Manual of Neonatal Respiratory Care

Steven M. Donn
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Fifth Edition

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In loving memory of my beloved wife, Paula, who was my inspiration, my support, my partner in life, and my true soulmate for more than half a century.

–Steven M. Donn

For my family, who have always supported me during my often-challenging career, and to babies, their doctors, and families everywhere.

–Mark C. Mammel

To my family, for their unconditional love and support.

–Anton H. L. C. van Kaam

Foreword

A successful transition from fetal to neonatal life is dependent upon the profound cardiorespiratory adaptation 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 in the 1950s, 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 non-invasive 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 last decade of the century ended in remarkable fashion with the introduction of exogenous surfactant therapy and recognition that the novel 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 40% in the smallest survivors of neonatal intensive care. This current fifth edition meets this dilemma head on by clearly acknowledging such issues as the need to optimize non-invasive 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 can diminish morbidity in NICU graduates. As addressed in this edition, we are grappling with novel techniques for exogenous surfactant therapy and automated delivery of supplemental oxygen while fine-tuning pharmacotherapy. All this requires our heightened attention toward the principles of evidence-based medicine and quality improvement.

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, which may evolve into mesenchymal stem cell therapy. 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 decreasing 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.

This latest comprehensive edition of the *Manual of Neonatal Respiratory Care* provides an important educational tool to address many of these challenges. This time, it is again thoroughly edited by an accomplished transatlantic team comprised of Steven Donn, Mark Mammel, and Anton van Kaam. Once again, they have assembled established and new 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 remarkable text that provides a strongly international insight into neonatal respiratory care in a user-friendly, practical format.

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Preface to the Fifth Edition

Much has transpired since the publication of the fourth edition of the *Manual of Neonatal Respiratory Care* in 2017. In this edition, we have attempted to incorporate many of the changes in pathophysiology, care practices, and respiratory devices. We have enhanced the chapters on noninvasive ventilation, deleted chapters on equipment that is no longer in use, and added chapters to address new devices and techniques.

Professor Sunil Sinha has retired from practice after serving as a co-editor of the first four editions. We are indebted to him for his many years of dedication and expertise and wish him well in his retirement. He has been replaced by two experienced and renowned neonatologists, Professor Mark Mammel and Professor Anton van Kaam, who helped us to maintain an international perspective.

Neonatal intensive care is as much "art" as "science," and care practices vary widely, not only among countries but within countries and even within regions. Our contributors represent many countries—Australia, Austria, Canada, Germany, Italy, the Netherlands, Norway, Poland, Spain, the United Kingdom, and the United States—and many viewpoints. Although most clinicians try to practice evidence-based medicine, not every question has a sufficient database to enable an answer, and clinical decisions must also be based on an understanding of pathophysiology and therapeutics.

We are indebted to many for the preparation of this edition. First and foremost are our contributors, who have given their time, energy, and expertise. We thank our publishing personnel at Springer, especially Miranda Finch and Sheik Mohideen K. We are grateful to many of our readers for providing valuable feedback to the fourth edition, and we hope the fifth edition continues to provide helpful bedside management.

Lastly, in the interval since the fourth edition, we have lost three dear friends and colleagues who had contributed valuable chapters in each of the first four editions. Malcolm Chiswick, William Meadow, and Anthony Milner were the epitome of the "gentleman and scholar." Each possessed a unique clinical savvy, scholarly inquisitiveness, and a special sense of humor, which made them exceptional physicians, medical educators, and humanitarians. They are sorely missed.

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Frequently Used Abbreviations

µm	micrometer
°C	degrees Celsius (Centigrade)
°K	degrees, Kelvin
A	alveolar
a	arterial
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
cAMP	cyclic adenosine monophosphate
CBF	cerebral blood flow
CBG	capillary blood gas
cc	cubic centimeter
CCAM	congenital cystic adenomatoid malformation

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	conventional mechanical ventilation
CMV	cytomegalovirus
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	cardio-pulmonary resuscitation
CPT	chest physiotherapy
CRP	C-reactive protein
CSF	cerebrospinal fluid
CST	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	gauge
g	gram
G	gravida
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
HCO3-	bicarbonate
HFJV	high-frequency jet ventilation
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, inertial
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
$\dot{V}$	flow
$\dot{V}$	rate of change of flow
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	deadspace volume
VD_{alv}	alveolar dead space
VD_{aw}	airway dead space
VD_{phys}	physiologic dead space
VDRL	venereal disease research laboratory
VECO2	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

Part I

Lung Development and Maldevelopment

1 Development of the Respiratory System

Vinod K. Bhutani and Vineet Bhandari

I. Introduction
   A. The neonatal respiratory system is a complex organ whose life-sustaining function depends 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 offer 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 sero-mucous glands and Clara (now known as club) 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, repair, and recovery.
   C. The complex process of mammalian lung development includes lung airway branching morphogenesis and alveolarization, together with vasculogenesis and angiogenesis.
      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, occur-

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ring as a result of aberrant lung development, have been neglected in the past because of a 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 (embryonic phase of lung development: approximately 4–7 weeks' gestation in humans).
   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 (pseudoglandular phase: 5–17 weeks' gestation in humans).
   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 (16–26 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. The saccular stage of lung development (24–38 weeks' gestation in humans) begins with the end of branching morphogenesis and the onset of development of the terminal saccules at the end of distal airspaces and the surfactant production/secretion system.
   5. The alveolar stage of lung development (36 weeks and extending up to 8 years) occurs next, giving rise to an eventual alveolar gas diffusion surface 70 m^2 in area by 1 μm in thickness.
   6. 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.
   7. 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.
   8. 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.
   9. In addition, physical forces play an important role in regulating lung formation (Fig. 1.1).
      (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 an intraluminal hydraulic pressure of approximately 1.5 cm water in the airways.

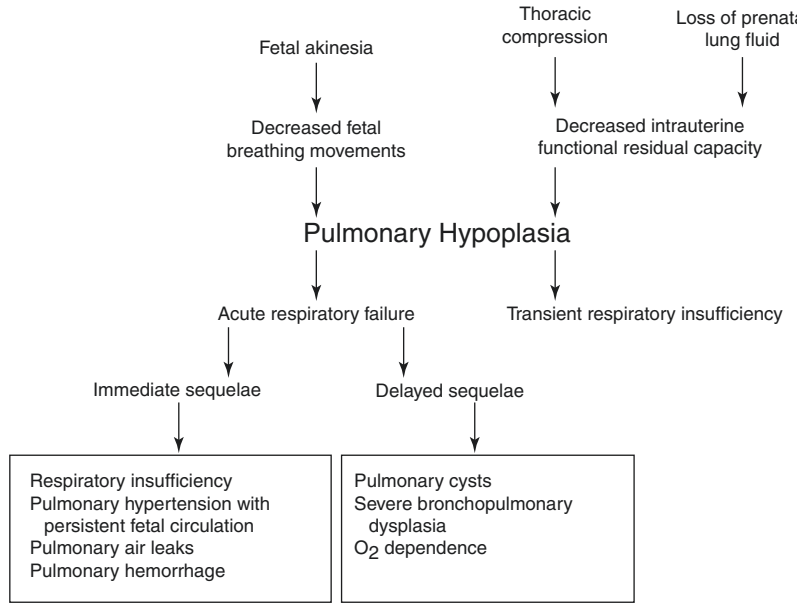

Fig. 1.1 Probable mechanisms and sequelae of pulmonary development during prolonged amniotic leak. (Modified from Bhutani VK, Abbasi S, Weiner S: Neonatal pulmonary manifestations due to prolonged amniotic leak. Am J Perinatol 1986; 3:225, © Thieme Medical Publishers, with permission)

(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 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
   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 comprising 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.

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

	30 Wks	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	50 m	300 m	6
Alveolar diameter: μm	32	150	300	10
Airway branching: number	24	24	24	0

PCA postconceptional age

Table 1.2 Stages of prenatal and postnatal structural lung development

Phase	Postconceptional age	Length: terminal bronchiole to pleura	Lung development
Embryonic	4–7 weeks	<0.1 mm	Budding from the foregut
Pseudoglandular	5–17 weeks	0.1 mm	Airway division commences and terminal bronchioles formed
Canalicular	16–26 weeks	0.2 mm	3 generations of respiratory bronchioles Primitive saccules formation with type I and II epithelial cells, Capillarization
Saccular	24–38 weeks	0.6 mm	Transitional saccules formed True alveoli appear
Alveolar	>36 weeks	11 mm	Terminal saccules formed True alveoli appear
Postnatal	Up to 2 months	175 mm	5 generations of alveolar ducts Alveoli form with septation
Early childhood	Up to 8 years	400 mm	Airways remodeled Alveolar sac budding occurs

3. Little is known about the effects of antenatal steroids on the transition and maturation of fetal lung development.

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 extramural, mural, and intramural factors.

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	

cAMP cyclic adenosine monophosphate, *FRC* functional residual capacity

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

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	

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, and filter air into the lungs. Also help to separate functions of respiration and feeding as well as share in the process of vocalization.

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 a significant role in controlling airway lumen size/patency.
2. In presence of respiratory volu−/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

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

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.
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 impact 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.

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 physiological 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 downward 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.

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 mo	112,000,000	8.4	27 (22–31)
~ 1 yr	129,000,000	12.2	19 (17–23)
~ 3 yr	257,000,000	22.2	19 (16–25)
~ 5 yr	280,000,000	32.0	18 (14–23)
Adult	300,000,000	75	15 (12–18)

E. At the same time, the laryngotracheal tube elongates downward 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 give 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 16–24, 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 three to six 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 club cells. Peripheral mesenchymal cells differentiate to form the visceral pleura, and 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 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*) (Table 1.2)

A. Embryonic phase (4–7 weeks). Initial budding and branching of the lung buds from the primitive foregut. Ends with the development of the presumptive bronchopulmonary segments.

B. Pseudoglandular phase (5–17 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 (16–26 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. Saccular phase (24–38 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 been 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 to 2 years after birth; thereafter, all components grow proportionately until adulthood.

2 Malformations, Deformations, and Disorders of the Neonatal Airway

Chad Sudoko, Janet Lioy, Steven E. Sobol, and Ryan Borek

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 partof 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.

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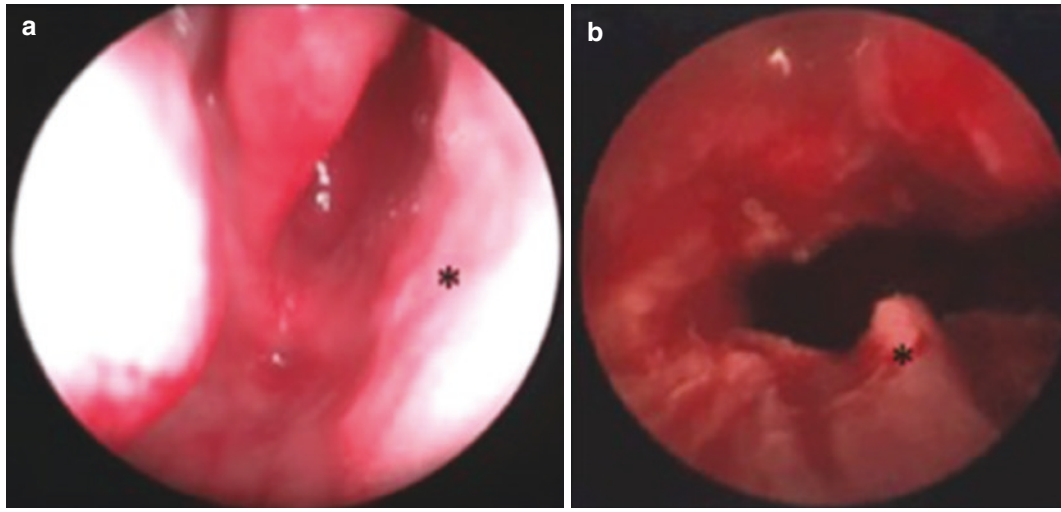

Fig. 2.1 (**a**) Choanal atresia of the right nasal cavity. (*) indicates the nasal septum. (**b**) Following surgical repair and posterior septectomy where (*) indicates the remnant of the inferior septum

2. Pathogenesis
   (a) Atresia occludes passage of air or drainage of nasal secretions.
   (b) Stenosis increases airway resistance.
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, and 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
   (a) Genetics: (associated syndromes: CHARGE, other craniofacial genetic malformations now diagnosable by mutation analysis)

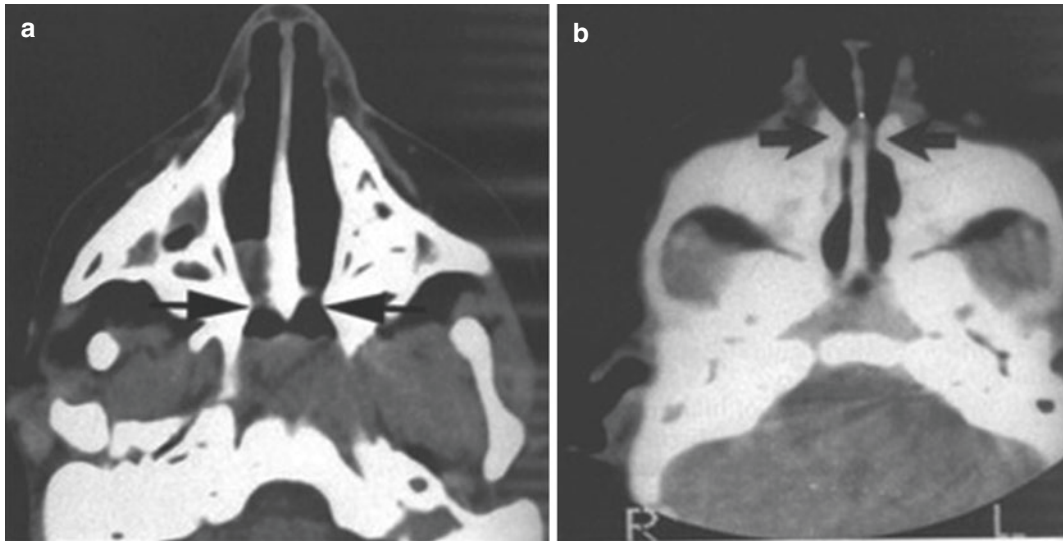

Fig. 2.2 CT scan of the head showing (**a**) choanal atresia and (**b**) piriform aperture stenosis. Note the differences in location of these embryologically different but similar clinical nasal obstructions

B. Piriform aperture and nasal stenosis (Fig. 2.2)
   1. Etiology and Epidemiology
      (a) Overgrowth of the nasal inlet or medial position of the nasal process of the maxilla atthe level of the piriform aperture bilaterally
      (b) Craniofacial or skull base anomalies are associated with partial obstruction of the nasal inlet.
      (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

C. Nasolacrimal Duct Cyst (Dacryocystocele) (Fig. 2.3)
1. Etiology and Epidemiology
   (a) Uncomplicated congenital nasolacrimal duct obstruction is a common anomaly that can occur in up to 6% of infants with a spontaneous remission rate of 85–96% at 1 year.
   (b) The duct is typically obstructed at the valve of Hasner, just lateral to the inferior turbinate
2. Clinical Presentation
   (a) If the duct is obstructed proximally, facial swelling inferior to the medial canthus of the eye may be seen.
   (b) If the duct is obstructed just lateral to the inferior turbinate, a round mass may be seen in the nasal cavity.
   (c) Dacryocystitis may develop, presenting with erythema, increased swelling, and tenderness over the dacryocystocele.
      1. May also mimic acute sinusitis if the obstruction is more distally located in the nasal cavity
   (d) Nasal obstruction and respiratory distress may occur if bilateral cysts are present.
3. Diagnostic Evaluation
   (a) Clinical evaluation is complemented by CT scan with contrast or MRI to help distinguish between piriform stenosis, bilateral nasolacrimal duct obstruction, choanal atresia, or other mass effects.
   (b) Should be evaluated by an ophthalmologist.

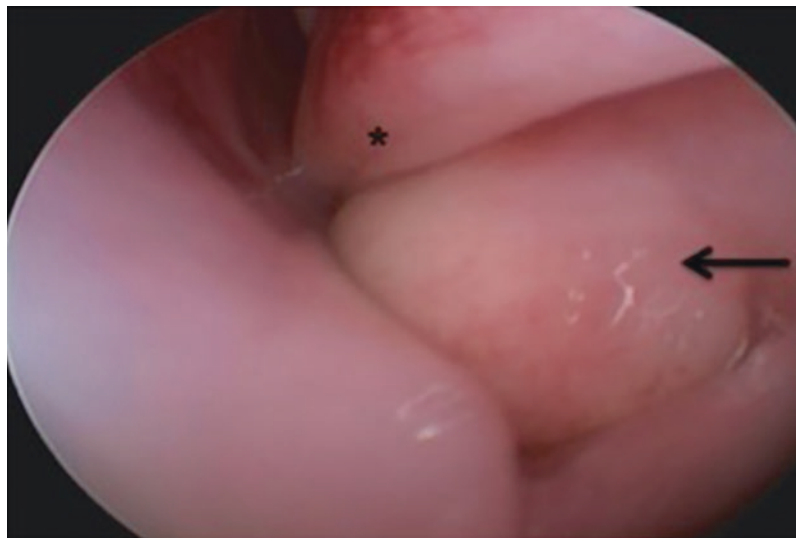

Fig. 2.3 Left-sided nasolacrimal duct cyst marked by the arrow. (*) indicates the inferior turbinate

4. Medical Management
   (a) Observation if minimally symptomatic.
   (b) If concern for acute dacryocystitis, systemic antibiotics and inpatient observation is warranted.
5. Surgical Management
   (a) Unilateral dacryocystoceles rarely need surgical intervention.
   (b) Bilateral obstruction may require surgery within the first few weeks of life due to nasal obstruction.
   (c) Surgical treatment can range from duct probing and balloon dilation to intranasal marsupialization and silastic stenting.
6. Multidisciplinary Collaboration
   (a) Ophthalmology: Depending on the location of the dacryocystocele and/or obstruction an ophthalmologist and otolaryngologist may be following

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; tongue base obstruction, (TBO), from severe retro-/micrognathia (Fig. 2.4) with glossoptosis (Fig. 2.5); nasopharyngeal mass extension; oropharyngeal mass; vallecular cyst; an undescended thyroid; or a thyroglossal duct cyst.

A. Glossoptosis or Macroglossia (Fig. 2.6)
   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
      (d) May also be caused by lingual tonsil hypertrophy (Fig. 2.7)

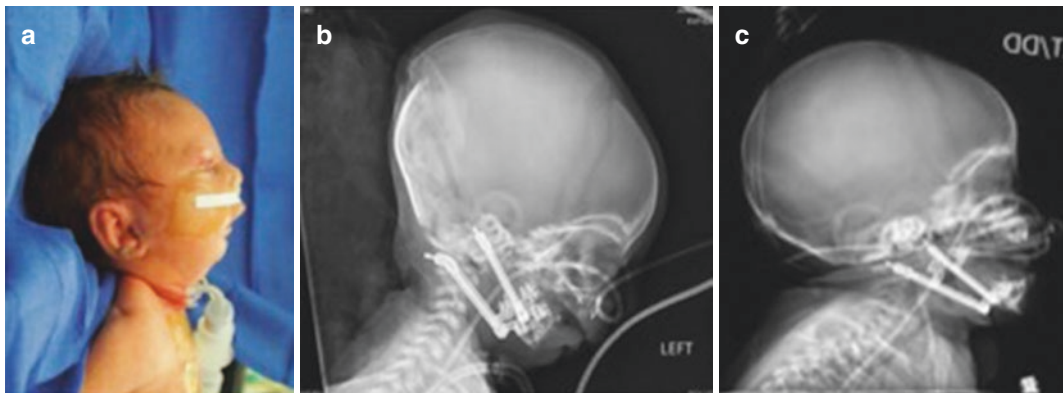

Fig. 2.4 (**a-c**)**:** Preoperative and postoperative photographs and radiographs of a patient undergoing mandibular distraction osteogenesis through a submandibular approach

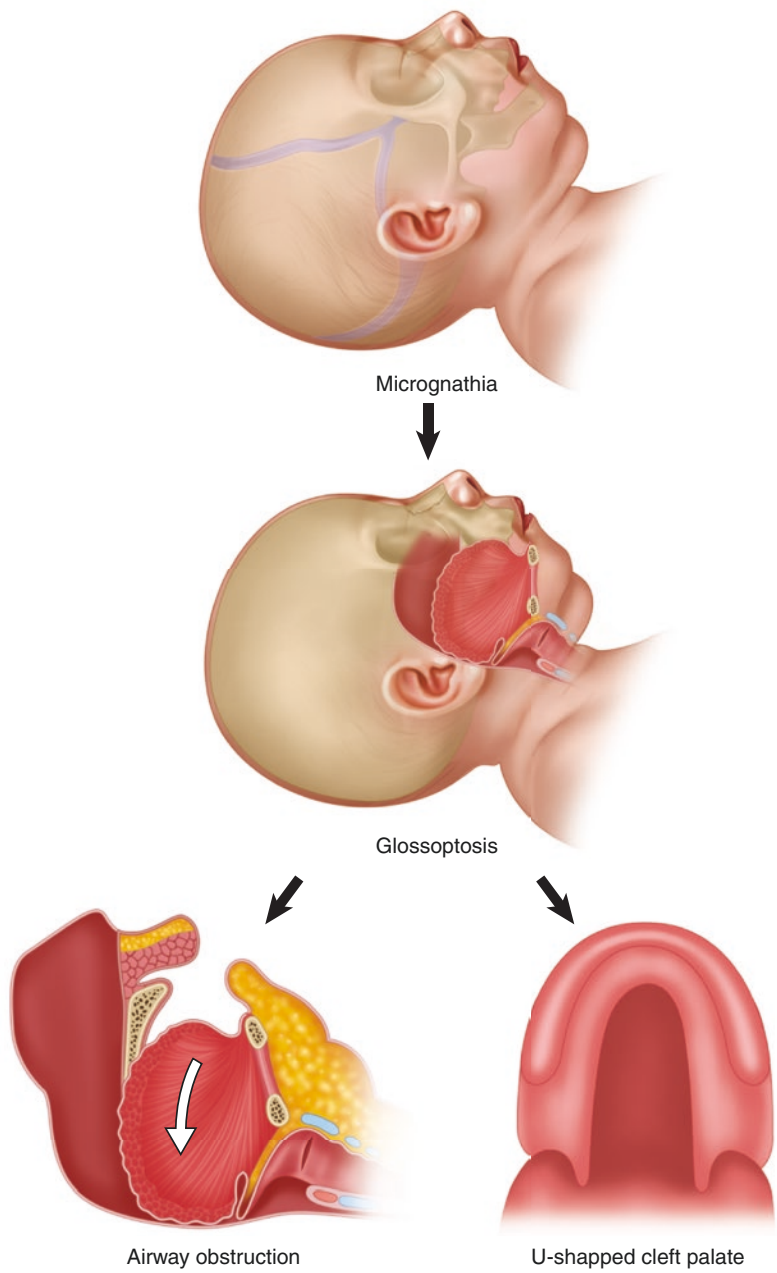

Fig. 2.5 The "domino effect" of Pierre Robin sequence

2. Pathogenesis
   (a) 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

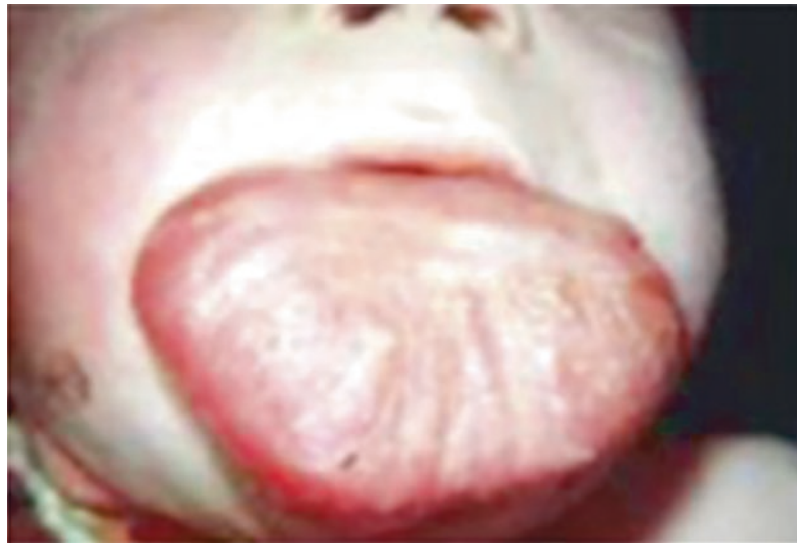

Fig. 2.6 Infant with Beckwith–Wiedemann syndrome showing extreme macroglossia

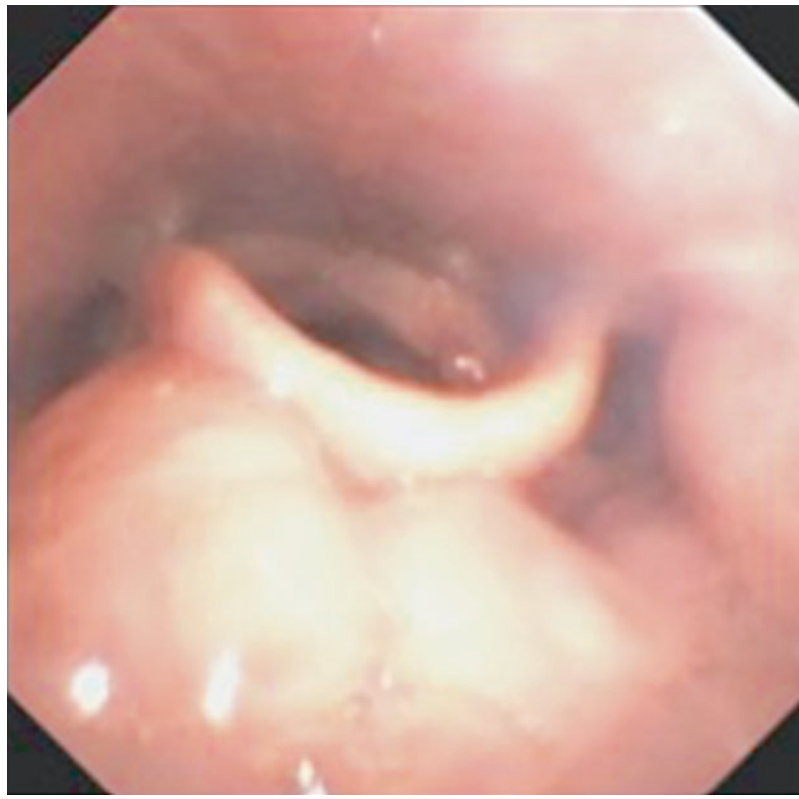

Fig. 2.7 Endoscopic view of a patient with lingual tonsil hypertrophy

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 (Fig. 2.8)
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

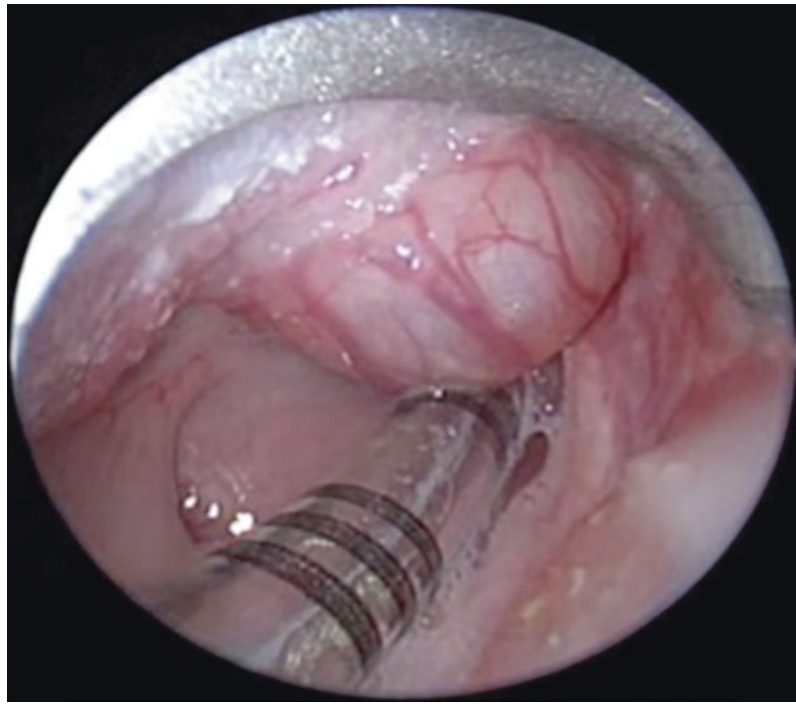

Fig. 2.8 Vallecular cyst obscuring the view of the epiglottis

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
   (a) 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, bifid epiglottis (Fig. 2.6), saccular cyst, and laryngeal cleft.

A. Laryngomalacia (Fig. 2.9)
   1. Etiology and Epidemiology
      (a) Most common cause of stridor in infants, resulting from dynamic collapse of the supraglottic structures into the laryngeal inlet during inspiration

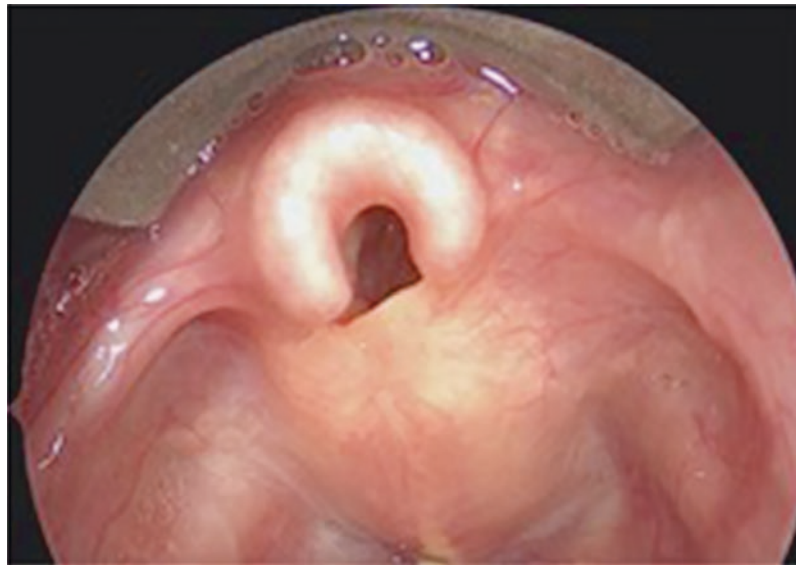

Fig. 2.9 Direct laryngoscopy of a patient with significant laryngomalacia (**a**) before and (**b**) after supraglottoplasty

2. Incidence is unknown but accounts for 70–95% of all neonatal stridor.
   (a) Incidence of synchronous airway lesions is ~15% (more frequent in severe cases).
3. Pathogenesis
   (a) 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 (Fig. 2.10)
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.

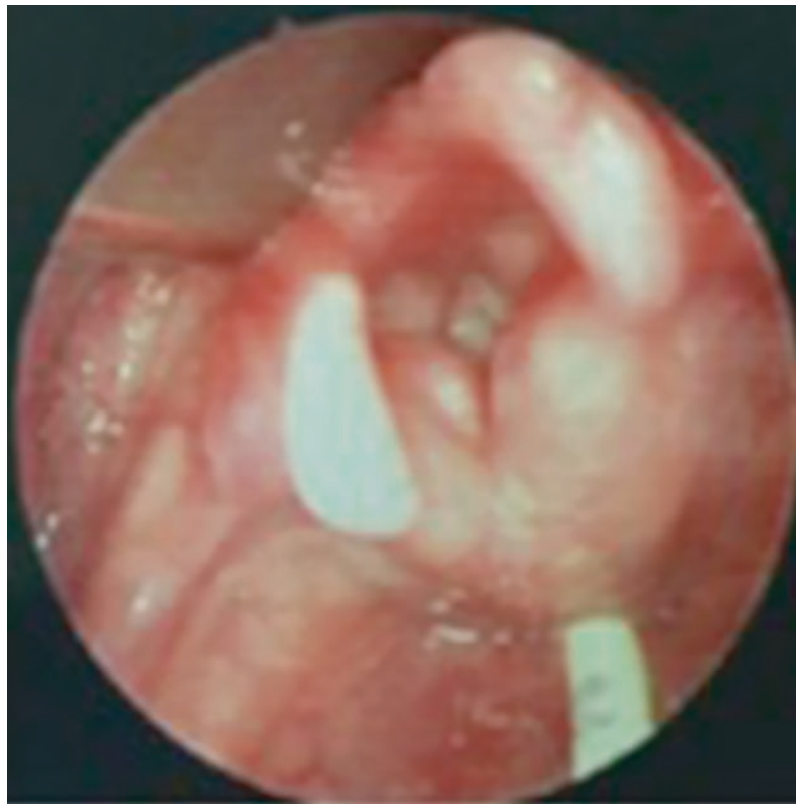

Fig. 2.10 Bifid epiglottis. A rare congenital airway anomaly potentially causing airway obstruction and early clinical signs

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. 2.11)
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.
   (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.

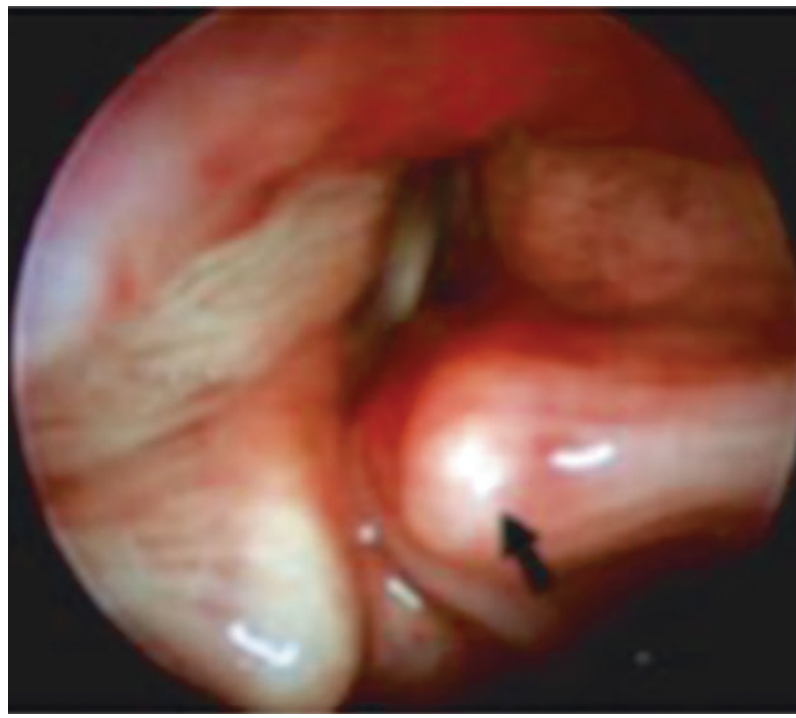

Fig. 2.11 Saccular cyst with a prolapsed arytenoid causing airway obstruction with stridor

(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
   (a) Speech therapy for evaluation and management of aspiration, if indicated

D. Laryngeal/interarytenoid cleft (Fig. 2.12)
1. Etiology and Epidemiology
   (a) Incidence is 1 in 10,000 to 1 in 20,000 live births with type 1 clefts being most common.
   (b) More common in boys than girls, with a M:F ratio of 5:3.
   (c) Can occur in isolation or as part of a syndrome including VATER/VACTERL, CHARGE, Pallister–Hall, and Opitz–Frias.

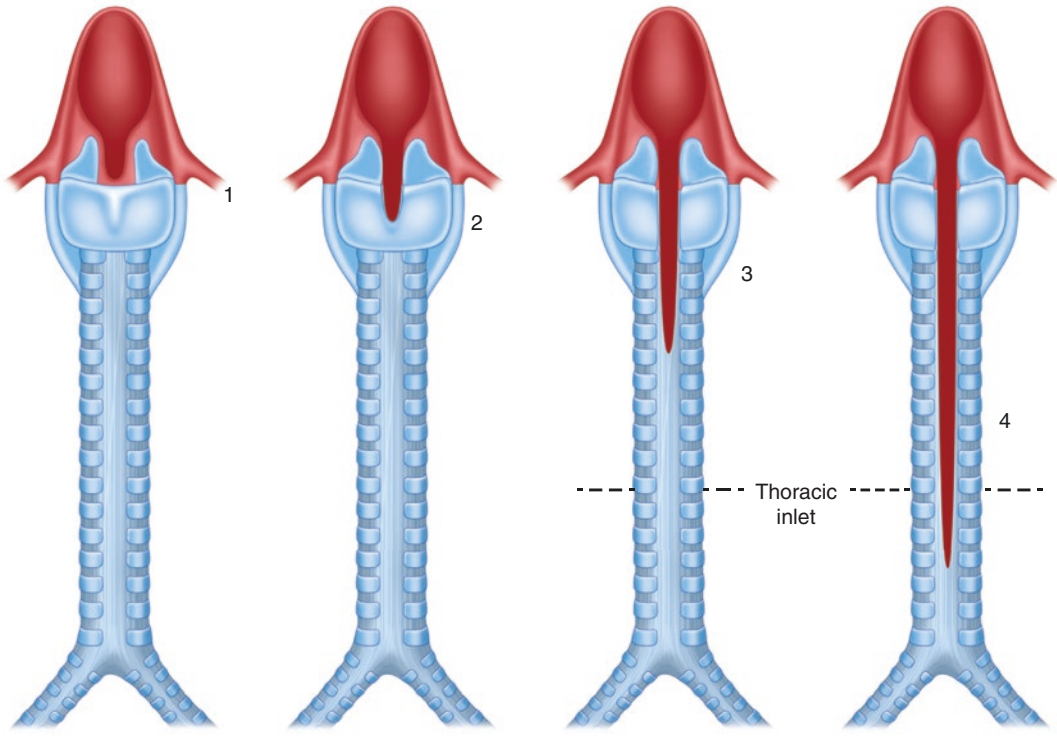

Fig. 2.12 The Benjamin and Inglis cleft classification

2. Pathogenesis
   (a) Branchial anomaly—failure of the cricoid (sixth arch) to fuse posteriorly
3. Clinical Presentation
   (a) Aspiration and/or chronic cough
   (b) Recurrent pneumonia
   (c) Respiratory distress
   (d) Hoarse voice
4. Diagnostic Evaluation
   (a) Videofluoroscopic swallow study
   (b) Microlaryngoscopy with suspension laryngoscopy and palpation of the interarytenoid space
   (c) Four types of clefts with the first two being the most common
      1. 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
      2. Type II cleft involves the superior posterior cricoid cartilage—incomplete fusion of the posterior cricoid ring.
      3. Refer to the section on "trachea" for types III–IV.
5. Medical Management
   (a) Trial of conservative management involves anti-reflux therapy, a thickened liquid feeding regimen, and maneuvers during feeding to prevent aspiration.
   (b) Typically only for type I and rarely type II clefts.
6. Surgical Management
   (a) 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 (Fig. 2.13), and open laryngeal cleft repair through a laryngofissure.
7. Multidisciplinary Collaboration
   (a) Speech therapy for evaluation and management of aspiration risk once cleft identified

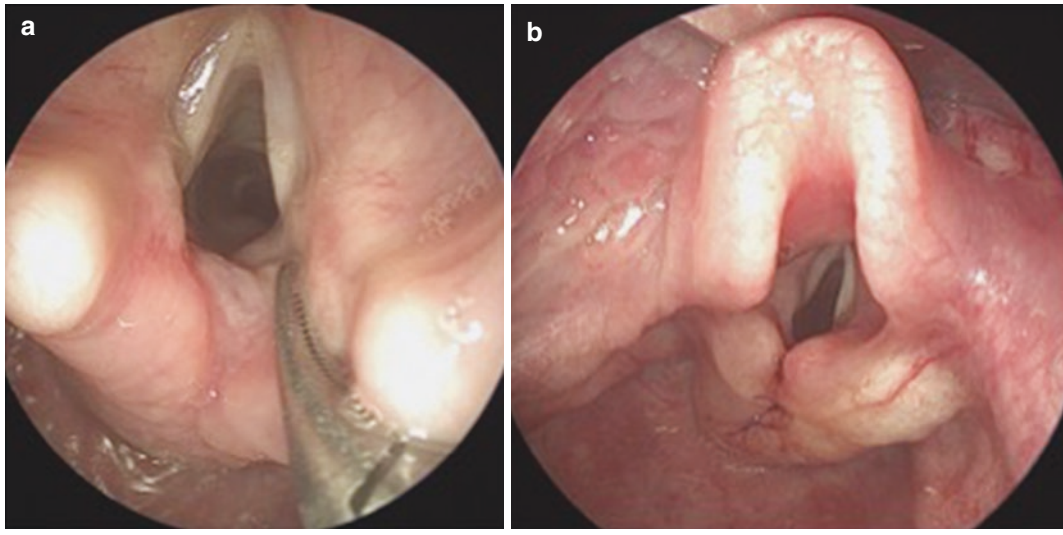

Fig. 2.13 Type I laryngeal cleft causing aspiration that is best seen in the operating room (**a**) with a deep interarytenoid notch on rigid palpation before and (**b**) after endoscopic repair

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. 2.14)

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.
   (b) Second most common cause of neonatal stridor.
   (c) Incidence of 0.75 cases per million births per year.
2. Pathogenesis
   (a) Bilateral abductor paralysis leads to medial position of the vocal cords which limits glottis 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.

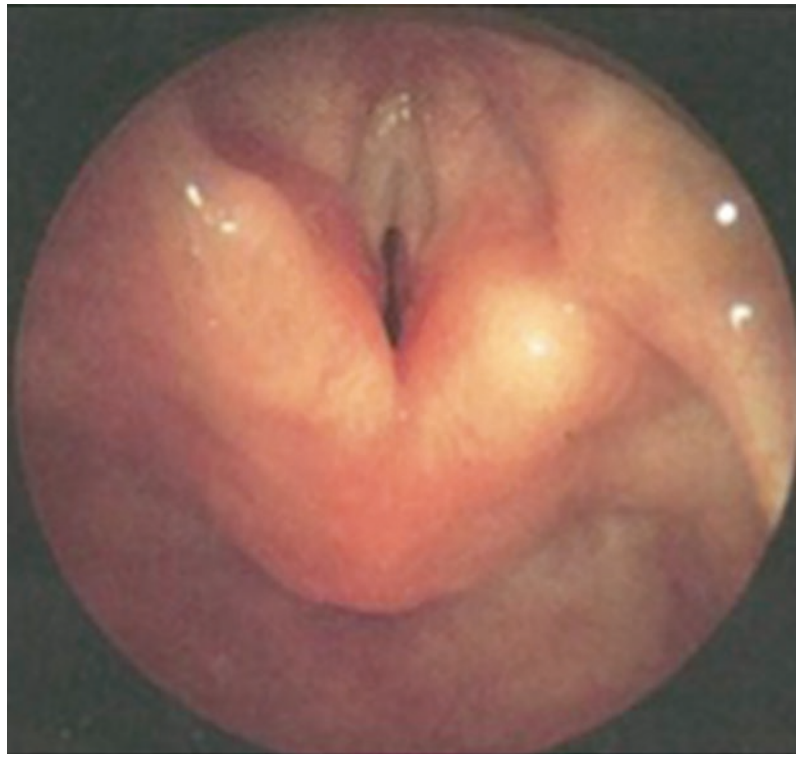

Fig. 2.14 Vocal cord paralysis causing airway obstruction at delivery

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 of 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. 2.15)
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
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

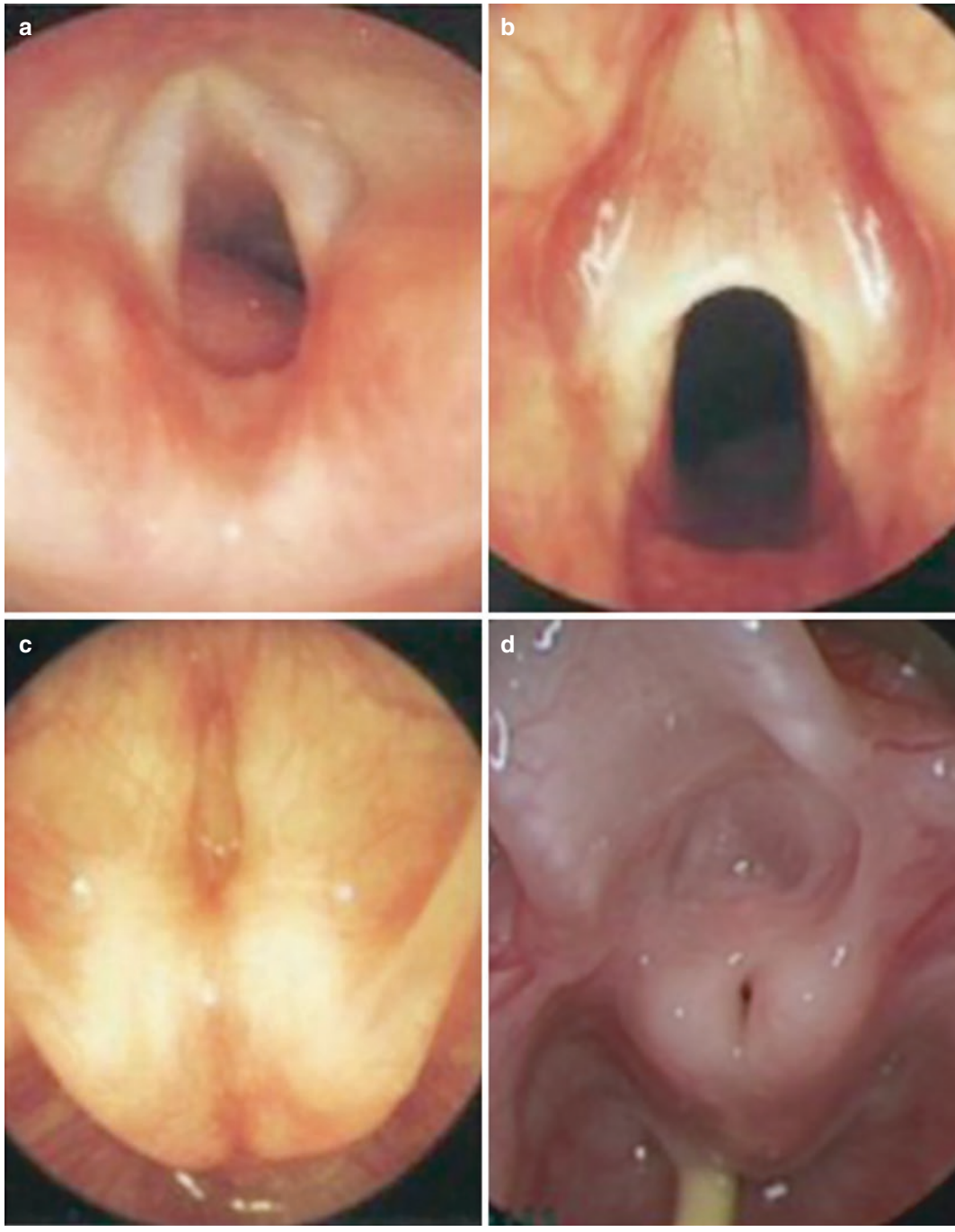

Fig. 2.15 MLB picture of congenital laryngeal anomalies causing airway obstruction. (**a**) Glottic lymphangioma; (**b**) laryngeal web; (**c**) tracheal atresia; (**d**) vocal cord atresia

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
   (a) 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
   (a) Congenital laryngeal atresia (Fig. 2.16) 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.

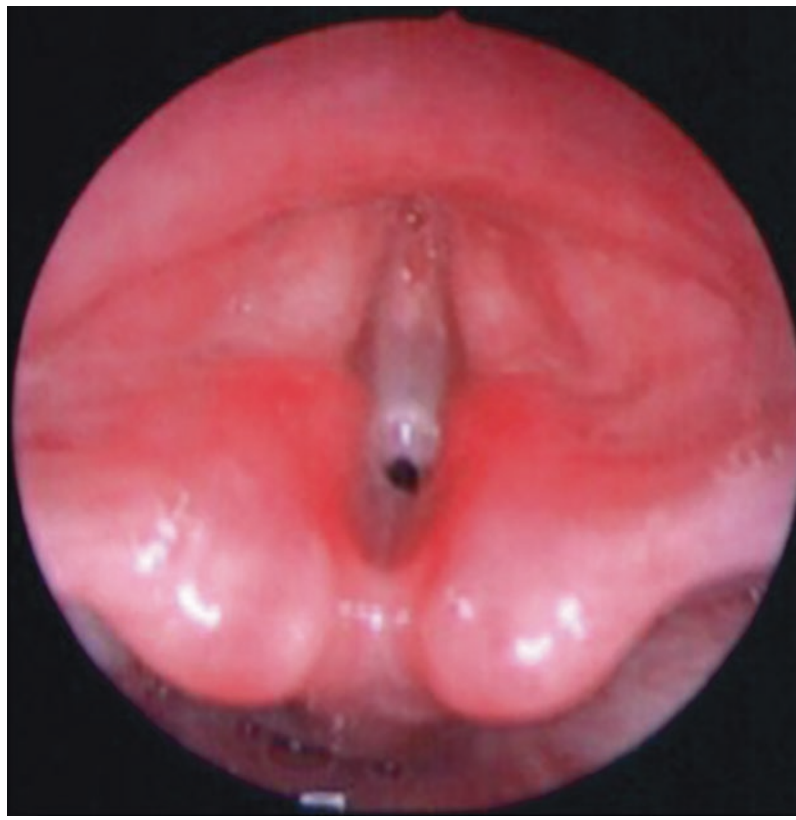

Fig. 2.16 Congenital laryngeal atresia with near-total fusion of the true vocal folds. Note the small glottic airway posteriorly

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.
   (c) Postnatally diagnosed cases are managed by emergent tracheostomy.
   (d) May consider laryngotracheoplasty in select cases for definitive management
6. Multidisciplinary Collaboration
   (a) 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. 2.17)
   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
      (a) Single or multiple cysts may occur as fixed lesions in the immediate subglottis, increasing airway resistance.

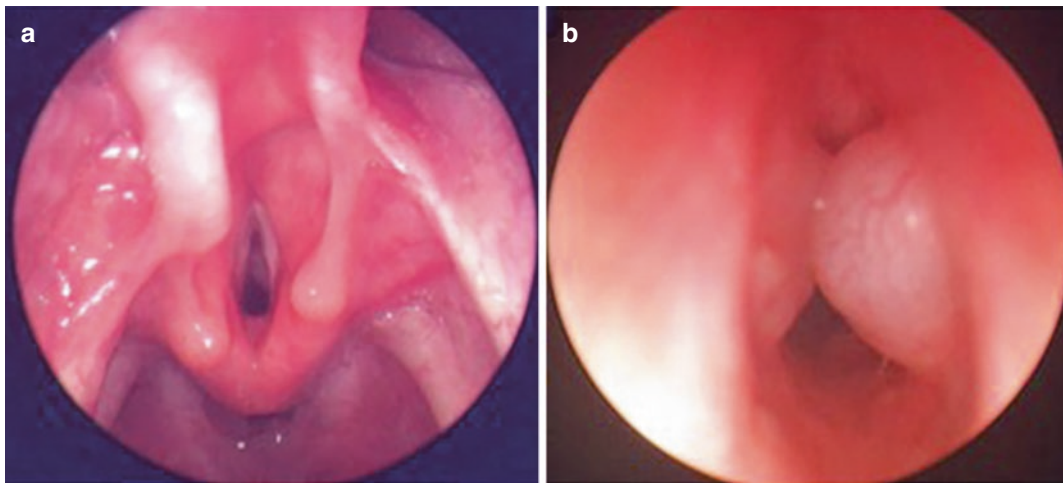

Fig. 2.17 Subglottic cysts viewed from (**a**) above the vocal cords and (**b**) below the vocal cords

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
   (a) Microlaryngoscopy and bronchoscopy demonstrate obvious cysts or asymmetric subglottic narrowing.
5. Medical Management
   (a) 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 CO2 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.

B. Subglottic stenosis (Fig. 2.18)
1. Etiology and Epidemiology
   (a) Membranous subglottic stenosis from embryologic failure of laryngeal recanalization

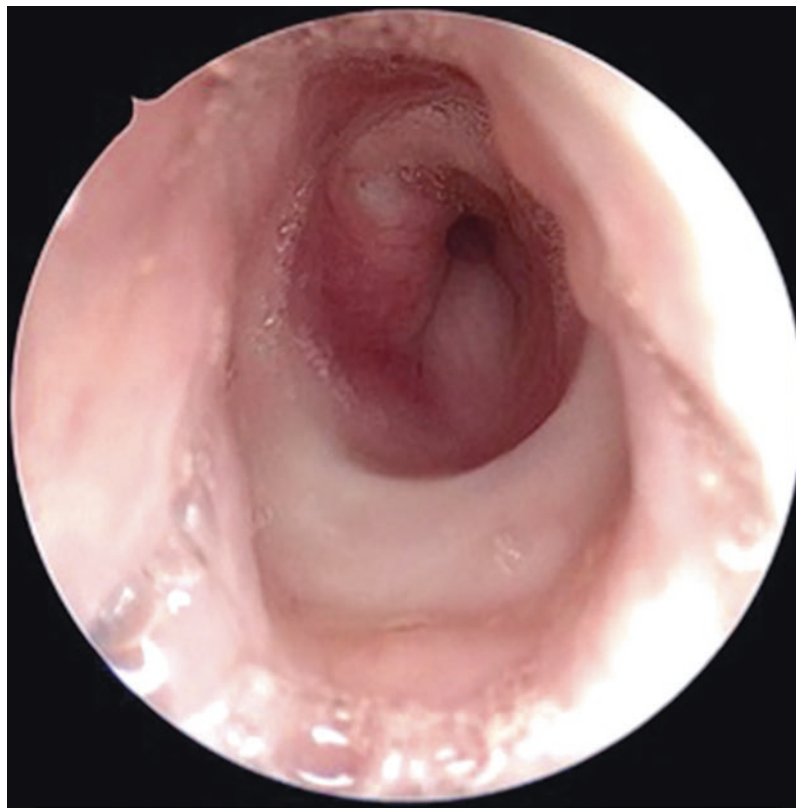

Fig. 2.18 Grade III subglottic stenosis and suprastomal collapse in a patient requiring a tracheostomy to maintain a stable airway

(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
   (a) 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 is most commonly staged by the Cotton–Myer classification
      1. Grade I: 0–50% obstruction
      2. Grade II: 51–70% obstruction
      3. Grade III: 71–99% obstruction
      4. Grade IV: 100% or complete obstruction with no discernable lumen
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 (Fig. 2.19).
   (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.
6. Multidisciplinary Collaboration
   (a) Pulmonary: often associated with lower airway pathology
   (b) Gastroenterology: acid reflux may potentiate or worsen stenoses.

C. Hemangioma (Fig. 2.20a,b)
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
   (a) 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.

