaDO_2 > 610$ mmHg × 8 h or > 605 mmHg × 4 h, if PIP > 38 cm H_2O
   2. Oxygenation index (OI)
      a. $$OI = \frac{100 \times (P\bar{a}w) \times (FiO_2)}{PaO_2}$$
         Pāw = mean airway pressure
      b. OI greater than 40 for three blood gases 30 min apart predictive of high mortality
   3. Unresponsive to treatment ($PaO_2 < 55$ Torr and pH < 7.25 × 3 h)
   4. Barotrauma (multiple or persistent air leaks)
   5. Uncontrollable hemodynamic instability

J. Denouement
   1. Patient switched to HFOV and given iNO, 20 ppm.
   2. OI greater than 50 for 3 h
   3. Started on continuous IV Flolan
   4. OI greater than 40 for 3 more hours
   5. Placed on veno-venous ECMO for 140 h
   6. Decannulated and extubated without difficulty
   7. Discharged with normal physical examination at 17 days of age.

Suggested Reading

Arensman RA, Short BL. Extracorporeal membrane oxygenation. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: Elsevier; 2010.

Bendapudi P, Rao GG, Greenough A. Diagnosis and management of persistent pulmonary hypertension of the newborn. Paediatr Respir Rev. 2015;157–61.

Jain A, McNamara PJ. Persistent pulmonary hypertension of the newborn: advances in diagnosis and treatment. Semin Fetal Neonatal Med. 2015;20(4):262–71. doi:10.1016/j.siny.2015.03.001. Epub 2015 Apr 2.

Kelly LK, Porta NFM, Goodman DM, et al. Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. J Pediatr. 2002;141:6.

Roberts JD Jr., Fineman JR, Morin FC III, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med. 1997;336:605.

Steinhorn, RH. Neonatal pulmonary hypertension. Pediatr Crit Care Med. 2010;S79–84.

UK Collaborative ECMO Trial Group. UK Collaborative randomised trial of neonatal extracorporeal membrane oxygenation. Lancet. 1996;384:75.

Case 4

IV. Baby D
- A. Prenatal Data
  1. Mother: 34 year-old G2P1 → 2 with good prenatal care
  2. 20 week ultrasound: interpreted as normal
  3. 28 week and 32 week ultrasound done for growth assessment secondary to two-vessel cord also interpreted as normal
  4. Prenatal labs: O+, hepatitis B negative, HIV negative, and GBS negative
  5. Spontaneous labor at level I hospital at 39 weeks' gestation
- B. Patient Data
  1. 3445 g male delivered by spontaneous vaginal delivery without complications
  2. Apgar scores: 8 (1 min), 9 (5 min), mild retractions noted at birth; heart rate >100.
  3. Tachypnea and retractions worsened over first 12 h of age.
- C. Physical Findings at 12 h of age
  1. Severe respiratory distress, deep retractions, and decreased breath sounds on the left
  2. Barrel shaped chest and scaphoid abdomen
  3. No murmur appreciated but heart sounds heard best on the right side of the chest
- D. Clinical Course
  1. Remained on room air and had appropriate saturation in the delivery room. Watched in nursery for resolution of what was thought to be transient tachypnea of newborn.
  2. Respiratory status worsened over the next 12 h and developed severe retractions and grunting with desaturation
  3. CBC, blood culture obtained, and antibiotics started
  4. CXR obtained in newborn nursery (Fig. 100.5)—bowel in left hemithorax consistent with congenital diaphragmatic hernia
  5. Intubated at 12 h of age after diagnosis
  6. Orogastric tube placed for decompression
  7. Transferred to level III NICU
  8. Placed on HFOV on admission to level III NICU
  9. Required 1.0 FiO_2, iNO started at 20 ppm—FiO_2 to 0.4
  10. Surgery consulted
- E. Diagnosis: Left Congenital Diaphragmatic Hernia
- F. Differential diagnoses:
  1. Cystic lesions of the lung
  2. Prior to one hemithorax showing bowel gas, a unilateral opaque lung may be confused with atelectasis or effusion.