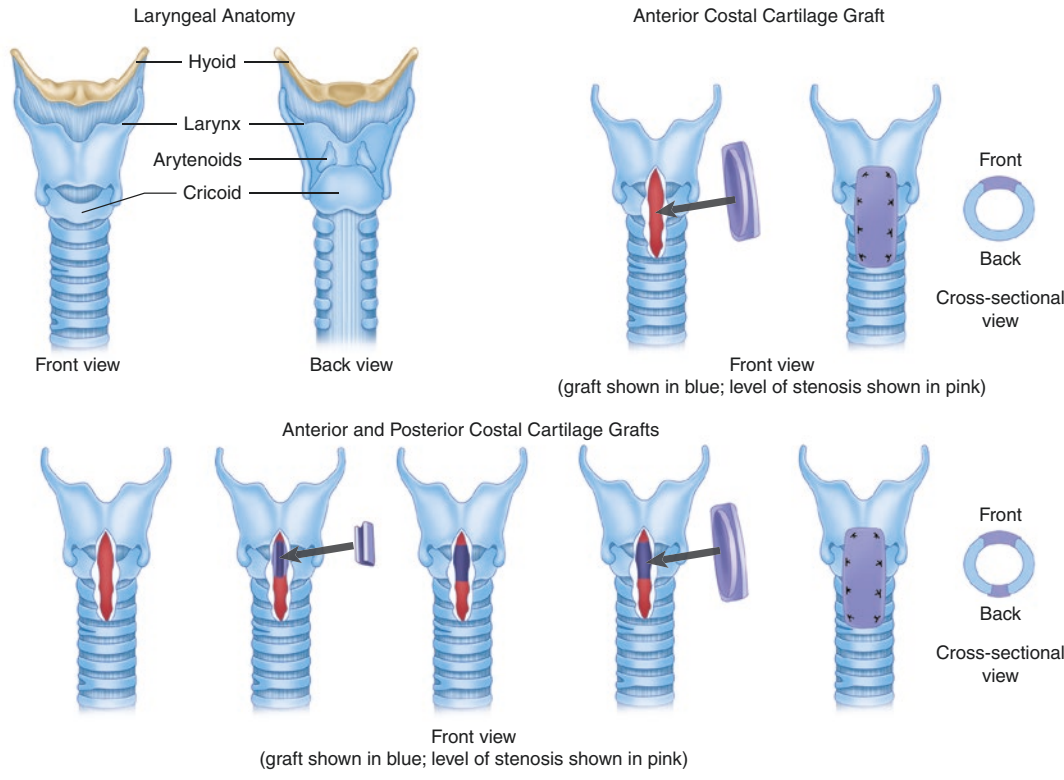

Fig. 2.19 Diagram of placement of anterior and posterior cartilage grafts during LTR, with resultant effect on the airway. (Permission granted for use of illustration by Brian Dunham, MD © 2008)

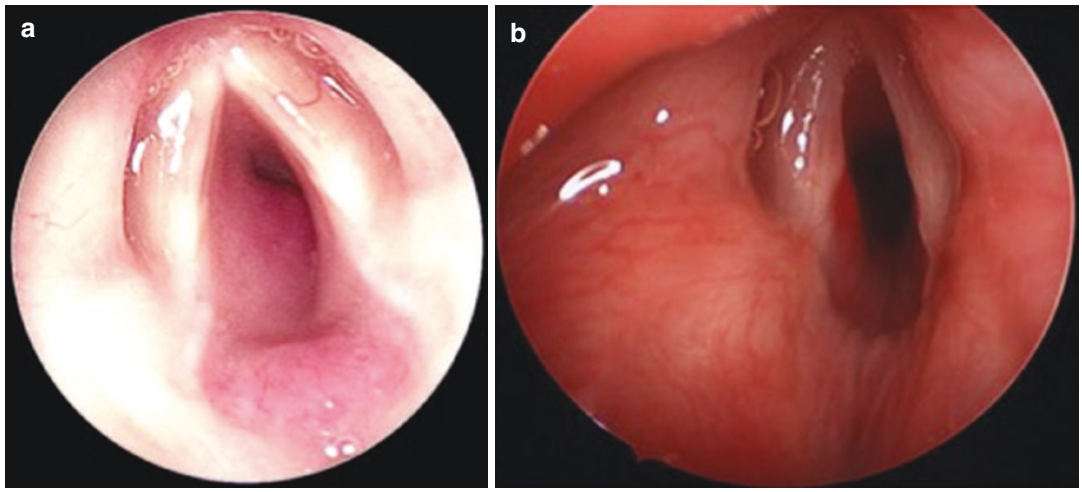

Fig. 2.20 Airway hemangiomas in the (**a**) posterior glottis and immediate subglottis causing inspiratory stridor and (**b**) glottic hemangioma along the left vocal cord with some extension posteriorly and inferiorly into the subglottis

(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
   (a) 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. 2.21a–c)
   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.
      (c) Associated with other malformations of the trachea.
      (d) Incidence estimated to be 1 in 64,500

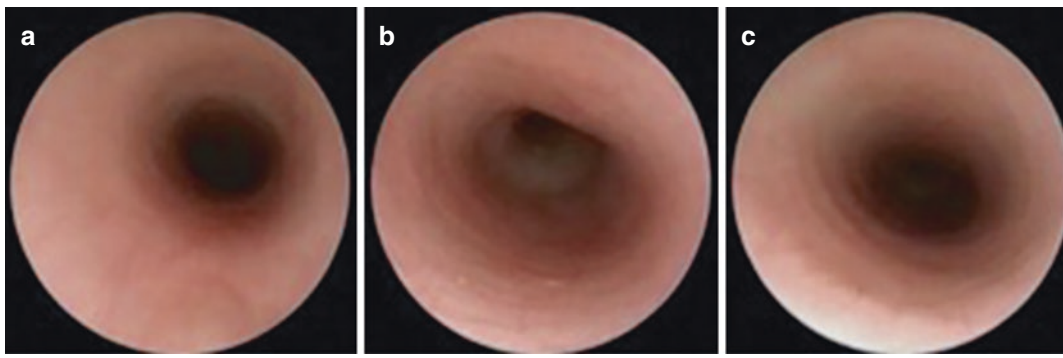

Fig. 2.21 Endoscopic view of a child with long-segment complete tracheal rings. (**a**) View showing the beginning of the rings; (**b**) view showing the midsection; (**c**) view showing the distal segment of the rings

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 (Fig. 2.22) 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).

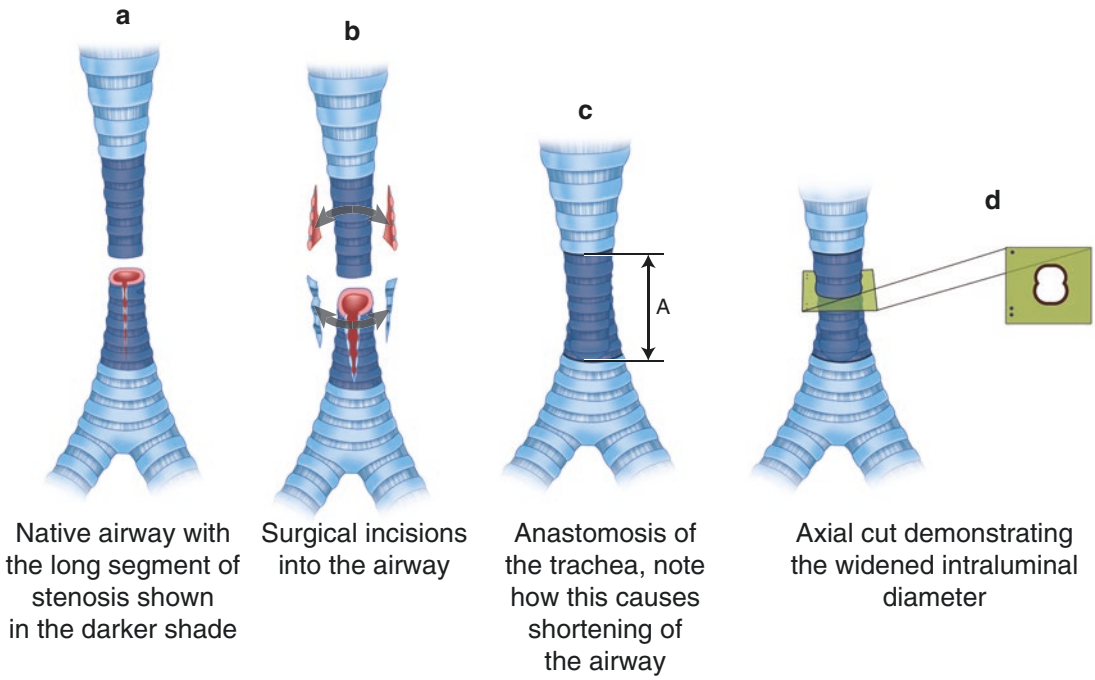

Fig. 2.22 Image showing the method in which a slide tracheoplasty widens the airway. (Permission granted for use of illustration by Brian Dunham, MD © 2009)

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. 2.23)

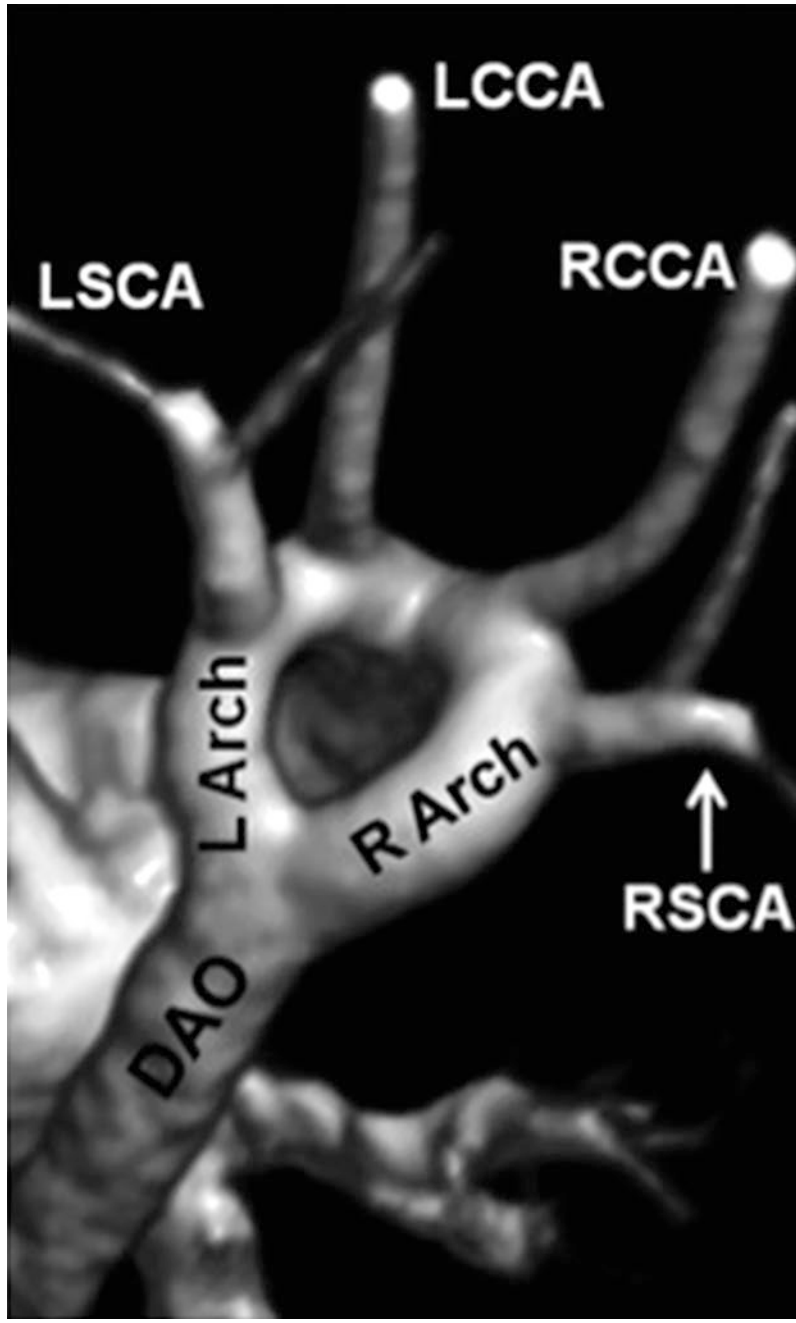

Fig. 2.23 Magnetic resonance angiogram of an unobstructed double aortic arch viewed from the right posterior oblique with cranial angulation. Note that the right aortic arch is slightly larger. *DAO*, descending aorta; *L Arch*, left-sided arch; *LCCA*, left common carotid artery; *LSCA*, left subclavian artery; *R Arch*, right-sided arch; *RCCA*, right common carotid artery; *RSCA*, right subclavian artery

1. Etiology and Epidemiology
   (a) Abnormal development of branchial arch system
   (b) Rare; frequently associated with other cardiac abnormalities
2. Pathogenesis
   (a) 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.
   (b) Rigid bronchoscopy and esophagoscopy for definitive evaluation and to identify synchronous tracheobronchial anomalies including complete rings and abnormal bronchial takeoff
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. 2.24a,b)
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.

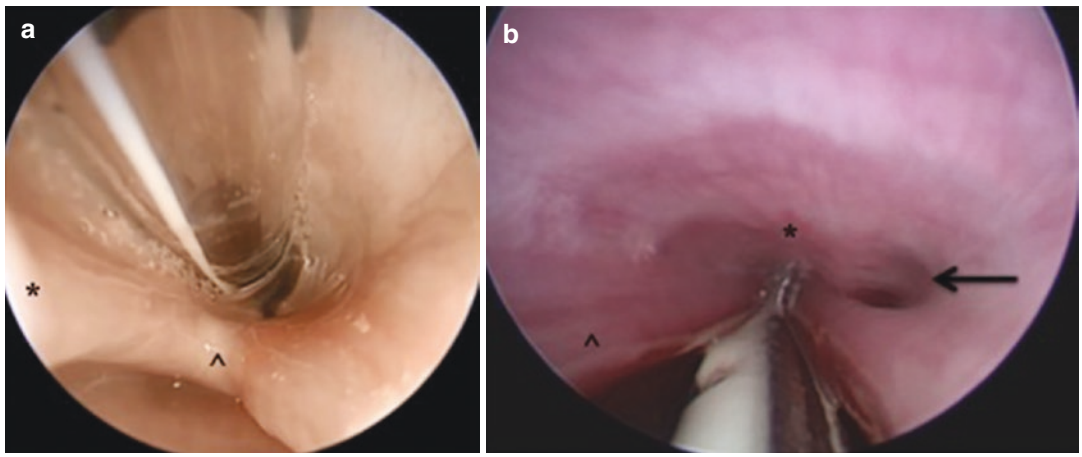

Fig. 2.24 (**a**) Type III laryngeal cleft where (*) is the cricoid cartilage and (^) is the cervical trachea. (**b**) Type IV laryngeal cleft where the arrow marks the right mainstem bronchus, (*) is the carina, and (^) is the tracheoesophageal septum that has failed to fuse

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) Types 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 (Fig. 2.25)
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.

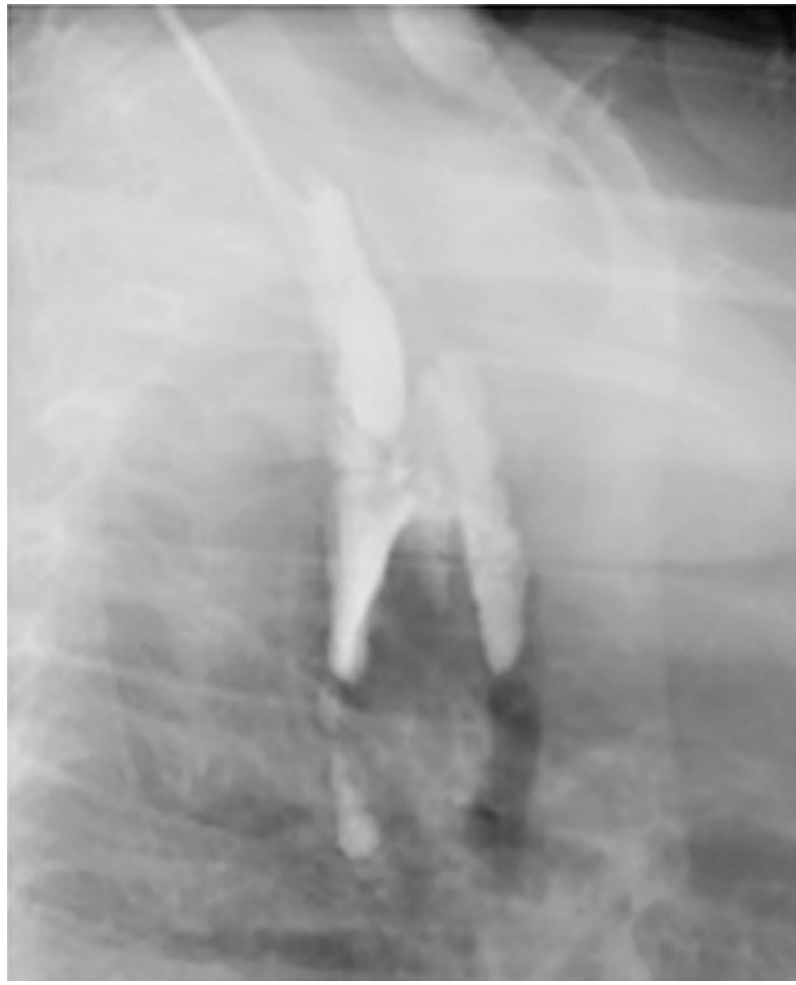

Fig. 2.25 Barium esophagram of a tracheoesophageal fistula. Note the extravasation of contrast from the esophagus and into the air column

3. Clinical Presentation
   (a) Most patients are symptomatic within the 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.
   (a) Type A—Esophageal atresia (EA) without fistula (6 %)
   (b) Type B—EA with proximal fistula (5 %)
   (c) Type C—EA with distal fistula (84 %)

(d) Type D—EA with double fistula (1 %)
(e) Type E—Tracheoesophageal 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. 2.26)
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.

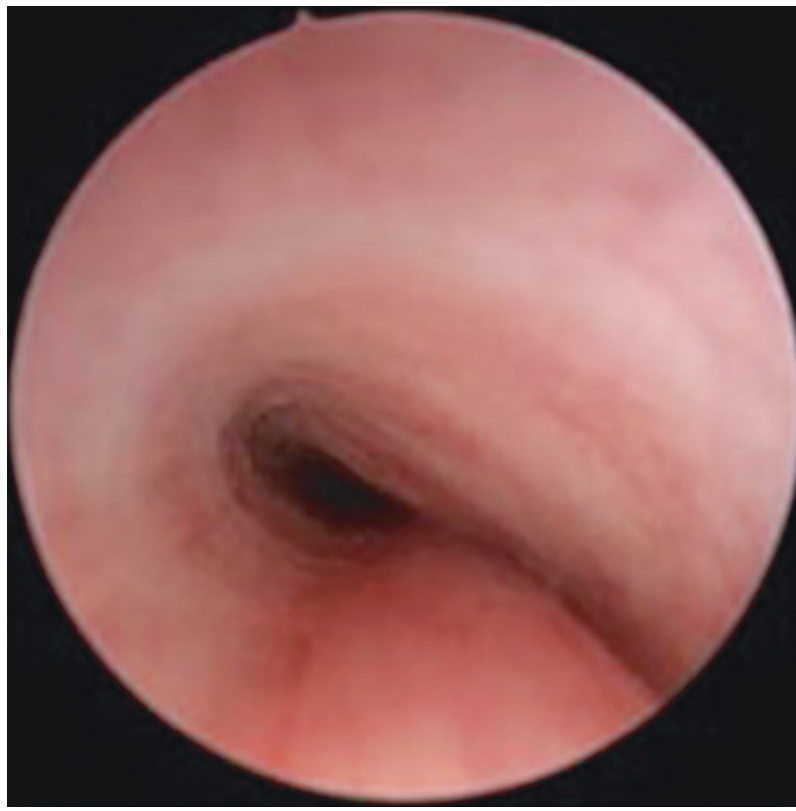

Fig. 2.26 Tracheomalacia in association with innominate artery compression and a large thymus

(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
   (a) 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, or 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

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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. Additionally, 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:
   1. Tracheobronchial tree
   2. Distal lung parenchyma
   3. Abnormalities in the pulmonary arterial and venous trees and the lymphatics

III. Malformations of the tracheobronchial tree
   A. Tracheoesophageal fistula (TEF)
      1. Occurs in 1 in 3000–4500 live births
      2. May result from failure of the process of division of the primitive foregut into the respiratory and alimentary tracts at 3–6 weeks of gestation.

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3. Usually found in combination with various forms of esophageal atresia. The most common combination is esophageal atresia with a distal tracheoesophageal fistula (about 85% of the cases).
4. Infants often present with respiratory distress secondary to airway obstruction from pooling of excess secretions or aspiration of gastric contents into the lung through the fistula.
5. Esophageal atresia itself is diagnosed by the inability to pass a catheter into the stomach. The diagnosis is confirmed by radiographic studies showing a distended blind upper esophageal pouch filled with air and the catheter coiled in the pouch.
6. TEF without esophageal atresia (H-type fistula) is extremely rare and usually presents after the neonatal period.

B. Laryngotracheoesophageal cleft
1. There is a long connection between the airway and the esophagus caused by failure of dorsal fusion of the cricoid, normally completed by the eighth week of gestation.
2. Affected infants have chronic aspiration, gag during feeding, and develop pneumonia.
3. The diagnosis is made by bronchoscopy.

C. Congenital high airway obstruction syndrome (CHAOS)
1. May be caused by laryngeal atresia, subglottic stenosis, a laryngeal web, or a completely occluding laryngeal cyst.
2. Prenatal diagnosis of upper airway obstruction could be inferred from secondary changes such as enlarged echogenic lung, flattened or inverted diaphragm, fetal ascites, or hydrops.
3. Fetal MRI may be helpful in localizing the level of obstruction.

D. Tracheal agenesis
1. Rare, but fatal, anomaly caused by displacement of the tracheoesophageal septum.
2. The length of the agenetic segment is variable.
3. Usually presents with tracheoesophageal fistula, and most are associated with other anomalies.
4. At birth, this anomaly is suspected when attempts at intubation are unsuccessful.

E. Tracheal stenosis
1. A malformation where the trachea is narrow, either because of intrinsic abnormality in cartilage formation or by external compression from vascular rings.
2. The major cause for intrinsic tracheal stenosis is an abnormality in cartilaginous ring formation, either from posterior fusion of the normal C-shaped rings or from formation of a complete cartilaginous sleeve as reported in children with craniosynostosis syndromes including Crouzon, Apert, and Pfeiffer syndromes.
3. Clinical manifestations: Biphasic stridor or expiratory wheezing.
4. Diagnosis is by bronchoscopy.

F. Tracheomalacia and bronchomalacia
1. There is absence or softening in the cartilaginous rings that cause the trachea to collapse on expiration. There is a reduction in the cartilage-soft tissue ratio.
2. The anomaly may be segmental or diffuse.
3. Infants with laryngomalacia present with variable inspiratory stridor that worsens with crying, feeding, and upper respiratory infections.
4. Tracheomalacia may be associated with other congenital anomalies like vascular rings and TEF.

G. Congenital bronchogenic cysts
1. Caused by abnormal budding and branching of the tracheobronchial tree.
2. Tend to lie in the posterior mediastinum, near the carina.

3. Cysts are filled with a clear, serous fluid unless they become infected. The walls of these cysts generally contain smooth muscle and cartilage.
4. It may appear as a space-occupying lesion on a chest radiograph obtained for investigation of respiratory distress.

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

IV. Malformations of the distal lung parenchyma

A. 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 bronchus 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.

B. 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, congenital diaphragmatic hernia, large pleural effusions, congenital anomalies of the neuromuscular system, and chromosomal anomalies, including trisomy 13, 18, and 21.

C. Congenital diaphragmatic hernia (CDH) (Chap. 72)
1. CDH occurs in 1 per 2000 to 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. The prenatal diagnosis is often made by ultrasonography, which is often precipitated by the occurrence of polyhydramnios.
8. 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.
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.

D. 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. 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 the cysts communicate with the airways, they fill with air, produce further compression of the adjacent lung, and result in worsening 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 if left untreated.

E. 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.

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

G. Other conditions that manifest as interstitial lung disease
1. Disorders (deficiencies and dysfunction) of surfactant protein (SP) B and C that are associated with lamellar body anomalies related to ABCA3 gene deficiency, thyroid transcription factor 1 (TTF1) deficiency, or alveolar epithelial 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 support.

V. Abnormalities in the pulmonary arterial, venous, and lymphatic vessels

A. Multiple anomalies in the pulmonary vasculature may compromise arterial supply or venous drainage of the lungs (such as total or partial anomalous pulmonary venous return) and may compress the airways (e.g., aberrant pulmonary arteries may compress the trachea, pulmonary artery sling).

B. Agenesis of a pulmonary artery may compromise the growth of the ipsilateral lung.

C. In Scimitar syndrome, there is partial anomalous venous drainage along with right lung hypoplasia and the right bronchial tree may exhibit a left-sided branching pattern.

D. Pulmonary arteriovenous malformations (also known as pulmonary arteriovenous fistulas or aneurysms) are associated with intrapulmonary right-to-left shunting.

E. Congenital pulmonary lymphangiectasis (CPL)
1. Extremely rare condition consists of markedly distended or dilated pulmonary lymphatics (but the number of vessels is normal), which are found in the bronchovascular connective tissue, along the interlobular septae, and in the pleura. It may be primary or secondary, and it can generalized.
2. This condition has been associated with Noonan, Ulrich-Turner, and Down syndromes.
3. Primary lymphangiectasis is a developmental defect in which the sluggish flow in pulmonary lymphatics fail to drain to the systemic lymphatics. Affected infants present with respiratory distress and pleural effusions.
4. Secondary lymphangiectasis is associated with cardiovascular malformations.
5. 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.

F. Other congenital anomalies of pulmonary lymphatics that present with chylothorax. These anomalies that include lymphangioma (focal proliferations of lymphatic capillaries that can be microcytic or macrocystic) and lymphangiomatosis (characterized by the presence of multiple lymphangiomas) that infiltrate different tissues, including the lungs and other thoracic tissues. Congenital chylothorax could also be idiopathic (not associated with lymphangiectasia or lymphangiomas) as part of congenital lymph dysplasia syndrome (Milroy disease) or as part of a syndrome that includes lymphatic dysplasia (such as Turner, Noonan, and Ehlers-Danlos).

Suggested Reading

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Part II

Principles of Mechanical Ventilation

Spontaneous Breathing

4

Vinod K. Bhutani and Vineet Bhandari

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 ($V = dV/dt$).
   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:

$$P = P_E + P_R + P_I$$

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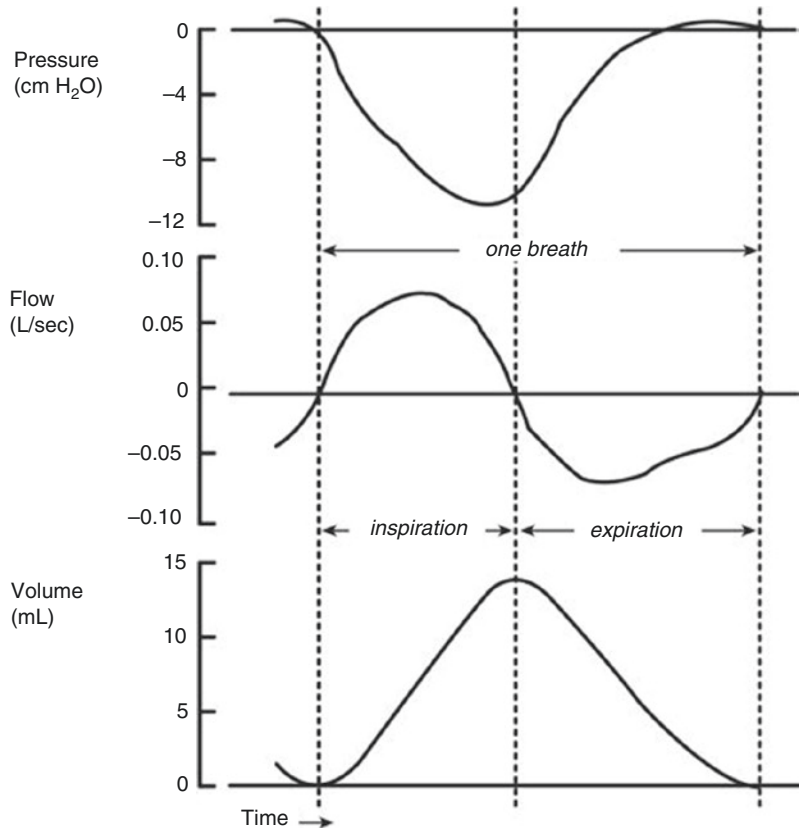

Fig. 4.1 Graphic representation of a respiratory cycle demonstrating pressure, flow, and volume waveforms. Volume is obtained by integration (area under the curve) of the flow signal (Modified from Bhutani VK, Sivieri EM, Abbasi S: Evaluation of pulmonary function in the neonate. In Polin RA, Fox WW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

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

$$P = EV + R\dot{V} + IV^{\cdot\cdot}$$

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:

$$\begin{aligned} P = EV + R\dot{V}\ or\ &\text{Pressure} \\ = &\text{Elastance} \times \text{Volume} + \text{Resistance} \\ &\times \text{Flow} \end{aligned}$$

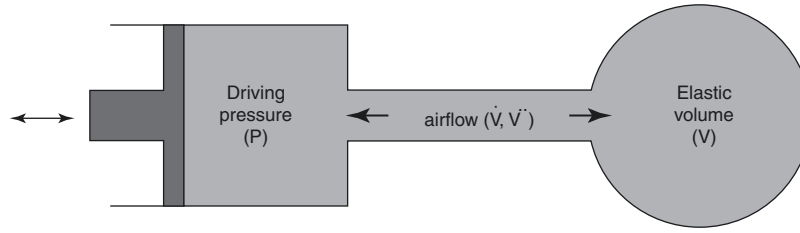

Fig. 4.2 Linear, first-order model of the respiratory system, where applied pressure causes gas to flow through a tube

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:

$$P = V/C + R\dot{V} \; or \; \text{Pressure} = \text{Volume} \times 1/\text{Compliance} + \text{Resistance} \times \text{Flow}$$

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.

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/periodic (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.
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.

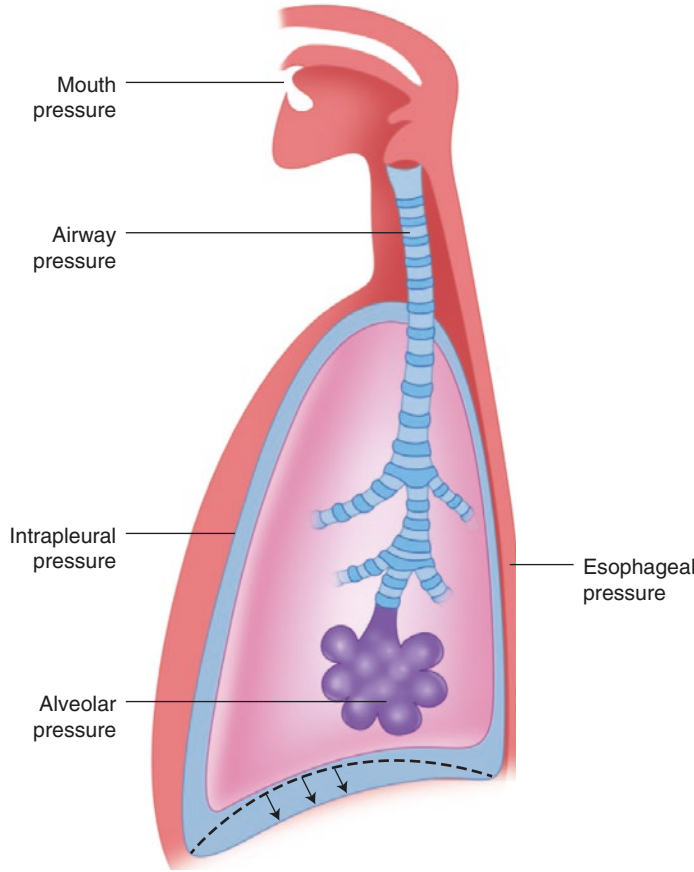

Fig. 4.3 Schematic representation of components of respiratory pressures used in pulmonary function studies. Esophageal pressure approximates intrapleural pressure (Modified from Bhutani VK, Sivieri EM, Abbasi S: Evaluation of pulmonary function in the neonate. In Polin RA, Fox WW [Eds.]: *Fetal and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

C. The 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.

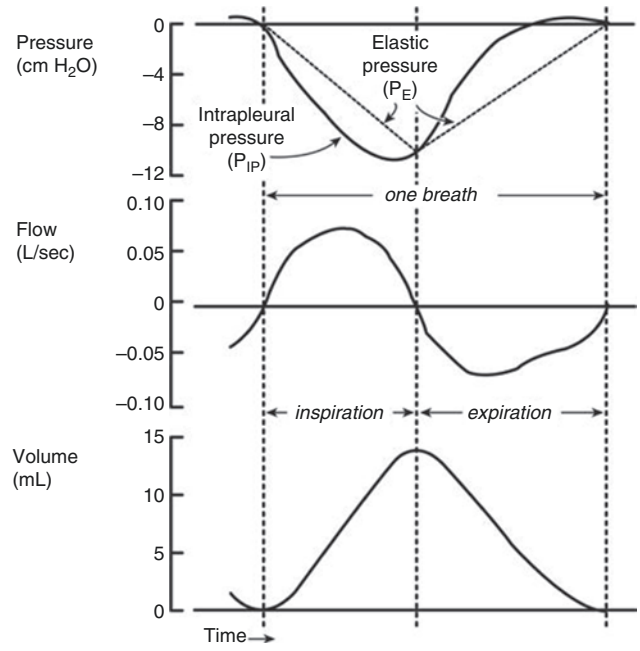

Fig. 4.4 During tidal breathing, airflow is zero at end-inspiration and end-expiration, where it reverses direction. The pressure difference between these two points represents the net elastic pressure at end-inspiration. The elastic component of intrapleural pressure at other points can be approximated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

Following are some physiologic observations of changes in intrapleural pressure during taneous breathing

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, 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.

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 (BPD) or during positive pressure ventilation), the intrathoracic airways are likely to be compressed during expiration (Fig. 4.6).

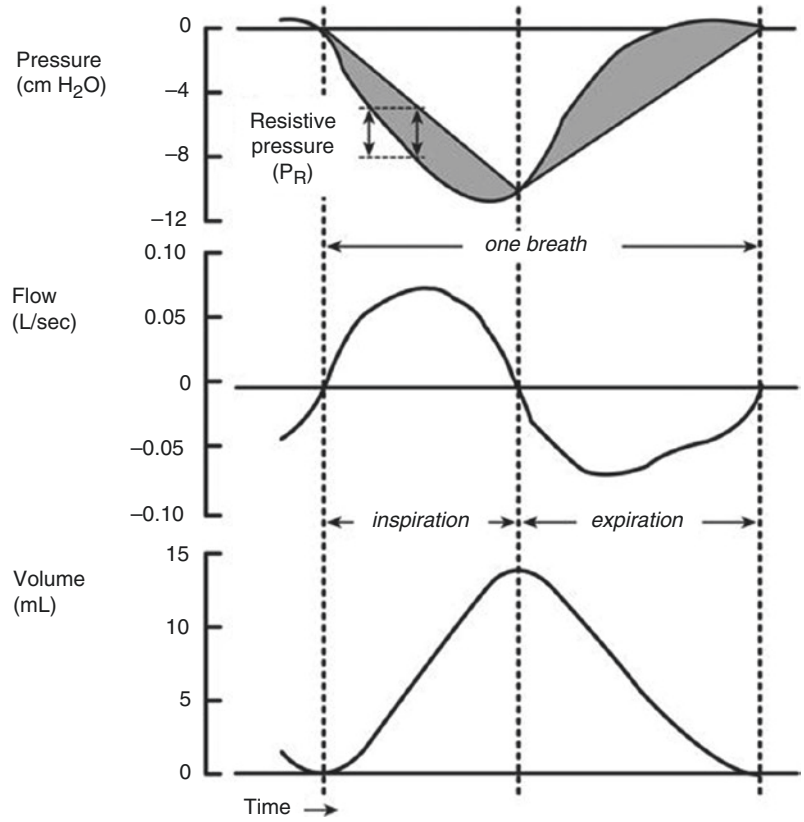

Fig. 4.5 The elastic component of intrapleural pressure can be estimated on the pressure tracing by connecting points of zero flow at end-expiration and end-inspiration with a straight line. The vertical distance between this estimate and the measured intrapleural pressure is the resistive pressure component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

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 musscle hyperplasia or a hyper-responsive smooth muscle should lead to a bronchospastic basis of airflow limitation.
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.

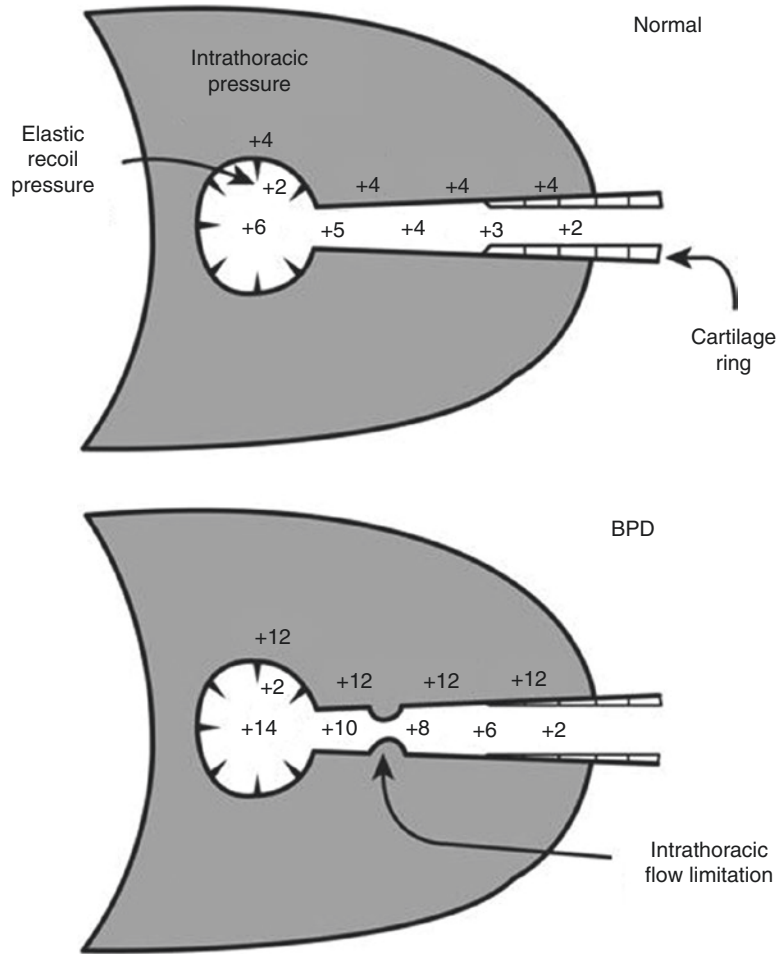

Fig. 4.6 Schematic comparison of normal and abnormal airflow. Infant with bronchopulmonary dysplasia (BPD) has higher transmural pressure generated during tidal breathing, and thoracic airways are likely to be compressed during expiration, resulting in a flow limitation (Modified from Bhutani VK, Sivieri 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)

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 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.

   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 (surfactant sufficient) 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 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

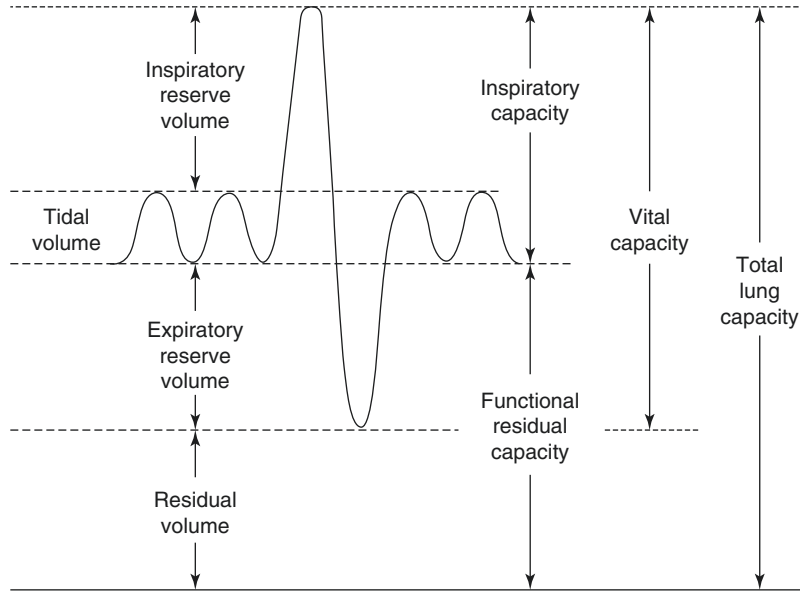

Fig. 4.7 Graphic representation of lung volumes and capacities (Modified from Bhutani VK, Sivieri EM: Physiological principles for bedside assessment of pulmonary graphics. In Donn SM [Ed.]: *Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications.* Armonk, NY, Futura Publishing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

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.

Expiratory Reserve Volume $(\mathrm{ERV}) = \mathrm{FRC} - \mathrm{RV}.$

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 and Vineet Bhandari

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 of the pulmonary vasculature include factors which control development and also provide insight into the genetic diversity of these cells. The development of the pulmonary vascular system and the airways is closely coordinated and share similar branching patterns.
   C. The two major ways pulmonary vessels develop are vasculogenesis (de novo formation of blood vessels from endothelial cells) and angiogenesis ("sprouting" and/or "intussusceptive," i.e., formation of new blood vessels from existing ones). The extrapulmonary artery and acinar arteries develop at 34 and 44 days, respectively. The pre-acinar arteries develop at 5–15 weeks, the intra-acinar at 18–25 weeks, alveolar duct arteries at 25 weeks–18 months, followed by the alveolar capillaries from 30 weeks to 18 years.
   D. Environmental signals and signaling molecules contribute to the terminal differentiation of specific vascular cells at the local level, and which confer unique properties to these cells. Among the molecular signaling pathways implicated are those involving sonic hedgehog, vascular endothelial growth factor, angiopoietins, and Wnts, to name a select few.
   E. Model systems using temporal-specific genetic cell lineage tracing using Cre-loxP techniques as well as transgenic reporter mice will 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.

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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.
I. In doing all of the above, we will come to a better understanding of the unique origins of the macro- and microcirculations 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.
1. In order to affect this transition, several physiologic changes occur
2. Adjustments in circulation
3. Pulmonary mechanics
4. Gas exchange
5. Acid-base status
B. 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.
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:

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

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:

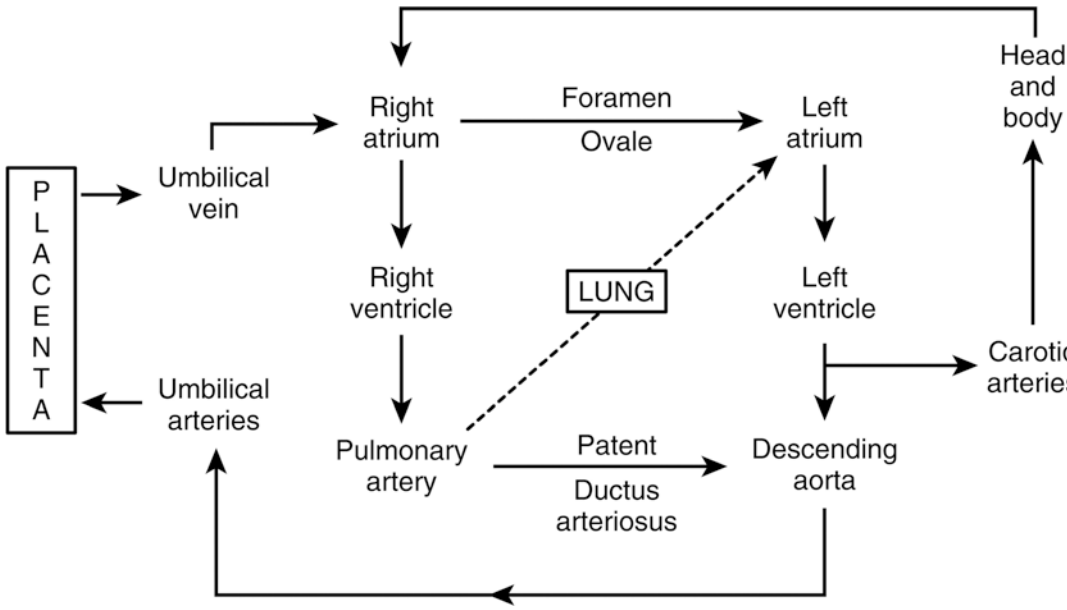

Fig. 5.1 Schematic representation of fetal circulation. (From Bhutani VK: Extrauterine adaptations in the newborn. Sem Perinatol 1997; 1:1–12, with permission)

Table 5.1 Salient features of extrauterine cardiopulmonary adaptations

Parameter	Mother (second trimester)	Fetus (before labor)	Newborn (before first breath)	Newborn (at about 6 hours)
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 signals	Rhythmic respiratory cycles based on chemoreceptors

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 mm Hg•273°K). Based on the product 310 × (760/273), we obtain the value 863 (in mm Hg) providing the constant for the relationship in the above equation.

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

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 seventh week.
   C. The branches of the pulmonary arterial system maintain a position next to the bronchial structures as both develop during the pseudoglandular and canalicular stages of lung development.
   D. By 18–25 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. 4.2).
    1. The effect of ventilation on reducing pulmonary vascular resistance (A).
    2. The effect of acidosis correction to enhance pulmonary blood flow (B).

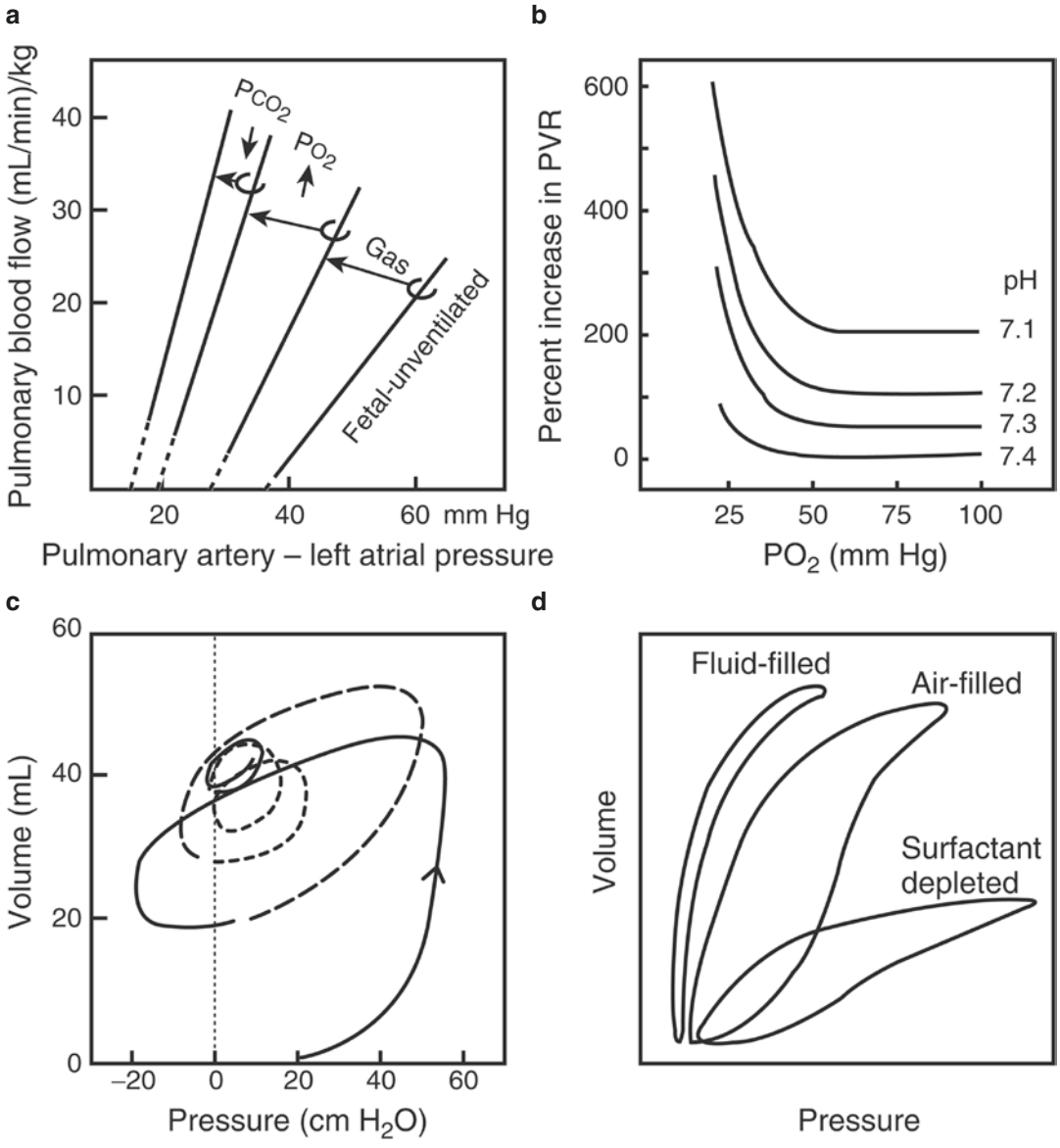

Fig. 5.2 Physiologic processes that facilitate onset of postnatal pulmonary gas exchange. (**a**) Effect of ventilation on reducing pulmonary vascular resistance (PVR). (**b**) Effects of acidosis correction on reducing PVR. (**c**) First breaths and establishment of optimal functional residual capacity. (**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)

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.

C. Maladaptation delays transition to adequate pulmonary gas exchange. (Maladaptation may 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 of:
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.

C. Respiratory failure can initially lead to increased respiratory effort in an attempt at compensation, followed by an inability to ventilate, or apnea.

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*

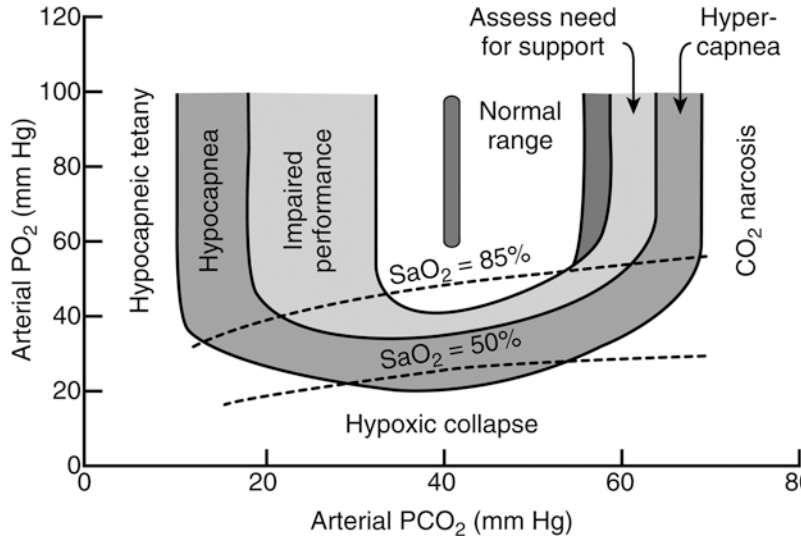

Fig. 5.3 The relationship between alveolar oxygen and carbon dioxide values and how these relate to hypoxemia and respiratory failure. (Modified from Bhutani VK: Differential diagnosis of neonatal respiratory disorders. In Spitzer AR [Ed.]: *Intensive Care of the Fetus and Neonate*. St. Louis, Mosby-Year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

Table 5.4 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

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 baro- 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 baro- and volutrauma.

Oxygen Therapy

6

Win Tin and Vrinda Nair

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 in 1951.
   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. The main factors relating to tissue oxygenation include:
      1. Effective breathing.
      2. Fractional inspired oxygen (FiO_2)
      3. Gas exchange mechanism within the lungs.
      4. Cardiac output (and the effects of shunts).
      5. Oxygen capacity of the blood: Maximum amount of oxygen that can bound to one gram of hemoglobin (1.34 ml × Hb level in grams).
      6. Oxygen Saturation: It is defined as percentage of Hb saturated with oxygen. Approximately 97% of oxygen transported to the tissue is carried by Hb and 3% is dissolved in plasma. It can be measured invasively from arterial blood (SaO_2) or noninvasively by pulse oximeter (SpO_2).
      7. Local tissue edema or ischemia.
      8. Altitude.

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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 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% to 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 to 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 to 50 torr and may remain high (20–40 torr) for days. The increase in *P* (*A*–*a*) O_2 is generally caused by:
      (a) Reduced 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):* OI is a commonly used index both clinically and in research because of its ease of calculation. It is a sensitive indicator for severity of pulmonary illness as mean airway pressure (Pāw) is taken into its calculation ($OI = Pāw \times FiO_2/PaO_2^* \times 100$) (*in mm Hg).
   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. Relationship between PaO_2 and oxygen saturation (SaO_2/SpO_2).
   1. For values of 80% and below, there exists a linear relationship between oxygen saturation and PaO_2. However, beyond 80% of oxygen saturation, smaller changes in saturation result in higher changes in PaO_2 (Fig. 6.1).
   2. 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).
   3. The correlation between PaO_2 and oxygen saturation is also influenced by several physiologic changes (quantity and quality of Hb, body temperature, acid-base status, PCO_2, and concentration of 2–3 DPG in red blood cells).

III. *Monitoring of Oxygen Therapy*

A. Noninvasive continuous monitoring.
   1. Pulse Oximetry (SpO_2): This is the most commonly used oxygen therapy monitoring system in neonates. It is based on the difference in absorption of infrared light by oxygenated and deoxygenated Hb. One of its major limitations is failure to detect hyperoxia and reduced reliability below 70–80% (Chap. 18).
   2. Transcutaneous PaO_2 ($tcPO_2$): The accuracy depends on skin thickness and perfusion status and sensor temperature. There is also a risk of local skin burns in very premature infants.

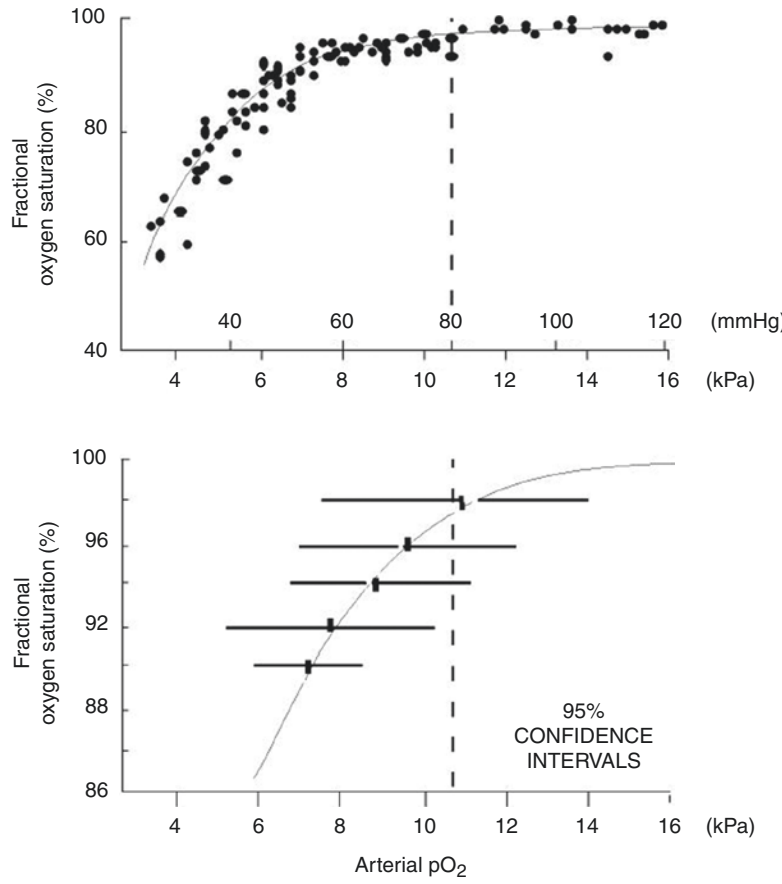

Fig. 6.1 The relation between fractional O_2 saturation measured with a pulse oximeter and arterial partial pressure (reproduced with permission from BMJ Books). The dashed line marks the TcO_2 above which there was an increased risk of ROP in the study reported by Flynn in 1992. The bars in figure show 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

3. Near-Infrared Spectroscopy (NIRS): It involves continuous noninvasive monitoring of regional oxygen saturation at tissue level. This is reflective of perfusion and oxygenation of the underlying tissues.

B. Invasive monitoring.
   1. Arterial blood gas analysis.
      (a) Intermittent arterial PO_2 by sampling via an indwelling arterial line.
      (b) Continuous online arterial blood gas analysis (Paratrend®) by inserting a blood gas sensor (catheter) in an arterial line.
   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.