G. Management:
   1. Gentle ventilation
      a. HFOV with Pāw to maintain adequate chest expansion (8–9 ribs on CXR). HFJV is an acceptable alternative.
      b. Maintain pH (7.30–7.35) and allow permissive hypercapnia as long as pH > 7.30.
   2. ECMO—if HFOV in conjunction with iNO unable to achieve adequate gas exchange. Use of iNO is also controversial in CDH.
   3. Elective surgery once patient stabilized on ventilator and preferably off ECMO (controversial)

H. Denouement
   1. Maintained with gentle ventilation on HFOV and iNO. No need for ECMO.
   2. CDH repaired at 1 week of life
   3. Extubated to nasal CPAP at 2 weeks of life and room air at 3 weeks life
   4. Discharged on full feeds at 1 month of age

Suggested Reading

Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. Prenat Diagn. 2008;28:592–603.

Keijzer R, Puri P. Congenital diaphragmatic hernia. Semin Pediatr Surg. 2010;19:180–5.

Migliazza L, Colombo A, et al. Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and pre-surgical stabilization. J Pediatr Surg. 2007;42(9):1526–32.

Puligandla PS, Grabowski J, Austin M, et al. Management of congenital diaphragmatic hernia: a systematic review from the APSA outcomes and evidence based practice committee. J Pediatr Surg. 2015 Sep 21. pii:S0022-3468(15)00593-X. doi:10.1016/j.jpedsurg.2015.09.010.

Case 5

V. Baby E
   A. Prenatal data
      1. 28 year-old G4 P2 → 3 mother with limited prenatal care
      2. Non-reassuring fetal status (meconium-stained amniotic fluid) at 39 4/7 weeks' gestation
   B. Patient data
      1. 3200 g male infant born by urgent Cesarean section at level II hospital
      2. Apgar scores 1 (1 min), 3 (5 min), and 7 (10 min)
      3. Intubated and ventilated in delivery room; no medications or chest compressions required
      4. Extubated → CPAP +6; pH 7.16 at 1 h of age → re-intubated
      5. Transported to level III NICU
   C. Physical examination on admission
      1. Depressed with limited respiratory effort and hypotonic and depressed reflexes
      2. Moderate respiratory distress: tachypnea, retractions, and rales at lung bases
      3. Liver 4 cm below right costal margin
   D. Chest radiograph on admission (Fig. 23.8)
      1. Hyperinflation
      2. Bilateral patchy alveolar opacities consistent with aspiration syndrome or retained lung fluid

E. Laboratory values
   1. Normal CBC with mild thrombocytopenia, normal renal and liver function panels
   2. Excellent arterial blood gases despite minimal ventilatory support ($P\bar{a}w = 7$ cm H_2O)

F. Clinical course
   1. Met criteria and placed on cooling blanket for encephalopathy for 72 h.
   2. Numerous technical problems with endotracheal tube thought to result from plugging, displacement.
   3. Heart murmur heard on day 3 → 2-dimensional echocardiogram → normal.
   4. Weaned off cooling on day 3 and attempts to extubate from day 4–7 unsuccessful despite appropriate low PIP and rate on conventional ventilator.

G. Extubation failure: Differential diagnosis (see Table 100.1)

Table 100.1 Major causes of extubation failure

I.	**Pulmonary**
	A. Primary lung disease not resolved
	B. Post extubation atelectasis
	C. Pulmonary insufficiency of prematurity
	D. Chronic lung disease
	E. Eventration, paralysis, or dysfunction of diaphragm
	F. Pneumonia
II.	**Upper airway**
	A. Edema and/or excess tracheal secretions
	B. Subglottic stenosis
	C. Laryngotracheomalacia
	D. Congenital vascular ring
	E. Necrotizing tracheobronchitis
III.	**Cardiovascular**
	A. Left to right shunt—patent ductus arteriosus
	B. Fluid overload
	C. Congenital heart disease with increased pulmonary flow
IV.	**Central nervous system (CNS)**
	A. Apnea, hypopnea (extreme immaturity)
	B. Intraventricular hemorrhage/periventricular leukomalacia
	C. Hypoxic ischemic brain damage/seizures
	D. Sedation, depressant, or narcotic drugs
	E. CNS infection
	F. Prolonged neuromuscular blockade
V.	**Miscellaneous**
	A. Unrecognized diagnosis (nerve palsy, myasthenia gravis, etc.)
	B. Sepsis/hyperthermia
	C. Metabolic abnormality/severe electrolyte disturbances/alkalosis
	D. Malnutrition/weakness
	F. Severe abdominal distention and elevated diaphragms

Modified from Goldsmith JP, Karotkin, EH, *Assisted Ventilation of the Neonate*, 5th Edition, p 123, 2010. Elsevier, Philadelphia. With permission

H. Repeat CXR and CT at 7 days of age (Fig. 23.36)
   1. Severe hyperinflation
   2. Volume loss in both upper lobes
I. Adjuncts to successful weaning and extubation
   1. Transition to pressure support ventilation or nasal CPAP
   2. Diuretics and bronchodilators
   3. Methylxanthines, racemic epinephrine, or systemic peri-extubation steroids
J. Differential diagnosis and denouement
   1. Possible laryngotracheomalacia from encephalopathy (would not have hyperinflation on CXR)
   2. Barium esophagoscopy, cardiac catheterization → true vascular ring with double aortic arch
   3. Surgical division of vascular ring and ductus arteriosus ligation accomplished without complication
   4. Patient successfully extubated post-operative day 2

Suggested Reading

Browne LP. What is the optimal imaging for vascular rings and slings? Pediatr Radiol. 2009;39: S191–5.

Halliday HL. Towards earlier neonatal extubation. Lancet. 2000;355:2091.

Sant'Anna GM, Keszler M. Weaning infants from mechanical ventilation. Clin Perinatol. 2012;39: 543–62.

Case 6

VI. Baby E
   A. Prenatal data
      1. Mother: 16 year-old G2 P1 → 3 with no prenatal care at 27 weeks' gestation
      2. Presents in active labor, complete and ready to deliver at level I hospital
      3. Unsuspected twins
   B. Patient data
      1. 890 g male second twin, vertex presentation delivered by spontaneous vaginal delivery
      2. Apgar scores: 4 (1 min) and 6 (5 min)
      3. Respiratory distress at birth
      4. Transport to level III NICU
   C. Physical findings
      1. Severe respiratory distress: deep retractions, poor air exchange, and wet rales
      2. Bruising of scalp, trunk
   D. Clinical course
      1. Placed on CPAP in the delivery room
      2. Progressive respiratory distress and increased work of breathing
      3. Intubated at 2 h of age; exogenous surfactant given two times 6 h apart
      4. Poor response to CMV; switched to HFOV secondary to CO_2 retention/acidosis
      5. Patent ductus arteriosus (PDA) murmur heard at 3 days; indomethacin tried, two courses → no effect
      6. Unable to wean from ventilator despite adequate nutrition, blood transfusions, and methylxanthines; patient requiring continuous sedation/analgesia

7. CXR at 27 days (Fig. 23.6): Areas of atelectasis alternating with cystic areas and interstitial edema consistent with early BPD
8. Repeat 2D echocardiogram shows persistent moderate sized PDA with L → R shunt

E. Diagnosis
1. CXR and clinical course consistent with BPD
2. NIH definition of BPD for infants <32 weeks' gestation at birth:
   a. Treatment with oxygen >21 % for at least 28 days plus
      (1) Mild BPD: Breathing room air at 36 weeks' PMA or discharge
      (2) Moderate BPD: Need for <30 % oxygen at 36 weeks' PMA or discharge
      (3) Severe BPD: Need for ≥30 % oxygen and/or positive pressure at 36 weeks' PMA
   b. Physiologic Test for Diagnosis of BPD
      (1) Infants at 35–37 weeks' PMA receiving mechanical ventilation, CPAP or >30 % oxygen with SpO_2 of <96 % have BPD
      (2) Infants receiving <30 % oxygen or ≥30 % oxygen with SpO_2 >96 % teste for oxygen need
         (a) O_2 progressively decreased to 21 %
         (b) No BPD if SpO_2 > 90 % in room air for 30 min
3. Patient now 31 weeks' PMA: does not strictly meet definition of BPD, but CXR suggestive of evolving transpulmonary process