IV. *Oxygen Toxicity* (Chap. 7)

A. Experimental and research work over more than a century have shown that oxygen can be toxic if not used judiciously. Oxygen toxicity can lead to oxidative stress and generation of reactive oxygen species. Preterm infants are far more vulnerable because of the immaturity of their antioxidant defense system.

B. Oxygen and Retinopathy of Prematurity (Chap. 84). One of the major tissues affected by harmful levels of oxygen is the retina. Fetal retina is initially avascular. New blood vessels start to develop from the center of the retina and progressively move to the periphery. Complete vascularization is nearly complete by 36 weeks of gestation. The vascularization process is hugely controlled by vascular endothelial growth factor (VGEF). Preterm infants are born with incomplete retinal vascularization. Treatment of these infants with oxygen lead to hyperoxia and vasoconstriction (suppression of VGEF) and at later stages vasoproliferation (increase in VGEF levels). These changes lead to aberrant vascularization, retinal fibrosis, retinal detachment, and blindness.

C. Oxygen and Bronchopulmonary Dysplasia (BPD) (Chaps. 78, 79, and 80). Oxygen toxicity is an important contributory factor in the pathogenesis of BPD. The reactive oxygen species can injure the pulmonary epithelium leading to interstitial edema, thickening, and fibrosis. Even if inspired oxygen concentrations are not high, oxidative stress can occur and contribute to tissue injury in the lung.

D. Oxygen and Brain. Reactive oxygen species can cause injury to the oligodendrocytes in white matter and result in periventricular leukomalacia (PVL). Oxidative stress is associated with impaired neurodevelopmental outcome in vulnerable infants even in the absence of intraventricular hemorrhage and PVL.

V. *Observational evidence of oxygen monitoring and clinical outcomes*

A. Pulse oximetry is the most commonly use oxygen monitoring technique in neonates. However, there is wide variation in SpO_2 monitoring policies among neonatal ICUs.

B. 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.

C. The STOP-ROP trial of preterm infants (median gestational age 25.4 weeks) with pre-threshold ROP looked at two different SpO_2 target ranges: 89–94% (conventional arm) versus 96–99% (supplemental oxygen arm). There was no difference in progression of ROP from pre-threshold to threshold ROP or the need for surgery. However, there were increased pulmonary complications including exacerbation of BPD in the supplemental oxygen arm.

D. The BOOST trial also showed that aiming to keep higher 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 healthcare resources.

VI. *Emerging evidence from the "Oxygen Saturation Targeting Trials"*

A. Five masked randomized controlled trials have been conducted to compare the clinical outcomes (primary outcome being death and/or 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. A meta-analysis of these trials showed that targeting the higher range (91–95%), compared to the lower range (85–89%), reduces the risk of mortality and necrotizing enterocolitis (NEC) but increases the risk of severe ROP.

C. A planned prospective individual participant data meta-analysis (NeOProM collaboration) showed that there was no significant difference in death or major disability at 18–24 months' corrected age between the lower (85–89%) and higher (91–95%) oxygen saturation range in extremely premature infants. However, targeting lower saturation range was associated with higher mortality and NEC but a lower risk of ROP and BPD (defined as oxygen requirement at 36 weeks' PMA).

D. In spite of the results from above studies, unanswered questions still remain. For instance, the saturation target ranges for more mature and term infants and at what age should transition to higher saturation range happen in extremely premature infants. The clinicians should be aware that the current oxygen trials may not give an answer to all the questions and controversies on "oxygen" – a powerful and the most commonly used "drug" in neonatal medicine.

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Oxygen Toxicity

7

Rønnaug Solberg and 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, in 1604 the Polish alchemist Michael Sendivogius 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. 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 1950s, oxygen was associated with the development of retrolental fibroplasia (today called retinopathy of prematurity, ROP), and at the end of the 1960s oxygen toxicity was associated with the 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 to recommend starting resuscitation of term or 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 a cell probably resistant to oxygen toxicity, and it is hypothesized that this was secondary to the fact that primitive organisms were

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forced through a "radiation bottleneck," making life resistant to both radiation injury and oxygen toxicity.
3. This prepared eukaryocytes 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.
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, proteins, and DNA. They are also important as signaling substances and therefore regulate physiologic processes such as circulatory aspects as well as growth and development. Therefore, it is important for the organism to tightly control the redox status and oxidative stress; even short deviations in oxidative stress indicators may trigger long-term effects.
5. The premature baby has less capacity to bind free iron, and thus these babies are more susceptible to damage through the Fenton reaction, which produces hydroxyl radicals.

D. Defense mechanisms
1. The body has a number of intracellular and extracellular antioxidants. In fetal life, activities of the intracellular anti-oxyenzymes superoxide dismutases, catalases, and glutathione peroxidases are low and increase toward term.
2. Extracellular defense is not so low in the premature and the first days after birth; for instance, vitamin C is high. Other important antioxidants in this period of life are bilirubin and uric acid.
3. DNA is protected against oxygen toxicity. 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 Neil 3, Mutyh, OGG1, and others.

E. Control mechanisms
1. HIF-1α is an important transcription factor, which is activated in hypoxia and closed down by normoxia or 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) NF-erythroid 2-related factor (Nrf2) is activated by hyperoxia and activates antioxidant response element (ARE) 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-κB 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) CCAAT/enhancer binding protein (CEBP) 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 oxidative stress because of its high content of unsaturated free fatty acids, which are easily exposed to peroxidation, the presence of free iron, low antioxidant enzymes, and vulnerable oligodendrocytes. A simultaneous exposure to inflammation will increase the oxidative stress even more.
2. Pre- and immature oligodendrocytes are especially vulnerable to hyperoxia and oxidative stress.
3. This vulnerability is probably time-dependent. The vulnerability of the rodent brain to hyperoxia seems to be confined to a short window postpartum, especially the first week of life. Whether such a vulnerable window exists in humans is not clear.
4. Microglia, which peak in white matter in the third trimester, when activated, generate free radicals and secrete cytokines.

B. Retina

1. The transition from intra- to extrauterine life increases oxygen tension and decreases VEGF not only in the retina but also in other tissues.
2. Angiogenesis in the retina of the immature baby is halted. However, after a few weeks, typically after 32 weeks' postconceptional age, the retina becomes hypoxic because of its increase in size without angiogenesis and consequently VEGF increases. This may lead to an uncontrolled vessel growth and development into stage II ROP (Chap. 84).
3. In order for VEGF to be active, insulin-like growth factor must reach a threshold level. Thus, the pathogenesis of ROP is complex, dependent on both hyperoxia and a number of other non-hyperoxic factors related to growth.
4. Several studies (NeoPROM), including one meta-analysis, strongly indicate that severe ROP can be significantly reduced by keeping the arterial oxygen saturation low 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 long period of time (days).
3. Hyperoxia-induced lung injury is also 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 caspase 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.
8. Hyperoxia has the potential to alter genomic activity via changes in DNA methylation and induce epigenetic changes in the lung with possible long-term consequences.
9. A recent meta-analysis of the NeoPROM studies indicates that BPD can be reduced by 20–25% by keeping arterial oxygen low.

III. Clinical implications
  A. Oxygen in the delivery room
    1. Term and late preterm infants. Recent international guidelines recommend starting resuscitation with air instead of supplemental oxygen. This is based on animal studies and 10 clinical human 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 by approximately 30 seconds, reduces the Apgar scores, and heart rate at 90 sec 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 non-healthy lungs (for instance, after meconium aspiration), oxygen supplementation may be needed, and no clinical data exist regarding optimal FiO_2 for such babies. 100% oxygen use impairs subsequent vasodilation with iNO, and high O_2 in combination with iNO may result in formation of peroxynitrite, so avoiding hyperoxemia may be as important as avoiding hypoxemia in the management of PPHN. In the rare event of the need of chest compressions (<1/1000 term or late preterm babies), the optimal initial FiO_2 is not known.
    3. If a pulse oximeter is available, arterial oxygen saturations (SpO_2) should be aimed to reach 80% within the first 5 minutes of life.
    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, advice, based on the limited data available, is to start ventilation with 21% or 30% oxygen and adjust FiO_2 to reach SpO_2 of 80% within 5 minutes of life.
    5. Hyperoxia and hypoxia are both involved in the development of neonatal diseases through contributing to increased mitochondrial ROS generation.
  B. Oxygen beyond the delivery room
    1. Term and late preterm babies should be weaned as quickly as possible, and this is often not difficult since their lungs are mostly mature.
    2. The optimal SpO_2 target of ELBW infants is not known. It is clear that especially severe ROP and also BPD (if defined as oxygen dependence at 36 weeks' PMA) are reduced by keeping the SpO_2 lower (85–89%) and avoiding fluctuations. On the other hand, recent data indicate that a low saturation target between 85% and 89% increases mortality and NEC compared with a higher target of 91–95%. Tight alarm limits are recommended in order to prevent fluctuations and hyperoxic peaks.

IV. Prevention of hyperoxia and hyperoxic injury
  A. The best prevention of oxidative stress injury of the newborn is to avoid hyperoxia and inflammation, especially the combination of these.
  B. Beta-carotene and vitamin A in one study were lower in preterm babies developing BPD. Postnatal vitamin A supplementation in the 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, and iNO has been linked to increased cancer risk.

E. A number of different antioxidants, such as allopurinol and erythropoietin, have been tested with some positive effects. Nutrients, such as omega-3 fatty acids, especially docosahexanoic 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 pre- and postnatally.

V. How to reduce hyperoxia/oxygen toxicity in the newborn
A. Early aeration of the lungs. Titrate O_2 and keep SpO_2 within the target ranges.
B. Late cord clamping/intact cord resuscitation contributes to earlier aeration, SaO_2 increase, and lower FiO_2.
C. Colostrum and breast milk (BM). The BM antioxidants are adapted to gestational age providing higher levels to infants with lower degree of maturation.
D. Lung ultrasound (LUS) <3 hrs. in newborns with RDS contribute to early identification of babies in need of surfactant treatment earlier than clinical signs alone and thereby reduced oxygen load.
E. Measure arterial PaO_2 in addition to SpO_2 in premature newborns to achieve the most appropriate FiO_2 for the specific child. NIRS is being investigated to measure tissue oxygenation index, TOI (in the brain, myocardium, and intestine).
F. Attenuation of oxidative damage after HI by targeting the deactivated mitochondrial complex I, which changes its conformation from active form (A) into the catalytically dormant deactive form (D). Reoxygenation may rapidly convert the D-form into the A-form and thereby increase ROS generation. Pharmacologically controlled gradual reactivation of complex I could therefore attenuate oxidative damage.

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8 Pulmonary Mechanics and Energetics

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

I. *Introduction*

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. 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. The only preventive measure is antenatal steroids, which will ameliorate both the structural and biochemical immaturity of the preterm lungs. Treatment mainly consists of respiratory support and exogenous surfactant. The basic aim is to restore pulmonary mechanics and FRC, thereby normalizing WOB and gas exchange. Bedsides, knowledge of respiratory physiology is key to select the optimal modality and level of respiratory support.

II. *Getting air in and out of the lung*

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 that requires a pressure difference between the airway opening and the alveolar space. 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 along the conducting airways. During mechanical ventilation, airflow is achieved by creating a positive airway pressure at the airway opening compared to ambient pressure outside the chest. The volume of air entering the lung as a result of the created pressure difference depends on the elastic and resistive properties of the respiratory system. Under normal conditions, exhalation is a passive process.

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III. *Elastic Properties*

A. *The elastic properties of the lung* parenchyma are dependent on 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 on 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 functional residual capacity.

C. *Pleural space*. 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 (i.e., the 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*

One way to characterize the elastic recoil forces of the lungs is to reconstruct a pressure-volume curve. Starting at residual lung volume, a known volume of air is stepwise injecting into the lungs in an incremental manner, until total lung capacity is reached. By simultaneously measuring the resulting airway pressure at each step, the inflation limb of the pressure-volume curve can be constructed. This usually contains a lower and an upper inflection point (Fig. 8.1). Between these points, the pressure-volume relationship is linear. By stepwise removing volume from the lung, the deflation limb of the pressure-volume curve, starting at total lung capacity, can be constructed. The deflation limb also has an upper inflection point (Fig. 8.1). 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. The volume difference between the inflation and the deflation limb at similar airway pressures is called lung hysteresis (Fig. 8.1). Elastic recoil forces will have a significant impact on the volumes and shape of the pressure-volume curves (Fig. 8.2).

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.

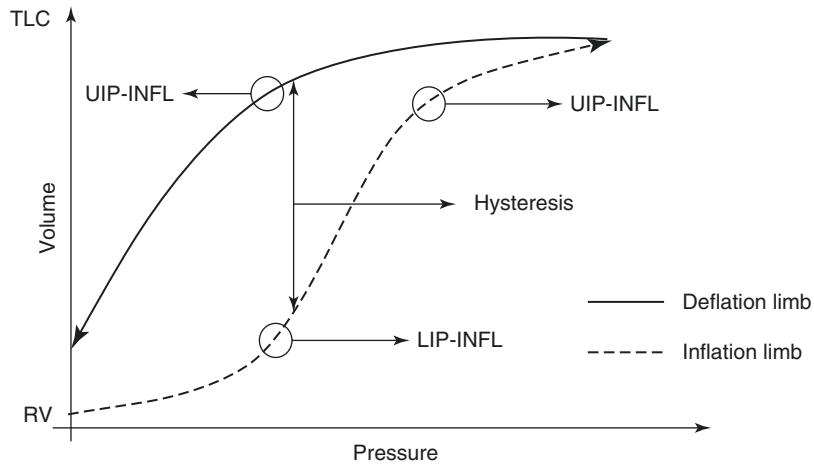

Fig. 8.1 Pressure-volume relationship of the lung inflated from residual volume (RV) to total lung capacity (TLC). Both the inflation limb (interrupted line) and the deflation limb (solid line) are displayed. Note the difference in lung volume between the inflation and deflation limb at similar pressures (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

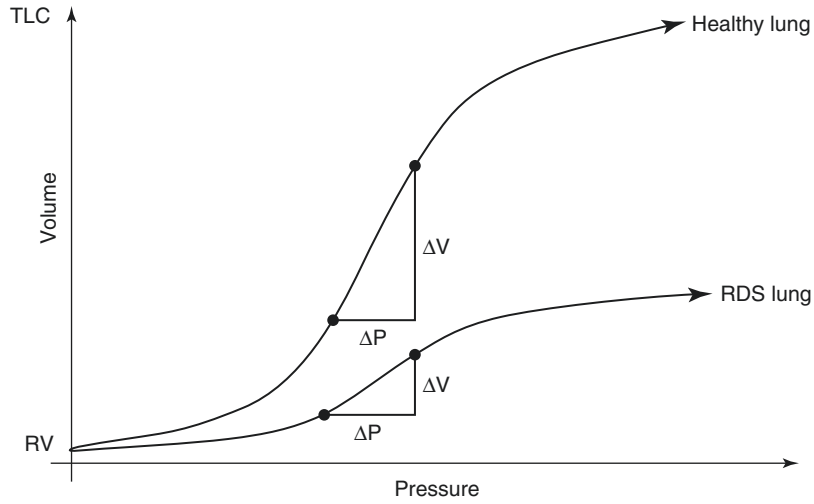

Fig. 8.2 The inflation limb of the pressure-volume relationship of a healthy lung and a surfactant deficient lung due to neonatal respiratory distress syndrome (RDS), inflated from residual volume (RV) to total lung capacity (TLC). Note the clear difference in shape and lung volumes. Per pressure unit,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

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

$$\text{Lung Compliance} = \text{change in lung volume} / \text{change in transpulmonary pressure}$$

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.

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.

2. 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 functional residual capacity. 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.
3. 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.
4. Lung compliance and pressure-volume relationships are determined by the interdependence of elastic tissue elements and alveolar surface tension. Tissue elasticity is dependent upon elastin and collagen content of the lung.
5. A typical value for lung compliance in a young healthy newborn is 1.5 to 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 FRC. This ratio is called the specific lung compliance. Specific compliance of a newborn infant is similar to that of an adult.
6. The surface-active substance (surfactant) 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 premature infants with respiratory distress syndrome (RDS), typically results in lungs that are stiff (low compliance) and prone to collapse (atelectasis) (Fig. 8.2).
7. 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.
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.
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 lower 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:

$$\text{Total Compliance} = \text{change in lung volume} / \text{change in transthoracic pressure}$$

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

$$\text{Elastance of the Respiratory System} = \text{Elastance of Lungs} + \text{Elastance of chest wall.}$$

this also means that

$$1 / \text{Total Respiratory System Compliance} = 1 / \text{Lung Compliance} + 1 / \text{Chest Wall Compliance}$$

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 (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. 8.3).
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 versus 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:

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

Therefore, resistance to airflow is defined as:

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

   4. Thus, the resistance to airflow increases by a power of four with any decrease in airway diameter.

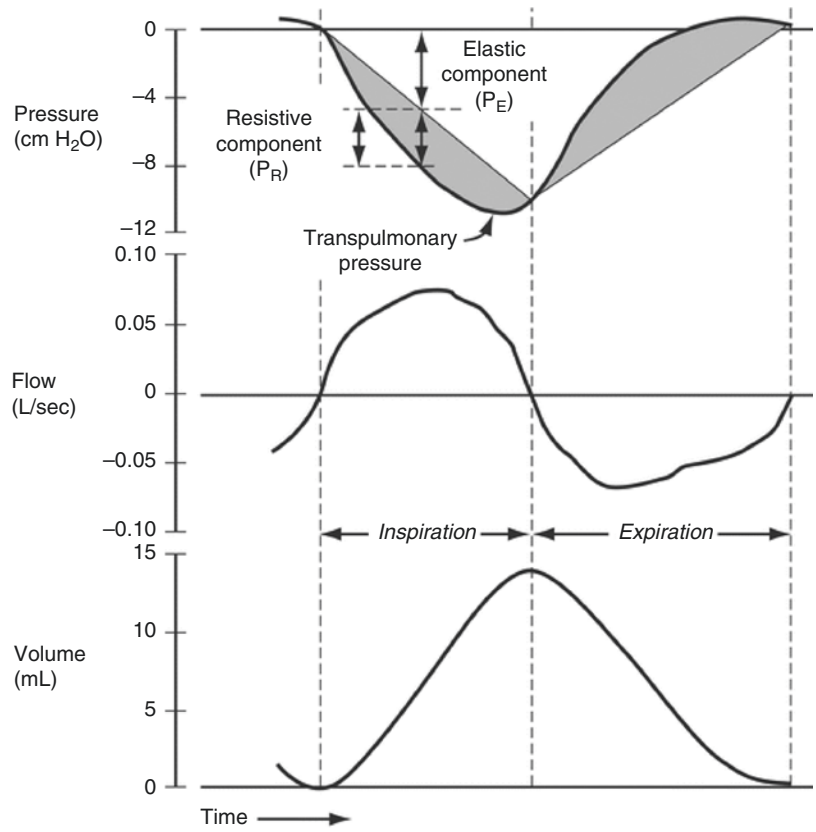

Fig. 8.3 The relative elastic and resistive components of transpulmonary pressure recorded from a typical single spontaneous breath. Pulmonary resistance is determined from simultaneous measures of the resistive component of pressure and the flow signal

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 to 40 cm H_2O/L/ sec (adults 1 to 2 cm H_2O/L/sec).

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 opposite 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.

VI. *Work of Breathing*

A. True work of breathing may be expressed as the energy required by the respiratory muscles to move 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:

$$\text{Work} = \int PV$$

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. 8.4). 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.
   2. The units of work of breathing correspond to the units of pressure times volume (cm H_2O•L), or equivalently, force times distance (kg•m), and is usually expressed the work per breath or respiratory cycle.

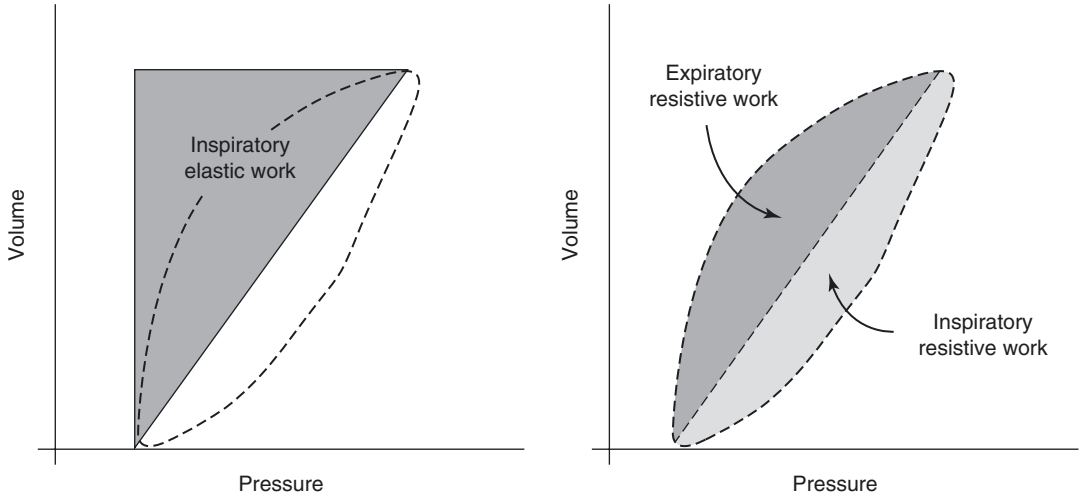

Fig. 8.4 Work of breathing is calculated as the area under the pressure versus volume curve (shaded areas)

VII. *Functional Residual Capacity*
- A. The volume remaining in the lungs after a normal passive expiration is called the FRC. In newborn infants, a normal FRC is estimated at 20–30 mL/kg.
- B. Preterm infants are prone for a low FRC, and this will have the following effects on lung physiology:
  1. Decreased compliance of the respiratory system.
  2. Increased airway resistance.
  3. Increased work of breathing.
  4. Increased intrapulmonary right-to-left shunt.
  5. Increased pulmonary vascular resistance.
  6. Impaired gas exchange.

VIII. *Select 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).
- D. 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 (Table 8.4).
- E. Pulmonary mechanics and energetics at term PMA of surviving infants with RDS who received surfactant replacement immediately after birth (Table 8.5).

Table 8.1 Calculated respiratory parameters

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

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

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

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 work (g cm/kg)	29 ± 19	29 ± 20	30 ± 19	25 ± 18

Suggested Reading

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9 Basic Principles of Mechanical Ventilation

Colm P. Travers, Waldemar A. Carlo, Namasivayam Ambalavanan, and Robert L. Chatburn

I. The ventilatory needs of a patient depend largely upon the mechanical properties of the respiratory system and the type of abnormality in gas exchange.
II. Pulmonary Mechanics
   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:

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

   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 (Fig. 9.1).
IV. Resistance
   A. Resistance describes the ability of the gas conducting parts of the lungs or respiratory system (including the chest wall) to impede airflow.

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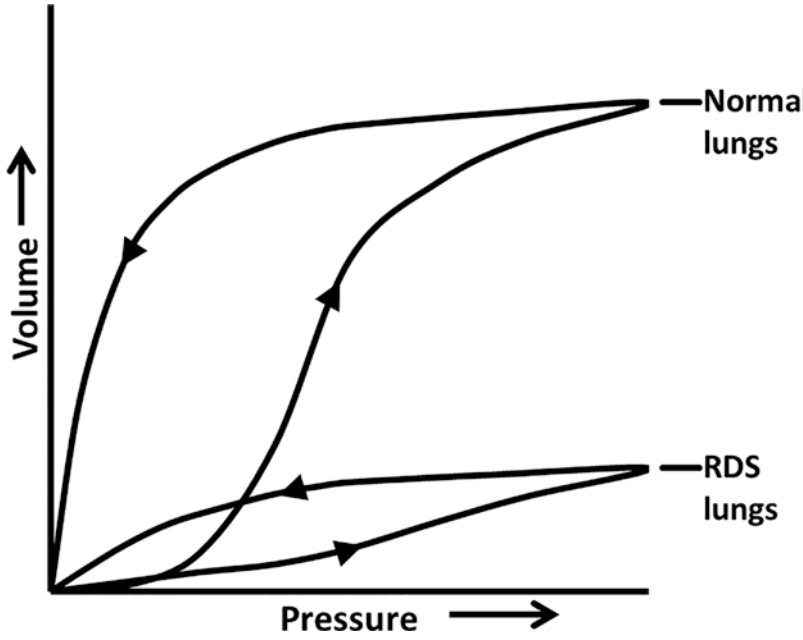

Fig. 9.1 Representation of pressure-volume relationship of the lungs for an infant with normal lung compliance and an infant with respiratory distress syndrome (RDS). The decreased lung compliance manifests as a decreased volume change for a given change in pressure

B. Pressure is needed to force gas through airways (airways resistance includes the nose, nasopharynx, larynx, trachea, and bronchi and accounts for approximately 55% of the total) and to exceed the viscous resistance of the lung tissue (tissue resistance from tissue moving against tissue accounting for 20% of the total) and chest wall (higher in neonates accounting for approximately 25% of the total).
C. It is calculated as follows:

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

D. Resistance in infants with normal lungs ranges from 25 to 50 cm H_2O/L/sec. Resistance is not markedly altered in infants with RDS or other acute pulmonary disorders but can be increased in infants with BPD.
E. Resistance can also be increased to 100 cm H_2O/L/sec or more by small endotracheal tubes. It is good practice to use appropriately sized endotracheal tubes and to cut tubes as short as practicable after insertion.

$$\text{Poiseuille's Law}: \text{Resistance} \propto L\eta / r^4$$
$$\left(L = \text{length}, \eta = \text{viscosity, and}\, r = \text{radius}\right)$$

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 stepwise changes in airway pressure (Fig. 9.2).

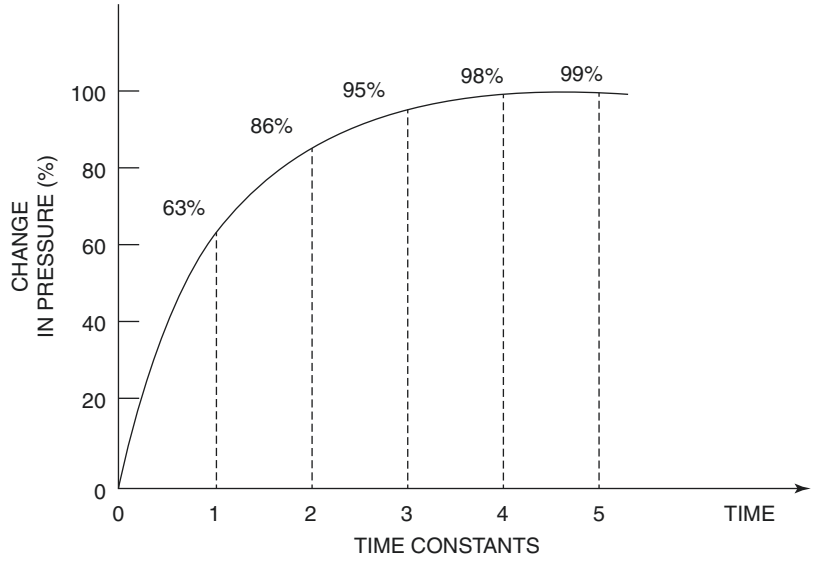

Fig. 9.2 Percentage change in pressure in relation to the time (in time constants) allowed for equilibration. As a longer time is allowed for equilibration, a higher percentage change in pressure will occur. The same rules govern the equilibrium for step changes in volume. Changes in pressure during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

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/sec, the time constant is calculated as follows:

$$\text{Time constant} = 0.002\,\text{L/cm}\,H_2O \times 40\,\text{cm}\,H_2O/\text{L/sec}$$

$$\text{Time constant} = 0.080\,\text{sec}$$

(Note that in the calculation of the time constant, compliance is not normalized to 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 airflow or volume change. Little further equilibration occurs beyond 3–5 time constants (Fig. 9.2). Thus, in the infant described above, inspiratory and expiratory duration should be around 240–400 msec each (or 0.24–0.4 sec).

D. The time constant will be shorter if compliance is decreased (e.g., in patients with RDS) or if resistance is decreased. The time constant will be longer if compliance is high (e.g., big infants with normal lungs) or if resistance is high (e.g., infants with BPD or airway obstruction).

E. Patients with a short time constant ventilate well with short inspiratory and expiratory times and higher 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).

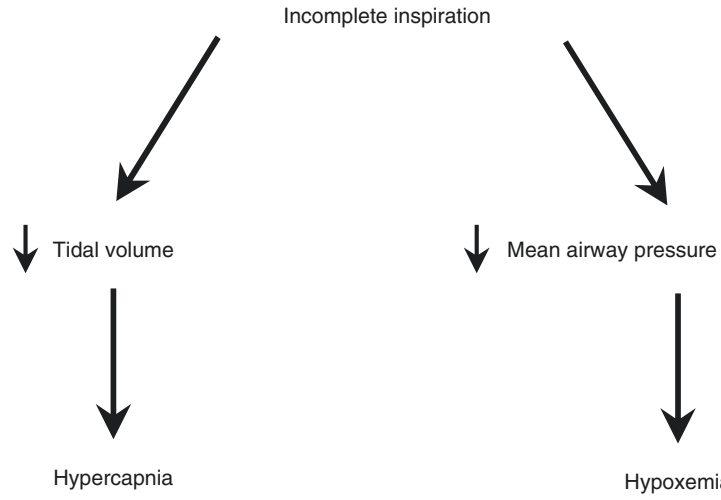

Fig. 9.3 Effect of incomplete inspiration on gas exchange. (From Carlo WA, Greenough A, Chatburn RL. Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH, editors. New therapies for neonatal respiratory failure: a physiologic approach. Cambridge: Cambridge University Press; 1994. p. 137, with permission)

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 (auto PEEP) (Fig. 9.4). The presence of auto PEEP decreases the driving pressure between airway opening and the alveoli, thus decreasing the tidal volume and potentially shifting the pressure-volume curve away from the PEEP of best compliance.

H. While the respiratory system is often modeled as being composed of a single constant compliance and resistance, it is known that lung mechanics vary with changes in the lung volume, differ from breath to breath, and even change somewhat between inspiration and expiration as resistance is higher during exhalation. In addition, in heterogeneous lung disease such as BPD, different areas of the lungs can have varying mechanical characteristics.

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. Inertance is a measure of the tendency of the respiratory system to resist changes in flow. In healthy adults and children, inertance is a minor component of the forces in the respiratory

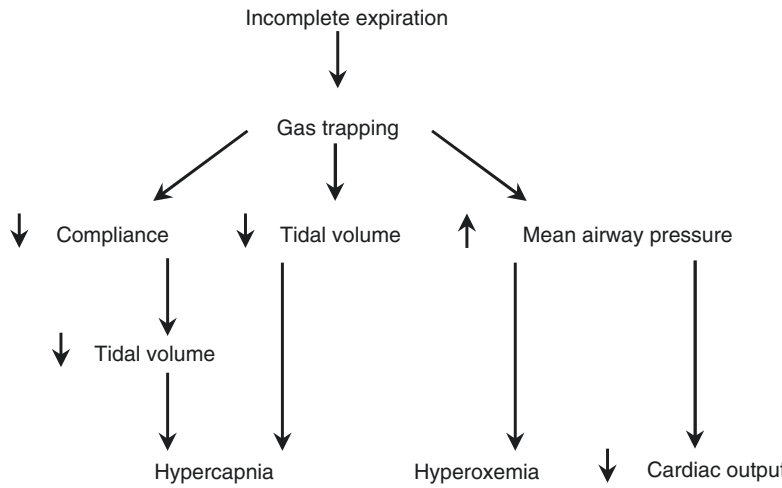

Fig. 9.4 Effect of incomplete expiration on gas exchange. (From Carlo WA, Greenough A, Chatburn RL. Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH, editors. New therapies for neonatal respiration failure: a physiologic approach. Cambridge: Cambridge University Press; 1994. p. 137, with permission

system. As the inertial component is small at physiologic flows, the last component (IV) can generally be neglected. However, it should be noted that inertance increases as ventilatory rates increase, as is more commonly seen in newborn infants.

C. The equation of motion above can be used to derive estimates of compliance and resistance. For example, between points of 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 msec during inspiration or expiration).

D. Reactance is a measure of the energy conservation in the respiratory system and includes the elasticity of the lung tissue (that determines lung compliance) and inertia in the airway tree and lung tissues to the forces of acceleration and deceleration of the air column.

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.
   - Low resistance placental circulation removed.
2. Pulmonary vascular resistance decreases.
   - Lung inflation causes reflex pulmonary vasodilation.
3. Pulmonary blood flow increases.
   - Patent foramen ovale functionally closes as left atrial pressure increases decreasing right to left shunting.
   - Oxygen exposure and nitric oxide production further dilate pulmonary blood vessels.
   - Higher oxygen levels assist PDA closure decreasing right to left shunting.

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 hours 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 x 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 as water vapor also exerts a partial pressure.

Partial pressure O_2 = fractional content x (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.

$$\text{Partial pressure of alveolar } O_2 = PiO_2 - PaCO_2\left(FiO_2 + \left[1 - FiO_2\right]/R\right)$$

where P_ACO_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 P_AO_2 = 713–40 = 673 mmHg

If FiO_2 is 0.21, then P_AO_2 = 0.21 × (760–47) – 40 × (0.21 + [1–0.21]/0.8) = 102 mmHg.

D. Practical examples of alveolar air equation:

1. Changing FiO_2: If the FiO_2 requirement changes, the CO_2 may also have changed.

For example, if the FiO_2 increases from 0.30 to 0.40 in an infant whose pCO_2 was 45 mmHg and assuming that the A-a DO_2 has not changed and the infant is at sea level, how high may the pCO_2 have increased to? The alveolar gas equation is used to determine the new P_ACO_2 (and pCO_2) as follows:

$$0.40 \times (713) - PaCO_2 / 0.8 = 0.30 \times (713) - 45 / 0.8$$
$$PaCO_2 = 0.8(285 - (214 - 56)) = 102\,\text{mm Hg}$$

Therefore, it is common practice to follow the CO_2 if there is an increasing FiO_2 requirement due to the potential of hypercapnia.

2. Changing altitude: If an infant moves from one altitude to a different altitude, the FiO_2 requirement may change as the barometric pressure changes.

   For example, what FiO_2 may be needed in a cabin (c) pressurized to 570 mmHg during air transport of an infant on FiO_2 = 0.3 at sea-level (s)? First, simplify the equation by solving as follows:

$$\begin{aligned}(Pc - PH2O)\,xFiO2c &= (Ps - PH2O)\,xFiO2s\\ FiO2c &= (760 - 47)\,x0.30 / 570 - 47\\ &= 214 / 523 = 0.41\end{aligned}$$

Therefore, infants may require additional supplemental oxygen to maintain partial pressure of oxygen during air transport in a pressurized cabin or when moving to a higher altitude.

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 (major component).

   Dissolved O_2 = 0.003 mL O_2 per mmHg of PaO_2

   Hemoglobin bound O_2 = O_2 Sat × 1.34/gm 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

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

C. CO_2 content of blood.

   CO_2 is carried in three forms: (1) as carbonic acid 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 mismatch, shunt, hypoventilation, and diffusion limitation (Figs. 9.5, 9.6, and 9.7):

A. Ventilation-perfusion ($\dot{V}/Q$) mismatch

   $\dot{V}/Q$ mismatch is an important cause of hypoxemia in newborns. Supplemental oxygen can largely overcome the hypoxemia resulting from $\dot{V}/Q$ mismatch by displacing nitrogen from the alveoli.

B. Shunt

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

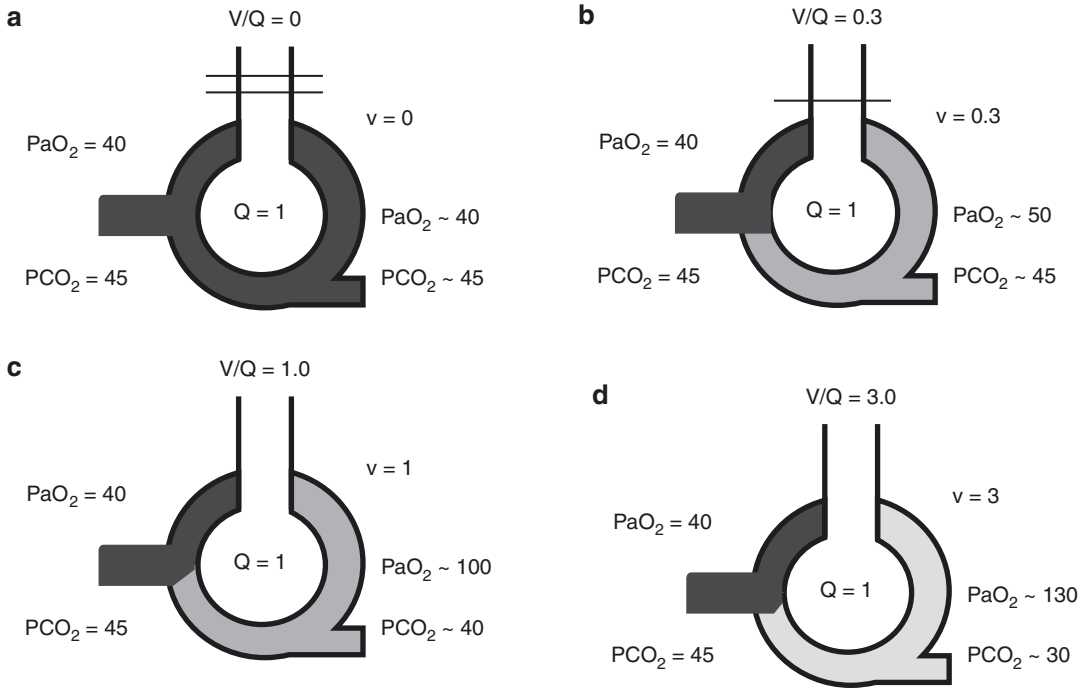

Fig. 9.5 Effects of various ventilation/perfusion ratios on blood gas tensions. (**a**) Direct venoarterial shunting ($V_A/Q = 0$). (**b**) Alveolus with a low V_A/Q ratio. (**c**) Normal alveolus. (**d**) Underperfused alveolus with high V_A/Q ratio

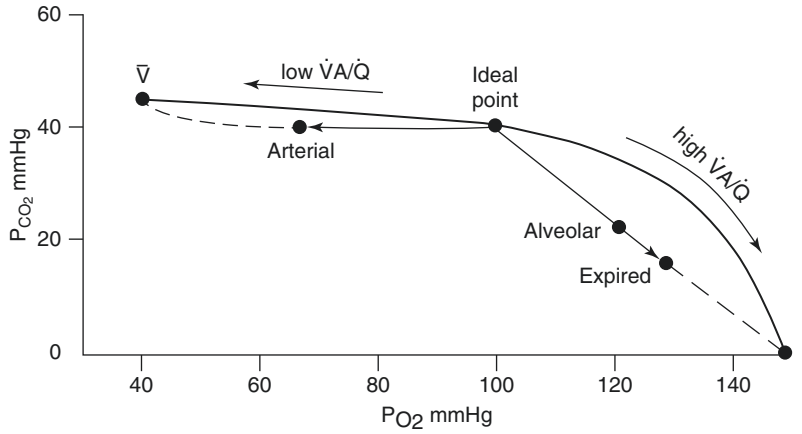

Fig. 9.6 O_2-CO_2 diagram showing the arterial, ideal, alveolar, and expired points. The curved line indicates the PO_2 and PCO_2 of all lung units having different ventilation/perfusion ratios. (From West JB. Gas exchange. In West JB, editor. Pulmonary pathophysiology: the essentials. Baltimore: Williams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

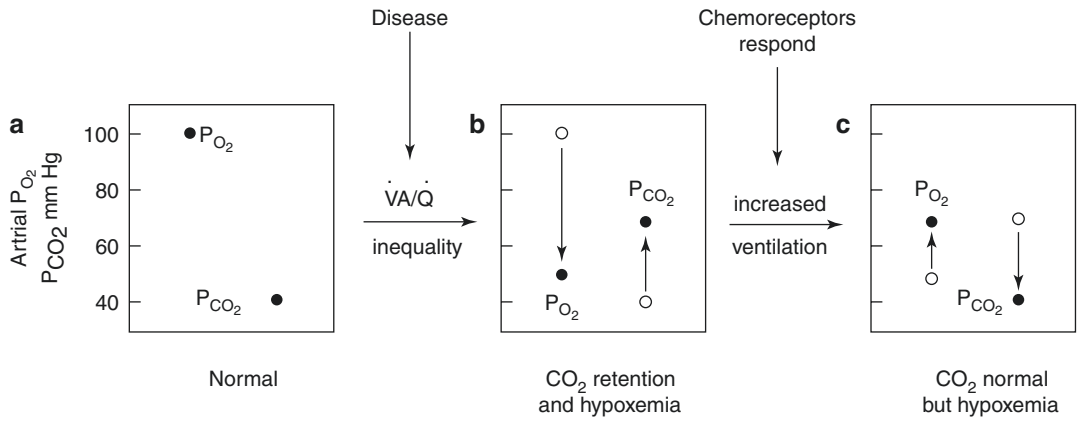

Fig. 9.7 PO_2 and PCO_2 in different stages of ventilation/perfusion inequality. Initially, there must be both a fall in oxygen and a rise in carbon dioxide tensions. However, when the ventilation to the alveoli is increased, the PCO_2 returns to normal, but the PO_2 remains abnormally low. (From West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

C. Hypoventilation

Hypoventilation results from a decrease in minute alveolar ventilation such that the metabolic consumption of oxygen exceeds the supply. Thus, alveolar PO_2 falls and PaO_2 decreases. It can be thought of as low $\dot{V}/Q$ and supplemental O_2 can overcome the hypoxemia easily (see alveolar air equation). Causes of hypoventilation include depression 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 in neonates, 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 blood flow to ventilated areas of the lungs (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 targeted modes, increasing any of the following will increase mean airway pressure: inspiratory flow (i.e., if it is adjustable and it indirectly decreases the pressure rise time), peak inspiratory pressure (PIP), the inspiratory to 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. Faster ventilator rates may also have an effect on mean airway pressure, as there are more "areas under the curve" in the same time interval.

D. Mean airway pressure maybe calculated as follows:

$$\textit{Mean airway pressure} = K\left(PIP - PEEP\right)\left[TI/\left(TI + TE\right)\right] + PEEP$$

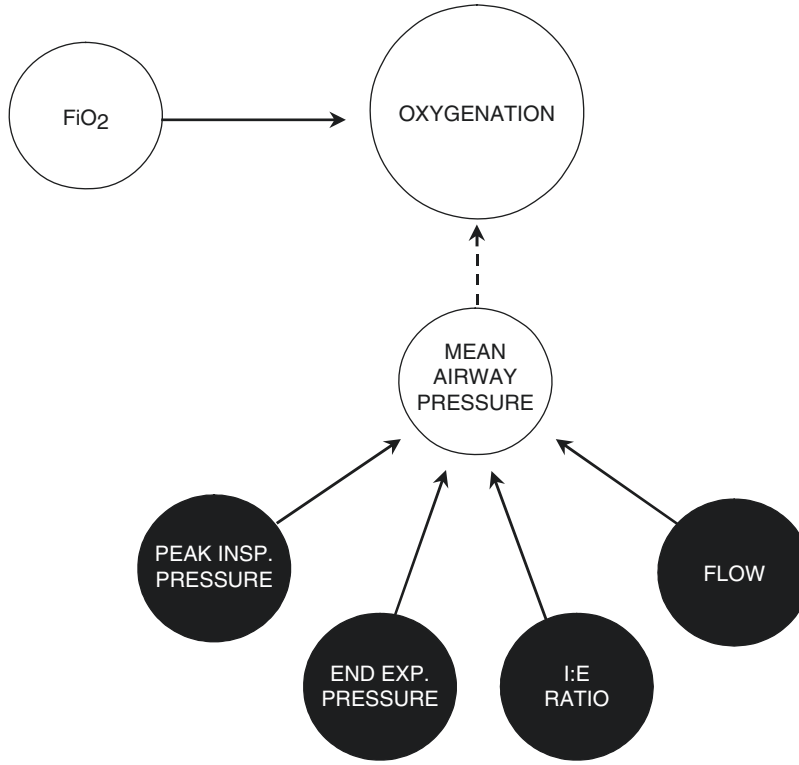

Fig. 9.8 Determinants of oxygenation during pressure-limited, time-cycled ventilation. Shaded circles represent ventilator-controlled variables. Solid lines represent the simple mathematical relationships that determine mean airway pressure and oxygenation, whereas dashed lines represent relationships that cannot be quantified. (From Carlo WA, Greenough A, Chatburn RL. Advances in mechanical ventilation. In Boynton BR, Carlo WA, Jobe AH, editors. New therapies for neonatal respiration failure: a physiologic approach. Cambridge: Cambridge University Press; 1994. p. 134, with permission)

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 to 0.9 during pressure targeted modes of ventilation); T_I is inspiratory time; and 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 across a patent ductus arteriosus or patent foramen ovale causing decreased pulmonary blood flow and decreased oxygen transport despite an adequate PaO_2.

XIV. Hypercapnia

The pathophysiologic mechanisms responsible for hypercapnia are $\dot{V}/Q$ 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 ventilation is calculated from the product of the frequency (number of breaths per minute) and the alveolar tidal volume (tidal volume minus dead space).

$$\text{Minute alveolar ventilation} = \text{frequency} \times \begin{pmatrix} \text{tidal volume} \\ \text{minus dead space} \end{pmatrix}$$

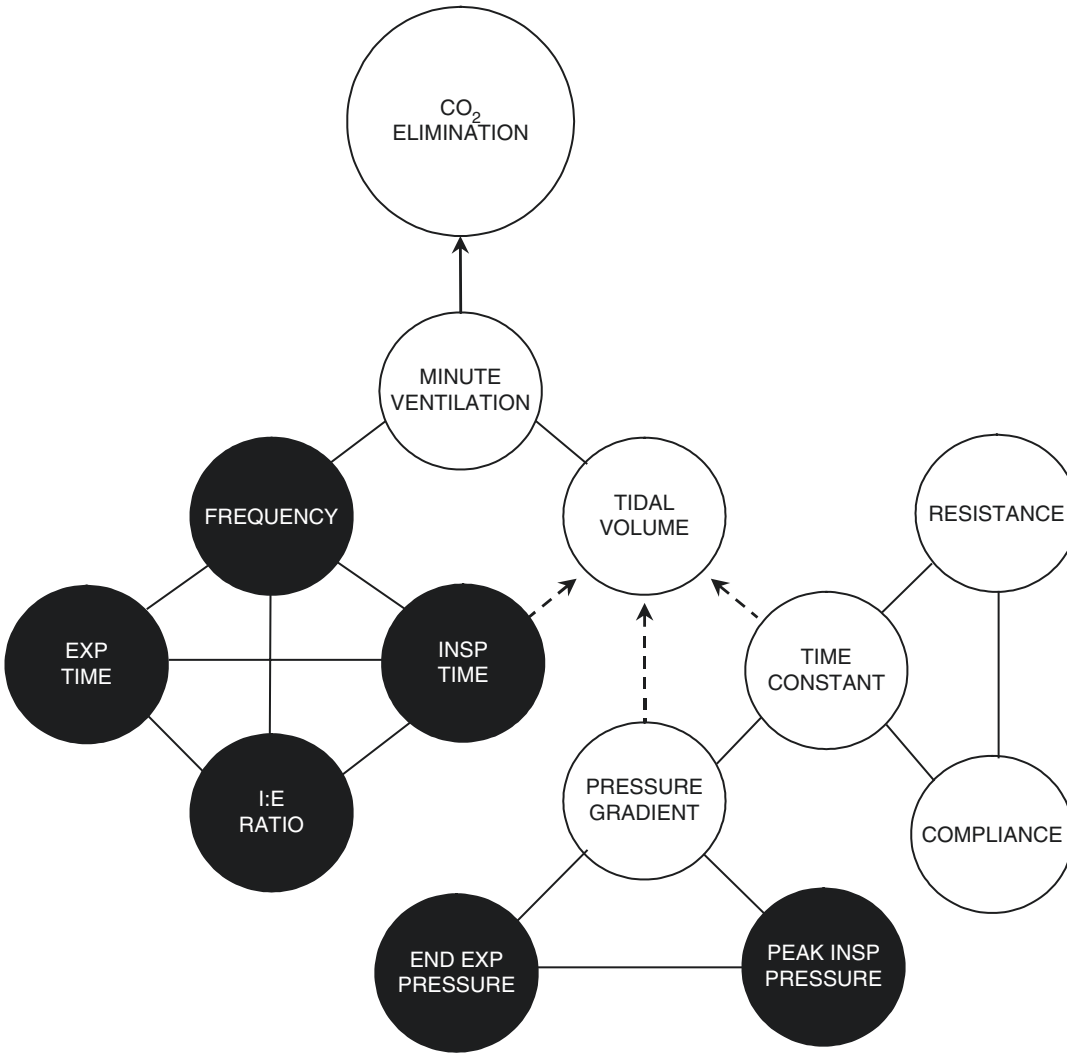

Fig. 9.9 Relationships among ventilator-controlled variables (shaded circles) and pulmonary mechanics (unshaded circles) that determine minute ventilation during time-cycled, pressure-limited ventilation. Relationships between circles joined by solid lines are mathematically derived. The dashed lines 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, editors. New therapies for neonatal respiration failure: a physiologic approach. Cambridge: Cambridge University Press; 1994. p.133, with permission)

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

B. During volume targeted ventilation (i.e., preset tidal volume and inspiratory flow), the desired tidal volume is preset. During pressure targeted 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 upon the time constant of the respiratory system (and the expiratory path of the patient circuit of the ventilator), an inspiratory time (T_I) that is too short may reduce the tidal volume, and an expiratory time (T_E) that is too short may cause gas trapping and inadvertent PEEP, thereby reducing 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.
E. Adequate PEEP prevents alveolar collapse and maintains lung volumes at end expiration. Mechanical ventilation without PEEP causes surfactant inactivation, decreased lung compliance, and atelectotrauma from recurrent shear forces from the 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 appropriate respiratory care (Table 9.1, Figs. 9.10 and 9.11, Chap. 20).

A. Respiratory acidosis (low pH, high $PaCO_2$, normal HCO_3).
   1. From $\dot{V}/Q$ mismatch, shunt, and/or hypoventilation.
   2. Secondary renal compensation begins within 6–12 hours.
      (a) Reduction in bicarbonate excretion.
      (b) Increased hydrogen ion excretion.

      Activation of alternative buffer systems may begin immediately (e.g., hemoglobin, albumin, globulin, and phosphate)
B. Respiratory alkalosis (high pH, low $PaCO_2$, normal HCO_3^-).
   1. From hyperventilation.

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	↑	↑	↑

From Carlo WA, Chatburn RL. Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL, editors. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers; 1988, p. 51, with permission

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

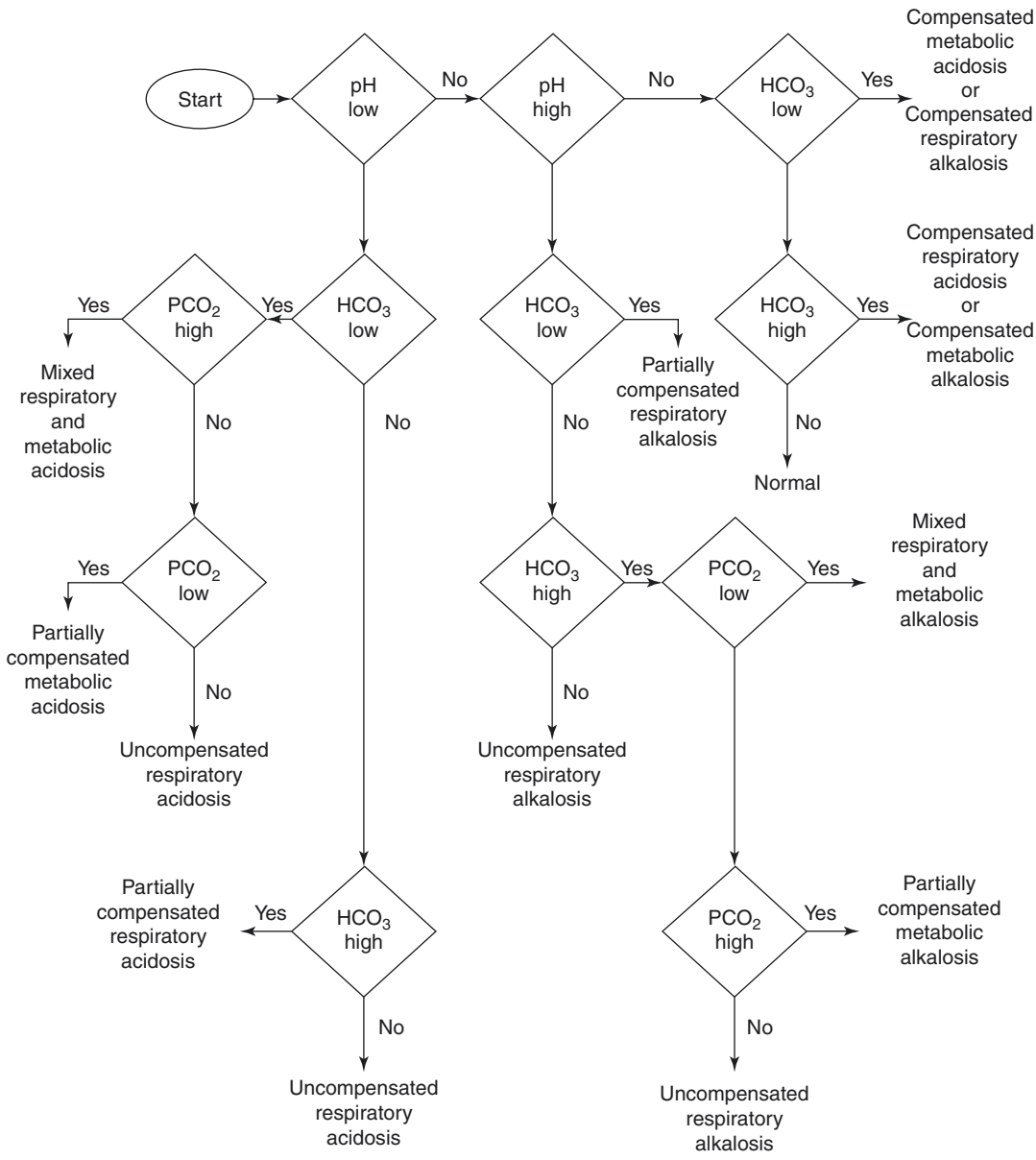

Fig. 9.10 A flow chart illustrating the algorithm through which a set of arterial blood gas values may be interpreted (From Chatburn RL, Carlo WA. Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL, editors. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers; 1998. p 56, with permission)

2. Secondary renal compensation begins within 6–12 hours.

   (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^-).

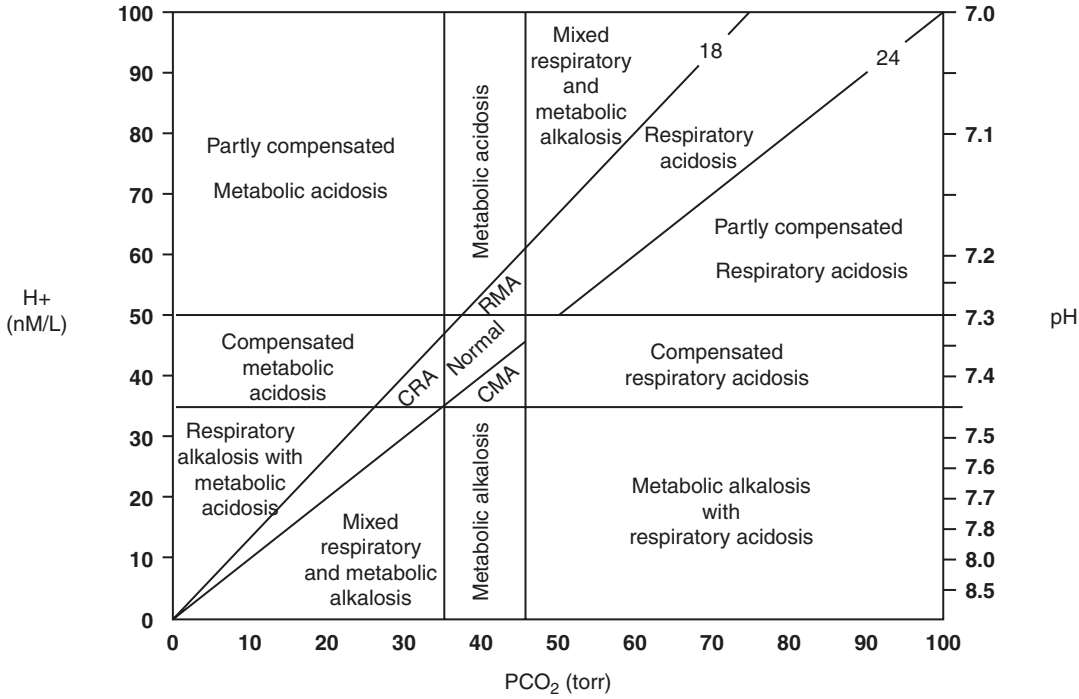

Fig. 9.11 A neonatal acid-base map. CRA compensated respiratory acidosis, CMA compensated metabolic acidosis, RMA mixed respiratory and metabolic acidosis. (From Chatburn RL, Carlo WA. Assessment of neonatal gas exchange. In Carlo WA, Chatburn RL, editors. Neonatal respiratory care. 2nd ed. Chicago: Year Book Medical Publishers; 1998. p 58, with permission)

1. From increased acid production (e.g., sepsis, inborn errors of metabolism) or intake (e.g., acidified human milk fortifiers), or excessive bicarbonate elimination (e.g., renal tubular acidosis, diarrhea).
2. Secondary pulmonary compensation may begin almost immediately – hyperventilation with decreased $PaCO_2$.
3. Activation of alternative buffer systems may begin immediately (e.g., hemoglobin, albumin, globulin, and phosphate).

D. Metabolic alkalosis (high pH, normal $PaCO_2$, high HCO_3^-)
1. From excessive $NaHCO_3$ or acetate administration, diuretic therapy, and loss of gastric secretions (e.g., gastric suctioning, emesis).
2. Secondary pulmonary compensation may begin almost immediately – hypoventilation with increased $PaCO_2$.

Suggested Reading

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Classification of Mechanical Ventilation Devices

10

Colm P. Travers, Waldemar A. Carlo, Namasivayam Ambalavanan, and Robert L. Chatburn

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) (Fig. 10.1). Microprocessor and sensor technology has increased the quality and quantity of ventilator output feedback available. These advances in the technology of targeting schemes warrant further classification.

II. Breath Control Variables. A modality 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 modality is pressure control. This includes modalities 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, then the control variable is volume.

A. Pressure control

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

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https://doi.org/10.1007/978-3-030-93997-7_10

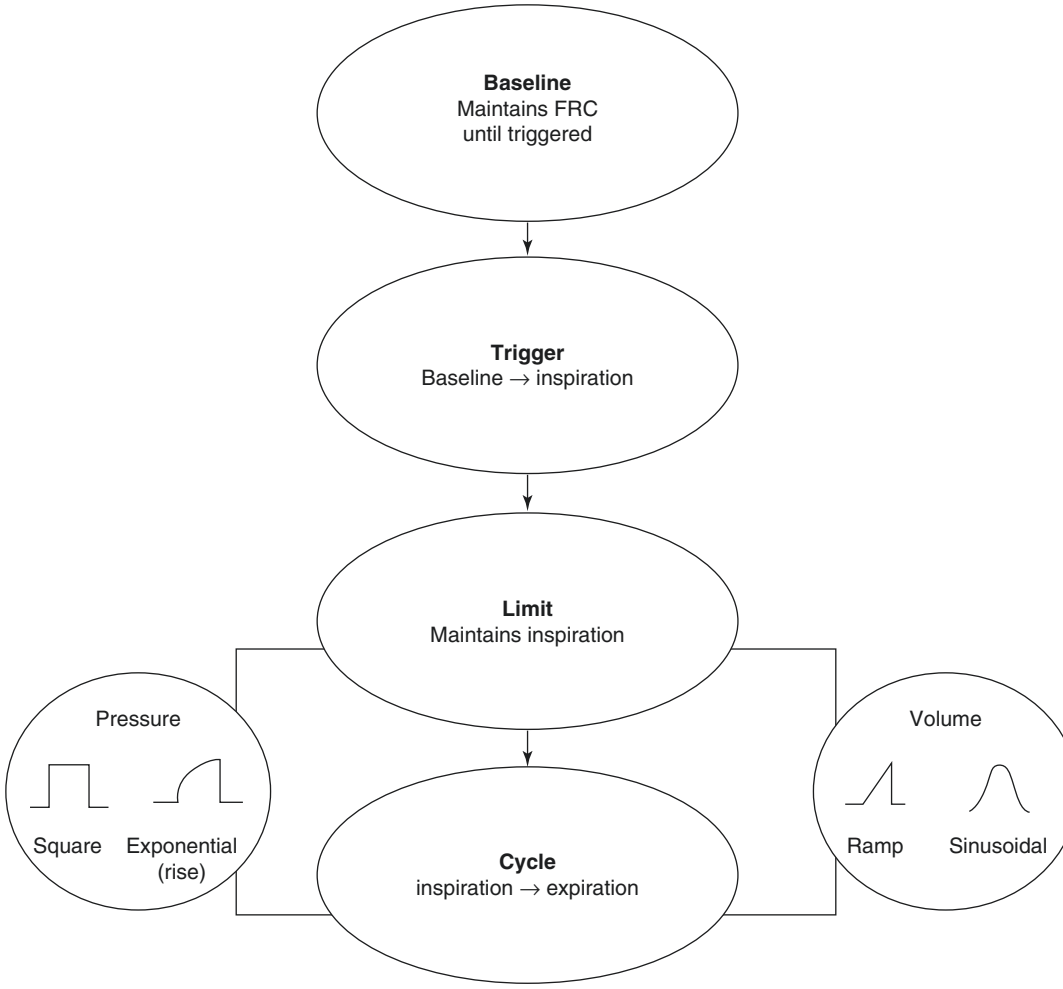

Fig. 10.1 Application of the equation of motion to the respiratory system. A common waveform for pressure and volume control is shown. Pressure, volume, flow, and time are also used as phase variables that determine the characteristics of each ventilator cycle (e.g., baseline pressure, trigger sensitivity, inspiratory time)

surface pressure (i.e., negative pressure ventilator); or (3) proportional airway pressure, making it rise proportional to inspiratory effort as sensed by the ventilator or the diaphragm (e.g., flow or electrical voltage). As the equation of motion above indicates, pressure is the independent variable, while volume and flow are dependent variables whose values are determined by elastance (or compliance) and resistance. Pressure control requires careful attention to changes in compliance through assessments of delivered volumes and chest rise.

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 the integral of flow) are the independent variables, and hence airway pressure depends on elastance (or compliance) and resistance. Control of tidal volume can be useful in circumstances of rapidly changing lung mechanics. Volume control is reliant upon the accuracy of flow sensors and requires careful attention to changes in chest rise and delivered pressures.

C. Time control

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

III. Cycle Control 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 cycle is determined by the patient independent of any ventilator settings. Spontaneous breaths may be assisted (as in pressure support) or unassisted. With mandatory breaths, the entire cycle is determined by the ventilator independent of the patient. 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) reach a preset threshold.
2. Trigger events may be either patient-initiated (spontaneous) or ventilator-initiated (mandatory).
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 flow (i.e., when a pre-defined flow is detected, the ventilator is triggered to assist). Pressure may also be used as a trigger (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-

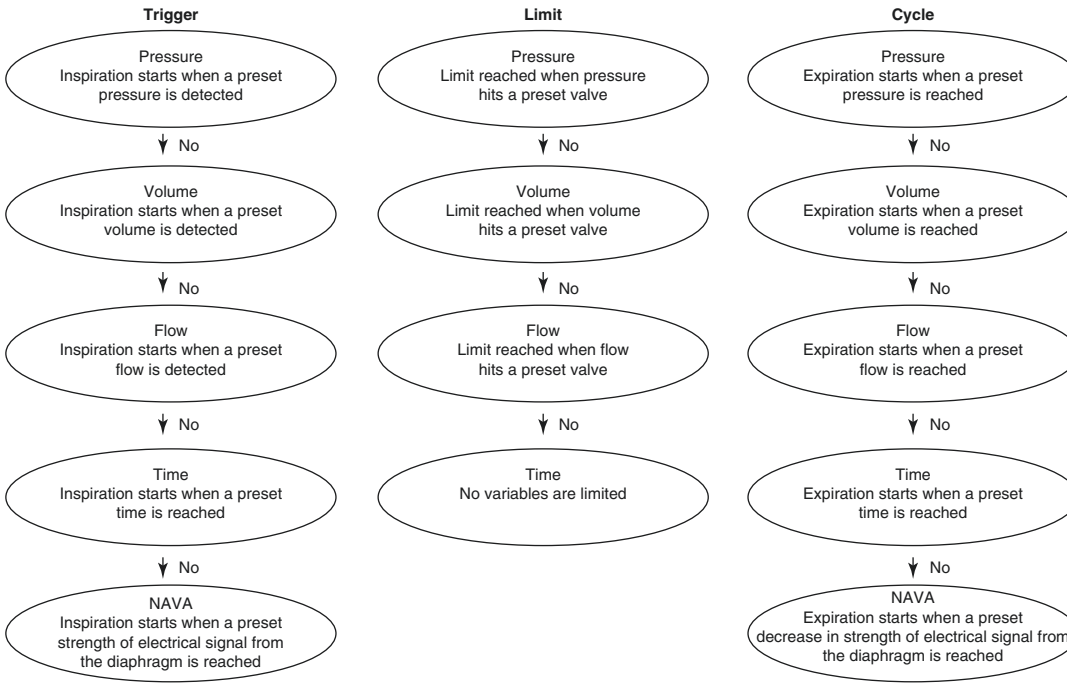

Fig. 10.2 Criteria for determining the phase variables during a ventilator-supported breath. This emphasizes that each control variable may have a different set of control and phase variables, depending on the mode of ventilation desired

triggering involves less patient effort and is more commonly used in infant ventilators. Neurally adjusted ventilatory assist (NAVA) triggers a ventilator breath by monitoring electrical signals from the diaphragm. NAVA is becoming more common as a trigger variable in infants.

B. Limit
   1. Pressure, volume, and flow increase during inspiration.
   2. A limit variable restricts the inspiratory increase to a preset 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 preset threshold.
   2. Cycling events may be either patient-initiated (i.e., by detecting changes in flow, pressure, or electrical signals from the diaphragm) or ventilator-initiated (i.e., based on the set inspiratory time or cycle time).
   3. Many neonatal ventilators, including high-frequency ventilators, are time-cycled (ventilator-initiated).

D. Baseline

E. The baseline variable maintains expiratory pressure and expiratory lung volume (e.g., positive end expiratory pressure on conventional ventilators or mean airway pressure on high-frequency oscillators).

IV. Targeting Variable

A target is a predetermined goal of ventilator output. The targeting variable describes the relationship between the selected ventilator settings and the ventilator output as detected by feedback control systems. Targets can be set between-breaths (i.e., end-tidal CO_2) or within-breaths (i.e., tidal volume). Within each ventilatory modality, there are also several targeting schemes that can be distinguished although some ventilators use more than one targeting scheme. The currently available targeting variables 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. This is the most common modality used in pressure control and time control ventilation.

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). This is the modality used by NAVA and proportional assist.

D. Adaptive (a)

   Ventilator automatically sets one target (pressure) in order to achieve another monitored target (volume). This is the most common modality used in volume control ventilation.

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.

V. Ventilatory Mode Classification

A. Because neonatal ventilators now offer dozens of modes and sometimes different names for similar modes, it is helpful and necessary to have a classification system (taxonomy) to understand ventilator modes and capabilities. Modes are classified using three basic characteristics (Fig. 10.3). First is the control variable (i.e., pressure-control or volume control as described above). Second is the cycle variable 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 this classification system is the targeting variable (as described above), which adds detail that allows us to distinguish between similar modes. Thus, to classify a mode, we specify the control variable, the cycle variable, and the targeting variable.

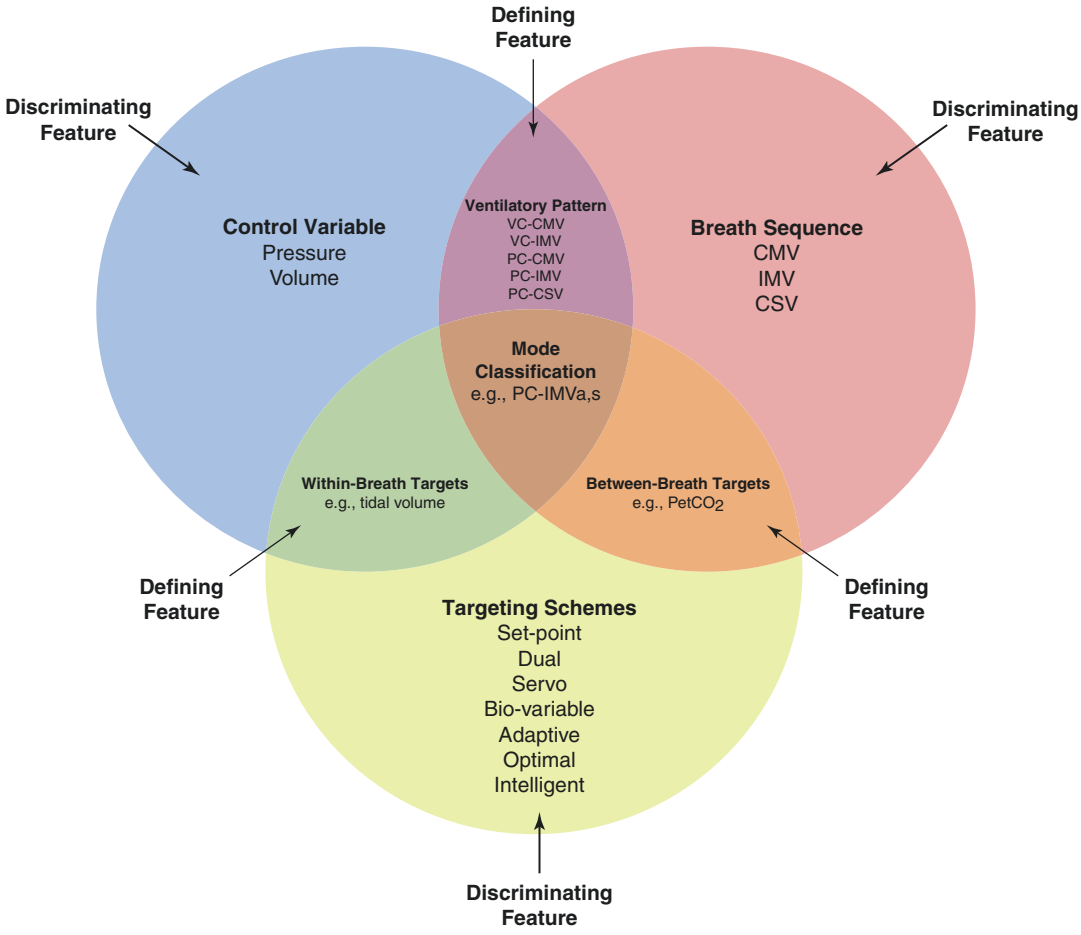

Fig. 10.3 Venn diagram illustrating how the mode taxonomy can be viewed in terms of discriminating features and defining features. (From Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. Respir Care. 2014;59(11):1747–63, with permission from 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

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

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

B. For example, the most common mode of ventilation used among neonates has historically been called “time-cycled pressure-limited.” Formally, this was classified as pressure control intermittent mandatory ventilation with set-point targeting, appreciated as PC-IMVs. More recently, the commonly used “synchronized intermittent mandatory ventilation + pressure support” is classified as PC-IMVs. Using the above classification system, high-frequency oscillatory ventilation would be classified as time control continuous mandatory ventilation with set-point targeting or TC-CMVs, and high-frequency jet ventilation would be classified as pressure control continuous mandatory ventilation with set-point targeting or PC-CMVs. NAVA ventilation may be classified as pressure control continuous spontaneous ventilation with servo targeting or PC-CSVr. “Patient-triggered ventilation” or “assist control” can use either pressure or volume control and is classified as continuous mandatory ventilation with either set-point (PC-CMVs) or adaptive targeting (VC-CMVa) respectively. “Volume guarantee” or “pressure regulated volume control” may be classified as pressure-control intermittent mandatory ventilation with both adaptive and set-point targeting or PC-IMVa,s.

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Ventilator Parameters

11

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I. Peak Inspiratory Pressure (PIP)
   A. Physiological effects
      1. PIP (peak inspiratory pressure relative to atmospheric pressure) in part determines the pressure gradient between the onset and end of inspiration (ΔP = PIP–PEEP) and thus, affects the tidal volume and minute ventilation.
      2. If tidal volume is not measured, PIP can be selected based on observation of the chest wall movement. If tidal volume is measured by a flow sensor that is remote from the patient, the tidal volume can be estimated by subtracting the volume detected in the circuit during brief clamping of the endotracheal tube from the measured volumes.
   B. Gas exchange effects
      1. An increase in PIP will increase tidal volume, assuming lung compliance remains unchanged, and thus increases CO_2 elimination.
      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. In pressure-targeted ventilation, it is important to adjust PIP based on lung compliance and ventilate with relatively small tidal volumes (e.g., 4–6 mL/kg) while avoiding excessive chest rise. Adjustment of PIP is particularly important in the setting of rapidly changing lung compliance (e.g., after surfactant treatment).

II. Tidal Volume
   A. Physiologic effects
      1. Tidal volume, in part, determines the minute ventilation (MV = $f \times V_T$). However, tidal volume (V_T) is affected by dead space volume (V_D), such that alveolar ventilation (AV) = f

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$\times (V_T - V_D)$. In addition, impairment of gas exchange increases the physiologic dead space. The dead space volume is relatively higher among infants with respiratory distress syndrome and bronchopulmonary dysplasia as they have impaired gas exchange. Dead space volumes may be further increased by the use of proximal flow sensors or other devices, such as capnometers.

2. During volume-targeted ventilation, an increase in tidal volume corresponds to an increase in PIP during pressure ventilation.

B. Gas exchange effects
1. An increase in tidal volume will increase ΔP, assuming lung compliance remains unchanged, and thus increase CO_2 elimination.
2. An increase in tidal volume will increase mean airway pressure and thus improve oxygenation.

C. Side effects
1. Ventilator-induced lung injury may be caused primarily by excessive tidal volume delivery (volutrauma) and lung overdistention rather than high PIP in the absence of excessive tidal volumes (barotrauma).
2. In volume-targeted ventilation, the targeted tidal volumes can be adjusted to simulate chest rise seen during spontaneous breathing (e.g., 4–6 mL/kg). During pressure-regulated volume control (PRVC), it is important to set a P_{Max} (maximum PIP allowed) approximately 3–5 cm H_2O above baseline delivered PIP in order to alert the care team to a change in clinical status and to avoid barotrauma/volutrauma secondary to flow sensor malfunction.

III. Positive End-Expiratory Pressure (PEEP)

A. Physiologic effects
1. PEEP, in part, determines lung volume at the end of the expiratory phase (functional residual capacity or FRC), prevents alveolar collapse, and improves ventilation/perfusion matching.
2. PEEP contributes to the pressure gradient between the onset and end of inspiration (ΔP = PIP–PEEP) and thus affects the tidal volume and minute ventilation.
3. A minimum "physiologic" PEEP of 2–3 cm H_2O should be used in most newborns to improve lung compliance and reduce the risk of atelectotrauma 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, usually improves ventilation/perfusion matching and oxygenation in patients whose disease state reduces expiratory lung volume.
2. An increase in PEEP will increase mean airway pressure, which may improve oxygenation in patients with respiratory distress syndrome.
3. The lowest pulmonary vascular resistance as well as the best lung compliance is found when the lung is neither under- nor overinflated. Optimal PEEP maximizes lung compliance and may allow the use of lower peak pressures to achieve the same tidal volume. Optimal PEEP also maximizes oxygenation for a given mean airway pressure.
4. Higher PEEP (7–9 cm H_2O) after extubation may reduce the risk of reintubation among preterm infants on nasal continuous positive 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. Higher PEEP has been associated with an increased risk of pneumothorax in surfactant-deficient lungs.

3. A very high PEEP may increase pulmonary vascular resistance and decrease cardiac output and oxygen transport.

IV. Frequency (or Rate)

A. Physiologic effects

1. The ventilator frequency (or rate), in part, determines minute ventilation ($MV = f \times V_T$) and thus, CO_2 elimination. Ventilation at high rates (≥60/min) may improve synchronization 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 noncompliant lungs (respiratory distress syndrome) tend to breathe faster to minimize work. When the spontaneous respiratory rate is low, excessive work is required by the respiratory muscles to overcome lung and chest wall elastic forces and to achieve larger tidal volumes. Therefore, more metabolically efficient alveolar ventilation can be achieved by increasing the respiratory rate rather than increasing the tidal volume.

B. Gas exchange effects

1. 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.
2. The relationship between frequency and CO_2 removal is relative to the baseline ventilator rate. The same absolute increase in the ventilator frequency among infants on higher rates and lower tidal volumes may not impact minute ventilation and CO_2 removal as would an increase in the ventilator rate at lower frequencies. Gas trapping may also increase the dead space at very high rates, thereby decreasing alveolar ventilation.

$$\Delta V_A = \left(V_T - V_D\right) \times \left(\Delta f\right)$$

For example, going from a rate of 20 to 30 breaths per minute leads to a 50% relative increase in alveolar ventilation: Baseline V_A = (4–2) × 20 = 40 mL/min and new V_A = (4–2) × (30) = 60 mL/min. Going from a rate of 120 to 130 breaths per minute leads to an 8% relative increase in alveolar ventilation: Baseline V_A = (4–2) × 120 = 240 mL/min and new V_A = (4–2) × (130) = 260 mL/min.

In contrast, increasing the volume by 1 mL/kg has a relatively similar impact on alveolar ventilation that is independent of the frequency: new V_A = (5–2) × 20 = 60 mL/kg or a 50% relative increase in alveolar ventilation and new V_A = (5–2) × 120 = 360 mL/min or a 50% relative increase in alveolar ventilation assuming dead space is constant.

C. Side effects. Use of very high ventilator frequencies may lead to insufficient inspiratory time and decreased tidal volume. In addition, very high ventilator frequencies may lead to insufficient expiratory time and gas trapping, which can negatively affect ventilation by decreasing lung compliance especially in infants with long time constants (bronchopulmonary dysplasia). Gas trapping generates auto-PEEP that decreases the pressure gradient between the airway opening and the lungs during pressure-targeted ventilation, thus decreasing V_T.

V. 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 times constants allows relatively complete inspiration.
3. T_I of 0.2–0.5 s is usually adequate for newborns with respiratory distress syndrome.

4. Infants with a long time constant (e.g., bronchopulmonary dysplasia) 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 increases the risk of pulmonary gas 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.
4. It is important to monitor pulmonary graphics and measured PEEP (available on most modern ventilators) for evidence of incomplete inspiration and expiration and adjust the T_I and T_E accordingly. This also allows selection of optimal ventilator frequency – the highest ventilator rate at which inspiration and expiration are completed.

VI. Inspired Oxygen Concentration (F_iO_2)

A. Physiologic effects
1. Changes in F_iO_2 alter alveolar oxygen pressure and thus, oxygenation.
2. Because both F_iO_2 and mean airway pressure determine oxygenation, the most effective and less adverse approach should be used to optimize FiO_2.
3. When F_iO_2 is above 0.6–0.7, increases in mean airway pressure are generally warranted.
4. When F_iO_2 is below 0.3–0.4, decreases in mean airway pressure are generally preferred.

B. Gas exchange effects. F_iO_2 directly determines alveolar PO_2 and thus PaO_2.

C. Side effects. A very high F_iO_2 can damage the lung tissue, but the absolute level of F_iO_2 that is toxic in infants has not been determined.

VII. Flow

1. Inspiratory flow is directly set during volume targeted modes. The higher the flow for a given V_T, the shorter the T_I.
2. Inspiratory flow is indirectly set during pressure-targeted modes and is a function of the set ΔP and the pressure rise time (during pressure control or pressure support), 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 preset constant flow through a pressure pop-off valve. This is referred to as "time-cycled pressure-limited" ventilation. At least one modern ventilator (AVEA, Vyaire Medical) still offers this modality. In this scenario, changes in the preset 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 Ti to maintain adequate flow for complete inspiration.
6. Excessive flow may contribute to turbulence, inefficient gas exchange, and inadvertent PEEP.

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

IX. Suggested Management Algorithm for RDS (Table 11.2 and Fig. 11.1).

Table 11.1 Desired blood gas goal and corresponding ventilator parameter changes ventilator parameter change

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

Table 11.2 Abbreviations and symbols used in the flowchart in figure

CO_2	Arterial carbon dioxide tension (mm Hg)
O_2	Arterial oxygen tension (mm Hg)
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 mm Hg

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

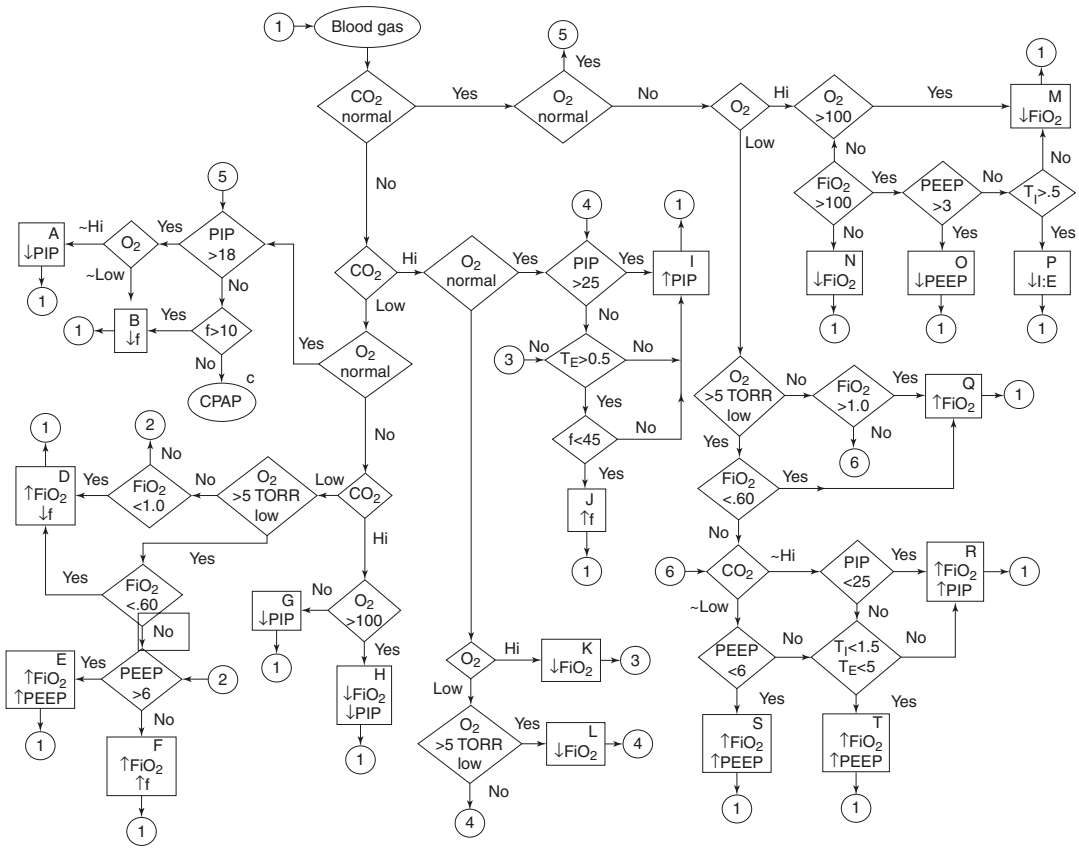

Fig. 11.1 Flowchart illustrating simplified version of ventilator algorithm. Symbols: I, calls for decisions; O, type and direction of ventilator setting changes. Abbreviations: CO_2, arterial carbon dioxide tension (mm Hg); O_2, arterial oxygen tension (mm Hg); FiO_2, fraction of inspired oxygen; PIP, 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

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Respiratory Gas Conditioning and Humidification

12

Andreas Schulze

I. Introduction
   A. Moisture depletion of the airway mucosa may lead to adverse effects 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, respiratory and systemic infection, and chronic lung disease.
      3. Heat loss.
   B. Humidifier malfunction may also impose risks.
      1. Flushing of contaminated condensate from the humidifier circuitry 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 (HMEs), may become clogged with water and secretions).
II. Structure and function of the airway lining tissue layers.
   A. Anatomy: 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

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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.

B. Physiology: 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 bypassed (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 mm Hg when air is fully saturated (100% relative humidity) at 37 ° C. This corresponds to 44 mg of water per liter (L) of gas (absolute humidity).
      (a) Absolute humidity (AH) is defined as the amount of water vapor (mg) per gas volume (L). 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.
      (b) 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,

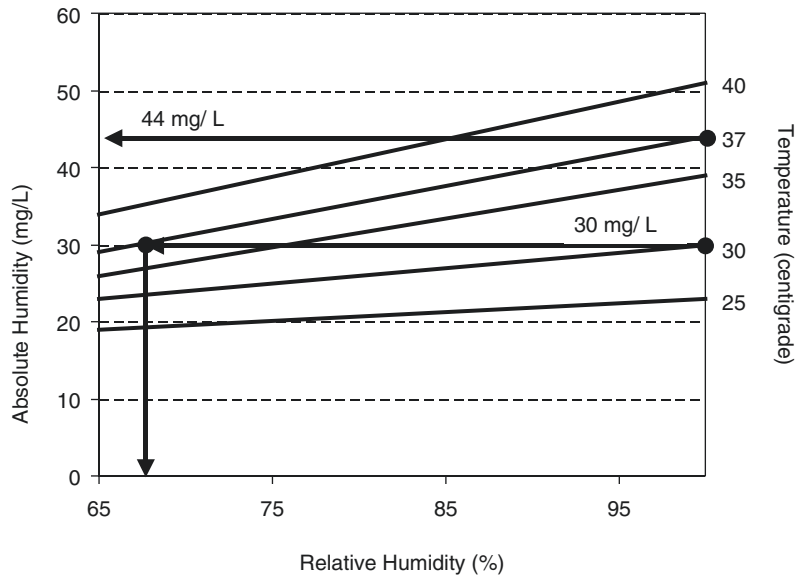

Fig. 12.1 Relationship between absolute humidity, relative humidity, and temperature of gases. The relative humidity depends on the absolute water content and the temperature of the gas. At 37.0 ° C and 100% relative humidity (BTPS, alveolar conditions), the respiratory gas has 44 mg/L absolute water 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 dry-heated to 37.0 °C, its relative humidity will fall to below 70%

vaporization consumes much energy, and thus vaporization of water from the airway lining 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. International standards and rational considerations on target levels of humidification.

A. Medical-grade compressed gases from cylinders or central supply systems have virtually negligible water content. Their temperature is below ambient temperature after decompression.

B. Standards on *minimum* required humidity levels to be provided with artificial respiratory support techniques were published separately for the UK and the USA: 33 mg H_2O/L and 30 mg H_2O/L, respectively. The International Organization for Standardization (ISO) stipulates that a minimum of 33 mg H_2O/L has to be provided at the patient connection port during invasive ventilation with the upper airway bypassed. The minimum requirement for noninvasive ventilation was defined at 12 mg H_2O/L.

C. The *optimum* level of respiratory gas humidity and temperature at the entry point to the natural human airway remains under discussion. It has not been specified for newly born infants in general or for their subgroups or disease entities. This is due in part to a paucity of evidence from clinical trials on the issue. It is rational, however, and acknowledged by ISO, to possibly avoid any additional necessity to provide heat and humidity from an endangered airway to bring up the inspired gas to BTPS conditions (e.g., alveolar conditions). Therefore, breathing gases should be delivered with a humidity as close to 44 mg H_2O/L as possible at body temperature. This strategy is particularly relevant during resuscitation, initial stabilization, and invasive mechanical respiratory support of premature infants in order to protect their lungs. It may help to avoid hypothermia.

D. The nasal cavity and pharynx are continuously purged due to inevitable leaks around nasal prongs or masks in infants during noninvasive positive airway pressure support modalities (high-flow nasal cannula therapy (HFNCT), CPAP, noninvasive mechanical ventilation). In addition, mouth leaks during positive upper airway pressure induce an *unidirectional* flow from the nasal cavity through the pharynx. Similarly, unidirectional leak flows occur with uncuffed endotracheal tubes along the intubated trachea. Such leak flow flushes the entire upper airway region. The leak flow rate increases with higher airway pressures. Whenever the respiratory gas is delivered to the infant at less than full water vapor saturation at 37 °C, it will have a capacity to cool and dry out this region. Gas delivery at or close to BTPS conditions is therefore necessary.

E. The MR850 heated humidifier (Fisher & Paykel Healthcare, New Zealand) attempts to saturate the gas mixture with water vapor at 37 °C only if "invasive mode" is chosen. Less humidity is provided with the "noninvasive" option assuming that the non-instrumented upper airway preserves its natural heat and moisture conserving capacity in adults. The manufacturer advices users to drive the device in the "invasive" mode *in infants undergoing noninvasive respiratory support*.

V. Inspired gas conditioning devices and procedures.

A. Devices are classified as active, passive, or hybrid humidifiers based on the external provision of heat and water or the utilization of moisture from the expired air ("artificial noses," also called Heat and Moisture Exchangers, HMEs). Hybrid humidifiers are HMEs with a small integrated heater. This latter type is currently not commercially available for infants.

Most active humidifiers are located in close proximity to the ventilator in the inspiratory limb of dual limb breathing circuits or between the gas source and the single limb inspiratory line. HMEs are placed immediately at the airway opening.

B. Cold pass-over and bubble-through humidification.

Such systems can achieve a maximum humidity level of approximately 18 mg H_2O/L (full saturation at 20 °C, see Fig. 12.1) provided the gas flow from the blender does not cool down the water reservoir below room temperature. This humidity level may suffice for low-flow (<2 L/min) supplemental oxygen therapy using small-bore nasal cannula in infants with chronic lung disease. Their peak spontaneous inspiratory airflow exceeds the supplemental oxygen flow, and therefore, ambient air is additionally entrained. The nasal and pharyngeal physiologic heat and moisture exchange is fully preserved. The humidity output of cold pass-over systems, however, is too low for patients exposed to positive airway pressure during HFNCT or CPAP when the upper airway is permanently purged and unidirectional leak flows occur through the nose and pharynx during open-mouth states.

Concern has been raised that bubble through humidification is associated with the generation of micro-aerosols and its potential to transmit infectious agents.

C. Heated humidifiers (HHs).

1. HHs are considered the standard of care for invasive and noninvasive, short-term and long-term mechanical ventilation in infants. Manufacturers are required to comply with the international standards imposed on safety and effectiveness of these devices. However, the technology is complex and device malfunction is not always immediately obvious. Consideration should be given to basic principles of operation common to all different brands of HHs. This should enable the clinician to better recognize gas conditioning deficits and the underlying problem in specific situations.
2. Heated water vaporizes inside a humidification chamber. The inspiratory gas mixture passes through the chamber alongside the water surface and gains heat and humidity. The chamber is placed on a hot plate (MR series, Fisher & Paykel Healthcare, New Zealand;

AIRcon, WILAmed, Germany; H900, Hamilton Medical, Switzerland; VHB20, Inspired Medical, Hong Kong), or a heating element is located inside the chamber ("Sophie" and "Stephanie" ventilators, Stephan Medizintechnik, Germany). The gas conditioning efficiency depends on water temperature and surface area. Means to increase the surface area include porous membranes (Vapotherm®, NH, USA), filter paper, or sponge-like material that acts as a "wick." The vaporizing capacity at a given water temperature may become insufficient at higher ventilator gas flow rates. Some HH brands measure the gas flow rates continuously and automatically adjust the water reservoir temperature (Fisher & Paykel MR series).

Note: The internal volume of the humidifier chamber dampens the pressure amplitude during high-frequency ventilation (HFV). Fisher & Paykel therefore distributes a small chamber with a low internal compressible volume specifically for HFV. The humidifier module of the Stephan series ("Stephanie" and "Sophie") is an internal component of the ventilator located proximal to the inspiratory/expiratory valves within the high-pressure side of the machine. Thus, the humidifier chamber is not part of the breathing circuit and does not dampen the oscillation during HFV.

3. A wide spectrum of breathing tube circuits is currently on the market with major differences in design and quality. Maintenance of humidity and temperature of the gas mixture on its way from the humidifier to the patient is a critical circuit-tube function. Rainout inside the tubing is almost always a sign of significant moisture loss of the gas mixture – contrary to the common believe that a wet tubing indicates proper moisturing. Rainout is to be avoided for other reasons as well: 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 auto-cycling in patient-triggered ventilators, malfunction of the expiratory ventilator valve, condensate buildup in expiratory filters). Removal of mobile condensate requires to break open the circuit which may lead to ventilator pressure loss and alveolar de-recruitment. Emptying of water traps may be associated with spilling infectious material into the environment. Strategies to limit this problem include:
   (a) Heated wires inside the inspiratory circuit tubing or integrated in the tube walls maintain or slightly raise the gas temperature to prevent rainout before the gas reaches the infant. Industrial standards, however, limit the maximum heat output of those wires in order to prevent a meltdown of tubing material. Thus, specific conditions may still lead to condensation: cool drafts around the tubing (air-conditioned rooms), low ambient room temperature, a large outer surface area of small diameter tubing (particularly if corrugated), and slow circuit gas flow through long tubing (long contact time of the gas at unfavorable outer conditions). Binding the inspiratory and expiratory limbs of the circuit closely may alleviate the problem especially if the expiratory limb is also equipped with heated wires.

Note: The respiratory gas temperature probe at the patient wye needs to be shielded from stronger external heat sources in its immediate vicinity, for example, from an overhead warmer. Otherwise, the sensor wrongly signals over-temperature which shuts down the chamber heater, followed by a decline of water vaporization. Fisher & Paykel recommends placing the patient temperature probe near the outside of the incubator wall if the temperature inside the incubator is >34 °C. For this condit ion, they provide unheated circuit extension tube segments for use inside the incubator.

   (b) The inspiratory circuit tube wall is fabricated from highly insulating material with the heated wires embedded. The expiratory limb wall consists of a vapor-permeable mate-

rial that allows moisture to diffuse freely out of the tube avoiding the formation of condensate inside (Evaqua 2™, Fisher & Paykel).

(c) The Vapotherm® technology for HFNCT humidifies the gas mixture inside a special cartridge to full saturation at a user-set target temperature. The flow passes subsequently through a center lumen of a delivery tube. Warm water circulates for insulation around the center lumen in channels covering the entire circumference of the tube.

4. Performance checks of HHs.
   (a) There is no "gold standard" hygrometric method for an evaluation of clinically used humidifiers. Complex techniques such as psychrometry or dew point hygrometry are impossible to apply under clinical routine care conditions.
   (b) An estimate of the humidity output under a specific clinical situation can easily be derived from the actual water consumption rate of the humidifier chamber (mL/hr) and the average ventilator circuit flow rate (Fig. 12.2). This calculation assumes that the humidity of the gas mixture delivered from the ventilator into the humidifier chamber is zero.

D. HMEs (artificial noses).
   1. Working principle: HMEs recover part of the heat and moisture contained in the expired air. A sponge-like material with a large surface area inside a clear plastic housing absorbs heat and condenses water vapor during expiration for subsequent release during inspiration.
   2. Variants: Some HMEs are additionally coated with bacteriostatic substances and equipped with bacterial or viral filters. Hygroscopic condenser humidifiers (HCHs) use hygroscopic compounds, such as CaCl2, MgCl2, and LiCl to increase the water retention capacity.
   3. Application: A very limited number of commercially available brands is designated by manufacturers for use in infants. The tidal volume range of low birth weight infants alone precludes the use of most of the available HMEs in this population. Moreover, leaks around uncuffed endotracheal tubes violate basic premises for HME function. The smallest HMEs may be appropriate for short-term conventional mechanical ventilation in infants, such as

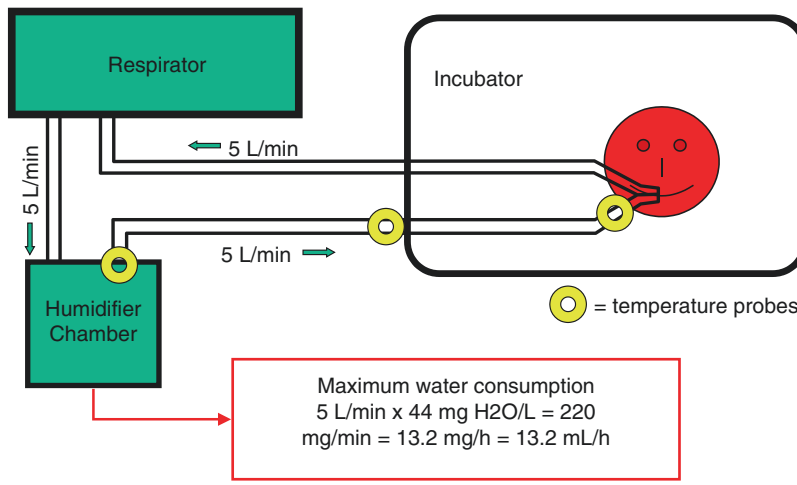

Fig. 12.2 Position of temperature probes of heated wire humidification systems for infants. The user sets the target temperature to be reached at the endotracheal tube adaptor. This temperature is commonly set at or slightly above 37.0 °C. The temperature inside the humidifier chamber must be high enough 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

during transport or minor surgical procedures. The safety and effectiveness during longer-term mechanical ventilation has not been established in infants. Significant advances in functional characteristics of infant HMEs have not been achieved in recent years. Thus, older infants with tracheostomies and larger tidal volumes remain as most appropriate candidates for use of infant HMEs.

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) Air leaks around an artificial airway impair the barrier effect of any HMEs/HCHs against moisture loss.
   (c) 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.

Note: HMEs/HCHs must not be used in conjunction with HHs, nebulizers, or metered dose inhalers. This may cause a hazardous increase in device resistance and/or leaching of the hygroscopic coating.

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.

E. Aerosol application for respiratory gas conditioning.

Water or normal saline nebulization offers no significant benefits for inspiratory gas conditioning compared to the use of HHs. It may entail a risk of over-humidification.

1. With appropriate use of HHs, 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) Increased airway resistance and narrowing or occlusion of small airways may develop if the aerosol deposition rate exceeds the water absorption capacity of the airway lining.
   (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.

F. 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.

VI. 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 hours or 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.

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Part III

Procedures and Techniques

Cardiorespiratory Examination

13

Avroy A. Fanaroff and Jonathan M. Fanaroff

I. Normal Physical Findings
   A. Respiratory rate 40–60/min.
      1. Irregular with pauses ≤5 seconds 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 hours.
         (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 between the upper (higher) and lower extremities is significant.

             Pulse oximetry screening for critical congenital heart disease is now routine. It is most likely to detect hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, transposition of the great vessels, total anomalous pulmonary venous return, truncus arteriosus, and tricuspid atresia in addition to coarctation of the aorta.
         (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.

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(c) Slowing of the heart is seen with hypoxia, hypothermia, seizures, heart block, and (rarely) increased intracranial pressure.
(d) Monitor artifacts may also produce bradycardia. The clinical diagnosis of neonatal sepsis may be preceded by abnormal heart rate characteristics of transient decelerations and reduced variability.

C. First and second heart sounds are often single; S_2 splits by 48 hours 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 indicate tachypnea.
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 if a non-synchronized mode (intermittent mandatory ventilation, IMV) is used. Though seldom used today, IMV may compromise oxygenation and increase the risk of air leaks and other pathologic events, such as intraventricular hemorrhage. Synchronization of the ventilator to the baby's own respiratory effort has been shown to decrease time on the ventilator and assists weaning.
  B. Unless a fully synchronized mode is used, 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 seconds, or if there are any gasping respirations, 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 seconds)
    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 depending on skin pigmentation (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 and if necessary, confirm hypoxemia by arterial blood gas analysis.
2. An arterial oxygen tension of 60–90 torr (8–12 kPa) results in a saturation of 94–98% and changes of 1–2% usually reflect a PaO_2 change of 6–12 torr (0.8–1.6 kPa). Below 40 torr (5.3 kPa), the saturation falls to <90%.
3. Saturations >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. Additionally, auscultation of the head will reveal a bruit.

X. Other Systems
A. Abdomen
1. Distention
   (a) Large amount of gas in the 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.
2. Scaphoid abdomen strongly suggests congenital diaphragmatic hernia.

B. Central Nervous System
1. Seizures – may be difficult to diagnose.
   (a) Common signs: eye movements, lip smacking, bicycling, and apnea.
   (b) Many movements that appear to be seizures are not confirmed with EEG, and many EEG documented seizures may only have subtle movements.

2. Tense fontanel when the newborn is not crying suggests increased intracranial pressure.
3. Abnormal tone – examine tongue for fasciculation, which indicate anterior motor neuron disease.
4. Abnormal level of consciousness (e.g., irritability, lethargy, coma). Review maternal chart regarding course of labor, instrument delivery, or maternal medications or drugs.

XI. Auditory Observations
- A. Listen to the baby. If he/she is crying vigorously, he/she is less likely to be seriously ill.
- B. Cry – May be a clue to diagnosis.
  1. High pitched or feeble may be a sign of intracranial pathology.
  2. Cri du chat – "cat's cry" may indicate a chromosomal anomaly.
  3. Aphonia may indicate vocal cord paralysis.
- C. Three important auditory clues.
  1. Grunting – a pathognomonic feature of neonatal lung disease – expiration against a partially closed glottis traps alveolar air and helps to 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 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. The following may be noted:
  1. Mediastinal shift (trachea, apical beat) with air leak, diaphragmatic hernia, and collapse (consolidation).
  2. Tense abdomen (tension pneumothorax or pneumoperitoneum, Fig. 13.1).
  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.

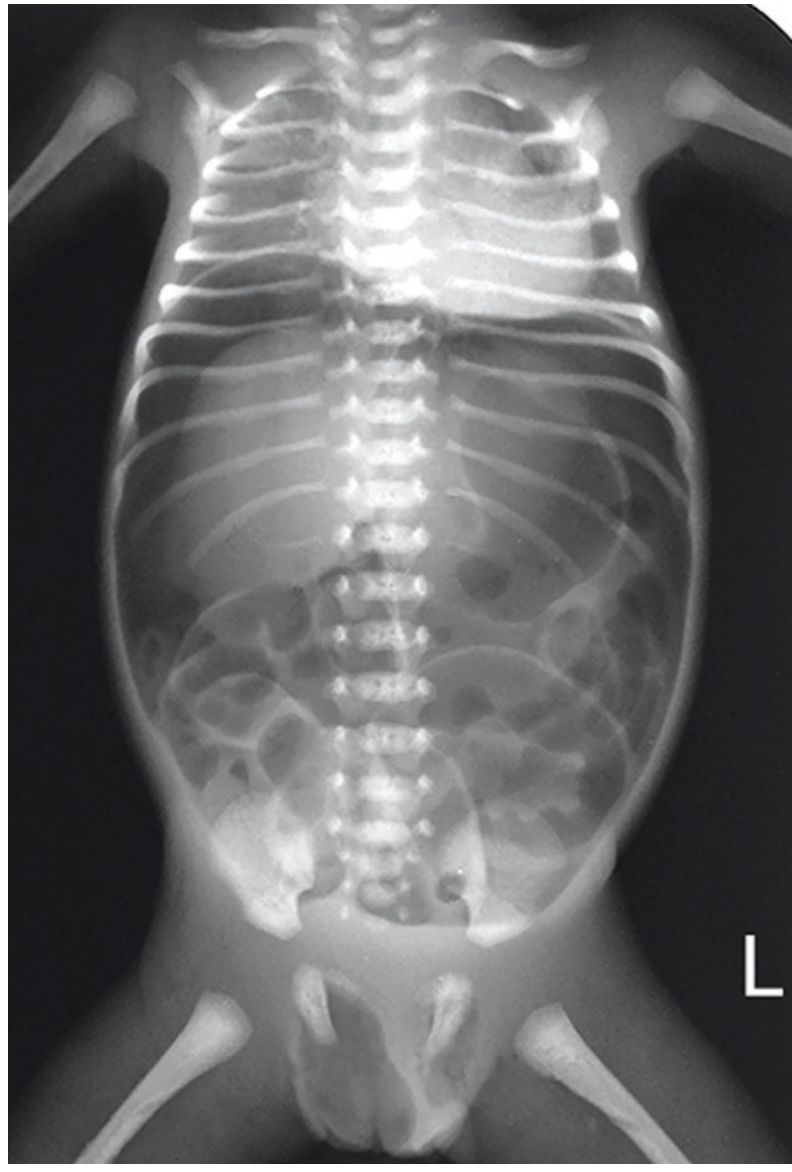

Fig. 13.1 Pneumoperitoneum ruptured viscus. Extensive free air under diaphragm with liver surrounded by large collection of air Pneumoperitoneum ruptured viscus – extensive free air under diaphragm with liver surrounded by extensive air

XIV. Auscultation

A. 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 seconds, 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 auscultation issues:
   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/pneumothorax.
      3. Pleural effusion.
      4. Misplaced endotracheal tube/spontaneous extubation.
      5. Unilateral pulmonary atresia (rare).
      6. The airway may also be obstructed in babies with micrognathia – Pierre Robin syndrome, where the tongue is the cause of the obstruction.
      7. Large tongues are seen with hypothyroidism, Beckwith-Wiedemann syndrome, hemangioma, and lymphangioma. Babies with trisomy 21 do not have large tongues but they protrude a lot because of a small mouth.

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 difficult to do a successful clinical examination under these circumstances. The tubing may 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 hours, with splitting of S_2 being present in 75% of babies by 48 hours.
  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 hours; 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 beyond 48 hours 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 hours 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 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 simplified.
- 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. May be measured with an automatic blood pressure recording device.
- 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 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. 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 seconds.
   5. Acid-base status (increased lactate with circulating insufficiency).
   6. Echocardiographic evaluation of cardiac function.
   7. Urine output (after the first 24 hrs.).

Suggested Reading

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Neonatal Resuscitation

14

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I. Anticipating resuscitation.
   A. Though most newborns make the fetal-to-neonatal transition without intervention, approximately 10–15% need assistance to establish spontaneous breathing in the first minutes of life. Among term newborns, 10% will respond to drying and stimulation, 3% will respond to positive pressure ventilation, 2% will require intubation, and 0.1% will receive chest compressions and/or drug therapy. When any moderate or high risk factor was present upon delivery, 20% of newborns were found to need positive-pressure ventilation (PPV). Given the large number of births each year, this represents a relatively frequent emergency and needs to be recognized by the healthcare teams, as even brief delays in initiating PPV increase the risk of death or prolonged hospitalization.
   B. With appropriate attention to identifiable risk factors, most neonatal resuscitations can be anticipated before birth. This allows a skilled team to be present at the time of birth. Despite the absence of risk factors, a small proportion (0.2–7%) will require unanticipated PPV. Achieving the best outcome requires an organized and efficient response from a highly reliable team.
   C. Because the need for resuscitation cannot always be predicted, every birth should be attended by at least one qualified individual with essential neonatal resuscitation skills. This individual's sole responsibility should be to provide care to the newly born infant, and, therefore, this provider must be competent in the initial steps of newborn care, basic airway management, and positive-pressure ventilation. If risk factors are identified (Table 14.1), additional personnel should be present to insert an advanced airway and obtain emergency vascular access as needed.

II. Normal postnatal transition. For the newborn to transition from the intrauterine environment, where the lungs are fluid filled and gas exchange is performed by the placenta, to the extrauterine environment, where aeration of the lungs and pulmonary gas exchange are essential, the following chain of events must occur:
   A. The newborn inhales and generates a large negative pressure that inflates the lungs. This is followed by a forceful exhalation that creates positive pressure within the alveoli that pushes fluid into the interstitial tissues.

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Table 14.1 Risk factors for neonatal resuscitation

Moderate risk	High risk
Late preterm (34–36 weeks' gestation)	Preterm (<34 weeks' gestation)
Intrauterine growth restriction	Major fetal anomalies or hydrops
Gestational diabetes mellitus	Fetal bradycardia
Chorioamnionitis	Acute or severe labor complication
Placental abruption	
Cord prolapse	
Maternal general anesthesia	
Meconium-stained amniotic fluid	
Category II or III fetal heart rate	
Instrumented delivery	
Emergency cesarean section	
Shoulder dystocia	
Abnormal fetal presentation (i.e., breech)	

B. Subsequent short, deep inspirations followed by exhalation against a closed or partially closed glottis results in a greater volume of air inspired than expired to establish a functional residual capacity (FRC). Carbon dioxide from the within the alveoli is exhaled.

C. Pulmonary vascular resistance decreases allowing pulmonary blood flow to increase. Pulmonary venous return fills the left atrium and ventricle. Flow through the ductus arteriosus changes from right-to-left to left-to-right. The foramen ovale closes.

III. Neonatal resuscitation supplies and equipment (Table 14.2)

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. Umbilical Cord Management: If there is no contraindication, delay umbilical cord clamping for most vigorous term and preterm newborns for at least 30–60 seconds. Deferring cord clamping until the newborn's lungs are aerated may improve cardiorespiratory transition.
   (a) If cord clamping cannot be delayed, intact umbilical cord milking may be a reasonable alternative; however, cord milking *is not recommended* for very preterm babies <28 weeks' gestation.
   (b) There is insufficient evidence to recommend whether umbilical cord clamping should be delayed in non-vigorous newborns, mono-chorionic multiples, or fetuses with alloimmunization.
   (c) Initiating resuscitation with an unclamped umbilical cord is an intervention that is currently being investigated.
2. Vigorous term newborns should be placed skin-to-skin on mother's chest or abdomen to monitor transition. Placing babies skin-to-skin after birth can improve newborn thermoregulation, breastfeeding success, and glucose homeostasis.
3. After the umbilical cord is clamped, preterm and non-vigorous term newborns should be placed on a flat surface under a radiant warmer.

Table 14.2 Resuscitation supplies and equipment

Warming
Pre-heated radiant warmer. Warm towels/blankets. Infant hat.
For preterm or very low birth weight
Polyethylene plastic wrap/bag (for preterm or very low birth weight newborns). Thermal mattress. Pre-warmed transport incubator.
Monitoring
Stethoscope. Pulse oximeter with neonatal sensor. Electronic cardiac (EC) monitor with neonatal chest or limb leads. Colorimetric CO_2 detector or capnometer. Measuring tape.
Ventilation
Bulb syringe. Suction device with range of catheter sizes (10–12F). Positive pressure ventilation device (self-inflating bag, flow-inflating bag, T-piece) with manometer and pressure regulator. Compressed gas source (air and oxygen) with adjustable flow meter and blender. Face masks (multiple sizes for term and preterm infants). Laryngeal mask (size 1) with 5 mL syringe (if needed to inflate). Orogastric feeding tube (8F).
Intubation
Laryngoscope handle and straight blades (sizes 0 and 1; size 00 optional). Video laryngoscope (optional). Tracheal tubes sizes 2.5, 3.0, and 3.5 (size 2.0 and 4.0 optional). Intubating stylette (optional). Waterproof tape and scissors or tracheal tube securing device.
Medications
Umbilical venous catheter (UVC) supplies. Intraosseous needle supplies. Epinephrine (0.1 mg/mL) with transfer device. Normal saline (with 20–60 ml syringes). 1 mL, 3 mL, and 5 mL syringes and stopcocks Surfactant (for preterm).