F. Therapeutic options
1. Rule out other causes of ventilator dependency
   a. PDA with pulmonary flow not allowing ventilator to be weaned
   b. Inadequate methylxanthine level
   c. CNS intact—cranial US negative for IVH/PVL
   d. Infection
   e. Anemia
   f. Electrolyte abnormalities
2. Goal is to extubate; may use nasal bubble CPAP or non-invasive ventilation to prevent atelectasis/apnea
   a. Ligate PDA
   b. Permissive hypercapnia
   c. Permissive hypoxemia (goal SpO_2 88–92 %)
   d. Bronchodilators (controversial)
   e. Adequate calories with fluid restriction (120–130 mL/kg/day) and/or diuretics (not a good long-term solution)
   f. Corticosteroids
      (1) Pros: Very efficient in weaning from ventilator
      (2) Cons: Short term—infection, hypertension, hyperglycemia, and adrenocortical suppression. Long term—associated with impaired brain and somatic growth and increased incidence of cerebral palsy
      (3) Parents informed of risks and benefits prior to giving corticosteroids
   g. Pressure support ventilation with low SIMV rate and patient-driven inspiratory time

G. Denouement
1. Patient switched to volume-targeted synchronized intermittent mandatory ventilation (SIMV) with pressure support (PS) at 12 cm H_2O and V_T of 4–6 mL/kg (Fig. 22.10)
2. Over next several days PS decreased, FiO_2 lowered; sedation and analgesia weaned, then discontinued.
3. Pulmonary mechanics study repeated

4. SIMV discontinued 1 week later and patient extubated to bubble CPAP within 48 h
5. Patient discharge at 76 days of age on oxygen by nasal cannula

H. Management controversy
Would earlier ligation of the PDA have prevented development of BPD?

Suggested Reading

Ambalavanan N, Schelonka RL, Carlo WA. Ventilation strategies (Chapter 15). In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: Elsevier; 2010. p. 265–76.

Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007;357: 1946–55.

Committee on Fetus and Newborn. Postnatal corticosteroid to treat or prevent chronic lung disease in preterm infants. Pediatrics. 2002; 109:330.

Donn SM, Becker MA, Nicks JJ. Special ventilation techniques: I: patient triggered ventilation (Chapter 12). In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 5th ed. Philadelphia: Elsevier; 2010. p. 220–234.

Ghanta S, Leeman KT, Christou H. An update on pharmacologic approach to bronchopulmonary dysplasia. Semin Perinatol. 2013;115–23.

Heuchan AM, Clyman RI. Managing the patent ductus arteriosus: current treatment options. Arch Dis Child Fetal Neonatal Ed. 2014;99(5): F431–6. doi:10.1136/archdischild-2014-306176. Epub 2014 Jun 5. Review.

Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics. 1999;104:1082.

Martin RJ, Fanaroff, AA. The preterm lung: past, present and future. Pediatr Neonatal. 2013; 228–34.

Walsh MC, Yao Q, Gertner P, et al. Impact of physiologic definition of bronchopulmonary dysplasia. Pediatrics. 2004;1305–11.

Appendix

Conversion Table A

Torr → kPa

Torr	kPa
20	2.7
25	3.3
20	4.0
35	4.7
40	5.3
45	6.0
50	6.7
55	7.3
60	8.0
65	8.7
70	9.3
75	10.0
80	10.7
85	11.3
90	12.0
95	12.7
100	13.3
105	14.0
110	14.7
115	15.3
120	16.0
125	16.7
130	17.3
135	18.0

Conversion Table B

kPa → Torr

kPa	Torr
2.5	19
3.0	22.5
3.5	26
4.0	30
4.5	34
5.0	37.5
5.5	41
6.0	45
6.5	49
7.0	52.5
7.5	56
8.0	60
8.5	64
9.0	67.5
9.5	71
10.0	75
10.5	79
11.0	82.5
12.0	90
12.5	94
13.0	97.5
13.5	101
14.0	105

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