B. Dry: Remove wet towels and dry term and late preterm newborns with warm towels/blankets. Preterm newborns (<32 weeks' gestation) should be placed in a polyethylene plastic bag (or wrap) without drying.
C. Stimulate: Rub the back or extremities, as necessary, to stimulate breathing.
D. Position: Establish an open airway. Position the newborn supine with the neck neutral, or slightly extended, and the baby's eyes looking upward directly toward the ceiling in the "sniffing" position (Fig. 14.2).
E. Suction, if necessary: Gently suction the mouth and nose with a bulb syringe if the baby is either not breathing, having difficulty breathing, or if positive-pressure ventilation (PPV) is anticipated.
    1. Routine oral, nasal, oropharyngeal, and endotracheal suctioning *are not recommended* even in the setting of meconium-stained amniotic fluid. Aggressive pharyngeal suctioning should be avoided.
    2. Oro-nasopharyngeal and/or tracheal suctioning may be necessary if there is evidence of airway obstruction during PPV.

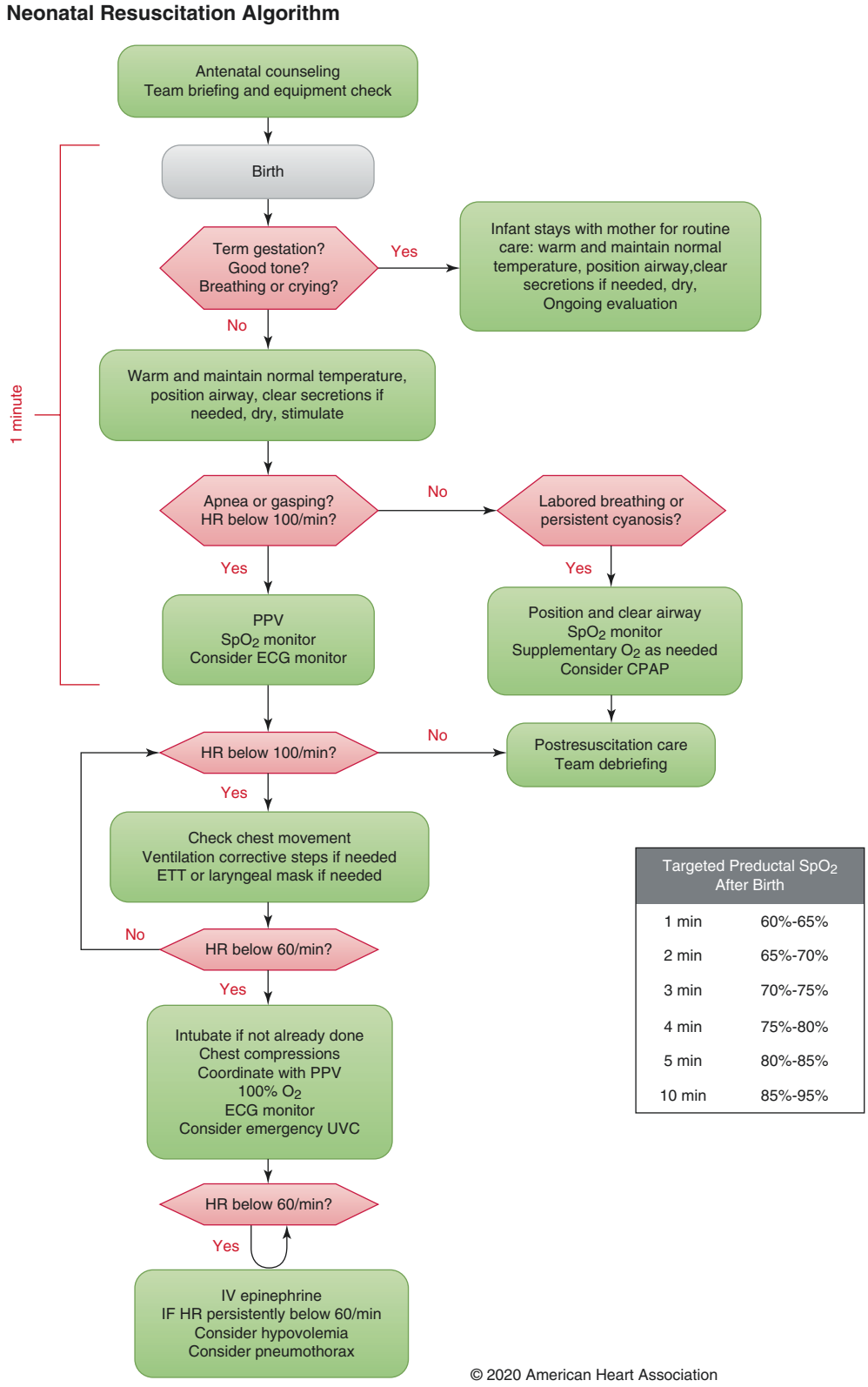

Fig. 14.1 Neonatal resuscitation algorithm

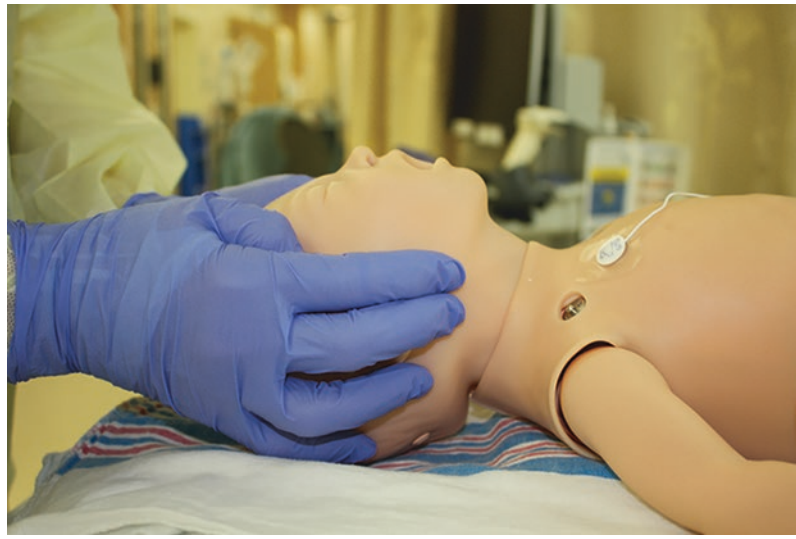

Fig. 14.2 Sniffing position

F. Evaluate response to the initial steps by assessing breathing and heart rate.
   1. If the baby is not breathing, is gasping, or the heart rate (HR) is <100 bpm by 1 minute of age, start PPV.
   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 or wrist) to assess the need for supplemental oxygen by comparing the baby's oxygen saturation with published *minute-specific* saturation targets.
   3. Heart rate is most accurately assessed by auscultation at the cardiac apex or by using an electronic cardiac (EC) monitor. Palpation of the umbilical pulse is unreliable and often inaccurate. Heart rate monitoring by pulse oximetry may be delayed secondary to poor perfusion. There is a small risk that the heart rate displayed by the EC monitor represents non-perfusing pulseless electrical activity (PEA). A handheld Doppler fetal HR monitor may be used to quickly assess heart rate and confirm blood flow.

VI. Positive-pressure ventilation.
- Most newborns requiring resuscitation will improve when their lungs are effectively oxygenated and ventilated.
  A. Place the baby supine. Consider putting a small towel or blanket under the baby's shoulders for a neck roll to prevent the occiput from flexing the neck resulting in airway obstruction but avoid hyperextension.
  B. Standing at the head of the bed, hold the baby's head and neck in the sniffing position, and apply an appropriate-sized 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 (Fig. 14.4) 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 recruit alveoli and establish and maintain FRC.
     2. The suggested ventilation rate is 40 to 60 breaths per minute.

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

Fig. 14.4 Face mask ventilation with two-hand hold and CO_2 detector

3. Use an inflation time (Ti) of 0.3 to 1 second. Though prolonged Ti (>1 second) may help to establish FRC more quickly, it has not been shown to be beneficial in randomized controlled trials and Ti >10 seconds may increase the risk of death and severe intraventricular hemorrhage in newborns <28 weeks' gestation.
4. Initiate ventilation with 21% oxygen (air) for term and late preterm newborns and 21–30% oxygen for newborns <35 weeks' gestation. Preterm newborns <30 weeks' gestation frequently need oxygen to meet saturation goals, and it is reasonable to begin with 30% oxygen.

5. Use pre-ductal pulse oximetry (right hand) during PPV to evaluate oxygenation and adjust the oxygen concentration (F_iO_2).
   (a) Use a target oxygen saturation table to guide supplemental oxygen (Fig. 14.1).
   (b) For newborns <32 weeks' gestation, it is important to achieve an oxygen saturation >80% and heart rate >100 bpm by 5 minutes.
6. Consider using warmed and humidified inspired gases for very preterm newborns to avoid hypothermia.

D. The baby's HR should promptly increase with PPV.
1. Once PPV is started, monitor the HR response. Consider using an EC monitor for accurate HR assessment.
2. If HR rapidly improves, continue PPV until the HR is at least 100 bpm and the baby is breathing effectively.
3. If HR does not increase within approximately 15 seconds, it is likely because effective ventilation has not been achieved. Ensure there is adequate chest rise with PPV. If chest rise 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. A carbon dioxide (CO_2) detector may help to assess PPV effectiveness. If gas is being exchanged within the lung, you should detect CO_2 at the mask.
5. If HR is not improving and chest rise cannot be achieved with face mask ventilation, insert an alternative airway (tracheal tube or laryngeal mask). If an alternative airway is needed, use an EC monitor to accurately and continuously monitor HR.
6. If intubation is to be performed, select the correct tracheal tube size, confirm tracheal intubation with capnography, confirm equal breath sounds by lung auscultation, and estimate the insertion depth using the nasal-tragus length (NTL).
   (a) The NTL is calculated by adding the distance (cm) from the nasal septum to the ear tragus and adding 1 cm (NTL (cm) = nasal septum-to-tragus distance +1).
   (b) 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 HR remains <60 bpm after 30 seconds of effective ventilation through a properly inserted tracheal tube or laryngeal mask, increase the F_iO_2 to 100% and proceed with 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 HR remains <60 bpm despite at least 30 seconds of effective ventilation with consistent chest movement.
1. Chest compressions should not be started until effective ventilation has been established.
2. In most cases, a baby that requires chest compressions should be intubated.
3. Once the alternative airway is secured, the operator should stand at the head of the bed with the person providing ventilations at the side (Fig. 14.5). This improves ergonomics and allows space for another provider to obtain emergency vascular access.

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 both thumbs (Fig. 14.6).
1. Compress the chest by one-third of the antero-posterior diameter.

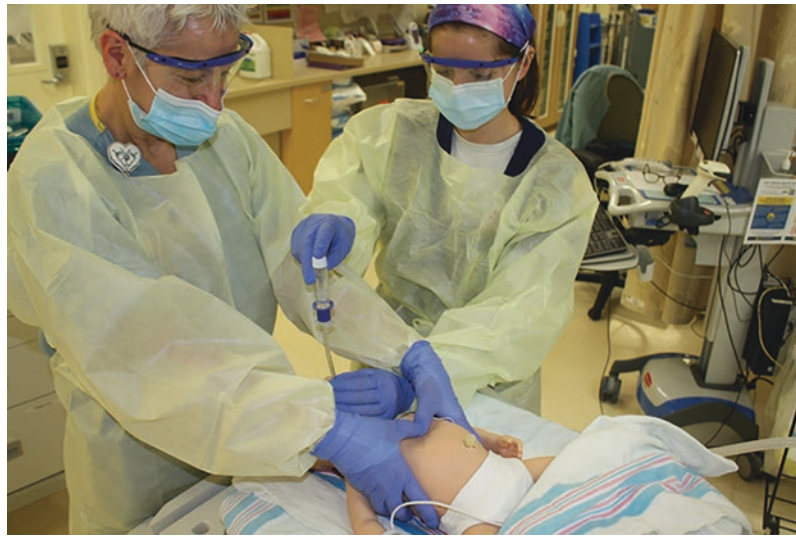

Fig. 14.5 Chest compressions from the head of the bed

Fig. 14.6 Hand placement for chest compressions. Hands encircle the chest with 2 thumbs placed on the sternum

2. PPV must continue during compressions. At present, synchronous chest compressions and ventilations are recommended even when ventilation is provided through a tracheal tube.
3. Give one lung inflation after every third compression (a ratio of 3:1) to achieve 90 compressions and 30 ventilations per minute.

C. 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).

D. Check the HR response after 60 seconds of compressions using an EC 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 synchronized compressions and effective ventilation, proceed to administration of epinephrine.

VIII. Medication.

A. Epinephrine (adrenaline).
   1. Indication: HR <60 bpm despite 60 seconds of synchronized compressions and effective ventilation through a tracheal tube.
   2. Preparation: 0.1 mg/mL (1 mg/10 mL).
   3. Route: UVC or ION, rapidly infused.
      (a) Attempting to start a *peripheral IV is not recommended*.
      (b) An emergency UVC only needs to be inserted until blood can be aspirated (approximately 3–4 cm in term newborns).
   4. Suggested initial dose: 0.02 mg/kg (0.2 mL/kg).
      (a) Recommended dose range: 0.01 mg/kg to 0.03 mg/kg (0.1 mL/kg to 0.3 mL/kg) per dose.
      (b) If starting at the lower end of the recommended range and there is not an acceptable response, consider increasing subsequent doses. Do not exceed the recommended maximum dose.
      (c) May repeat epinephrine every 3 to 5 minutes if HR remains <60 bpm.
   5. Flush each UVC/ION dose with a minimum of 3 mL normal saline.
   6. 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 (0.05 mg/kg to 0.1 mg/kg) is recommended. This larger dose should not be administered intravenously.
      (a) Repeated endotracheal administration is not recommended.
      (b) If the baby does not respond to the initial endotracheal dose, an intravascular (UVC or ION) dose should be given as soon as access is obtained.
   7. *Use caution to use ONLY the diluted (0.1 mg/mL) preparation of epinephrine* (Fig. 14.7). Use of a cognitive aid that shows how to assemble the epinephrine syringe and prepare the correct dose based on estimated weight may decrease the risk of dosing errors (Table 14.3).

B. Volume expansion. Routine volume expansion during and after resuscitation are 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: 10–20 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 radiograph, and evaluate each of the following:

Fig. 14.7 Correct neonatal epinephrine concentration (0.1 mg/mL) with delivery device

Table 14.3 Suggested dose of epinephrine (0.1 mg/mL) based on estimated weight

Weight (kg)	IV/IO epinephrine (preferred) 0.02 mg/kg = 0.2 mL/kg	Endotracheal epinephrine 0.01 mg/kg = 1 mL/kg
0.5	0.1 mL	0.5 mL
1	0.2 mL	1 mL
2	0.4 mL	2 mL
3	0.6 mL	3 mL
4	0.8 mL	4 mL

1. Is the tracheal tube in the esophagus?
2. Is there is 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. Variables to consider include uncertainty about the duration of asystole, whether all steps of resuscitation have been completed and optimized, the baby's gestational age, the timing of events leading to cardiorespiratory arrest, the availability of critical care and therapeutic hypothermia, and the family's desires and values. Although previous case series suggested that absence of HR after 10 minutes predicted mortality or serious morbidity in late preterm and term newborns, recent reports suggest that outcomes may not be as poor as previously reported. Given the limitations of evidence and the difficulty assessing key variables during the time and pressure of a complex resuscitation, in most circumstances it is reasonable to continue resuscitative efforts if HR remains undetectable for up to 20 minutes.
2. Prolonged bradycardia (HR < 60 bpm) without improvement: Assuming that prolonged bradycardia reflects cardiorespiratory compromise (not congenital heart block) and resus-

citative 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 important and multiple methods may be required to avoid hypothermia. For preterm newborns <32 weeks' gestation, increase the room temperature to 23 °C to 25 °C (74 °F to 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 of 36.5 °C to 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. Use the lowest inflation pressure required to maintain a HR >100 bpm and oxygen saturation within the target range.
      4. Resuscitation of newborns <35 weeks' gestation begins with 21–30% oxygen. Preterm newborns <30 weeks' gestation frequently need oxygen to meet target saturation goals, and it is reasonable to begin with 30% oxygen.
   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.
      3. Ventilate with low peak pressures (<25 cm H_2O) to avoid pneumothorax.
      4. Goal pre-ductal saturation is >80–85%.
      5. Obtain central arterial and venous access. UVC may be difficult if the liver is herniated into the chest.
   C. Abdominal wall defects.
      1. Gastroschisis.
         (a) Place the newborn in a polyethylene bag to cover the defect and reduce evaporative heat losses.
         (b) Exposed bowel contents should be placed to the infant's right side to avoid vascular compromise.
         (c) Prompt placement of a gastric sump suction tube (Replogle) should be prioritized to decompress the bowel.
         (d) A longer umbilical cord segment should be left to allow for suture-less closure.
         (e) Obtain IV access to support fluid resuscitation.
      2. Omphalocele.
         (a) Prompt placement of gastric sump suction tube (Replogle) should be prioritized to decompress bowel.
         (b) Obtain IV access to allow for fluid resuscitation.
         (c) Perform a thorough physical exam to evaluate for associated congenital anomalies. If Beckwith-Wiedemann syndrome is suspected (large tongue, large for gestational age, hemi-hypertrophy), monitor for hypoglycemia.
   D. Neural tube defects.
      1. All equipment should be latex-free.
      2. Roll a blanket into a doughnut shape or cover a pre-formed latex-free foam ring with a towel. This will be used support the newborn's back and off-load pressure on the defect if the baby needs to be positioned supine.

3. Avoid placing newborns with spinal defects flat on their back. Position the newborn sidelying, prone, or on the "doughnut" made from towels or latex-free foam with the defect within the open "doughnut hole."
4. Once the newborn is stable, cover the defect with non-latex, transparent plastic wrap, and surround the baby's abdomen/waist with the plastic wrap.

E. Congenital heart disease (CHD).
1. Good communication between the neonatologist, maternal-fetal medicine specialist, and pediatric cardiologist is recommended to determine the mother's care needs, stratify the newborn's risk of hemodynamic instability in the early postnatal period, and appropriately plan delivery room care for newborns with known CHD. Several risk stratification systems based on prenatal echocardiographic findings exist.
2. No increased risk of hemodynamic instability in the delivery room:
   (a) Examples include atrial septal defect (ASD), atrioventricular septal defect (AVSD), mild-moderate valve abnormalities, and ventricular septal defect (VSD).
   (b) In the absence of other maternal or newborn risk factors, routine delivery room care in the local hospital is appropriate. There are no anticipated hemodynamic issues in the delivery room and no special precautions or interventions are needed. The newborn's oxygen saturation in the delivery room is expected to be normal (>90%).
   (c) Plan cardiology consultation either before discharge or as an outpatient.
3. Low to moderate risk of hemodynamic instability in the delivery room:
   (a) Examples include: Coarctation of the aorta, d-Transposition of the great arteries (d-TGA) with ASD (*see below*), hypoplastic left heart (HLHS) without restricted atrial shunting, pulmonary atresia with intact ventricular septum, tetralogy of Fallot (TOF) with severe pulmonary stenosis, and total anomalous pulmonary venous return (TAPVR) without obstruction.
   (b) Delivery should occur at or nearby a location with high acuity neonatology and pediatric cardiology resources and expertise. If delivery occurs at a location without these resources, the referral center and critical care transport team should be alerted.
   (c) In the absence of other maternal or newborn risk factors, routine delivery room care is anticipated with cardiology evaluation shortly after birth. Although these newborns may rely on patency of the ductus arteriosus (DA) for pulmonary or systemic blood flow, most will not require any special interventions immediately after birth. The DA often closes between 12 and 72 hours after birth. Most of these newborns can have a brief period of bonding time with their mother.
   (d) Prostaglandin E1 infusion (PGE) may be indicated shortly after birth.
   (e) The predictive ability of prenatal echocardiography to identify infants with d-TGA who will have restricted atrial shunting is limited; therefore, all newborns with d-TGA are at some risk of restricted atrial shunting that interferes with the flow of oxygenated blood to the systemic circulation and requires emergent intervention.
4. High risk of hemodynamic instability in the delivery room:
   (a) Examples include d-TGA with restrictive or intact atrial septum (R/IAS), HLHS with R/IAS, TAPVR with obstruction, TOF with absent pulmonary valve and evidence of airway obstruction (lobar emphysema), fetal arrhythmia with heart failure or hydrops, and congenital heart block (heart rate < 55 bpm) with heart failure or hydrops.
   (b) Delivery should occur at a location with immediate access to specialized neonatology and pediatric cardiology resources. Rapid intervention, including cardiac catheterization, cardioversion, transcutaneous pacing, surgery, or ECMO may be necessary.
   If necessary, critical care transport should be arranged prior to birth,
   (c) Coordination and planning with maternal-fetal medicine, neonatology, pediatric cardiology, and cardiothoracic surgery are important to plan care immediately after birth.

F. Fetal hydrops (hydrops fetalis).
   1. Delivery should occur at a high risk center with capabilities to resuscitate critically ill newborns.
   2. Prior to delivery, assign roles and prepare equipment for endotracheal intubation, emergency vascular access, thoracentesis, and paracentesis.
   3. Intubation may be difficult because of soft tissue edema or a neck mass.
   4. Once ventilation is established, vascular access with UVC and UAC should be obtained.
   5. If ventilation is impeded by pleural effusion, a thoracentesis or thoracostomy tube placement may be required in the delivery room.
   6. Infants may require careful volume resuscitation with normal saline or packed red blood cells secondary to prolonged anemia.

XI. Post-resuscitation care.
   A. Vital signs should be monitored at regular intervals.
   B. Perform a thorough physical examination to evaluate for ongoing respiratory distress, cyanosis, and congenital anomalies.
   C. Evaluate for hypoglycemia from perinatal stress.
   D. A neurological examination should be performed on all infants requiring prolonged resuscitation to evaluate for encephalopathy.
      1. Assess alertness, tone, sucking, pupillary response, and reflexes.
      2. Infants with evidence of encephalopathy should be evaluated for therapeutic hypothermia using protocols similar to those in randomized trials.

Suggested Reading

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15 Laryngoscopy, Tracheal Intubation, and Laryngeal Mask Airway

Steven M. Donn and Meera S. Meerkov

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. Maintain airway patency.
      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. It is critical to avoid face mask ventilation which leads to delivery of air into the gastrointestinal tract. Immediate intubation following delivery should be performed.

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

Tube size (mm) inner diameter	Weight (grams)	Gestational age (wks)
2.5	<1000	<28
3.0	1000–2000	28–34
3.5	2000–3000	34–38
3.5–4.0	> 3000	>38

   B. Depth of insertion may be estimated by measuring the distance from the nose to the tragus (NTL), in cm (Fig. 15.1).
      1. Orotracheal route: Depth = NTL + 1 cm
      2. Nasotracheal route: Depth = Orotracheal route +2 cm = NTL + 3 cm.

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Fig. 15.1 Nose to tragus length (NTL)

III. Use of Pre-intubation Medications.
   A. Anesthesia or analgesia should be provided except in emergency situations.
   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. Improved first attempt intubation success.
      2. Decreased intubation related airway trauma.
      3. Faster intubation.
      4. Increased hemodynamic stability.
      5. Less hypoxemia.
      6. Less rise in intracranial pressure.

C. Premedication regimens (Chaps. 59 and 62). The goal of premedication is to eliminate pain and discomfort and minimize physiologic abnormalities of the procedure. Optimal regimens should decrease the chance of traumatic injury to the newborn and cause no adverse events.
   1. Vagolytic agents (e.g., atropine) – prevent bradycardia during intubation and decrease bronchial/salivary secretions.
   2. Analgesics (e.g., fentanyl) – reduce pain and discomfort of intubation.
   3. Paralytic agents (e.g., succinylcholine, rocuronium, pancuronium) – minimizes increase in intracranial pressure that occurs during intubation and has been shown to facilitate successful intubation. 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 can be provided.
   4. Sedatives (e.g., midazolam). This category of agents may not be necessary as studies have not demonstrated a reduction in physiologic changes during intubation when sedatives have been administered.
   5. Adjunctive or reversal agents.
      (a) Neostigmine: reverses the effects of non-depolarizing muscle relaxants.
      (b) Naloxone: competitive antagonist at all opioid receptors.

IV. Oral Intubation with Direct Laryngoscope or Video Laryngoscope Device – intubation attempt should last ≤30 seconds.

A. Collect all equipment you will need and place in a convenient location (Fig. 15.2). Necessary equipment includes:
   1. Laryngoscope handle or video laryngoscope device, *if using.*
   2. Laryngoscope blades appropriate for patient. (Size 1 for term infant, Size 0 for preterm newborn. Consider Size 00 for very preterm newborn.)
   3. Endotracheal tubes (ETT). Prepare tube appropriate for patient size and have available smaller ETTs.
   4. Stylet.
   5. CO_2 detector.
   6. Suction set-up with appropriate-sized suction catheters.
   7. Measuring tape.
   8. Securement device – e.g., waterproof adhesive tape or NeoBar®.
   9. Stethoscope.
   10. Positive pressure device.
   11. Magill forceps *(*if performing nasotracheal intubation*).*

B. Position the baby on a firm flat surface. Infant's head should be midline, neck slightly extended into "sniffing position," and body straight. Consider placing a small roll or blanket under the baby's shoulders (not the neck). If possible, adjust the height of the bed so that the infant's head is at the level of the operator's upper abdomen/lower chest. This improves the view of the airway when intubating.

C. Open the baby's mouth with the index finger of your right hand (Fig. 15.3). Holding the laryngoscope in your left hand, insert the blade carefully into the right side of the baby's mouth, and slide the blade over the right side of the tongue toward midline (Fig. 15.4).

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 using a video laryngoscope device, position device's monitor to allow for easy visualization throughout the entire procedure (Fig. 15.5).

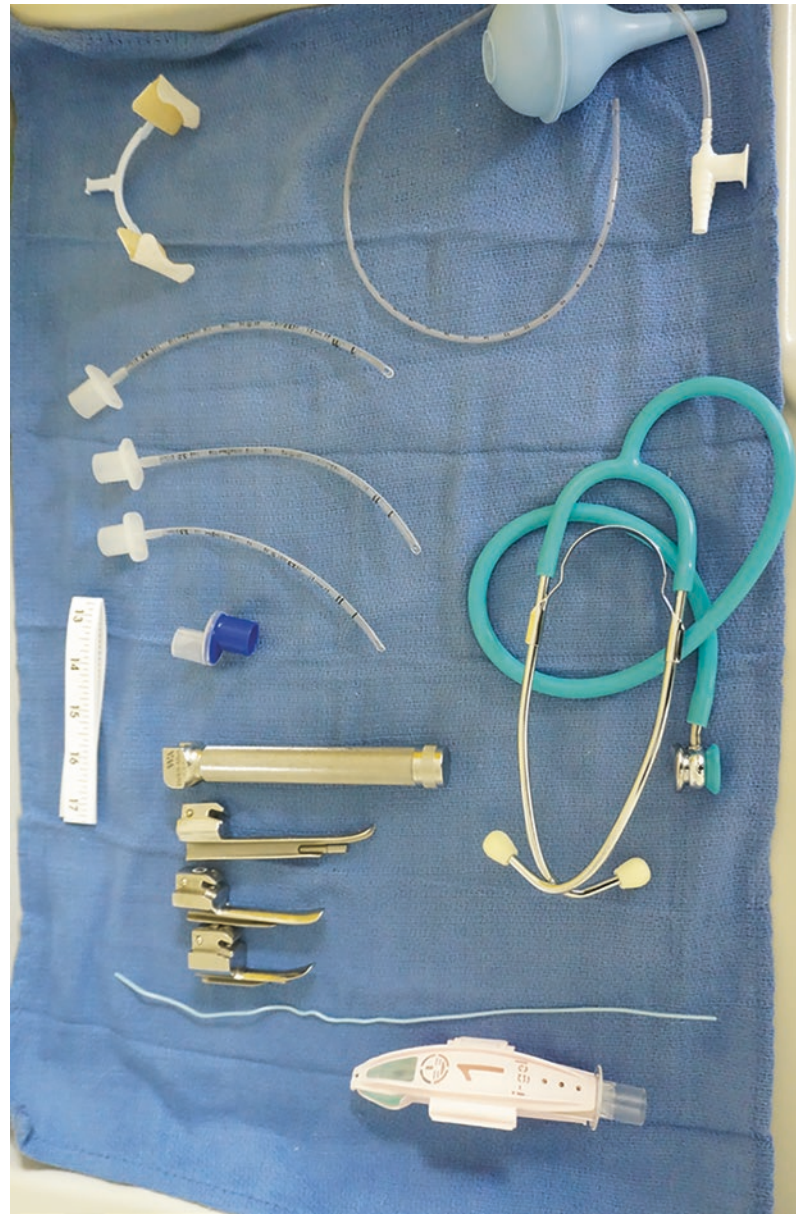

Fig. 15.2 Intubation procedure equipment

F. Insert the blade further until the blade tip lies in the vallecula (space between the tongue and epiglottis) or the blade is overlaying the epiglottis.
   1. 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.
   2. 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.

G. Lift the laryngoscope in the direction of the handle without allowing the intubator's wrist to bend ("rock"), which will lever the end of the laryngoscope blade against the infant's jaw, which could potentially damage the dental alveolus and developing teeth.

Fig. 15.3 Infant position to insert laryngoscope blade

H. Slight external backward/upward/rightward pressure on the cricoid should bring the larynx into the center of the field of view. Vocal cords should be visible and appear in the shape of an inverted letter "V" (Fig. 15.6).
I. With the ETT in your right hand, insert the ETT into 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.
J. Insert the tube 1–2 cm through the cords. *If necessary, wait for the cords to relax*. Several commercially available tubes have markings to indicate where the ETT should align with the vocal cords (Fig. 15.7).
K. Hold ETT against infant's hard palate with your right index finger.

Fig. 15.4 Inserting laryngoscope

L. Carefully remove laryngoscope blade and stylet (if applicable).
M. Inflate the lung using a positive pressure device.

V. Oral intubation without a Laryngoscope (Digital Intubation): 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 seconds
   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.

Fig. 15.5 Operator's position when using video laryngoscopy

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.
I. Hold ETT against infant's hard palate with your right index finger.
J. Inflate the lungs using positive pressure device.

VI. Nasotracheal intubation: Nasal intubation is not normally used for emergency intubation, but many neonatologists perform this procedure in non-urgent settings. Nasal intubation is often preferred in situations when it is difficult to maintain an oral tube in appropriate position, or based on neonatologist's preference.
A. Provide adequate oxygenation in preparation for the procedure.
B. Administer pre-intubation medications (see Sect. III).
C. Position the baby supine with the shoulders supported on a small towel roll (see Sect. IV.B.) 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 toward 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. Lubricate the end of the tracheal tube, thread it over the feeding tube, and insert it through the nostril and into the nasopharynx.

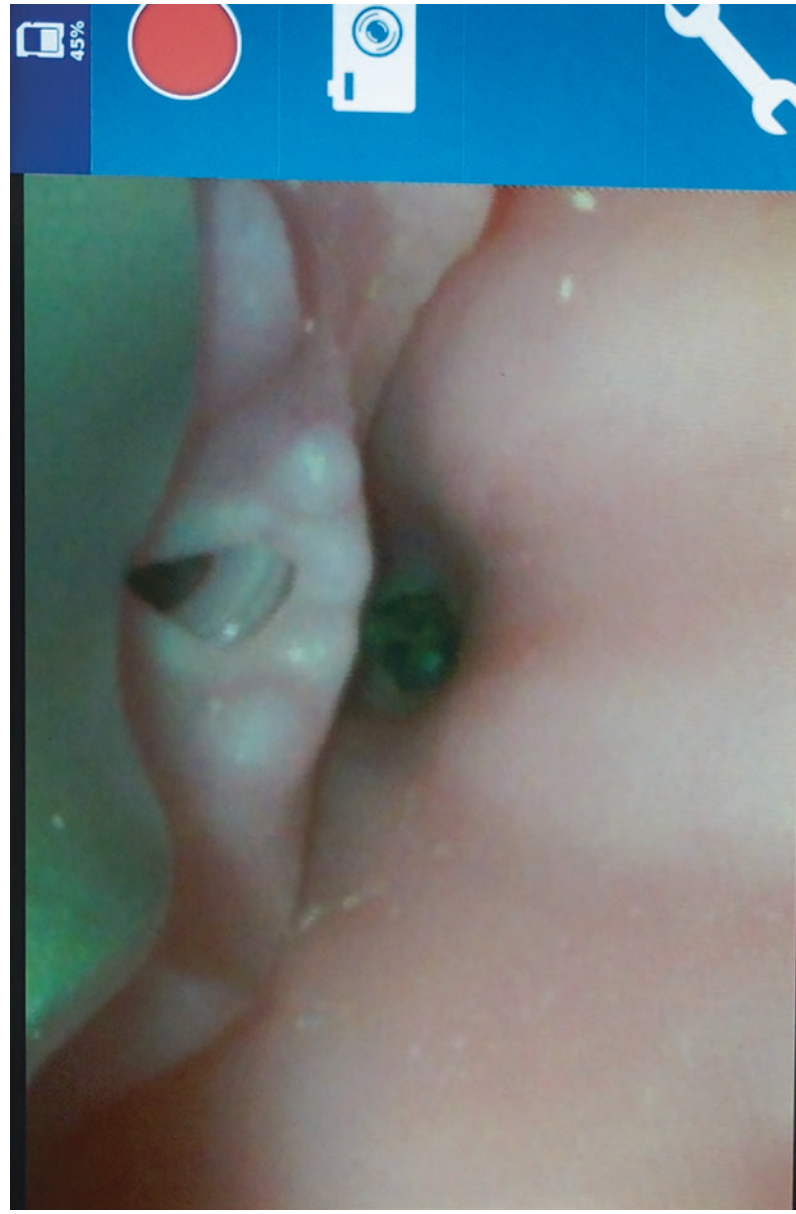

Fig. 15.6 View of larynx/vocal cords during intubation attempt

F. Remove the feeding tube.
G. Loosen the attachments of the oral tube (if present) and have an assistant prepare to remove it when requested.
H. Visualize the larynx with the oral tube in place (if present) using a laryngoscope. Identify the nasal tube within the nasopharynx.
I. Ask an assistant to remove the oral tube (if present). Grasp the nasal tube with a small pair of Magill or crocodile forceps and position the end of the tube into the laryngeal opening.
J. 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

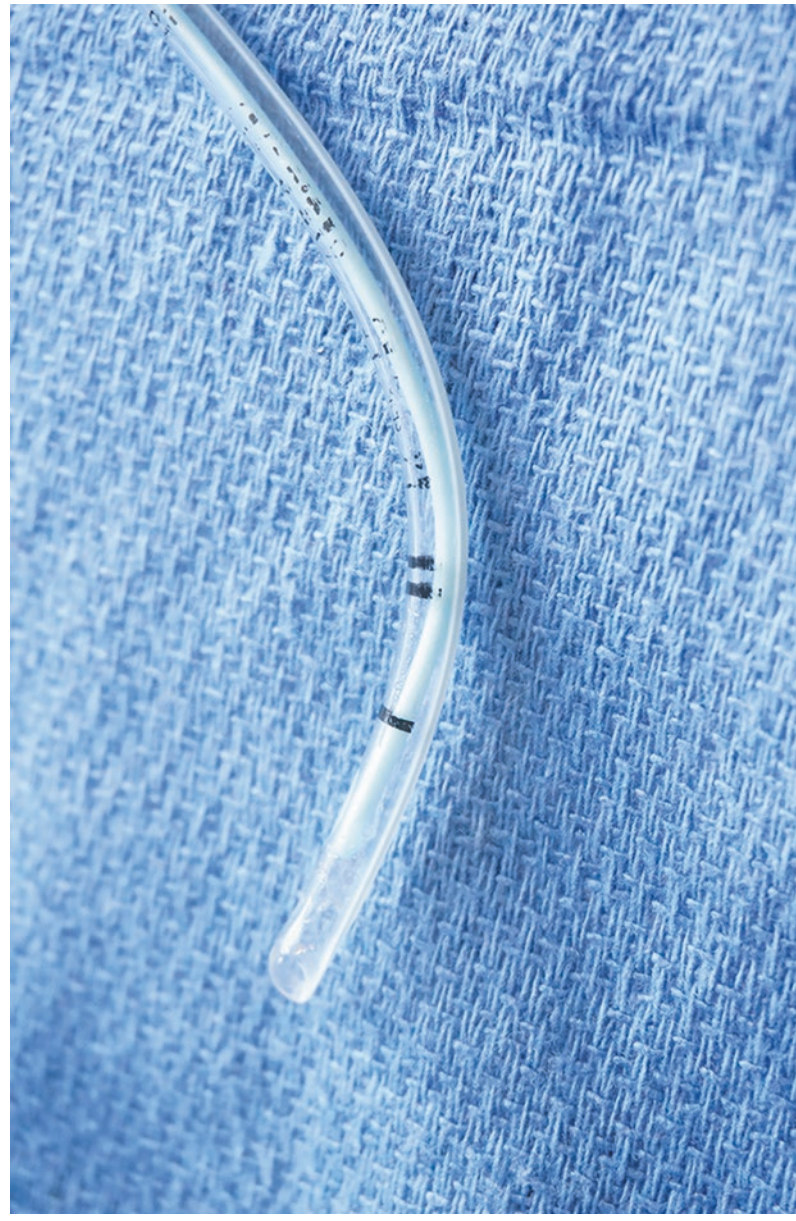

Fig. 15.7 ETT line markers

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

K. Inflate the lungs using positive pressure device.

VII. Confirming Tube Position – the primary methods of confirming appropriate ETT position are detection of exhaled CO_2 and rising heart rate.

A. Clinically.

1. Equality of breath sounds bilaterally.
2. Absence of phonation.
3. Good chest excursions, symmetrical.

4. Appropriate physiologic responses (HR, SpO_2).
5. Presence of vapor in the ETT.

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, typically at level first or second thoracic vertebra.

C. Exhaled CO_2 detection via colorimetric devices or capnography.
1. Colorimetric devices changes from purple to yellow in the presence of exhaled CO_2.
2. Capnography is an electronic monitor that displays CO_2 concentration with each breath.
3. False-negative results may occur with reduced pulmonary blood flow (e.g., after cardiopulmonary resuscitation, cardiac anomalies) or with severe airway obstruction.

VIII. Securing the Endotracheal Tube.

A. Dry face thoroughly.

B. Use waterproof tape or other securement devices (e.g., NeoBar®) to maintain appropriate ETT position.

IX. Replacing the Endotracheal Tube Following a Trial of Extubation.

A. Despite meticulous post-extubation care, use of methylxanthines, and a trial of CPAP, about 20–30% of babies require re-intubation. The immediate goal is to quickly re-intubate and provide assisted ventilation to stabilize the 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 (see Sect. II).
3. Use of pre-intubation medication (see Sect. III).
4. Insert ETT by previously described techniques (see Sects. IV–VI).
5. Before fixation, assess for correct ETT placement by assessing air entry, chest wall movement, appropriate colorimetric devices or capnography changes, and improvement in oxygen 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 or video 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.
7. A radiograph is necessary only if there is a question of suitable placement.

VI. Laryngeal Mask Airway (LMA) – device that can be used as an alternative to face mask or ETT. Multiple designs are commercially available, but they all have an airway tube with a standard (15 mm) connector at one end (to attach to a positive pressure device) and at the other end

is a small/flexible mask. In appropriate position, the small/flexible mask covers the glottis to create a "seal" against the hypopharynx (Fig. 15.8).

A. Clinical Indication for LMA.
   1. See Sect. I.
   2. Unable to insert ETT and face mask ventilation is insufficient. Common clinical situations include:
      (a) Unable to visualize vocal cords.
      (b) Newborns with anomalies involving upper airway, mouth, lip, tongue, and palate/neck.

B. Limitations of LMA.
   1. Difficult to effectively suction oral secretions.
   2. Increased air leak between pharynx and mask.

Fig. 15.8 Example of LMA

3. Possibly less effective means of administering intratracheal medications.
4. Size limitations – smallest LMA device is appropriate only for infants ≥1.5 kg.

C. LMA Insertion Technique.
1. If device has an inflatable cuff surrounding the mask, attach syringe to the inflation port and completely deflate the cuff.
2. Consider lubricating the back of the mask with a water-soluble lubricant.
3. Position infant as for oral intubation (see Sect. IV.B.).
4. Hold the device with inner curve pointed toward infant's toes. Device can be held in left or right hand (Fig. 15.9).

Fig. 15.9 LMA insertion

5. Open infant's mouth and insert the mask as it follows the curve of the infant's palate.
6. Advance device inward following the contour of the mouth/palate. Advance until you feel resistance (Fig. 15.10).
7. If necessary, inflate cuff surrounding the mask.
8. Attach connector at the end of the airway tube to colorimetric device and positive pressure device to inflate lungs.

Fig. 15.10 Final position of LMA

9. Confirm appropriate placement by:
   (a) Equality of breath sounds with auscultation.
   (b) Good chest excursions, symmetrical.
   (c) Appropriate physiologic responses (HR, SpO_2).
   (d) Appropriate changes on colorimetric and capnography devices.
   (e) (Of note, phonation will likely continue; LMA does not obstruct vocal cords.)
10. Secure device by placing a piece of tape across the LMA's tube fixation tab.

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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.

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6. Air embolus.
7. Hypertension (renal artery thrombosis).

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) Inotropes, TPN, or hypertonic glucose administration.
   (c) Frequent blood sampling in unstable patient without other access.
3. Exchange transfusion.

B. Procedure.
1. Use sterile technique.
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 or with ultrasound.
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).
8. Cardiac tamponade. Bleeding or accumulation of infused fluids can occur. Suspect if narrowed pulse pressure, muffled heart sounds, and impaired perfusion.

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 or ultrasound 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 or ultrasound 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 the ankle
      (f) Supratrochlear, superficial temporal or posterior auricular veins of the scalp
   2. Apply tourniquet if placing in extremity.
   3. Clean area with antiseptic.
   4. Attach syringe to cannula and fill with saline, and 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

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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 the 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.

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Part IV

Monitoring the Ventilated Patient

18 Continuous Monitoring Techniques

Christian F. Poets

I. *Transcutaneous partial pressure of oxygen ($PTcO_2$) 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 need calibration every 4–8 h. Fluorescence quenching, a new optical technique to measure $PTcO_2$, does not require calibration. With either technique, sensors require a 10–15 min. Warm-up period after application.

   B. Factors influencing measurements
      1. Sensor temperature. Good agreement with PaO_2 only at 44 ° C, but then frequent (2–4 hourly) repositioning necessary. The above optical method may already show good agreement with PaO_2 at 43 °C.
      2. Probe placement. $PTcO_2$ 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, $PTcO_2$ will be higher on upper than on lower half of the thorax.
      3. Peripheral perfusion. $PTcO_2$ depends on skin perfusion. If the latter is reduced, e.g., from hypotension, anemia, acidosis (pH <7.05), hypothermia, or marked skin edema, $PTcO_2$ 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, $PTcO_2$ 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%.

   D. Technique is better for trending than determining absolute value.

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II. *Pulse oximetry (SpO_2)* (Chap. 19)

A. Principle of operation

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. Early devices determined arterial absorption component by identifying the peaks and troughs in absorbance over time, thereby obtaining a "pulse-added" value that is independent of the absorbance characteristics of the non-pulsating parts of the tissue. Current instruments use additional techniques, e.g., scan through all red-to-infrared ratios found, 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 physiologic 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 every 6–8 hours. Highly flexible sensors (usually disposable) provide better skin contact and thus better signal-to-noise ratio.
2. Peripheral perfusion. Oximeters require a pulsating vascular bed; performance at low perfusion may be impaired. Some manufacturers provide continuous information about perfusion conditions so that users can check signal quality.
3. Response and averaging times. The former largely depends on the latter. Longer averaging times will increase response times and may reduce alarm rates, although the latter are more effectively reduced by introducing an alarm delay (e.g., 10 sec). The relationship between desaturation rate and averaging time has been described mathematically, so that rates observed with one averaging time can be translated into those theoretically obtained with another averaging time.
4. Movement artifact. Most frequent cause of false 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 toward 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.

C. Detection of hypoxemia and hyperoxemia

In the absence of movement, pulse oximeters have a high sensitivity for the detection of hypoxemia. Because of the shape of the O_2 dissociation curve, they are less well suited for detecting hyperoxemia. The upper alarm setting at which a $PaO_2 > 80$ mmHg (10.7 kPa) can be reliably avoided is at 95–96%.

III. *Transcutaneous partial pressure of carbon dioxide ($PTcCO_2$) monitoring*
   A. Principle of operation
      $PTcCO_2$ 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 ($CO_2 + H_2O$ / $HCO3^- + H^+$), 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 repositioning.
   B. Factors influencing measurements
      1. Sensor temperature. Optimal sensor temperature is 42 ° C, but if sensors are used in combination with a $PTcO_2$ sensor, a sensor temperature of 44 ° C can be used without jeopardizing the precision of the $PTcCO_2$ measurement.
      2. Sensor placement and skin thickness. $PTcCO_2$ measurements are relatively independent of sensor site or skin thickness, but $PTcCO_2$ may be falsely high if pressure is applied onto the sensor.
      3. Peripheral perfusion. $PTcCO_2$ may be falsely high in severe shock. Precision may already be affected if $PaCO_2$ is >45 mmHg (6 kPa) 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 sec.
   C. Detection of hypocarbia and hypercarbia
      Sensitivity to both hypocarbia and hypercarbia is 80–90%.
   D. Technique is better for trending than determining absolute value.

IV. *End-tidal carbon dioxide ($ETCO_2$) monitoring (capnometry)* (Chap. 21)
   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 (i) CO_2 equilibrium is achieved between end-capillary blood and alveolar gas, (ii) $ETCO_2$ approximates the average alveolar CO_2 during a respiratory cycle, and (iii) 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. Also provides information on thoraco-abdominal asynchrony during spontaneous breathing. 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. *Regional lung aeration using electrical impedance tomography (EIT)*
   A. EIT calculates cross-sectional (i.e., tomographic) images of the chest.
   B. Very small alternating electrical currents are applied through electrode pairs and the resulting voltages measured on the remaining electrodes.
   C. By repeating this process at a rate of about 50 images/sec, information on lung function under dynamic conditions can be sampled, as the method is sensitive to changes in conductivity in the tissue underneath the electrodes. For example, a higher lung volume reduces conductivity, while more blood or fluid volume increases it.
   D. Using this technique, continuous information about local tidal volumes, the spatial distribution of the inspired gas within the thorax or the effects of changes in PEEP on lung aeration can be obtained.

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.

Clinical Controversies in Pulse Oximetry

19

Samir Gupta, Prakash Loganathan, and Win Tin

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 (performing arterial blood gas with co-oximetry) and SpO_2 measures 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.

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H. Minimal effect of motion, light, perfusion, and temperature with the advent of "Signal Extraction Technology" in pulse oximetry which removes the noise from the artifact signals.

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.
   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:

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

      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 Met Hb). 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.

$$\textit{Fractional saturation} = \frac{\mathrm{HbO_2}}{\mathrm{HbO_2 + Hb + CoHb + MetH}} \times 100$$

      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.*
   C. Averaging time. Pulse oximetry oxygen saturation values are obtained by averaging from (period ranging from 2–16 secs) preceding measurements. This is displayed as a single oxygen saturation value, a running average of preceding measurements. Shorter averaging time detect lower saturation and frequency of desaturation episodes.

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 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 (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 pigments
   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 the probe should be confirmed by a good plethysmographic waveform and/or heart rate similar to that on the 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.
   3. Attaching the sensor to the infant and then to the extension cable of the oximeter provides slightly earlier readings (mean difference of 10 seconds).
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 like "adaptative probe off detection technology" 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 an 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. Advances in Pulse Oximetry
A. Perfusion index (PI): The new-generation pulse oximeters provide PI, which is the ratio of pulsatile signal (arterial blood) indexed against non-pulsatile signal (venous blood, skin, and tissues). Trend of PI provides relative assessment of pulse strength and indicator of

peripheral perfusion. The normal PI in term newborn infants has been reported at 0.7 (tenth percentile) and 0.5 (third percentile).

B. Pleth variability index (PVI): This has been used to assess the fluid status in adults, but there are no data evaluating its use in newborn infants.

C. Oxygen saturation histogram: provides graphical representation of distribution of oxygen saturation in different ranges over a time period. Trend of oxygen saturation histogram could help in weaning respiratory support and titration of oxygen.

D. Other measurements: A few of the new-generation pulse oximeters have incorporated non-invasive measurement of co-oximetry to provide continuous hemoglobin measurements (SpHb). This has been shown to have moderate correlation with total hemoglobin measured from the laboratory. Some of the monitors have additional measurement of end tidal carbon dioxide. All of these parameters need to be validated in further studies.

VIII. 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 other neonatal morbidities like sepsis. This has been adopted by pediatric societies around the world as part of the routine newborn evaluation.

IX. 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 gases if saturation is persistently below 80%.

H. Remember that high SaO_2 may indicate significant hyperoxemia.

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Interpretation of Blood Gases

20

Steven M. Donn and Kate Wilson

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 seconds.
      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:

$$(\text{Frequency}) \times \left(\begin{array}{c}\text{Volume of the high} \\ \text{frequency ``breaths''}\end{array}\right)^2$$

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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
	$PaCO_2$	35–45
	PaO_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

C. Acid-base status (Table 20.1).
   1. The pH of arterial blood is determined primarily by:
      (a) P_aCO_2.
      (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_aCO2 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.

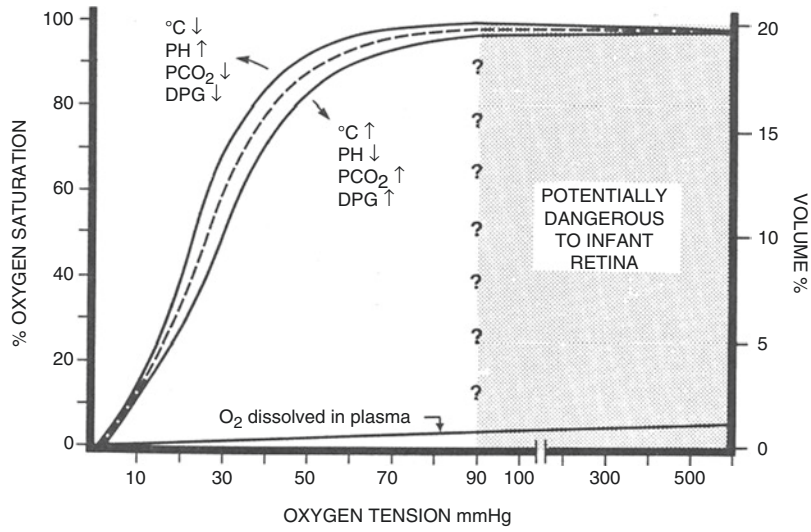

Fig. 20.1 The oxyhemoglobin dissociation curve. (From Klaus MH, Fanaroff AA. Care of the high risk neonate. Philadelphia: WB Saunders CO.; 1986. p. 173. Used by permission)

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.

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 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 are 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 overestimate 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 postoperative babies or other larger babies with only minimal lung disease. For patients who are small, 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. PaCO2 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 is 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 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 BJPD, 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 P_{50} and will supply more oxygen to tissues than a baby with more fetal hemoglobin, all other things being equal.

IX. Umbilical Cord Blood Gases
   A. Umbilical cord blood gas analysis is the most objective determination of the condition of the fetus immediately before birth.
      1. The umbilical vein carries oxygenated blood from the placenta to the fetus, thus venous cord blood values reflect the maternal condition and placental acid-base status.
      2. The umbilical arteries carry deoxygenated blood from the fetus to the placenta. Thus, the arterial cord blood values reflect the fetal acid-base status.
   B. Fetal Acid-Base Physiology. Understanding the basics of acid-base physiology in the fetus aids in interpretation of cord blood gas analysis.
      1. Carbon dioxide (CO_2) is the major acid and by-product of carbonic acid (H_2CO_3) via oxidative metabolism. Carbon dioxide and oxygen both diffuse across the placenta. Diffusion rates are primarily limited by blood flow. The rate of CO_2 production correlates with the rate of fetal oxygen consumption.
      2. Bicarbonate (HCO_3^-) is the major buffer to maintain pH within a desired range. The placenta helps buffering by maintaining HCO_3^- levels. The primary measure of change in buffering capacity is the base deficit or excess. Base deficit is a calculated value from the measured pH and PCO_2 in the blood.
      3. Hypoxemia and ischemia impair oxidative metabolism resulting in anaerobic metabolism and the production of metabolic acids, lactate, and H^+. Lactate is the most produced anaerobic acid. The accumulation of lactic acid is proportional to the degree and duration of hypoxemia.
      4. Fetal physiology is unable to react to acidosis by ways of respiratory and renal compensatory mechanisms. In response to acidemia, the fetus primarily relies on the placenta for compensation. However, as the buffering capacity is diminished, the fetus is unable to neutralize the accumulation of lactic acid, and metabolic acidosis worsens.

   C. Indications. Umbilical cord blood analysis can be routine, although not practical for all vigorous newborns, or if indicated based on certain clinical scenarios. Both the AAP and ACOG recommend analysis after any delivery in which a suspected fetal metabolic abnormality such as acidemia may result.
      1. Additional indications for cord blood collection and analysis include, but are not limited, to the following scenarios:
         (a) Maternal intrapartum fever.
         (b) Severe intrauterine growth restriction.
         (c) Multiple gestation.
         (d) Preterm gestation.
         (e) Abnormal fetal heart rate tracing.
         (f) Cesarean delivery for fetal distress.
         (g) Abruptio placentae.
         (h) Low (<5) 5-minute Apgar score.
   D. Sampling. Ideally both arterial and venous cord blood should be sampled for blood gas analysis and interpretation. Caution should be exercised in interpretation of a single cord blood gas analysis, as sampling from an unintended vessel is not uncommon.
      1. Differentiation between arterial and venous sampling is aided by the following:
         (a) Arterial pH should be at least 0.02 units lower than the venous pH.
         (b) Arterial pCO_2 is usually >4 mmHg higher than the venous pCO_2.

(c) Similar values probably indicate sampling from the same vessel, likely the vein since its large size makes it easier to sample.

2. Proper blood sampling should lead to accurate measurements. The following steps should be taken to ensure proper sampling.
   (a) Umbilical cord is double-clamped immediately after delivery.
   (b) Samples are drawn within 15 minutes of delivery.
   (c) Samples are placed into a syringe that contains the appropriate amount of heparin. Residual air bubbles, if present, should be removed from the syringe.
   (d) Samples are analyzed within 30 to 60 minutes.

E. Reliability. The effects of various sampling methods on the reliability of umbilical cord blood analysis have been reported in several studies. Sampling methods include but delayed cord clamping, delayed sampling, and delayed analysis.

1. *Effect of delayed cord clamping (DCC)*: DCC has been defined as clamping of the umbilical cord after a duration of time has elapsed. The duration can vary from 30 seconds to 2 minutes. When compared to early cord clamping, some studies found variations in the parameters such as decreased pH and HCO_3 and increase in base deficit in DCC samples, whereas other studies found no difference. A recent systematic review concluded that DCC up to 120 seconds in vaginally delivered term infants has either no effect or a small effect on acid-base parameters.
2. *Effect of delayed sampling*: Delayed sampling refers to sampling of a clamped cord at room temperature at a time other than immediately after birth. Several studies have reported that most parameters do not change over 30–60 minutes. However, a few studies have argued that at least two parameters, lactate and base excess, may not be reliable 20 minutes after delivery.

F. Parameters and Target Ranges. Components of sampled umbilical cord blood include pH, pO_2, pCO_2, HCO_3^-, and lactate. Recommended normal arterial and venous umbilical cord blood gas values are displayed in the following table (referenced from Goldsmith 2020). Ranges represent the mean and 2 standard deviations.

	Arterial cord blood	Venous cord blood
pH	7.18–7.38	7.25–7.45
pCO_2 (mmHg)	33–65	27–49
pO_2 (mmHg)	6–30	18–40
HCO_3^- (mmol/L)	17–27	16–24
Base excess (mmol/L)	0 to −8	0 to −8

G. Clinical Interpretation. The following umbilical cord blood gas parameters, pH, pCO_2, HCO_3^-, and base deficit (BD), are used for analysis and clinical interpretation. Emphasis is placed on delineating whether the gas represents an underlying acidemia (↓ pH) or alkalemia (↑ pH) and the presence of a change or disturbance in the respiratory (pCO_2) and metabolic (HCO_3^-) components. BD is useful to further differentiate acidosis. Thus, umbilical cord blood gases can then be categorized into the following disorders: respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis, mixed acidosis, and mixed alkalosis.

1. The following table represents values used to define and classify disorders of acidosis.

Classification	pCO_2	HCO_3^-	BD
Metabolic	Normal	↓	↑
Respiratory	↑	Normal	Normal
Mixed	↑	↓	↑

H. Clinical Implications. Umbilical cord blood gas analysis provides insight into the acid-base status and environment of the fetus prior to delivery. Fetal acidosis, as supported by the findings of metabolic acidosis on cord blood analysis, has been associated with adverse neonatal outcomes.
   1. The risk for neonatal morbidity is inversely related to pH. Several studies have reported a pH threshold of <7.0 to be strongly associated with an increased risk for neonatal encephalopathy and death. Additionally, a pH of <7.0 along with a base deficit of >16 mmol/L has been associated with moderate to severe neurologic deficits.
   2. The pattern of acidosis, whether arterial or venous, may provide insight into the underlying etiology of the fetal acidosis. Examples include the following:
      (a) ↓ arterial pH/↓ venous pH: Hypoxemia of a prolonged duration and usually secondary to an underlying metabolic acidemia.
      (b) ↓ arterial pH/normal venous pH: Interruption of umbilical blood flow such as cord compression or brief fetal hypoxia.
   3. Key points to remember regarding umbilical cord blood gas analysis and clinical outcomes:
      (a) Primary metabolic acidosis (↓ pH/↓ HCO_3^-) with increased lactate and a severe base deficit has been associated with an increased risk of neonatal encephalopathy and/or neurologic deficit.
      (b) Primary respiratory acidosis (↓ pH /↑ pCO_2) is not believed to be detrimental to the fetus or associated with adverse neurologic outcomes.
   4. When paired samples are unavailable, the umbilical cord venous gas can be used to predict the umbilical cord arterial gas (Cantu).

Suggested Reading

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21 Volumetric Capnography in Critically Ill Neonates and Children

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Abbreviations

Pa-ACO_2	Arterial to alveolar CO_2 gradient
$PACO_2$	Partial pressure of alveolar CO_2
$PaCO_2$	Partial pressure of arterial CO_2
Pa-$etCO_2$	Arterial to end-tidal CO_2 gradient
$PECO_2$	Partial pressure of mean expiratory CO_2
$PetCO_2$	Partial pressure of end-tidal CO_2
VCO_2	Expiratory CO_2 volume per minute
VD_{alv}	Alveolar dead space
VD_{aw}	Airway dead space
VD_{phys}	Physiologic dead space
$VECO_2$	Expiratory CO_2 volume per breath
Vte	Expiratory tidal volume
SpO_2	Pulse oximetry
SpO_2/FiO_2	Ratio of pulse oximetry and fraction of inspired oxygen concentration
OSI	Oxygen saturation index (=100*Paw*FiO_2/SpO_2)
V/Q	Ventilation/perfusion ratio
RSV	Respiratory syncytial virus

I. *Definitions*
   A. Time-based capnography: Expired CO_2 concentration plotted against time.
   B. Volume-based capnography: Expired CO_2 concentration plotted against the expired gas volume of a single breath (SBT-CO_2).

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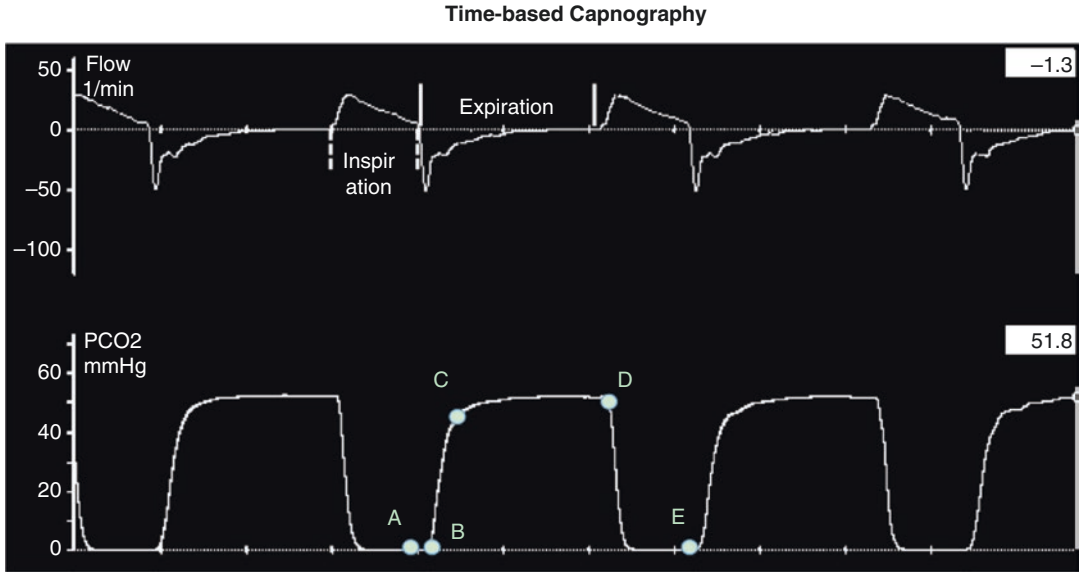
II. *Baseline Information*
   A. Shows airway integrity and alveolar ventilation.
   B. Allows hemodynamic (cardiac output) and metabolic (CO_2 production) monitoring.
   C. Provides noninvasive, easy to obtain, breath-by-breath assessment of ventilation.
   D. Graphically displays airway dead space and allows calculation of physiologic and alveolar dead spaces.
   E. Helps optimizing ventilator settings.

III. *Mainstream Technology for Gas Measurement*
   A. Infrared (IR) absorption technique.
   B. Capnostat 5 sensor.
      (i) Consists of an IR source and IR detector.
      (ii) The beam of IR radiation passes through the cuvette and the fraction of IR radiation absorbed is measured by the detector.
   C. Airway adapters.
      (i) Infants (dead space <1 mL).
      (ii) 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.
      (i) Hamilton G5, C1neo, C3 (Hamilton Medical, Reno, NV).
      (ii) Draeger VN 500 (Draeger, Telford, PA).
      (iii) Avea (CareFusion, Yorba Linda, CA).
      (iv) Servo-i (Maquet Critical Care, Wayne, NJ).

V. *Graphic Waveforms*
   A. Time-based waveform (Fig. 21.1).
      (i) A-D: Expiration.
      (ii) A-B: Early phase of expiration (mostly CO_2-free air of the upper airways).
      (iii) B-C: Mixed air of lower conductive airways and early-emptying alveolar units.
      (iv) C-D: CO_2-rich air of the alveolar units.
      (v) D: Partial pressure of end-tidal CO_2.
      (vi) D-E: Inspiration.
   B. Volume-based waveform (Figs. 21.2 and 21.3).
      (i) Phase I: Represents the first portion of the expired air and is therefore more or less free of CO_2.
      (ii) 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 (S II) of the capnogram is normally very steep, because more and more CO_2 streams out of the alveolar units.
      (iii) 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 ($etCO_2$).
      (iv) Slope CO_2: The slope of phase III (S III) represents the mean value of the ascent of phase III. Therefore, phase III is divided into three parts, in the midsection 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).

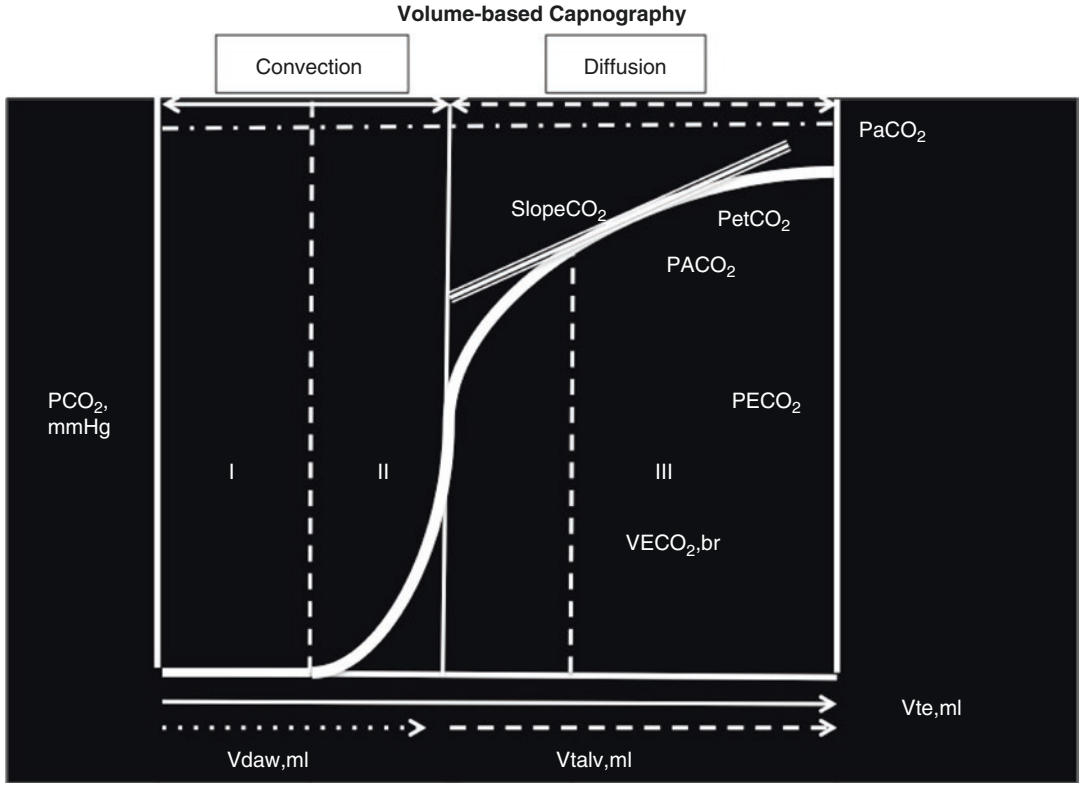


A-B: Early stage of expiration (CO_2-free air of the upper respiratory tract)
B-C: Mixed air of the lower respiratory tract and the early emptying alveolar units
C-D: CO_2 rich air of the alveolar units
D: Partial pressure of endexpiratory CO_2
D-E: Inspiration

Fig. 21.1 Time-based capnography

VI. *Dynamic Measurements/Calculations*

A. $PetCO_2$ (mmHg): End-tidal partial pressure of CO_2 in the expired air.
B. $PECO_2$ (mmHg): Mixed-expired partial pressure of CO_2, which is used to calculate the physiologic dead space (Bohr equation, see below).
C. $PACO_2$ (mm Hg): Mean alveolar partial pressure of carbon dioxide.
D. VCO_2 (mL/min): Volume of CO_2 eliminated per minute. In steady-state conditions, VCO_2 is equal to metabolic CO_2 production.
E. $VECO_2$ (mL): Breath-by-breath elimination of CO_2.
F. SIII (= Slope CO_2 [CO_2 vol%/L]): mean value of the ascent of phase III (see above).
G. Dead Spaces and Equations.
   (i) Airway dead space fraction (VD_{aw}/Vte,%).
   (ii) Physiologic dead space fraction (VD_{phys}/Vte.%).
      1. $VD_{phys}/Vte = VD_{aw}/Vte + VD_{alv}/Vte$.
      2. Bohr equation: $(PACO_2\text{-}PECO_2)/PACO_2$.
      3. Bohr-Enghoff equation: $(PaCO_2\text{-}PECO_2)/PaCO_2$.
   (iii) Alveolar dead space fraction (VD_{alv}/Vte,%).
H. Pa-$etCO_2$ (mm Hg): Arterial-to-end tidal gradient of PCO_2. Some investigators use this index as a parameter for the alveolar dead space fraction (normal values: 3–5 mmHg).
I. Pa-ACO_2 (mm Hg): Arterial-to-alveolar PCO_2 gradient. Is a more accurate index for gas exchange than Pa-$etCO_2$ (normal values: 4–8 mmHg).



Phase I: CO2-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 CO2 associated with an increase in the expired CO2 volume (VECO2,br)

Fig. 21.2 Volume-based capnography

VII. *Indications*

A. Endotracheal intubation.
   (i) Shows expiratory gas flow immediately after endotracheal intubation, confirming the tube placement.

B. Optimizing ventilatory parameters.
   (i) Respiratory rate (RR).
   (ii) Peak inspiratory pressure (PIP).
   (iii) Positive end expiratory pressure (PEEP).
   (iv) Inspiratory time (Ti).
   (v) Synchronization.

C. Evaluation of infant's spontaneous effort.
   (i) Respiratory pattern.
   (ii) Readiness for extubation.

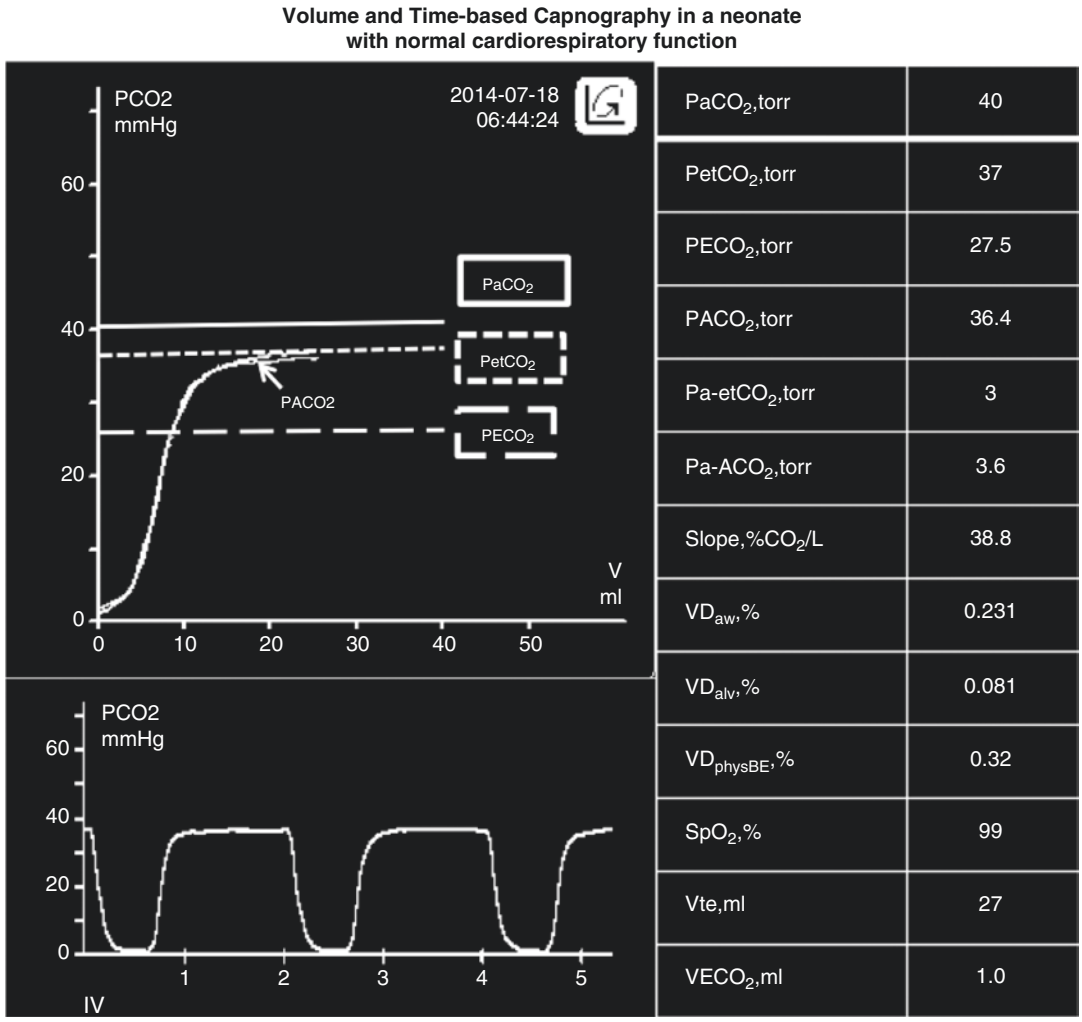


Fig. 21.3 Time- and volume-based capnography in a neonate with normal cardiorespiratory function

D. Therapeutic response to pharmacologic agents.
   (i) Bronchodilators.
   (ii) Inhaled pulmonary vasodilators.
   (iii) Surfactant.
E. Disease evaluation.
   (i) Restrictive.
   (ii) Obstructive.
   (iii) Severity.
   (iv) Recovery.

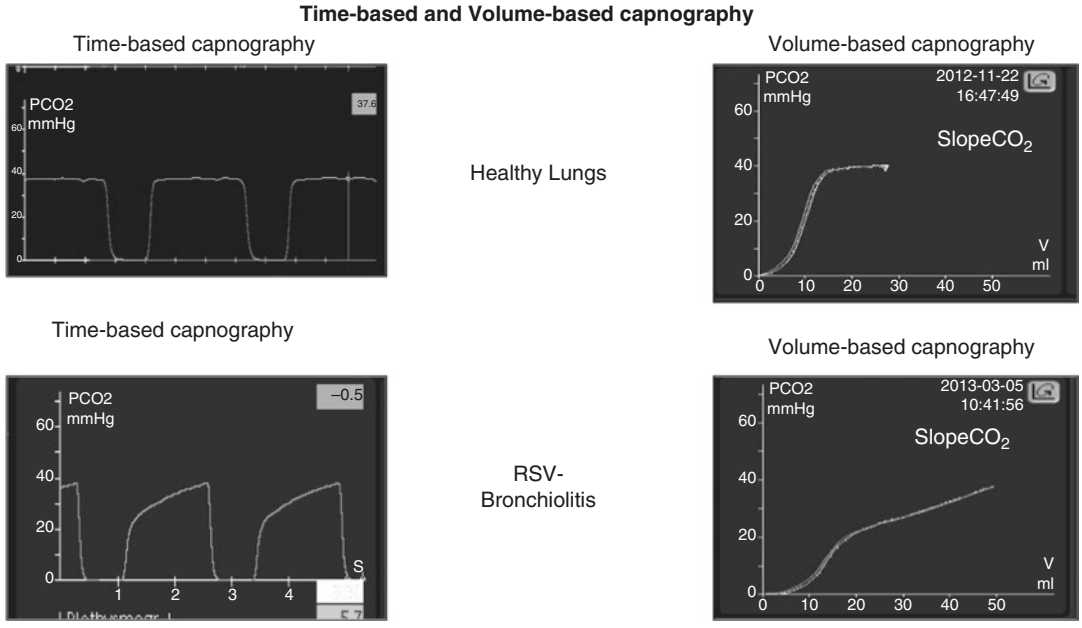


Fig. 21.4 Time- and volume-based capnography in an infant with healthy lungs and an infant with severe RSV-bronchiolitis. In severe RSV-bronchiolitis, phase II is elongated and SII is not as steep as in normally ventilated lungs. The transition between phases II and III is difficult to determine and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

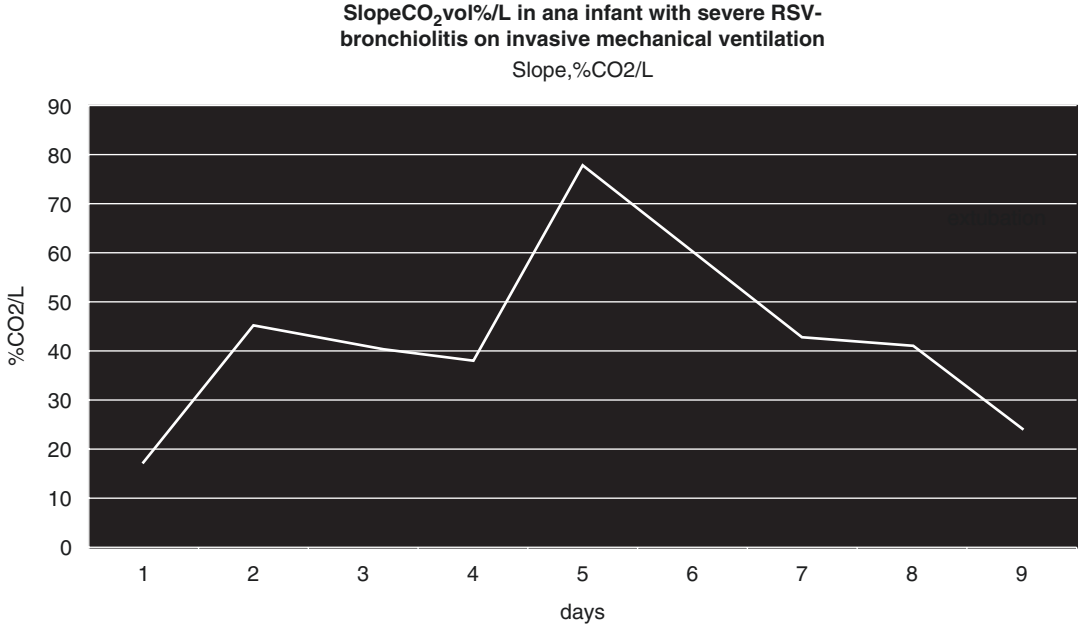


Fig. 21.5 The course of slope CO_2 (vol%/L) in an infant with severe RSV-bronchiolitis on invasive mechanical ventilation. The changes of slope CO_2 over time in an infant with severe RSV bronchiolitis show that maximum values of slope CO_2 are usually reached within 4 to 6 days. When peripheral airway obstruction improves over time, slope CO_2 decreases

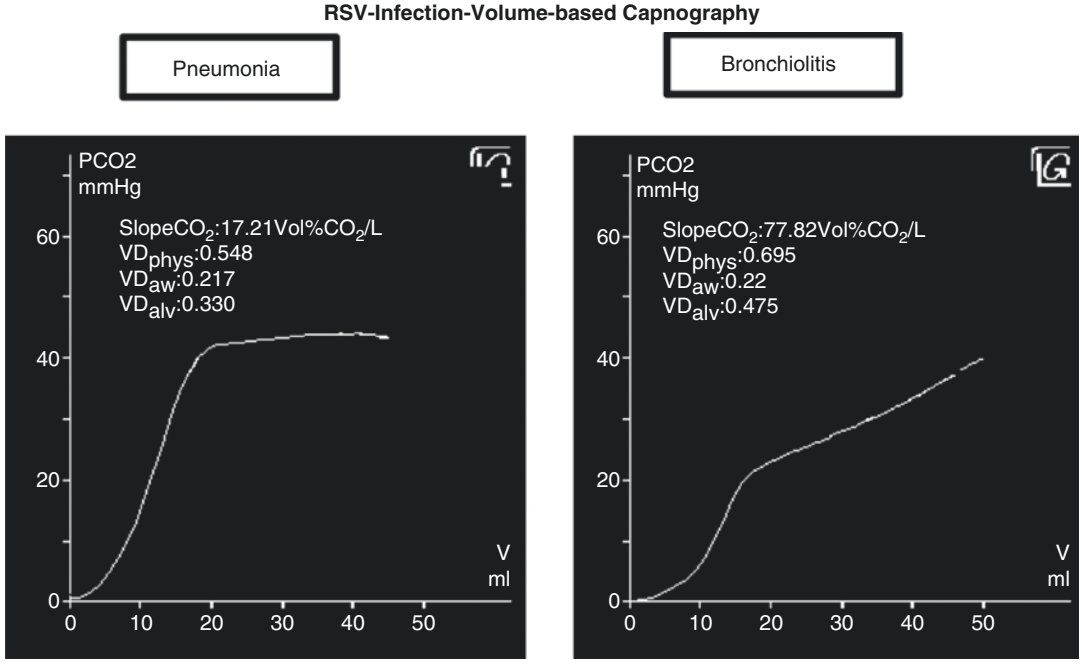
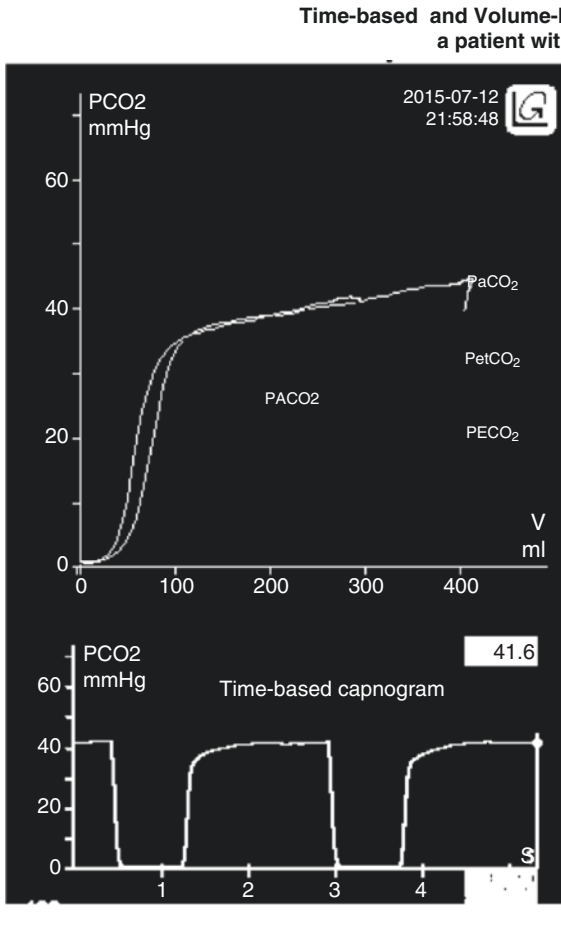


Fig. 21.6 Volume-based capnography to define severe respiratory RSV-infection. Whereas volume-based capnogram looks normal in an infant with severe RSV-pneumonia, there are significant changes in phases II and III in an infant with severe RSV-bronchiolitis



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 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)

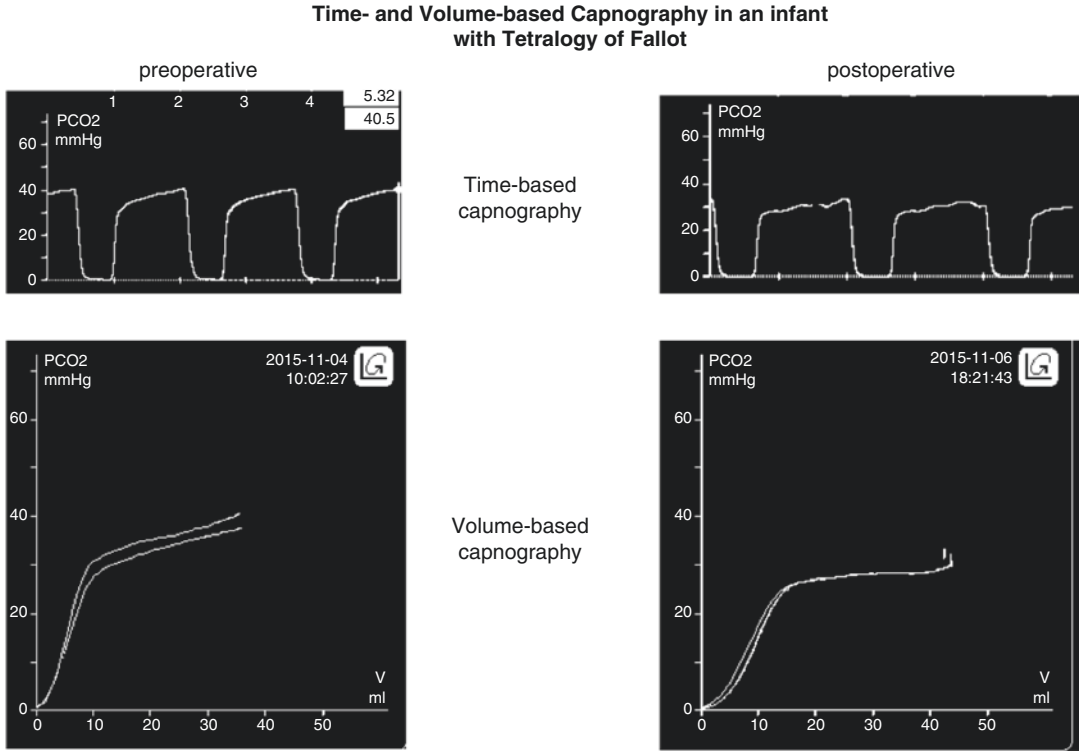


Fig. 21.8 Pre- and postoperative time- and volume-based capnography in an infant with the tetralogy of Fallot. Improved postoperative pulmonary perfusion can be seen on both time- and volume-based capnograms

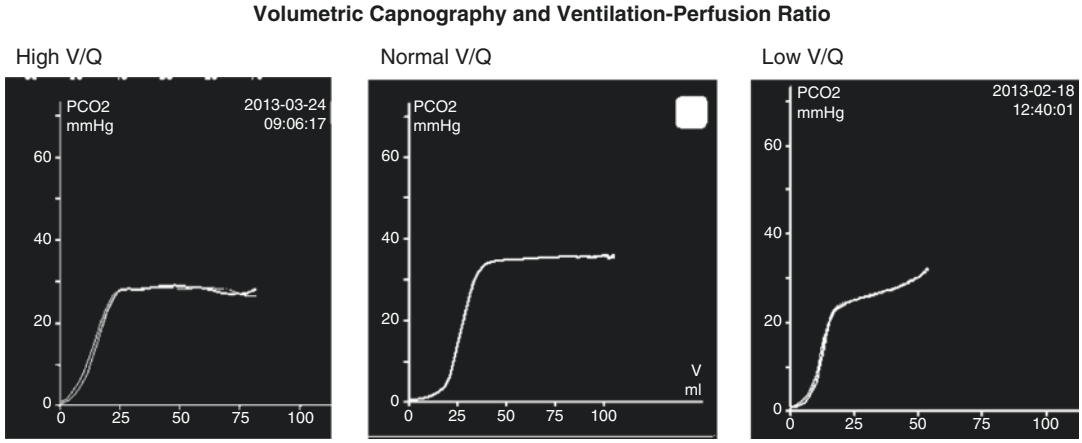


Fig. 21.9 Volume-based capnography and ventilation-perfusion matching. Three different volume-based capnograms with high, normal, and low ventilation-perfusion matching

Suggested Reading

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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
   D. Evaluation of respiratory waveforms, loops, and mechanics
      1. Waveforms
         (a) Pressure
         (b) Flow
         (c) Volume

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https://doi.org/10.1007/978-3-030-93997-7_22

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 (GUI)

A. Graphical user interfaces 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 two decades 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. The 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. 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.
4. Respiratory impedance plethysmography is an evolving technique.

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 and 980 (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)

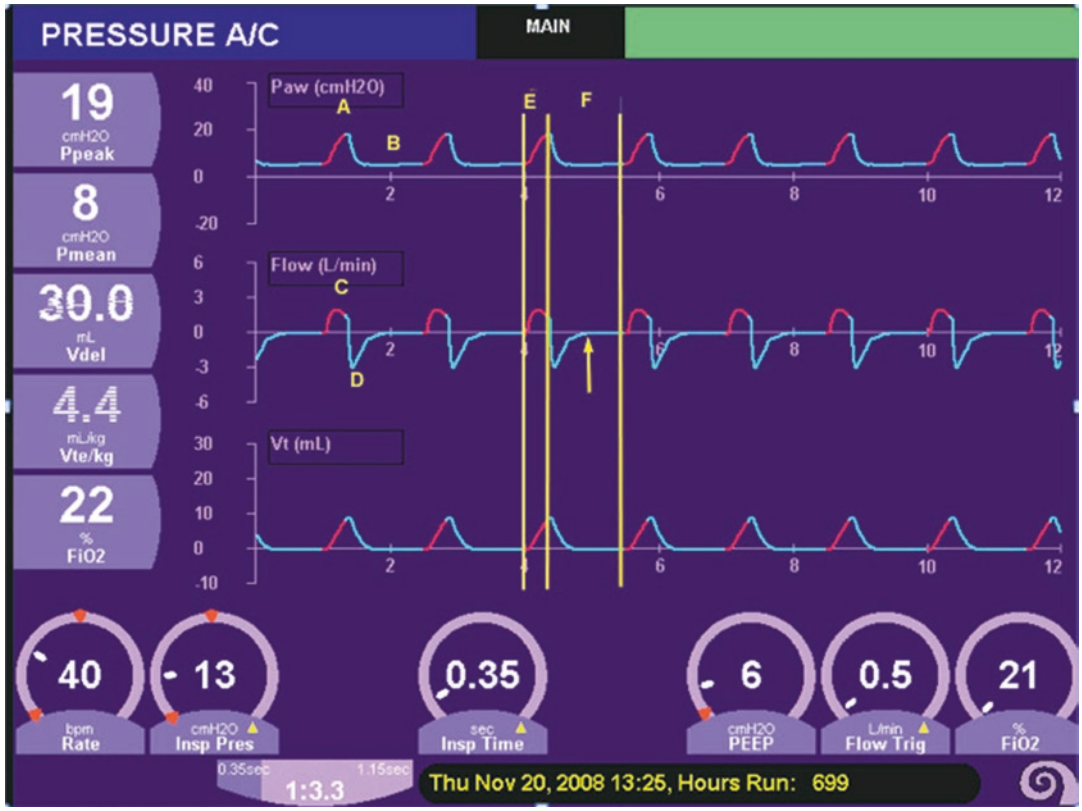

Fig. 22.1 The pressure waveform. See text for full description

8. Fabian (Acutronic)
9. Others

G. Neonatal-pediatric ventilators that are still in use, but not currently being manufactured
1. VIP BIRD/GOLD with Bird Graphic Monitor (CareFusion Healthcare, 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 upsweep of the waveform represents inspiration and the downsweep 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).

B. Flow
1. Flow waveform (Fig. 22.1 center waveform)
   (a) Horizontal line is the zero flow point. Upsweep of the flow waveform above this line is inspiratory flow, and downsweep is expiratory flow.
   (b) Greatest deflection above reference equals peak inspiratory flow (C).

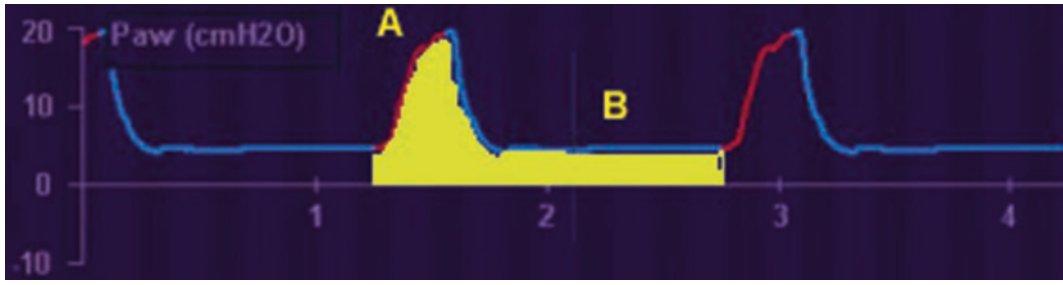

Fig. 22.2 Graphic display of mean airway pressure

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

(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

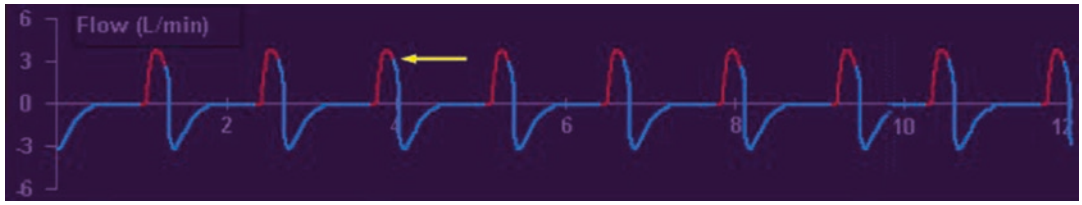

Fig. 22.4 This flow waveform illustrates flow cycling. Red shows inspiration, blue expiration. Arrow shows end-inspiration above zero flow baseline

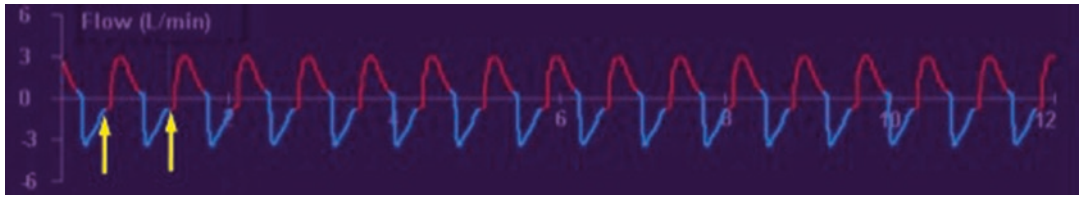

Fig. 22.5 Flow waveform demonstrating gas trapping

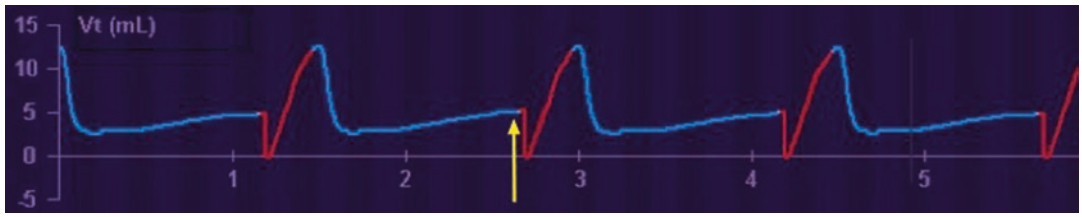

Fig. 22.6 Flow waveform demonstrating an endotracheal tube leak. Note that expiratory flow does not completely returns to baseline before the next breath

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. 22.1 F). When expiratory flow returns to zero, lung deflation is complete.

(h) If flow has not reached zero before the next breath is delivered, gas trapping may occur (Fig. 22.5, arrow).

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.

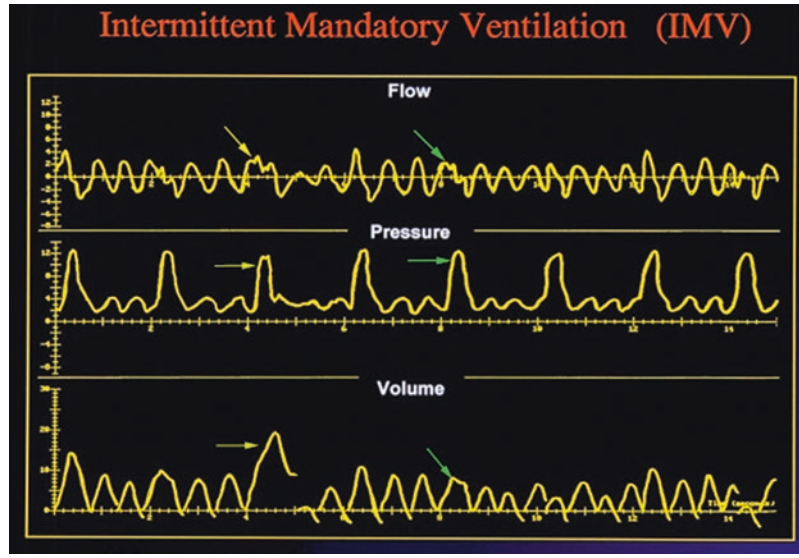

Fig. 22.7 Intermittent mandatory ventilation. Yellow arrows show patient effort augmenting the ventilator breath, with very high Vt. Green arrows show patient beginning exhalation during machine inspiration

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; red arrows show an non-augmented spontaneous breath.
   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; 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 upsweep from the baseline (PEEP) terminating at PIP. Expiration is the downsweep 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.

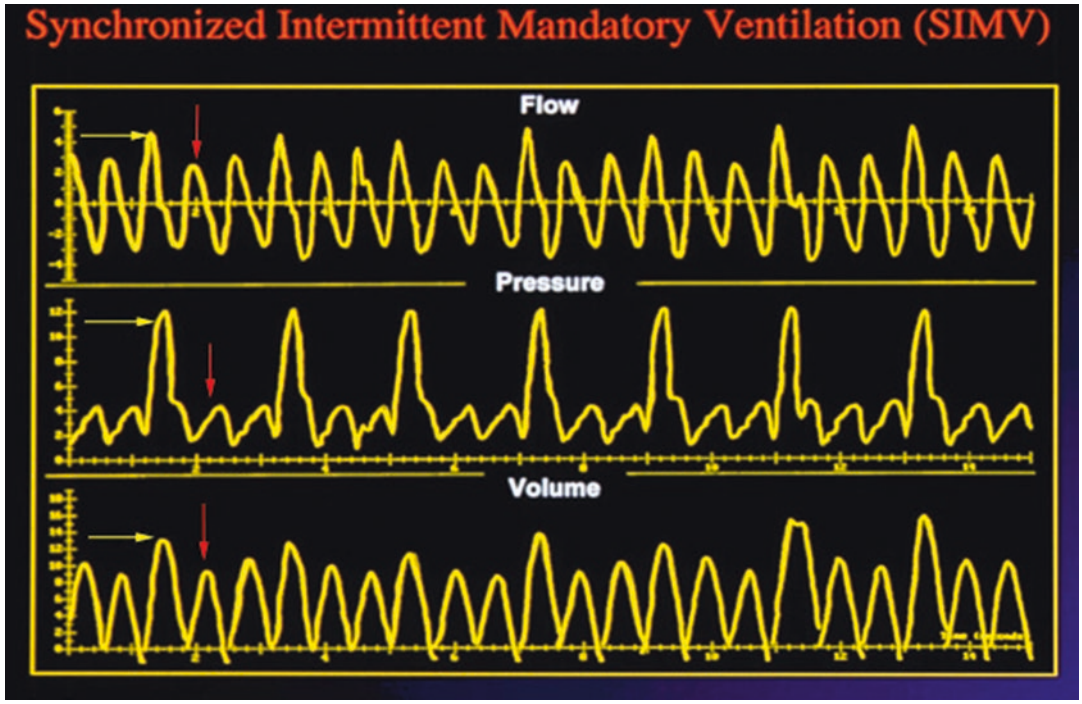

Fig. 22.8 Synchronized IMV. Yellow arrows show a synchronized machine breath, red arrows show an unaugmented spontaneous breath

(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.

(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-eight" 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 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.

(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 need for suctioning or draining water from circuit (Fig. 22.19).

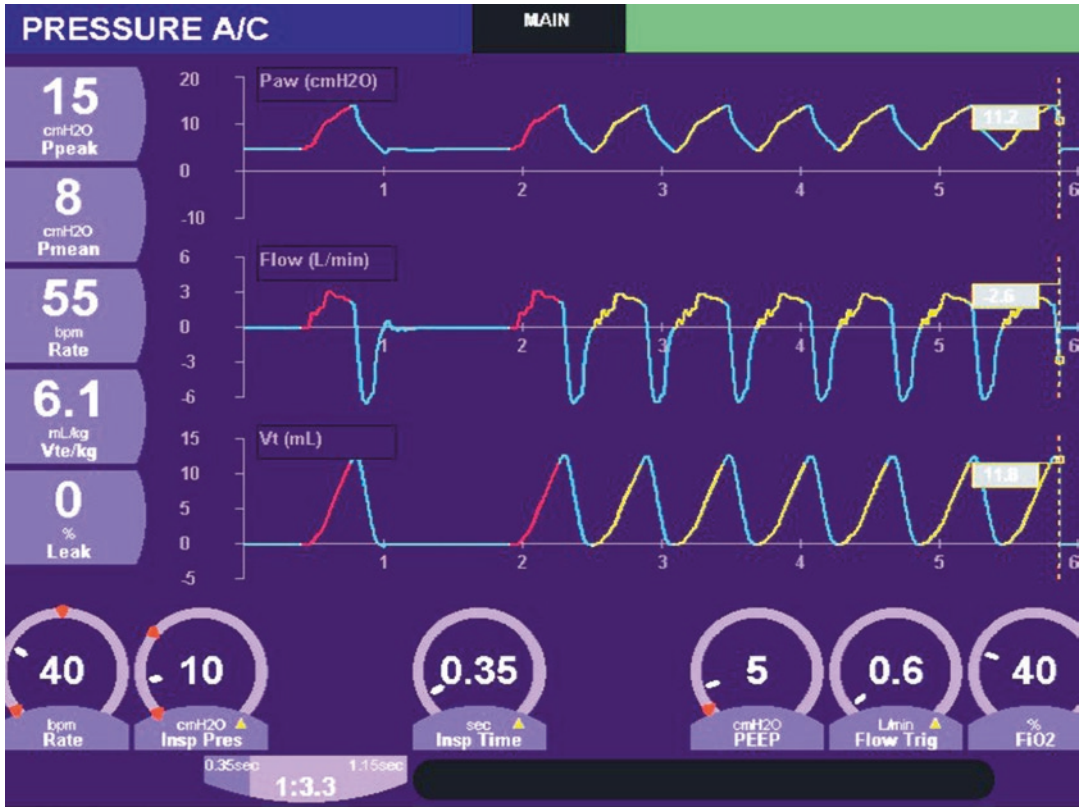

Fig. 22.9 Assist/control. Red shows a time-cycled machine delivered breath during apnea, and yellow shows patient initiated breaths

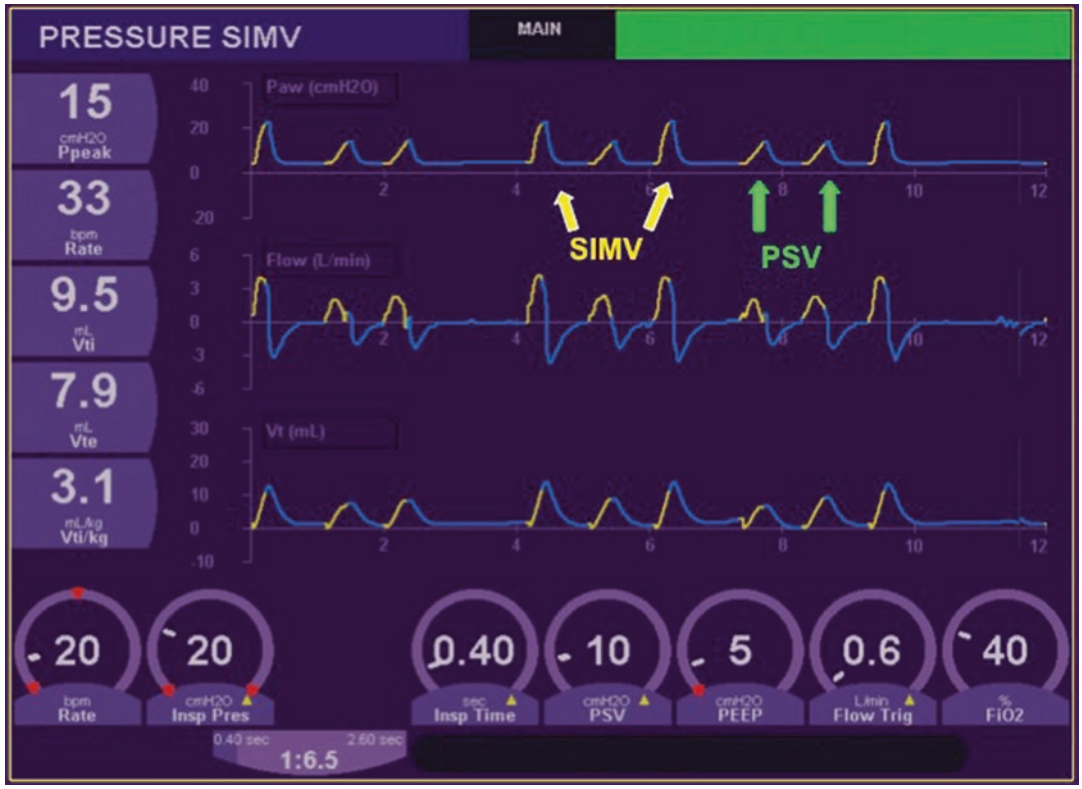

Fig. 22.10 Pressure support during SIMV

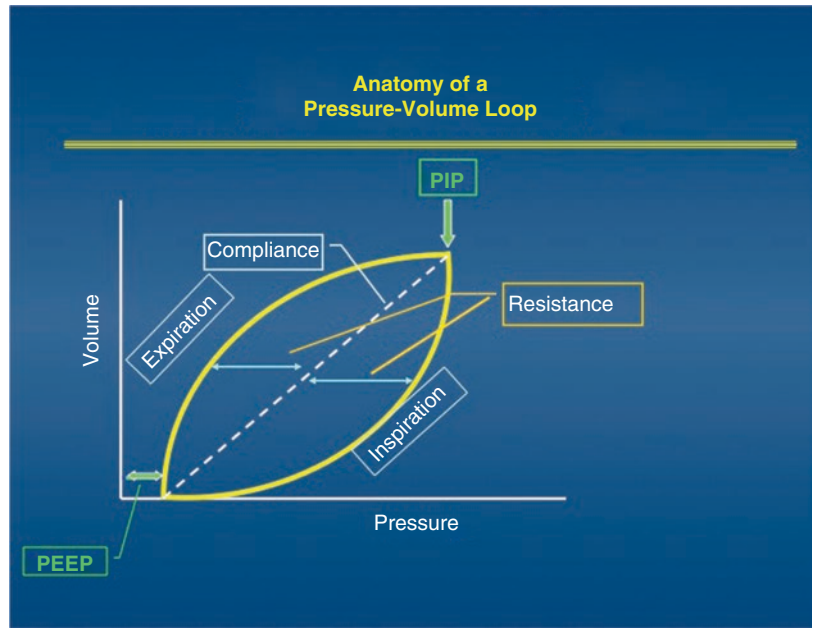

Fig. 22.11 The pressure-volume loop

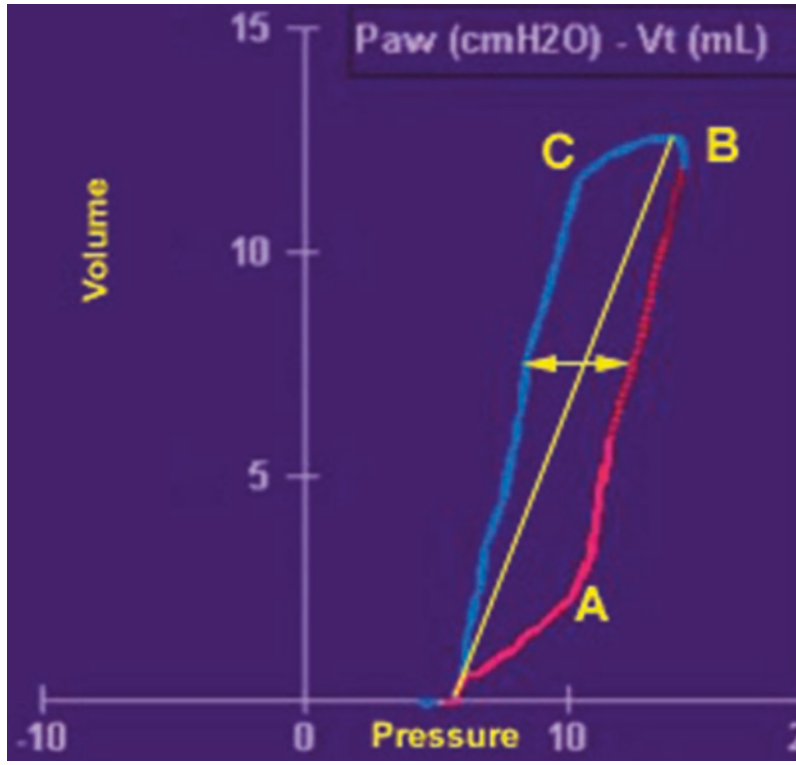

Fig. 22.12 PEEP assessment using the *P-V* loop

2. Be aware that the flow-volume loops are not standardized among manufacturers. Some devices "draw" the loop in a clockwise direction, while others do it in a counterclockwise direction.
3. Large endotracheal tube leaks can alter the appearance and accuracy of loops.
4. Proper scaling of axes is also necessary.

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.

$$C_D = \frac{V_{Ti}}{\text{PIP-PEEP}}$$

2. Static compliance is the measurement based on static pressure

$$C_{ST} = \frac{V_{Ti}}{\text{PIP-PEEP}}$$

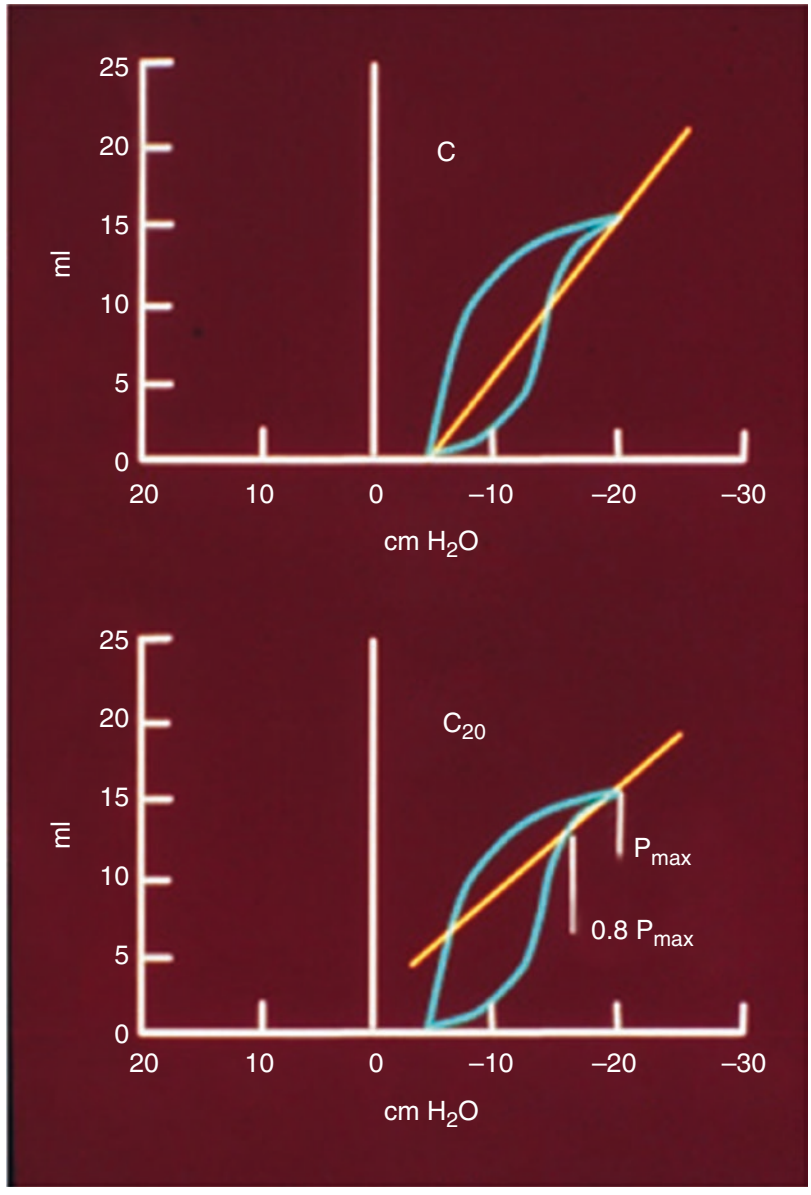

Fig. 22.13 Lung overdistension as assessed by the C_{20}/C ratio

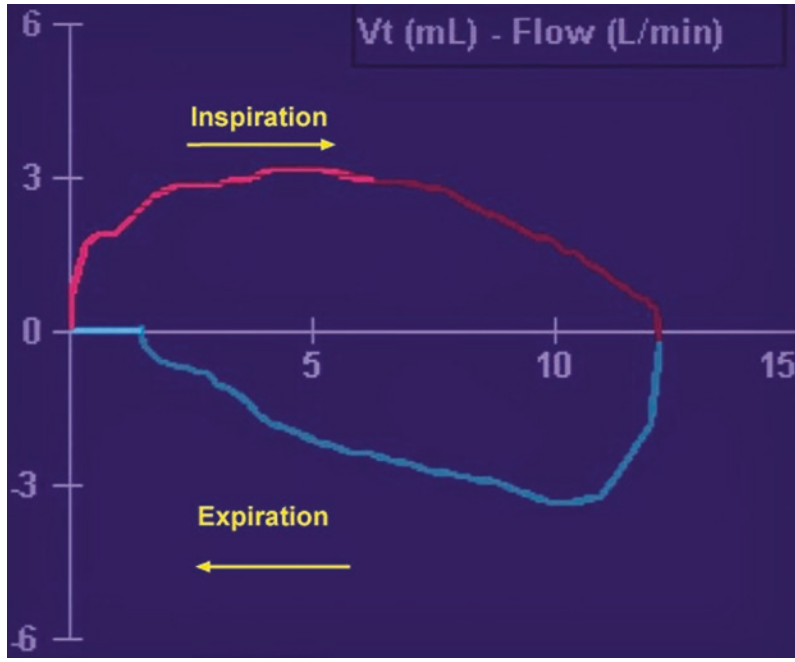

Fig. 22.15 The flow-volume loop

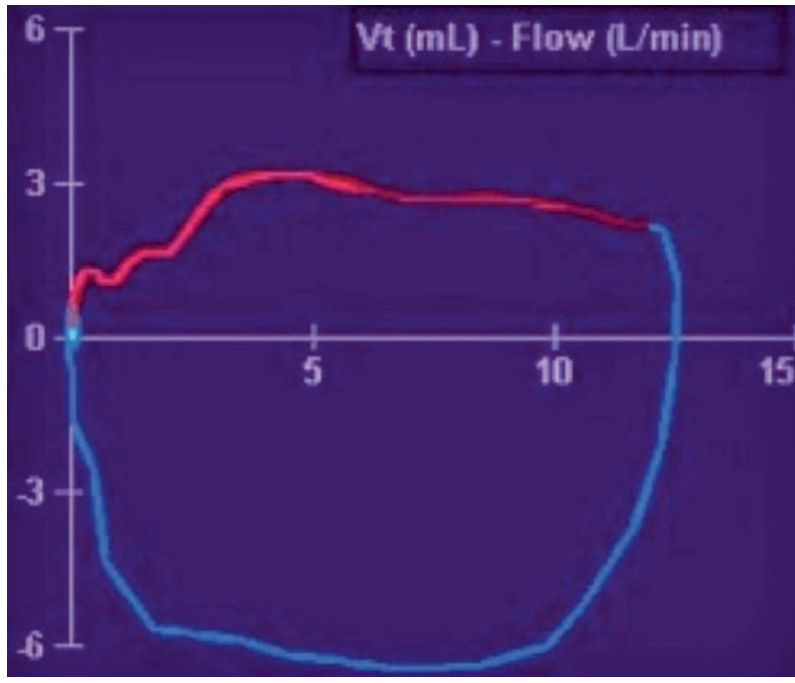

Fig. 22.16 $\dot{V}$ -*V* loop showing increased inspiratory resistance

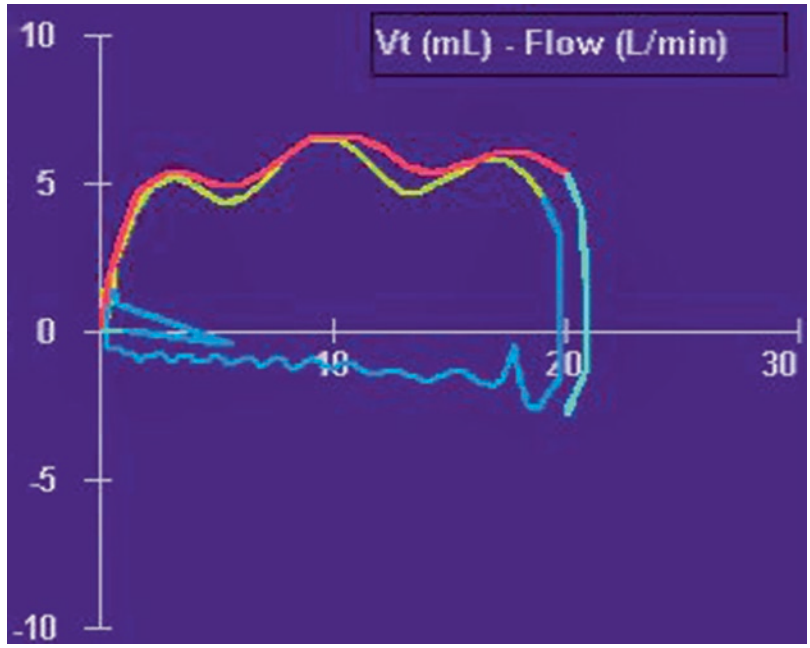

Fig. 22.17 $\dot{V}$ -V loop showing increased expiratory resistance

Fig. 22.19 Flow-volume loop on an infant in need of suctioning

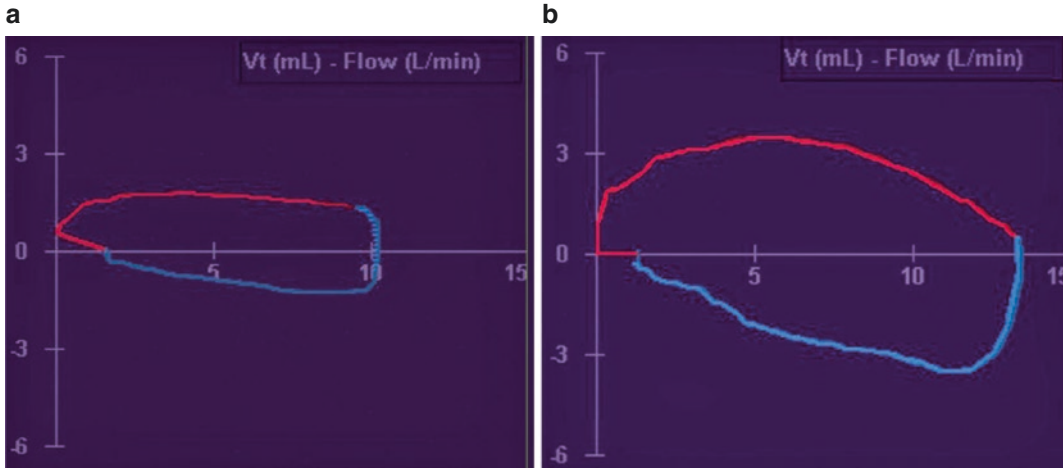

Fig. 22.18 $\dot{V}$ -*V* loop showing bronchodilator effect. A, pretreatment. B, posttreatment

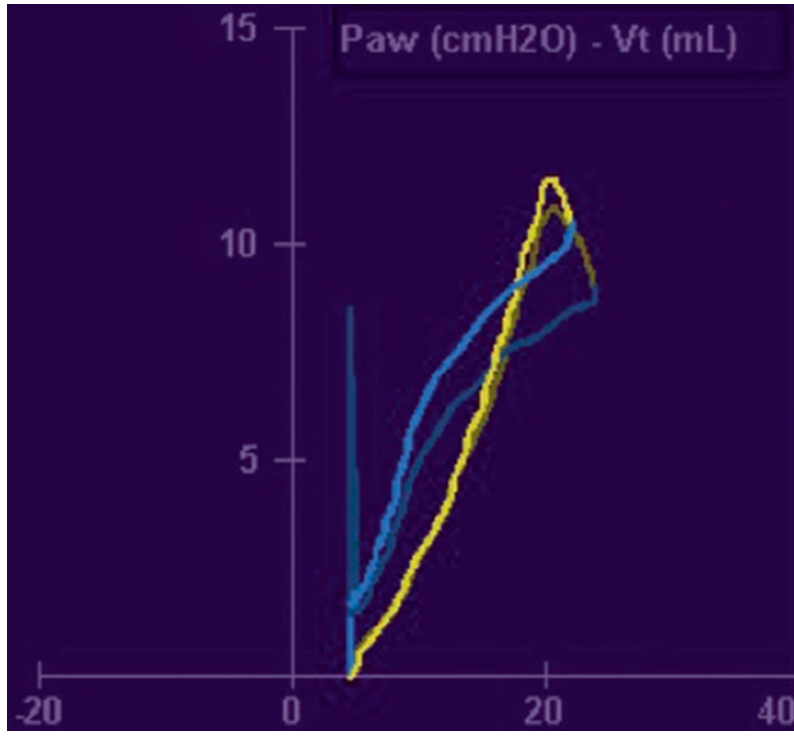

Fig. 22.14 *P-V* loop showing inadequate inspiratory flow resulting in figure 8 appearance

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.

$$R_{AW}\left(\text{cm}\,H_2O/\text{L}/\text{sec}\right)=\frac{\text{PIP-PEEP}}{\text{Flow}}$$

Suggested Reading

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Diagnostic Imaging

23

Jane S. Kim, Jonathan Zember,
and Ramon Sanchez-Jacob

I. Introduction
   A. Conventional chest radiography is the primary imaging modality used for evaluation of the neonatal chest.
   B. Computed tomography (CT), magnetic resonance imaging (MRI), 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 performed 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, which decrease radiation exposure without affecting image quality. This technology also allows almost immediate availability of images and different visualization options, such as magnification, electronic archiving, and network transmission.
      5. The anteroposterior (AP) view is the primary projection used. Lateral and cross table views can be obtained in selected cases for improved delineation of support devices, additional evaluation of pneumothoraces, pneumomediastinum, and pleural effusions.
   B. Common Indications
      1. Respiratory distress
      2. Abnormal blood gases
      3. Sepsis and/or pneumonia
      4. Cardiac anomalies

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S. M. Donn et al. (eds.), *Manual of Neonatal Respiratory Care*,
https://doi.org/10.1007/978-3-030-93997-7_23

5. Suspected congenital anomalies
6. Postsurgical evaluation
7. Assessment of catheters and tubes

III. CT

A. Introduction. A thin X-ray beam is projected through the body and measured by detectors. The X-ray beam and the detectors rotate 360° 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 parenchymal disease
5. Postsurgical evaluation
6. Imaging guidance for percutaneous procedures
7. Evaluation for interstitial lung disease

C. Advantages
1. Excellent characterization of lung parenchyma.
2. Short acquisition times with newer generation multidetector scanners 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 and/or anesthesia and possibly intravenous iodinated contrast administration

IV. 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 postsurgical evaluation of cardiovascular anomalies incompletely evaluated on echocardiogram including suspected vascular rings
2. Mediastinal masses
3. Further characterization of congenital anomalies detected on prenatal sonography

C. Advantages
1. *No ionizing radiation*
2. Exquisite soft tissue characterization
3. Multiplanar and 3D capabilities
4. Dynamic evaluation (multiple phases of contrast, cardiac motion, functional assessment).
5. Can be performed in utero

D. Disadvantages
1. Limited evaluation of lung parenchymal disease.
2. Requires transport to the scanner.
3. May require sedation and/or anesthesia and possibly intravenous gadolinium-based contrast administration.

4. Long acquisition time makes continuous monitoring of vital signs difficult.
5. Cold environment requires monitoring of patient temperature.
6. Requires specialized nonmetallic monitors secondary to magnet incompatibility with standard monitor equipment.
7. Limited availability at some institutions.
8. Expensive.

V. US
   A. Introduction: US waves propagate similarly to sound waves through a medium. Transmitted US waves reflect from tissue interfaces back to the detection transducer. Different tissues have different acoustic properties. With diagnostic US, a body part is exposed to sound waves to produce images of the inside of the body. US *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 performed.
   D. Disadvantages
      1. Operator dependent.
      2. Superimposed structures such as air, dressing, hardware, and osseous structures can limit the field of view and cause imaging artifacts.
      3. Incomplete coverage; limited by scan planes and points of access.
      4. Imaging appearance of lung parenchymal pathology is often nonspecific.

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), with images transferred in real time to a television-like monitor screen.
   B. Common Indications
      1. Esophagogram for tracheal, esophageal, or vascular anomalies
      2. Pre- and postsurgical evaluation of tracheoesophageal anomalies
      3. Evaluation of diaphragmatic motion
      4. Airway evaluation for tracheobronchomalacia or subglottic stenosis
      5. 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

VII. Common Clinical Applications
  A. Lung Disease in the Preterm Infant
    1. Respiratory Distress Syndrome (RDS)
      (a) Typical radiographic pattern is diffuse, bilateral, and symmetric granular opacities 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).

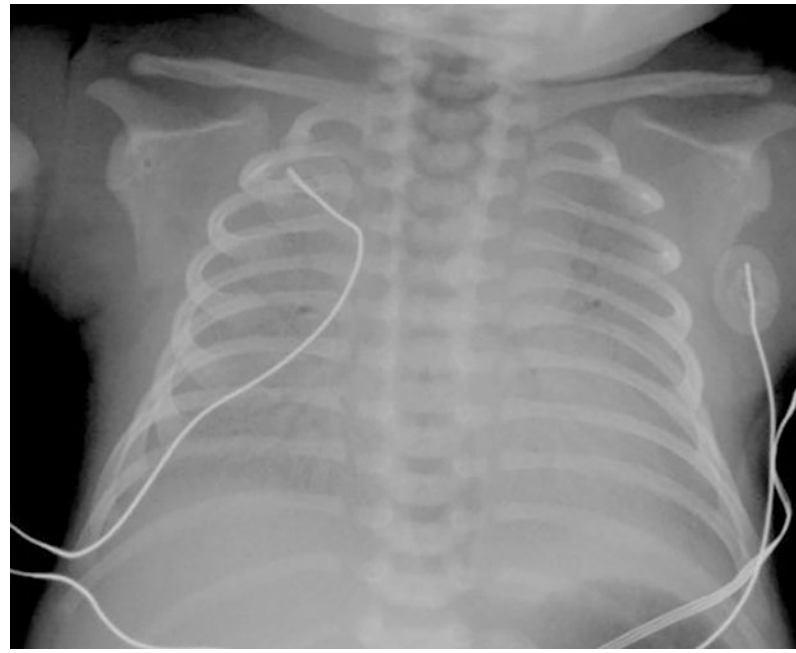

Fig. 23.1 RDS. Frontal chest radiograph shows symmetrically underinflated lungs with bilateral granular opacities and air bronchograms

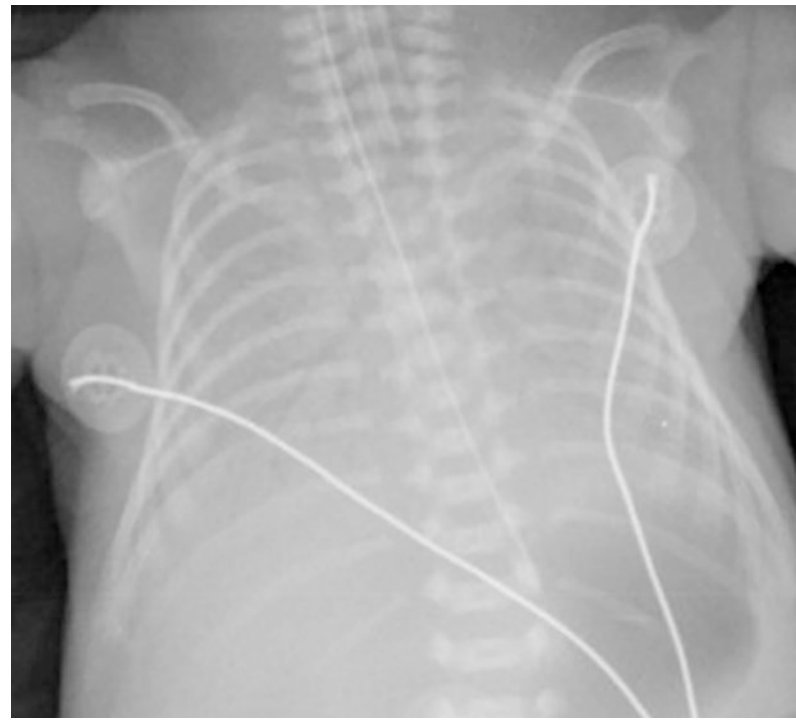

Fig. 23.2 RDS. Frontal chest radiograph shows complete opacification of lungs with indistinctness of the cardiomediastinal silhouette secondary to atelectasis

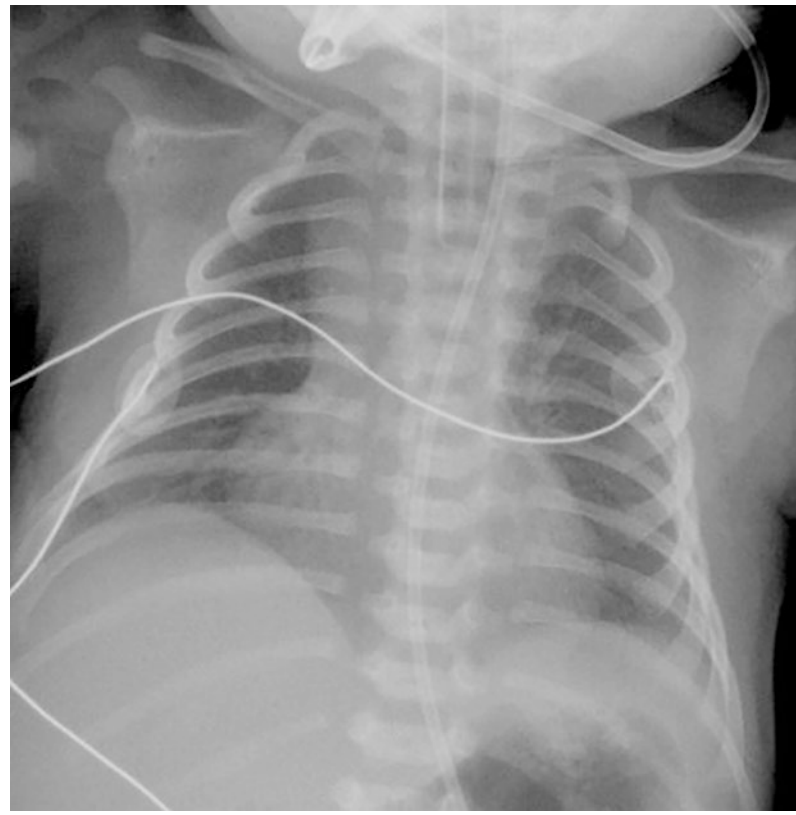

Fig. 23.3 RDS. Frontal chest radiograph performed 24 hours later after endotracheal intubation and surfactant treatment. Lung aeration has improved with mild residual bilateral granular pattern and air bronchograms

(c) Assisted ventilation may produce a radiographic appearance of normal aerated lungs (Fig. 23.3).
(d) Nonhomogeneous distribution of surfactant may cause an asymmetric appearance of the typical radiographic pattern (Fig. 23.4).
(e) A patent ductus arteriosus (PDA) with a left-to-right shunt may cause worsening of the radiologic pattern despite adequate treatment (Fig. 23.5).

B. Bronchopulmonary Dysplasia (BPD)
1. A form of chronic lung disease (CLD) common in low birth weight premature infants treated with mechanical ventilation.
2. The most common radiographic appearance is diffuse, coarse, bilateral interstitial markings with lung hyperinflation and parenchymal pseudocysts with little change over time (Fig. 23.6).
3. If pulmonary hypertension is present, cardiomegaly can occur.
4. Early stages simulate and overlap RDS. End-stage disease progresses to pseudocystic lung changes with linear opacities representing atelectasis and septal thickening.
5. Limited thin slice low-dose high-resolution chest CT can be performed to evaluate 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, which are more common on the right (Fig. 23.8).

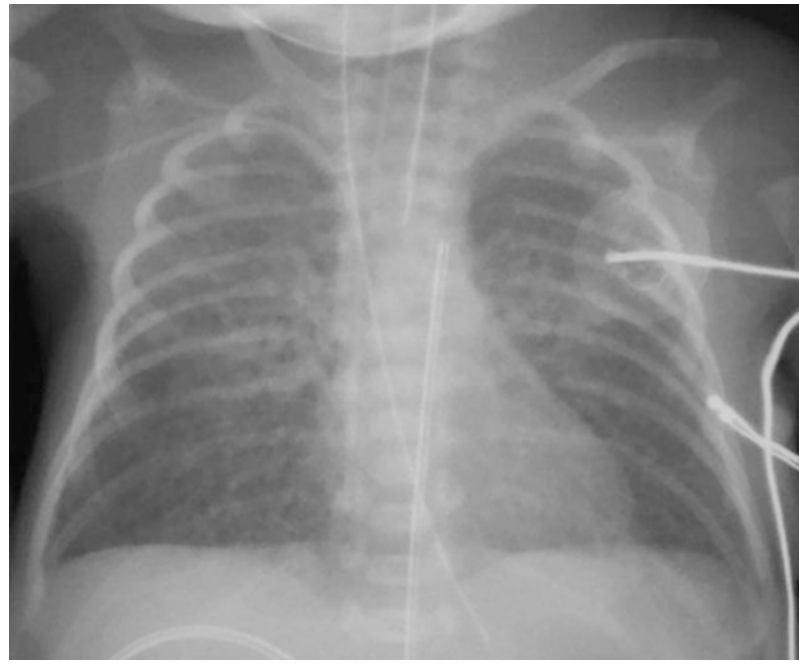

Fig. 23.4 RDS. Note the improved aeration of lower lobes compared to the upper lobes secondary to heterogeneous distribution of surfactant

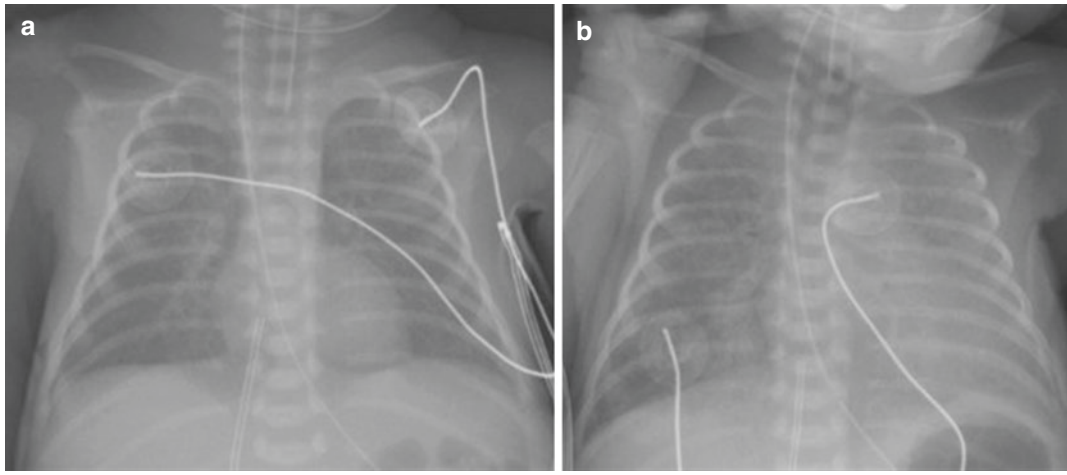

Fig. 23.5 RDS. (**a**) A 4-day old neonate with a diffuse bilateral and symmetrical granular pattern consistent with RDS. (**a**) On day of life eight, there was significant worsening of respiratory status. Diffuse, bilateral airspace opacities and cardiomegaly are present secondary to a large PDA with a significant left-to-right shunt

2. Findings are usually symmetric and the heart may be mildly enlarged.
3. Radiographic findings usually resolve in 12–24 hours 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 rope-like perihilar and patchy nodular opacities representing atelectasis and lung consolidation (Fig. 23.9).

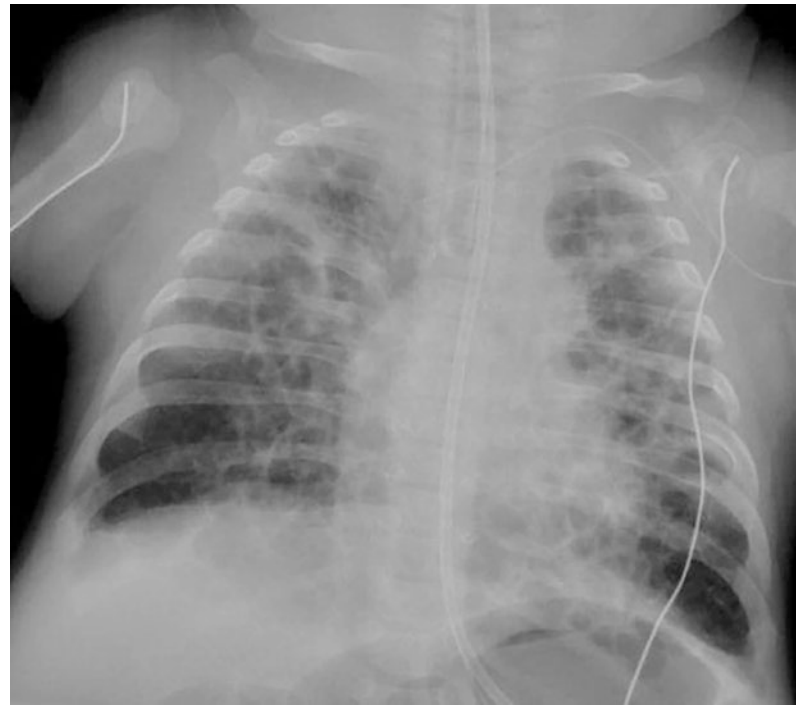

Fig. 23.6 BPD. Hyperinflated lungs with diffuse, bilateral interstitial coarse opacities and pseudocystic changes are typical radiographic findings

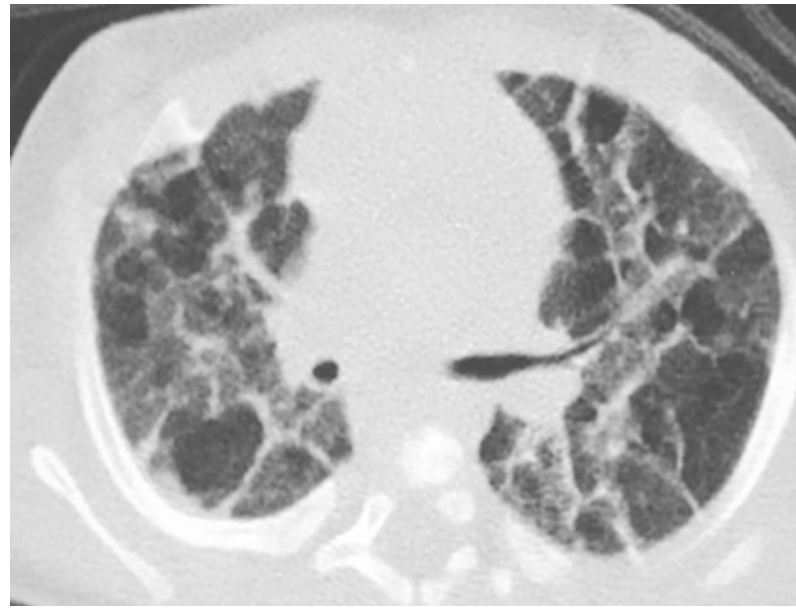

Fig. 23.7 BPD. Axial high-resolution CT in a 3-month-old male shows the presence of multiple linear opacities of septal thickening and parenchymal bands, diffuse ground-glass opacities (denser areas), and scattered areas of air trapping (darker areas)

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. PPHN. Idiopathic PPHN manifests as hyperlucent lungs with decreased pulmonary vascularity (Fig. 23.10).

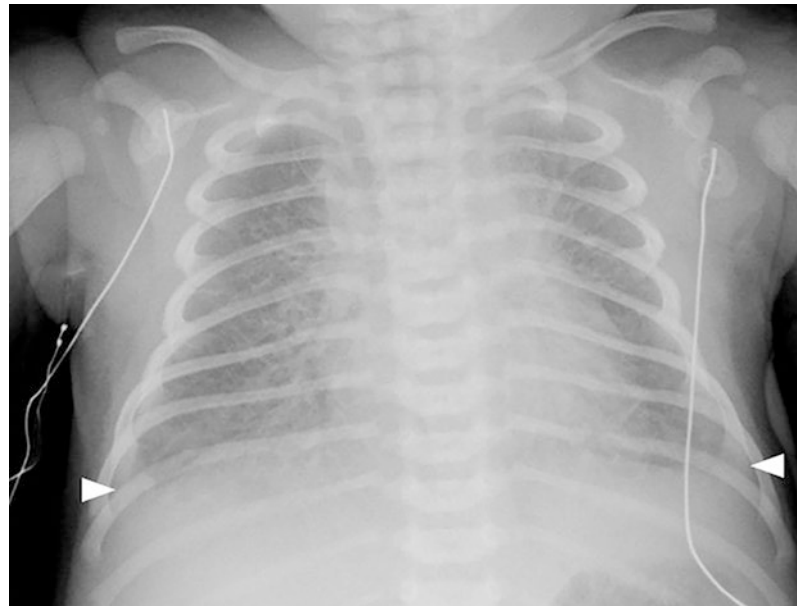

Fig. 23.8 TTNB. Frontal radiograph shows diffuse, bilateral, and symmetric prominent interstitial markings as well as small pleural effusions, with bilateral costophrenic angle blunting (arrowheads)

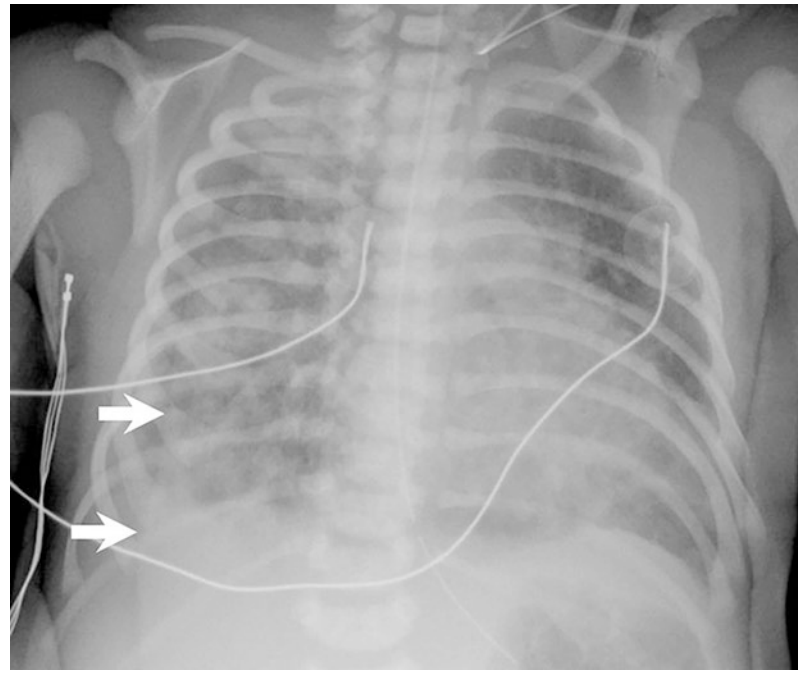

Fig. 23.9 Meconium aspiration. Diffuse, bilateral patchy opacities representing atelectasis and consolidation are seen on this chest radiograph. Note that the heart is mildly enlarged. The vertically oriented linear density (arrows) projecting over the right hemithorax extending below the diaphragm represents a skin fold mimicking a pneumothorax

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 appearances include a diffuse granular pattern similar to RDS, bilateral coarse, or scattered mixed air space-interstitial opacities (Fig. 23.11). Lungs are usually normally aerated, and pleural effusions may also be present.

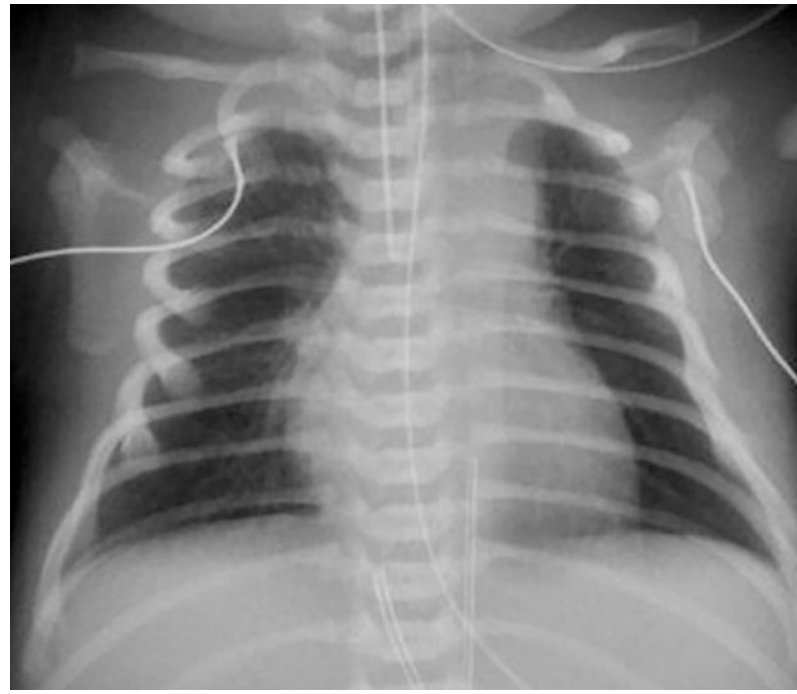

Fig. 23.10 PPHN. Radiograph shows symmetrical hyperlucent lungs and decreased pulmonary vascularity in a 1-day-old neonate

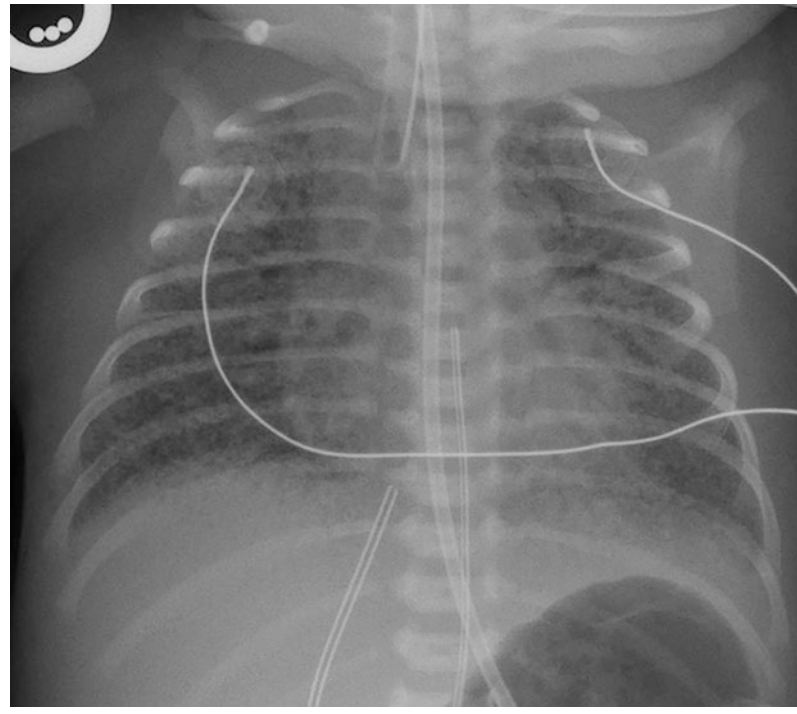

Fig. 23.11 Neonatal pneumonia. Neonate with group B streptococcal pneumonia. Note the diffuse and bilateral mixed interstitial and alveolar opacities. Thickening of the minor fissure is also seen

3. Isolated air space opacities with air bronchograms are uncommon in this age group but may be seen.
4. US can be used to differentiate focal lung consolidation from other lung parenchymal opacities and can identify the presence of pleural fluid.
5. CT may be used in specific circumstances to rule out rare complications, such as lung abscess (Fig. 23.12) and bronchopleural fistula formation.

B. Atelectasis
1. Atelectasis may be segmental, lobar, or total. On radiographs, atelectasis manifests as lung opacification with signs of volume loss including fissure displacement, diaphragmatic elevation, and mediastinal shift proportional to degree of lung collapse (Fig. 23.13).

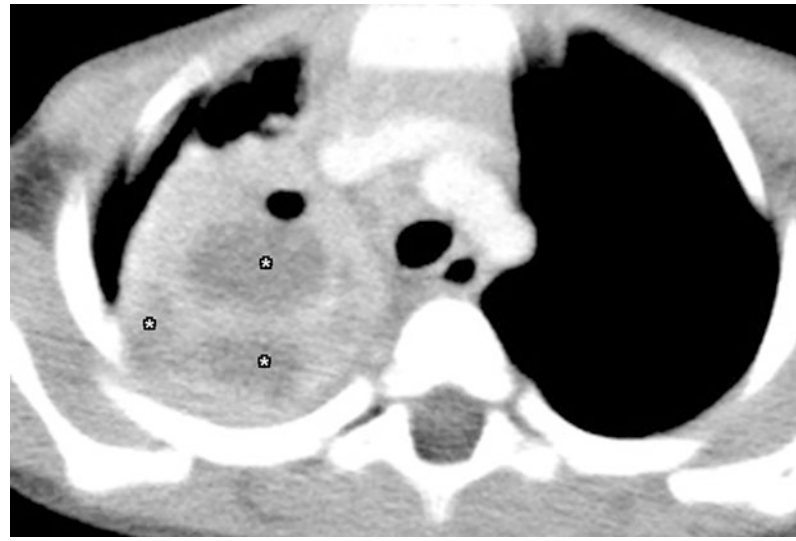

Fig. 23.12 Pneumonia. Axial CT image performed after intravenous contrast administration. Note a right upper lobe air space opacification with non-enhancing areas (*) and an air-fluid level representing necrotizing pneumonia

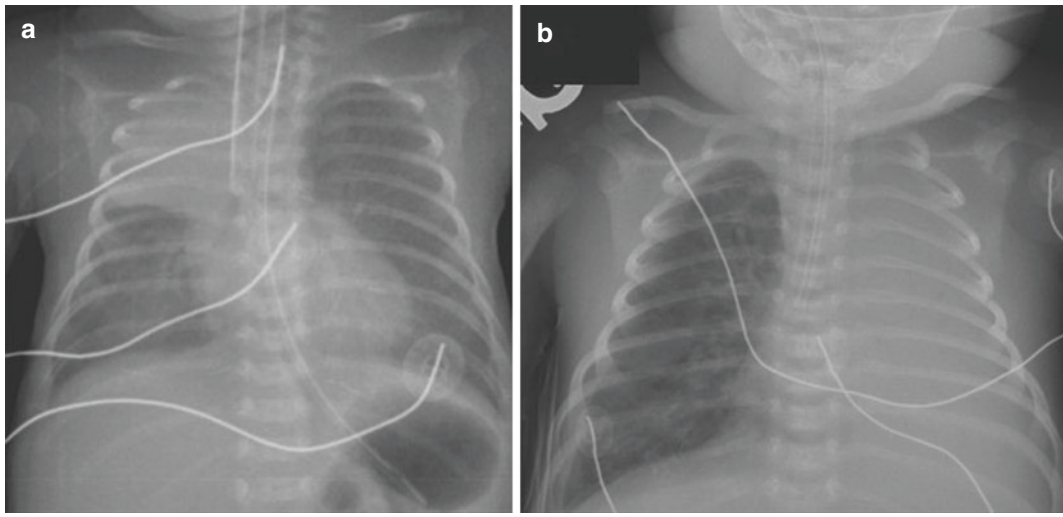

Fig. 23.13 Atelectasis. (**a**) Right upper lobe atelectasis (arrow). Note the trachea is slightly deviated to the right and there is also obscuration of the right upper mediastinum. (**b**) Left lung collapse with complete opacification of the left hemithorax and obscuring of the left heart border and upper mediastinum. Note the position of the ETT tip below the carina

This usually occurs with endotracheal tube (ETT) malposition and after extubation and typically resolves rapidly.

2. Rapid resolution differentiates atelectasis from other causes of lung opacification.
3. Poor radiographic technique (expiratory images, rotation, and underexposure) may simulate atelectatic lungs as well as cardiomegaly (Fig. 23.14).
4. A normal thymus may simulate lung atelectasis. US has been used to differentiate atelectasis from normal thymus simulating a collapsed lobe (Fig. 23.15).

C. Pleural Effusion

1. Supine films underestimate the amount of pleural fluid, and small effusions may be subtle. Increased lung density, blurring of the diaphragm and heart contour, thickening of the

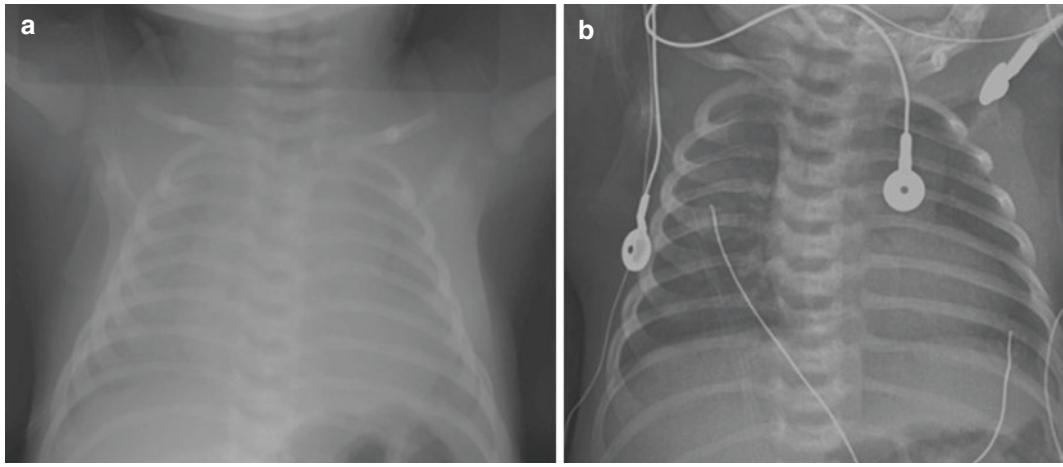

Fig. 23.14 (**a**) Simulated bilateral lung atelectasis and cardiomegaly secondary to expiratory film and underexposure. (**b**) Short-term follow-up X-ray with adequate radiographic technique and degree of inspiration

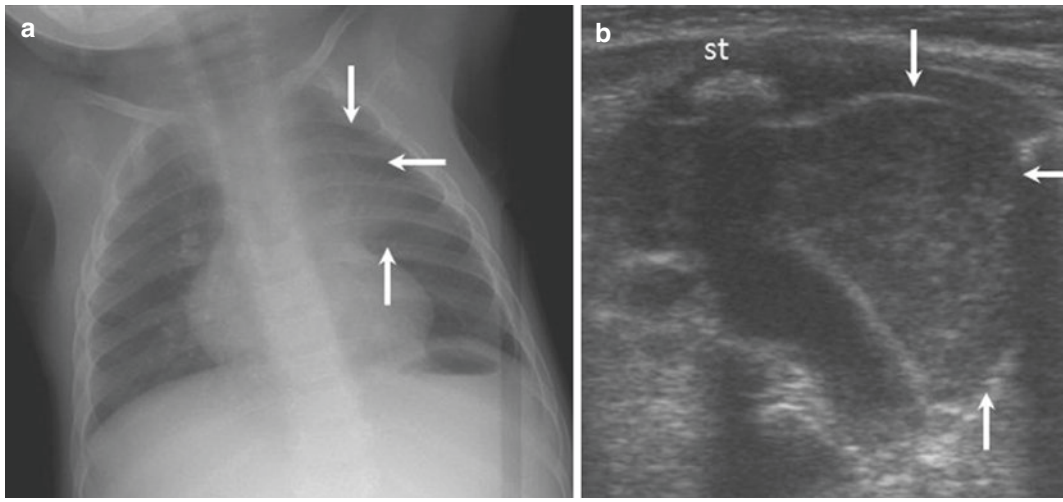

Fig. 23.15 Normal thymus simulating atelectasis. (**a**) Chest radiograph shows a left upper lobe opacity (arrows) mimicking lung collapse. (**b**) Transverse US image at the level of the upper mediastinum shows that the area of lung opacity on radiograph corresponds to normal thymus (arrows). ST = sternum. On US, the thymus has a homogeneous relatively hypoechoic echotexture with internal echogenic strands

fissures, and costophrenic blunting are typical findings. US can be used to detect, quantify, and better characterize pleural effusions (Fig. 23.16).

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. 23.17). US is now considered a better imag-

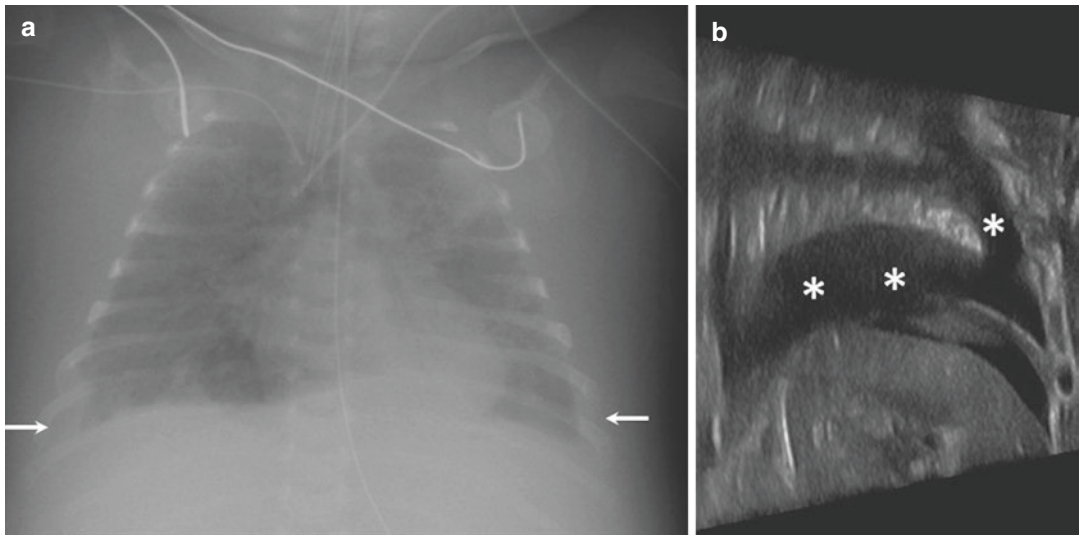

Fig. 23.16 Pleural effusion. (**a**) Supine chest radiograph shows diffuse bilateral lung haziness and bilateral costophrenic blunting (arrows). (**b**) Chest US performed a few minutes after the chest X-ray shows a large amount of anechoic pleural fluid (*) surrounding the atelectatic lung

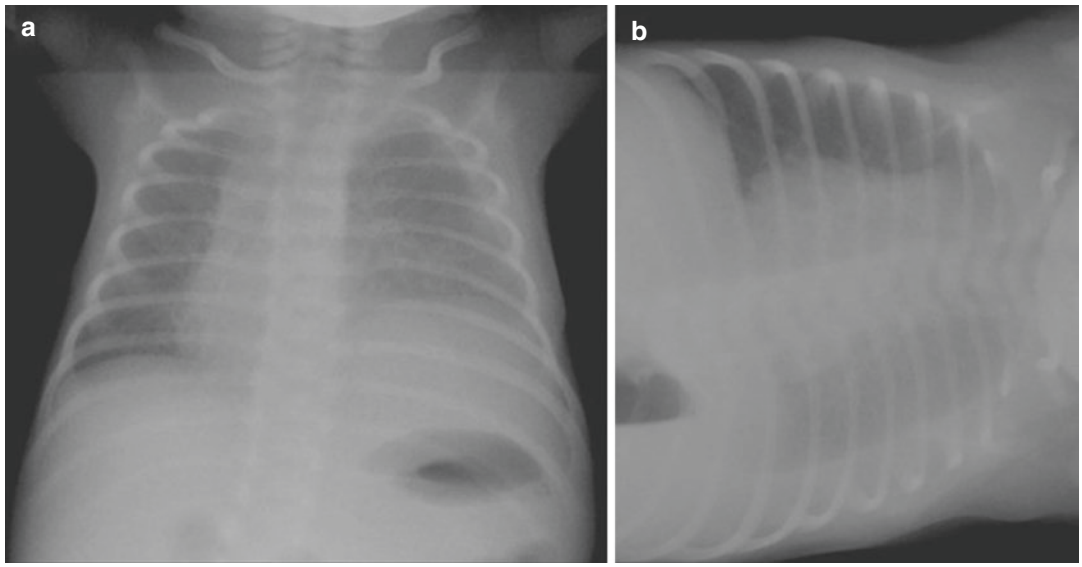

Fig. 23.17 Pleural effusion. Supine view (**a**). Shows an underinflated left lung with left lateral pleural thickening, contralateral mediastinal shift, and simulated elevation of the ipsilateral diaphragm (note the increased distance between the gastric bubble and the "pseudo" diaphragm) caused by a large predominantly subpulmonic pleural effusion. Left lateral decubitus film (**b**) better delineates the presence of left-sided pleural effusion

ing modality to detect pleural effusion and should substitute, when available, for the lateral decubitus films.

3. Large pleural effusions manifest as increased opacification of the ipsilateral hemithorax with adjacent lung collapse and contralateral mediastinal shift (Fig. 23.18).
4. Echogenic debris and septations are seen in complex pleural effusions (Fig. 23.19).

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 areas without associated vascular markings, lateral to a pleural line (Fig. 23.20).
   (c) Small pneumothoraces can be subtle on supine views, since air accumulates anteriorly and may manifest as increased sharpness of the mediastinal edge, hyperlucent lung, and occasional mild mediastinal shift (Fig. 23.21a). Medial pneumothorax can be difficult to differentiate from a pneumomediastinum.
   (d) Decubitus views can be useful in some circumstances and are preferred to cross table lateral views, which do not differentiate laterality and are limited by overlying structures (Fig. 23.21b).
   (e) Normal skin folds may mimic pneumothoraces and usually extend beyond the lung edge (Fig. 23.9).
   (f) Signs of tension pneumothorax include contralateral mediastinal shift, depression of the diaphragm, and splaying of the ribs (Fig. 23.22).
2. Pneumomediastinum
   (a) Mediastinal air collections tend to occur as a result of hyperventilation, are usually asymptomatic, and almost never require intervention.

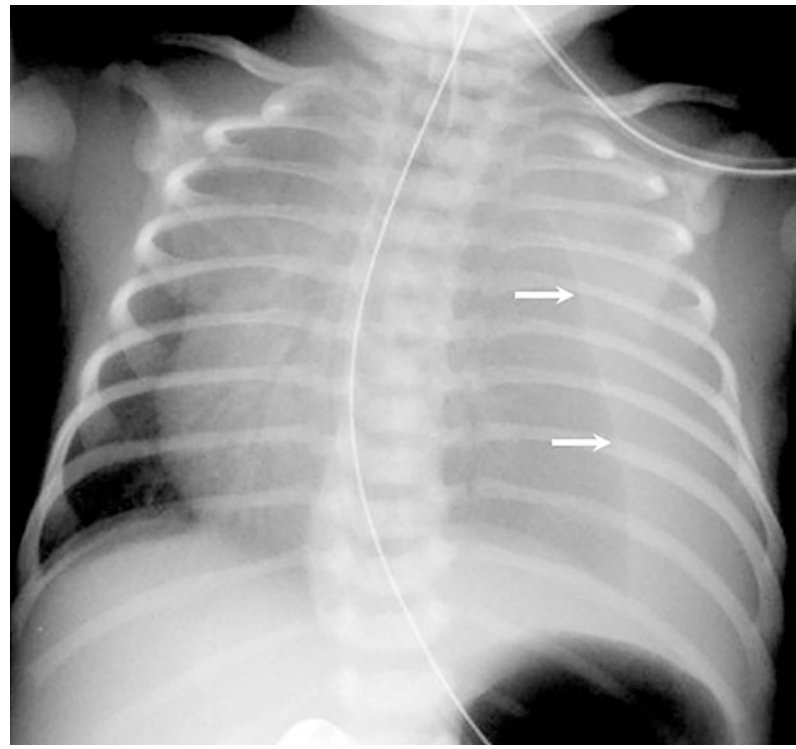

Fig. 23.18 Neonate with large left-sided pleural effusion. Supine radiograph of the chest shows diffuse left lung haziness with a moderate left pleural effusion (arrows). Note the contralateral mediastinal shift and the compressive right upper lobe atelectasis

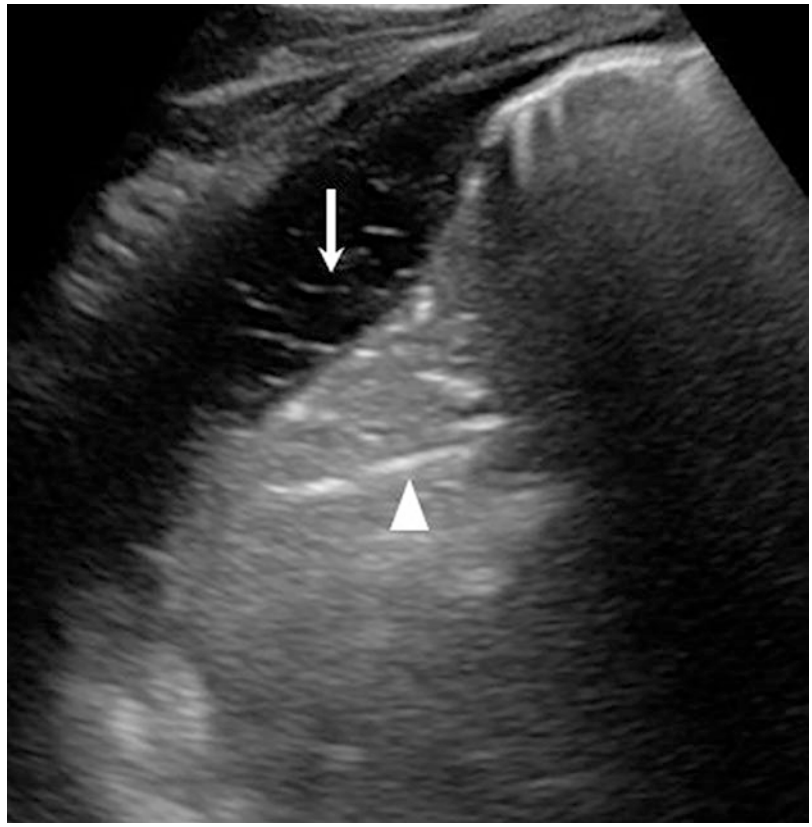

Fig. 23.19 Pleural effusion. US image shows a pleural effusion with multiple internal thin septations (arrow) representing fibrin bands in a patient with empyema. Note the "hepatization" of the underlying lung with the presence of air bronchograms (arrowhead)

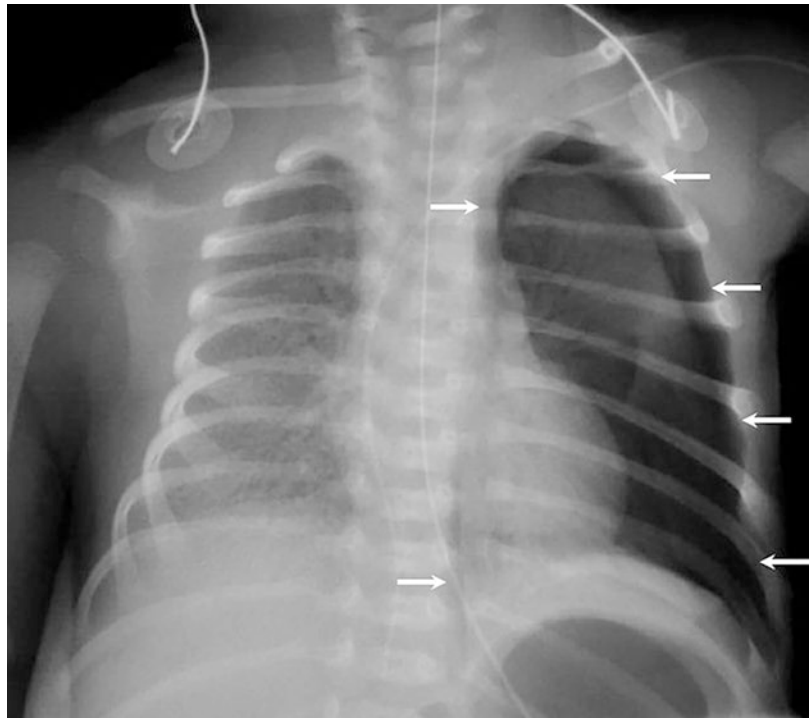

Fig. 23.20 Pneumothorax. Supine view of the chest in a patient with left pneumothorax (arrows). The left hemithorax appears hyperlucent compared to the contralateral side. Note the presence of diffuse, bilateral granular opacities and air bronchograms and a left upper extremity PICC extending into the IVC

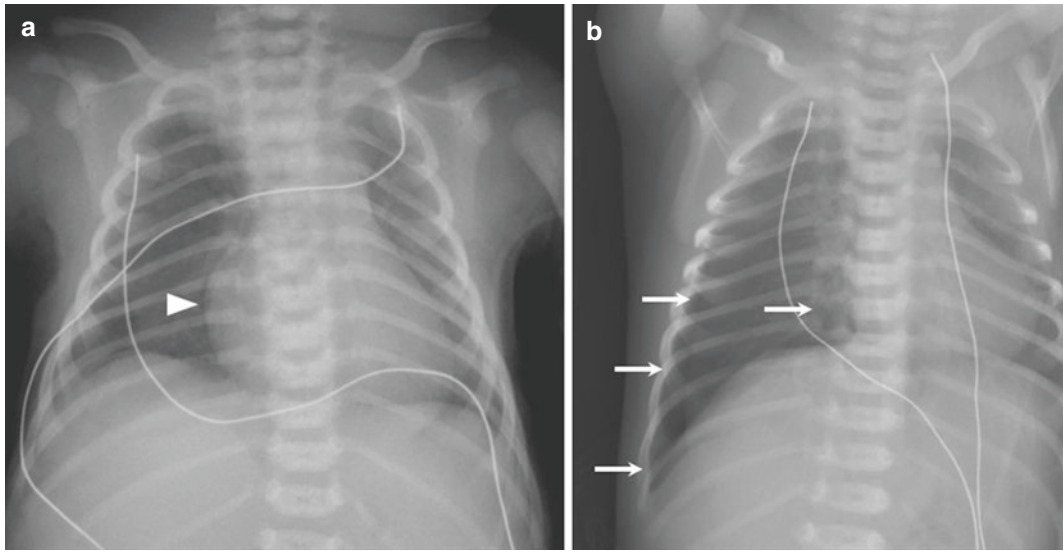

Fig. 23.21 Pneumothorax. (**a**) Supine view of the chest in a patient with right pneumothorax. The right hemithorax appears hyperlucent, and there is increased sharpness of the right heart border (arrowheads). (**b**) Left lateral decubitus view in the same patient better delineates the presence of a pneumothorax (arrows)

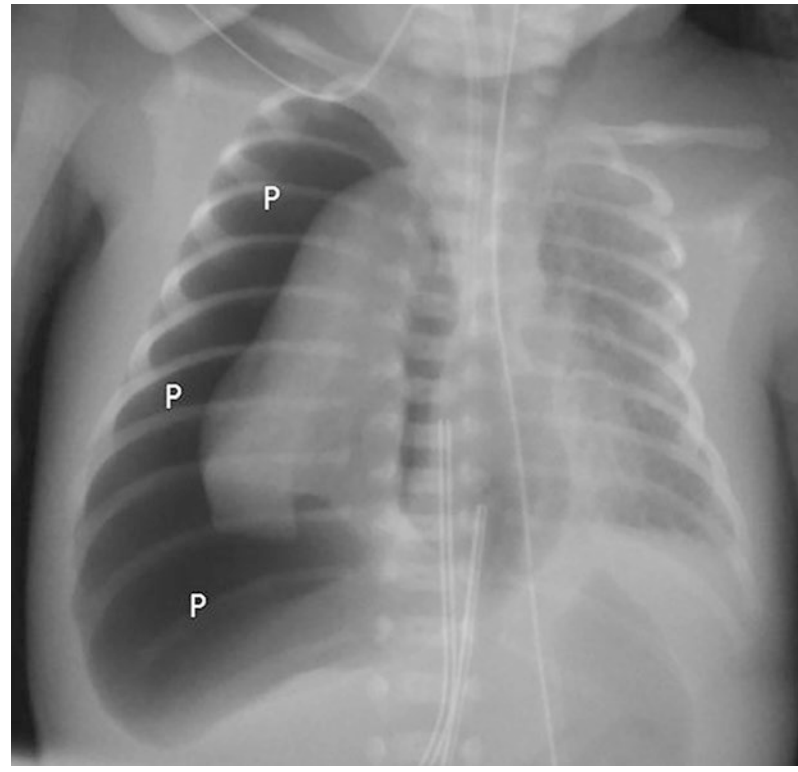

Fig. 23.22 Pneumothorax. Note the presence of a right tension pneumothorax (P), which causes right lung collapse, inversion of the right diaphragm, and mediastinal shift to the left

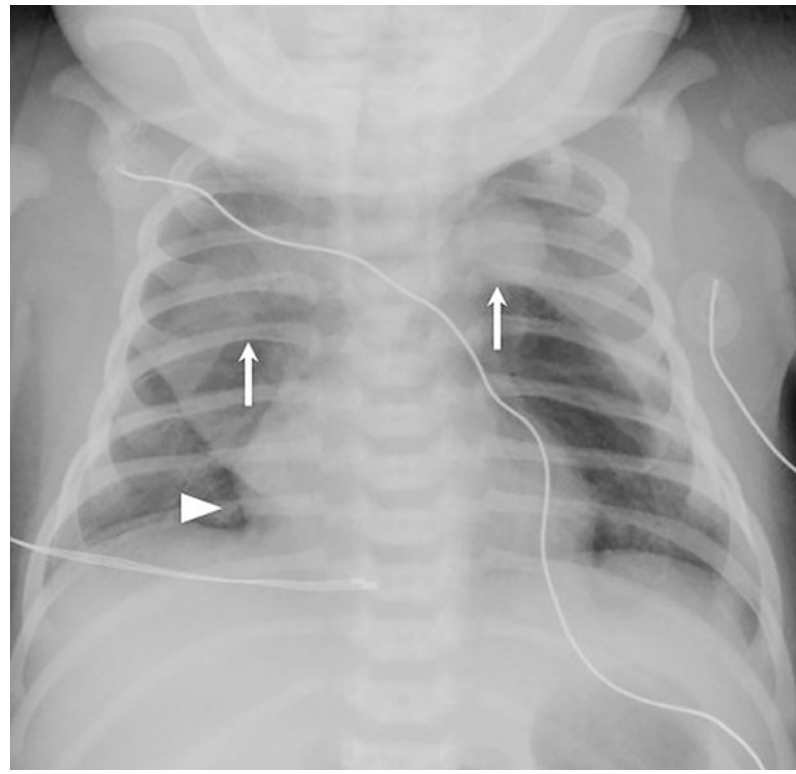

Fig. 23.23 Pneumomediastinum. Air in the mediastinum displaces the thymus ("spinnaker" sign) superiorly (white arrows). Associated right pneumothorax is present (arrowhead)

(b) Anteriorly located pneumomediastinum usually outlines or delineates the thymus due to uplifting and separation from the heart ("spinnaker" sign) (Fig. 23.23).
(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.

3. Pulmonary Interstitial Emphysema (PIE)
   (a) On radiography, PIE is seen as linear and cystic lucencies radiating from the hilum toward the periphery of the lung (Fig. 23.24).
   (b) May be localized, unilateral, or bilateral and may cause significant mass effect and mediastinal shift. It usually occurs in the first week of life and may be fleeting. Localized PIE may mimic congenital pulmonary airway malformation (CPAM), and careful review of prior radiographs and prenatal imaging may help to differentiate CPAM and PIE. CT can also be used to differentiate these two entities (Fig. 23.25).
4. Pneumopericardium. Pneumopericardium manifests as curvilinear lucency completely surrounding the heart, which conforms to the pericardial sac (Fig. 23.26).

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. 23.27a); lateral views also help to assess heart size (Fig. 23.27b). Determination of cardiac chamber enlargement on radiography is usually not very useful or accurate.
   (b) Expiratory films with low lung volumes may accentuate the heart size and simulate cardiomegaly (Fig. 23.14a).

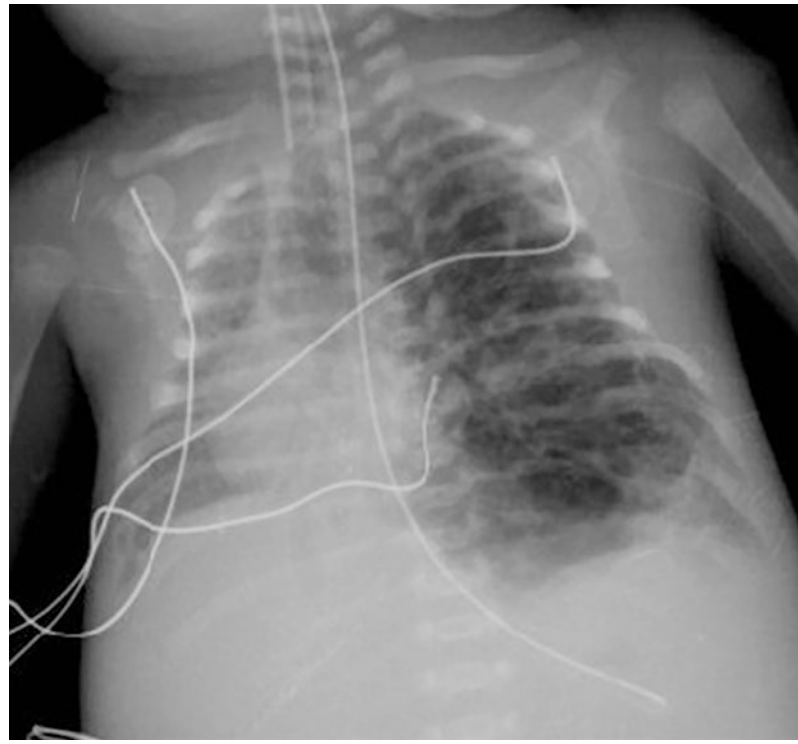

Fig. 23.24 PIE. Multiple linear and cystic lucencies are identified in the entire left lung. Note the hyperexpansion of the left lung with flattening of the diaphragm and mediastinal shift to the right

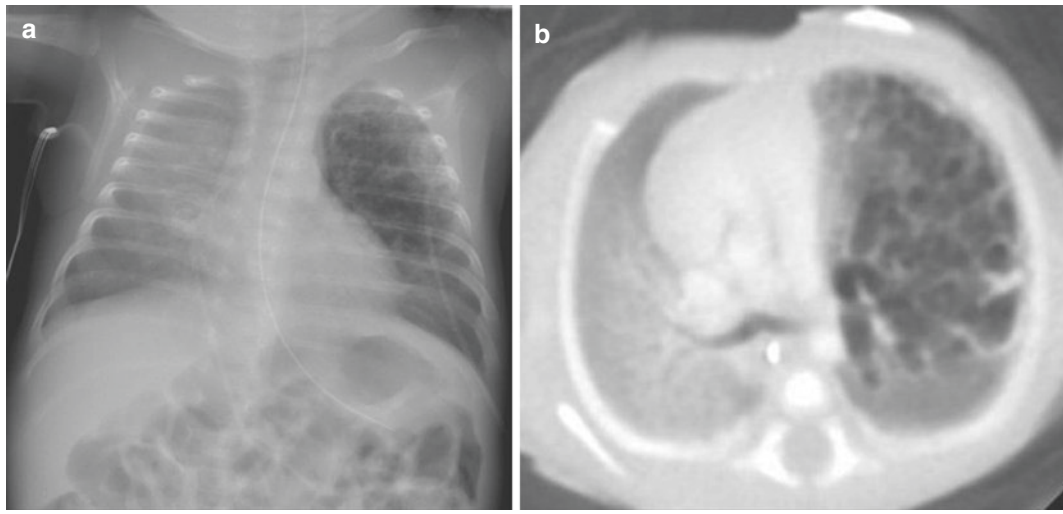

Fig. 23.25 PIE. Chest radiograph (**a**) and axial CT image (**b**) show the presence of localized left upper lobe PIE seen as multiple linear and cystic lucencies, which can mimic CPAM

(c) A normal thymus can extend inferiorly and may mimic cardiomegaly (Fig. 23.28).
(d) The aortic arch may be hidden by the thymus, but the descending aorta is usually visible (Fig. 23.28). 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 and midline in the presence of a right aortic arch.

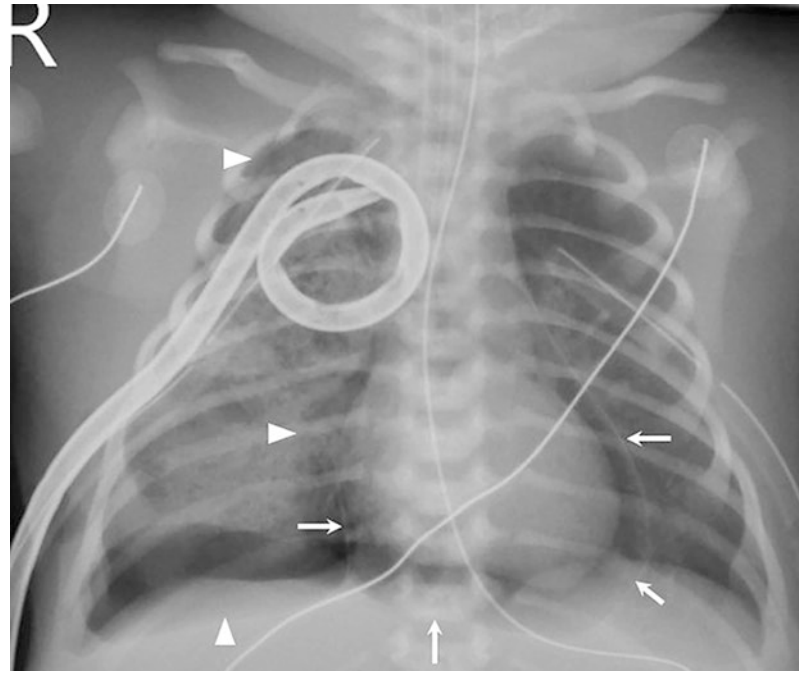

Fig. 23.26 Pneumopericardium. The heart is completely surrounded by air (white arrows). Note the presence of an associated right-sided pneumothorax (arrowheads)

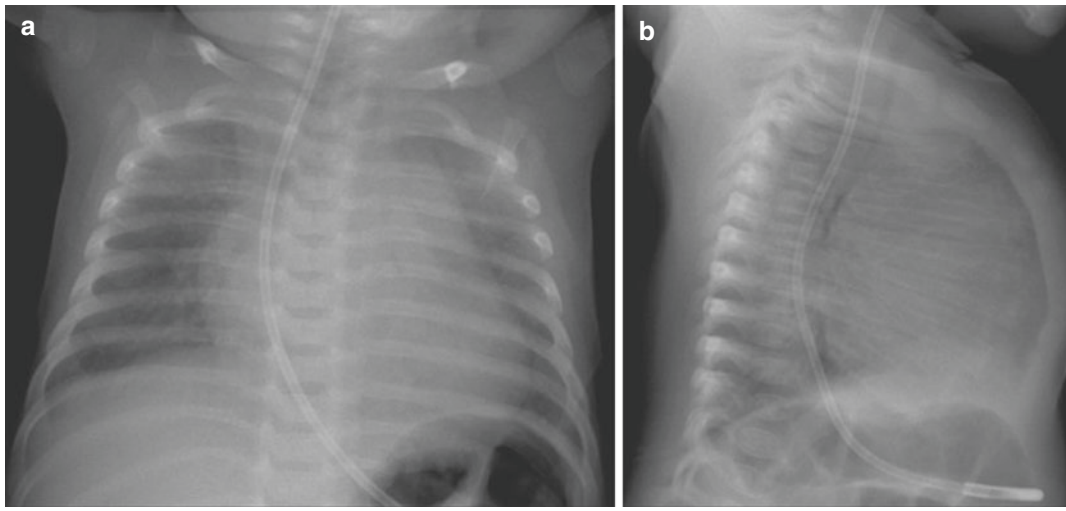

Fig. 23.27 Frontal (**a**) and lateral (**b**) chest radiographs show cardiomegaly. Note on the lateral view the posterior displacement of the esophagus by an enlarged heart, which extends to the level of the spine

(e) Left-to-right shunts >2:1 usually cause increased pulmonary vascularity (Fig. 23.29a) 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. 23.29b). These radiographic changes may not be apparent in the first week of life.

(f) Skeletal abnormalities, cardiac apex position, tracheal position, and abdominal situs should also be assessed.

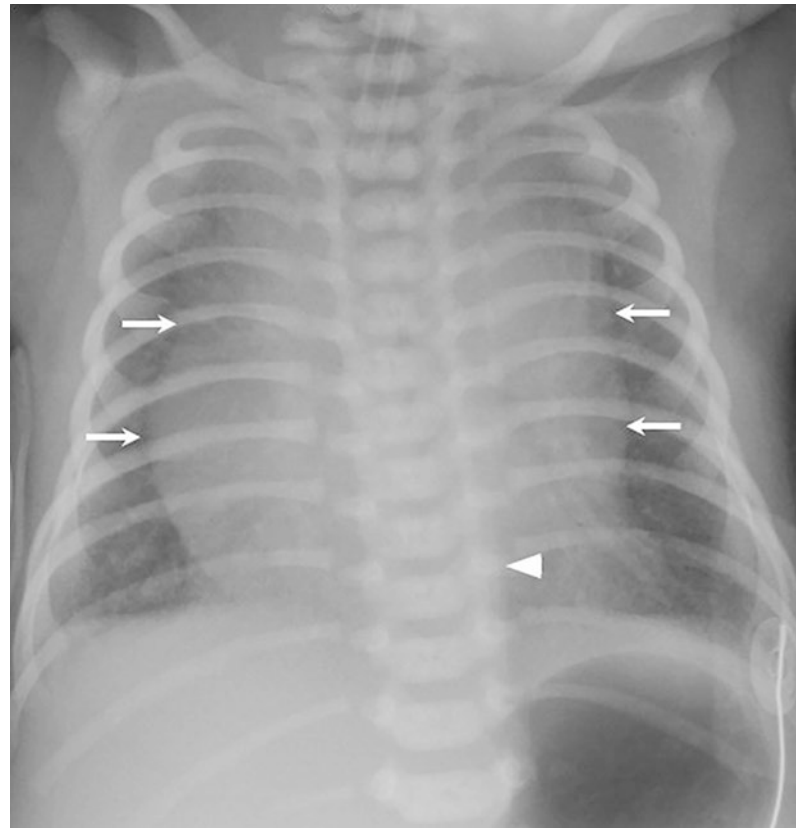

Fig. 23.28 Thymus simulating cardiomegaly. The heart and mediastinum appear widened secondary to the presence of a prominent thymus. Note the undulating appearance of the lateral aspect of the thymus secondary to the impressions caused by the ribs (white arrows). Descending aorta is indicated (arrowheads)

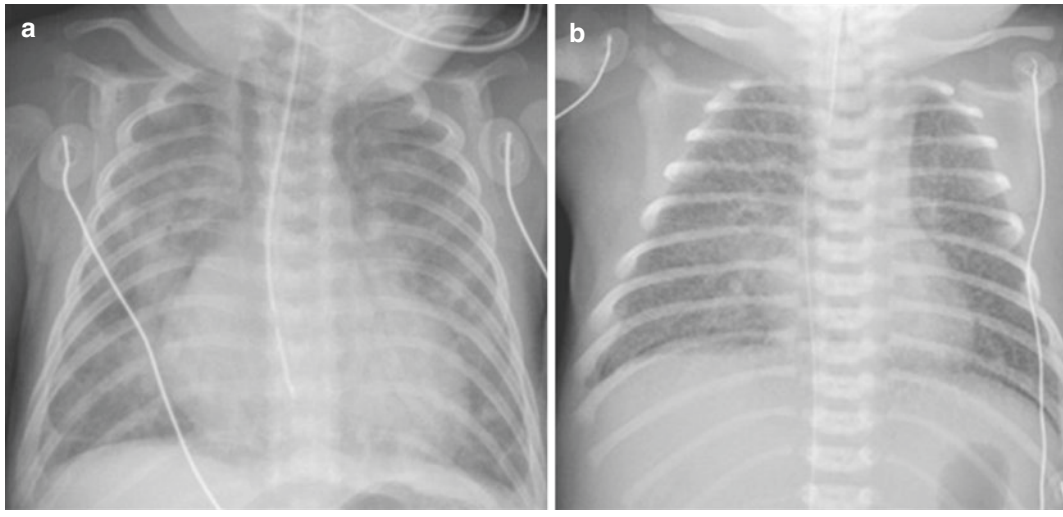

Fig. 23.29 Increased vascular flow. (**a**) Neonate with a ventricular septal defect. Chest radiograph shows cardiomegaly and increased vascular flow. Note that the tip of the nasogastric tube (NGT) is malpositioned in the distal esophagus. (**b**) Chest radiograph in a neonate with total anomalous pulmonary 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

2. Esophagram. An esophagram may diagnose a vascular anomaly causing airway compression (Fig. 23.30).
3. US. Chest US can be performed to evaluate for diaphragmatic paralysis (Fig. 23.31) following cardiac surgery.
4. CT and MRI
   (a) Echocardiography remains the primary imaging modality for cardiovascular anomalies in the neonate.
   (b) MRI and CT are excellent imaging modalities for 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.

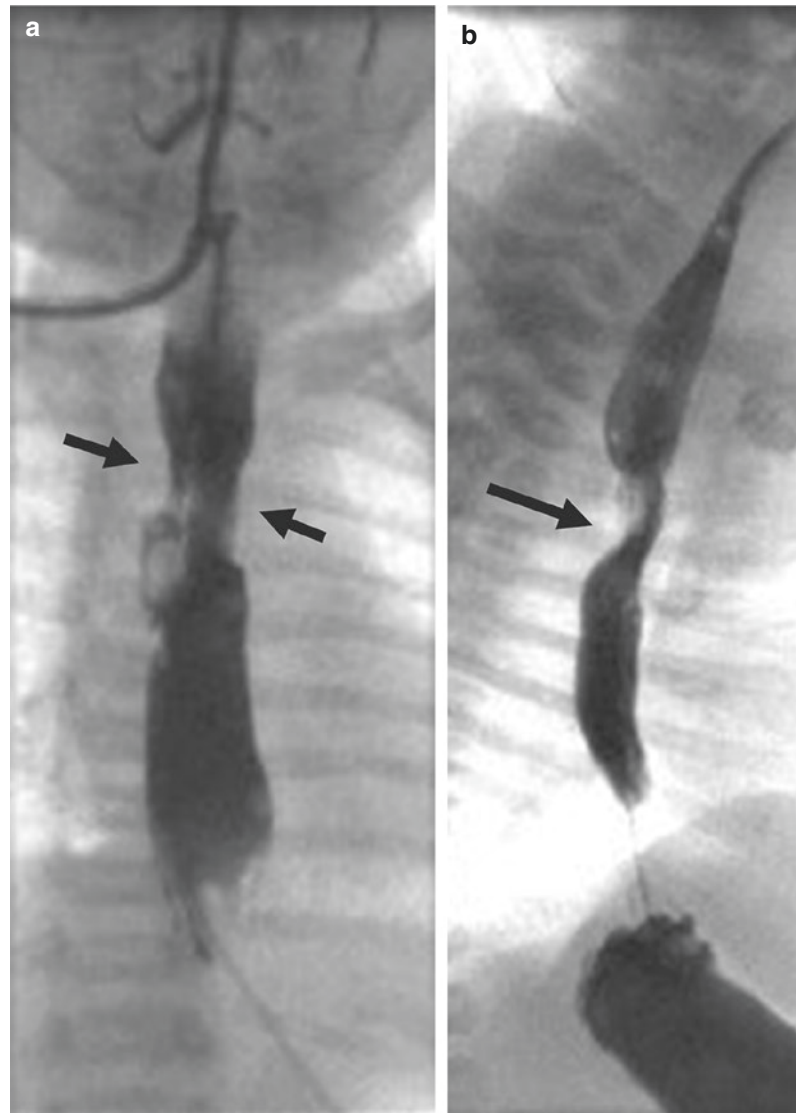

Fig. 23.30 Double aortic arch. AP (**a**) and lateral (**b**) views from an esophagram show extrinsic compressions (arrows) posterior and to both sides of the esophagus caused by a double aortic arch

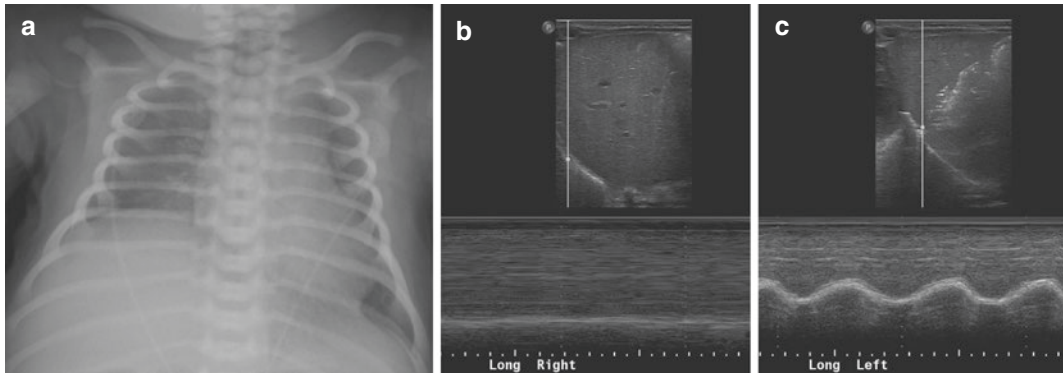

Fig. 23.31 Diaphragmatic paralysis. (**a**) Chest radiograph shows asymmetric elevation of the right diaphragm following birth injury. (**b**) M-mode Doppler interrogation of the right diaphragm shows loss of the normal motion with a flat tracing. (**c**) M-mode Doppler interrogation of the left diaphragm shows normal waveform movement during the respiratory cycle

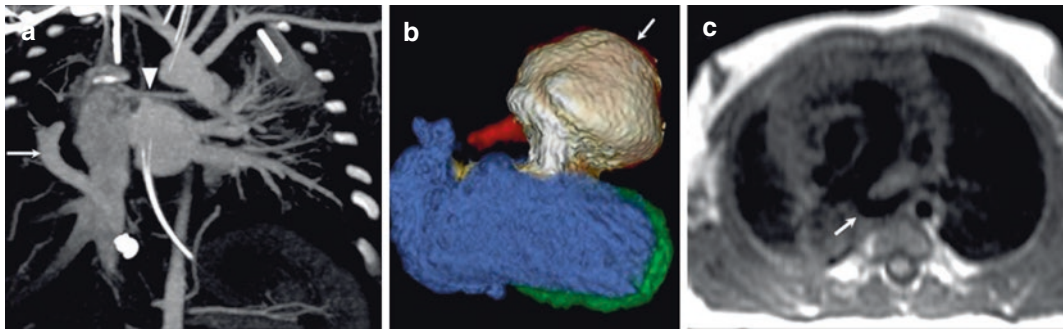

Fig. 23.32 Congenital cardiovascular anomalies. (**a**) Coronal CT angiogram in a patient with scimitar syndrome. Anomalous pulmonary vein draining into the infradiaphragmatic IVC (arrow) and hypoplastic right pulmonary artery (arrowhead). (**b**) Three-dimensional CT angiogram reformat in patient with 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

F. Developmental Lung Anomalies
   1. Congenital Pulmonary Airway Malformation (CPAM)
      (a) Previously referred to as congenital cystic adenomatoid malformation (CCAM).
      (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.
      (c) Presurgical evaluation with CT is performed to evaluate size and location usually with intravenous contrast administration to evaluate the vascular anatomy as well as the presence of a sequestration component (Fig. 23.33b).
      (d) It is often diagnosed on prenatal US. Pre- or postnatal MRI can also be performed to evaluate anatomy and extension (Fig. 23.34).

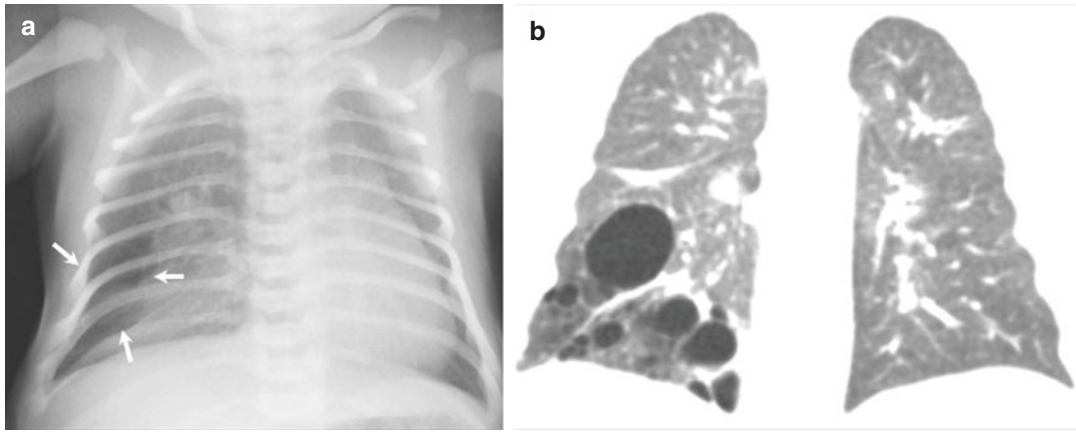

Fig. 23.33 CPAM. (**a**) Chest radiograph shows a large dense right lower lobe opacity with associated multicystic lesion (arrows). (**b**) Coronal CT image shows multiple well-defined air-filled cystic lesions (arrows) involving middle and lower lobes

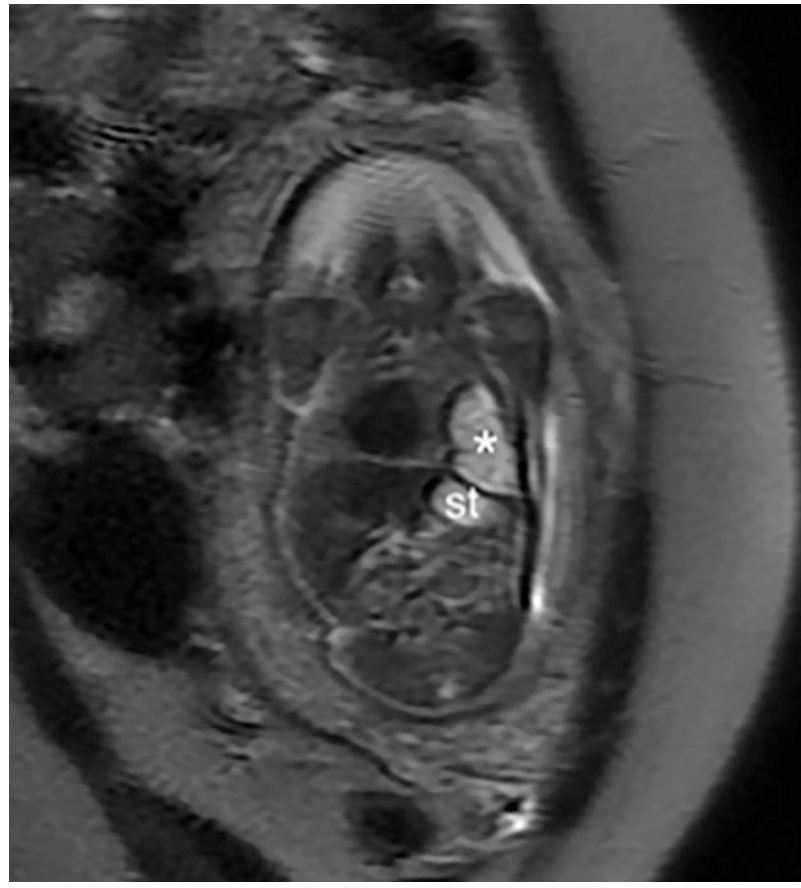

Fig. 23.34 CPAM. Coronal T2-weighted fetal MRI image shows a large cystic structure (*) in the left lower chest above the stomach (st)

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 pleural lining with systemic venous return. Intralobar sequestrations have pulmonary venous drainage and are invested within the pleura.
   (b) On conventional radiography, sequestrations are seen as dense and persistent focal masses (Fig. 23.35a).
   (c) Presurgical evaluation with CT, MRI, and US is performed to evaluate the extent and lobar involvement and identify the systemic vascular supply, which arises from below the diaphragm in 20% of cases (Fig. 23.35b).
   (d) Pulmonary sequestration may occur in conjunction with CPAM ("hybrid lesions") as well as cardiac, diaphragmatic, skeletal, and other lung anomalies.
   (e) It is also often diagnosed on prenatal US. Fetal MRI also allows evaluation of anatomy and extension (Fig. 23.36).
3. Congenital Lobar Overinflation
   (a) Formerly referred to as congenital lobar emphysema (CLE). It occurs secondary to bronchial obstruction with a ball-valve mechanism leading to lobar hyperinflation.
   (b) Initially, after birth, the overdistended lobe is filled with fluid and may be opaque (Fig. 23.37a). Subsequently, the typical appearance is that of an overdistended lobe, which, depending on the size, may cause adjacent atelectasis and contralateral mediastinal shift (Fig. 23.38a).
   (c) CT may be performed for presurgical evaluation to better evaluate the anatomy (Figs. 23.37b and 23.38b).

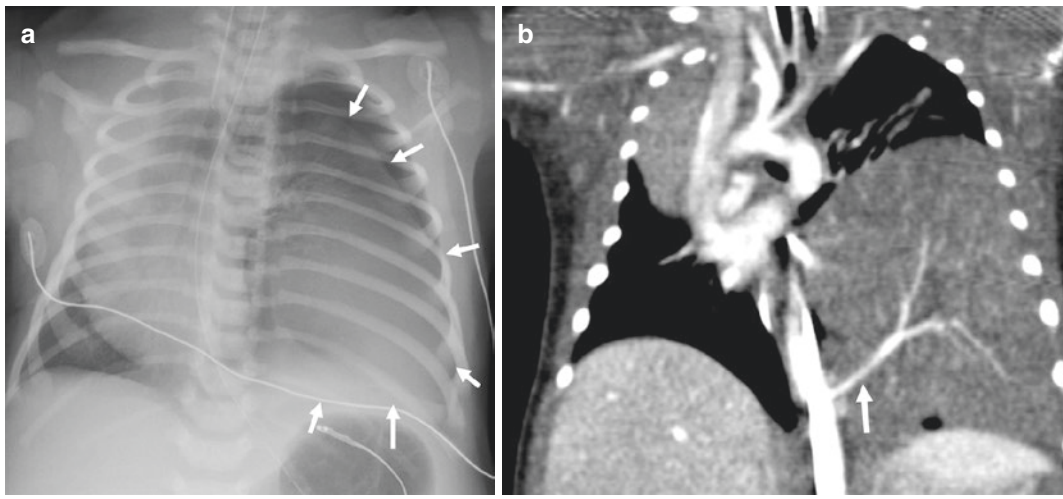

Fig. 23.35 Pulmonary sequestration. (**a**) Chest radiograph shows a well-defined left lung opacity (arrows) and significant mediastinal shift to the right. (**b**) Coronal CT image shows a large left lower lobe solid mass and a feeding vessel (arrow) arising from the aorta

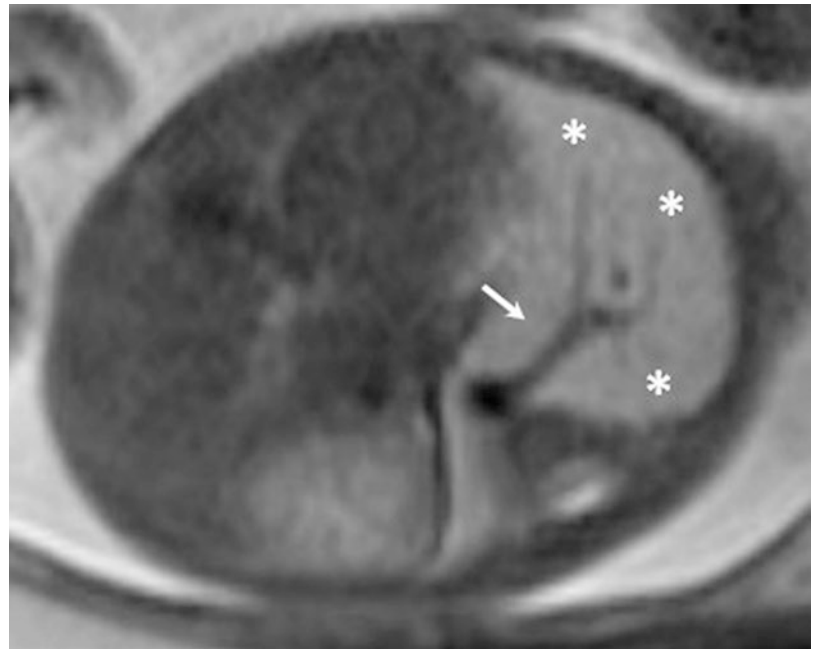

Fig. 23.36 Pulmonary sequestration. MRI performed prenatally in the same patients as Fig. 23.35. Axial T2-weighted image shows a large left lower lobe mass (arrowheads) and a feeding vessel arising from the thoracic aorta (arrow)

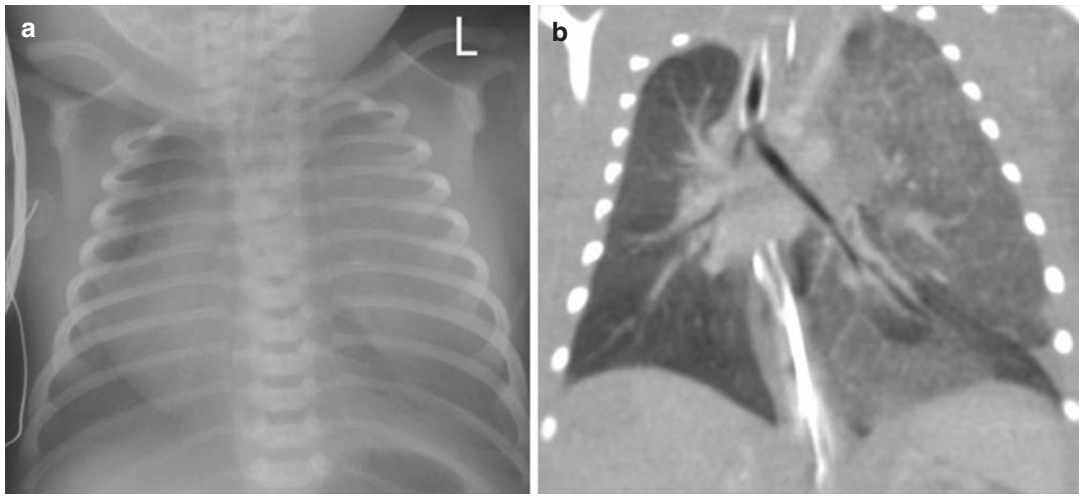

Fig. 23.37 Congenital lobar overinflation associated with bronchial atresia: (**a**) Chest radiograph shows an ill-defined left upper opacity and significant mediastinal shift to the right. (**b**) Coronal CT image shows left upper lobe ground-glass opacity density secondary to retained fluid

G. Congenital Diaphragmatic Hernia (CDH)
   1. CDHs are frequently diagnosed on prenatal US.
   2. Fetal MRI now plays an important role in the presurgical and initial neonatal management. MRI characterizes the herniated structures, quantifies the degree of lung hypoplasia, and evaluates for the presence of associated anomalies (Fig. 23.39).
   3. On initial radiographs, herniated abdominal contents are seen as an opaque mass, more common on the left side, with ipsilateral lung hypoplasia and contralateral mediastinal

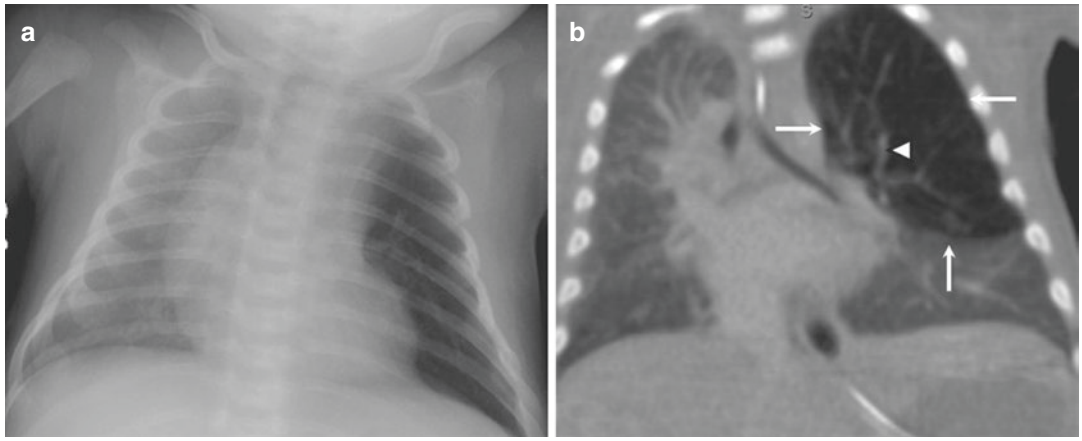

Fig. 23.38 Congenital lobar overinflation: (**a**) Chest radiograph shows left upper lobe lucency with mediastinal shift to the contralateral side and compressive right lung atelectasis. (**b**) Coronal CT image in the same patient. Marked hyperinflation of the left upper lobe (arrows) with significant mediastinal shift and right lung atelectasis. Note that the vascularity (arrowhead) in the affected lobe is attenuated

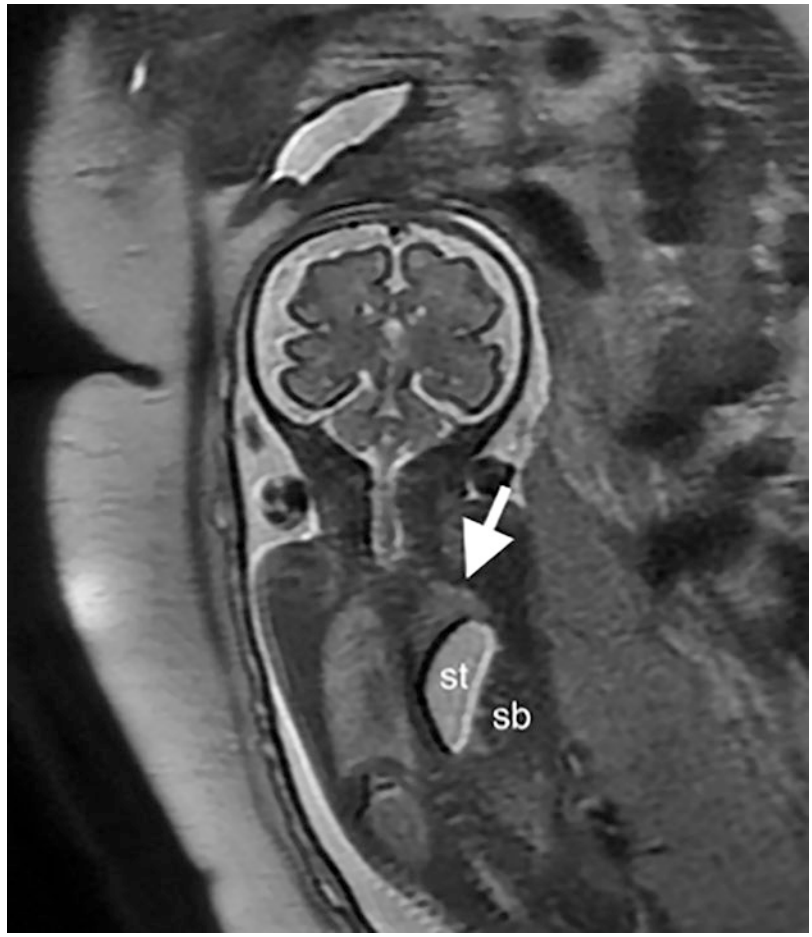

Fig. 23.39 Left-sided CDH. Coronal T2-weighted fetal MRI image shows herniation of part of the stomach (st) and small bowel (sb) into the chest. Note the presence of a hypoplastic left lung (arrow)

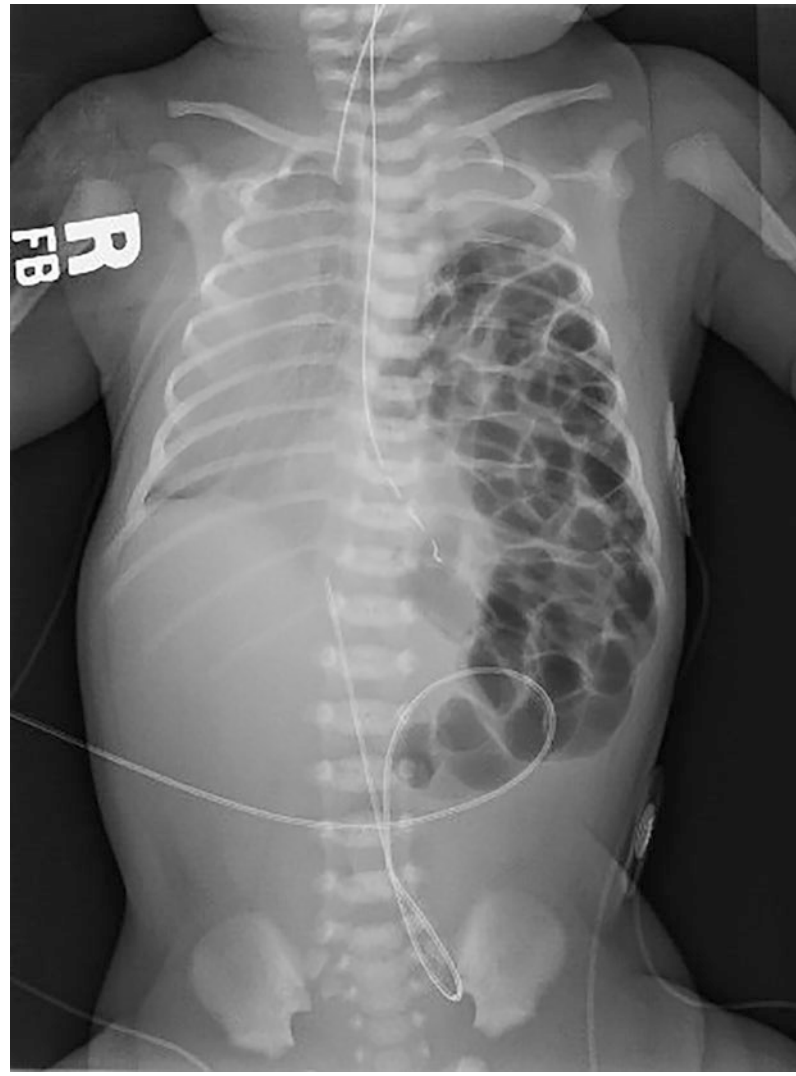

Fig. 23.40 Left-sided CHD. Radiograph of the chest and abdomen shows multiple gas-filled loops of bowel occupying the left hemithorax. The mediastinum is shifted to the right

shift. During the hours following birth, air fills the herniated loops of bowel giving the typical appearance of multiple bowel-like lucencies in the chest (Fig. 23.40).

4. After surgical correction, *ex vacuo* pneumothorax is a frequent finding.

H. Esophageal Atresia, Tracheoesophageal Fistula, Abnormal Tracheal-Bronchial Tree Anomalies

1. A coiled gastric tube in the proximal esophagus suggests esophageal atresia in the appropriate clinical setting. The presence of abdominal bowel gas suggests an associated distal tracheoesophageal fistula (Fig. 23.41). 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 is suspected, and for postsurgical evaluation (Fig. 23.42).

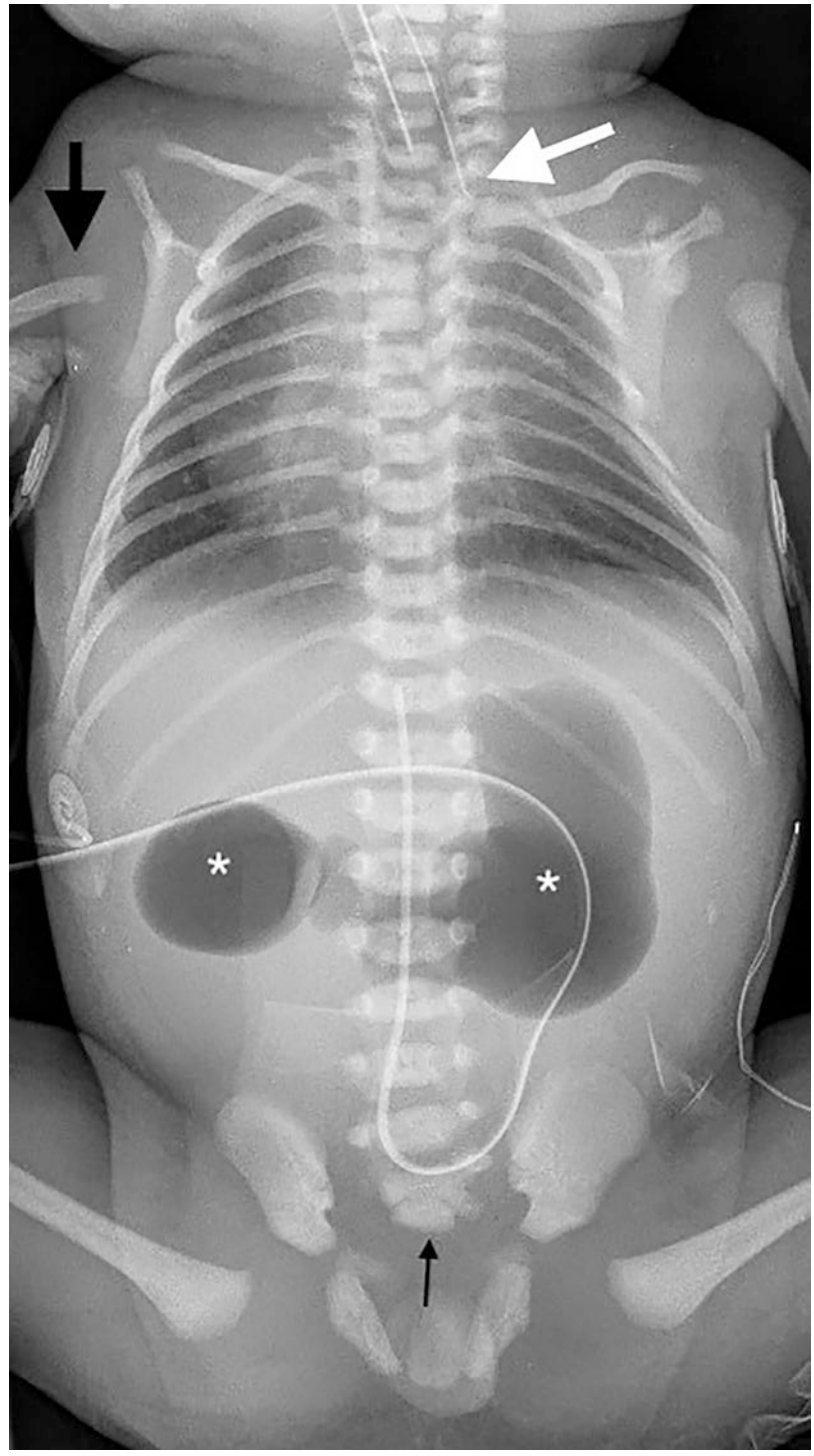

Fig. 23.41 Esophageal atresia and distal tracheoesophageal fistula. Radiograph of the chest and abdomen shows a feeding tube in the upper esophagus (white arrow) in this patient with esophageal atresia. The presence of abdominal bowel gas indicates the presence of a tracheoesophageal fistula; however, there is also a double bubble sign of duodenal atresia (*). Note the sacral vertebral anomalies with the absence of the inferior sacrum (thin black arrow) and hypoplasia of the right humerus (thick black arrow) in this patient with VACTERL spectrum

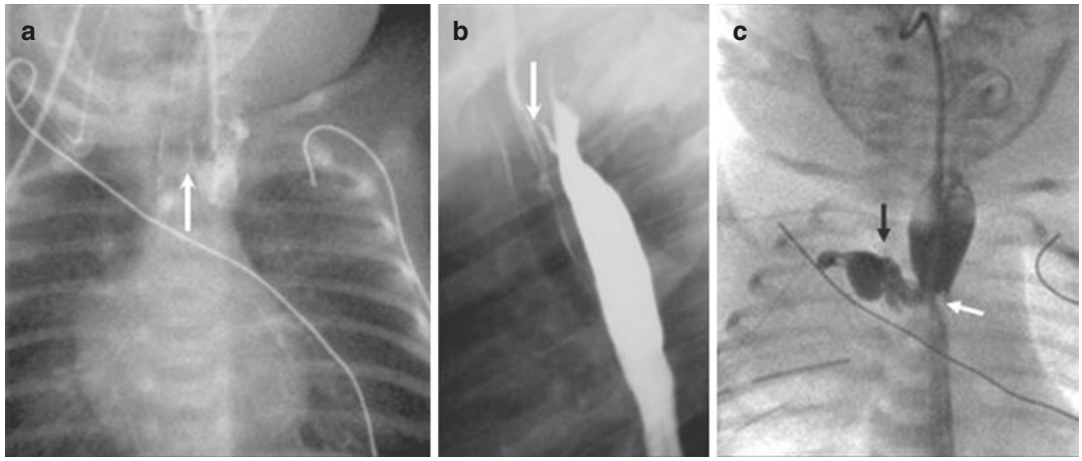

Fig. 23.42 Esophageal atresia and tracheoesophageal fistula. (**a**) Esophagram performed through the pouch in a patient with esophageal atresia reveals the presence of a proximal tracheoesophageal fistula (arrow). (**b**) Esophagram in neonate with aspiration pneumonias shows the presence of a tracheoesophageal 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

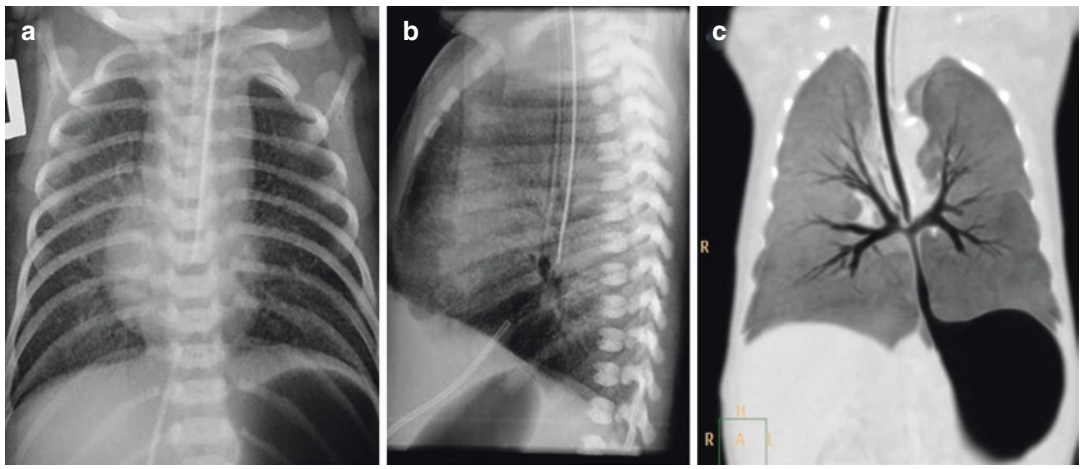

Fig. 23.43 Neonate with type II (Floyd classification) tracheal agenesis. Frontal (**a**) and lateral (**b**) views in a patient with severe respiratory distress reveal the presence of an ETT in the mid-distal esophagus with symmetrical hyperinflated lungs. (**c**) Coronal CT reconstruction shows the presence of total tracheal atresia with normal bronchi fusion in the midline at the level of the carina

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. 23.43a, b).
4. Rapid acquisition time, multiplanar, and volumetric capabilities make CT an excellent diagnostic tool when airway anomalies such as tracheal stenosis (Figs. 23.43c and 23.44), abnormal tracheal-bronchial tree development, or extrinsic compression are suspected.

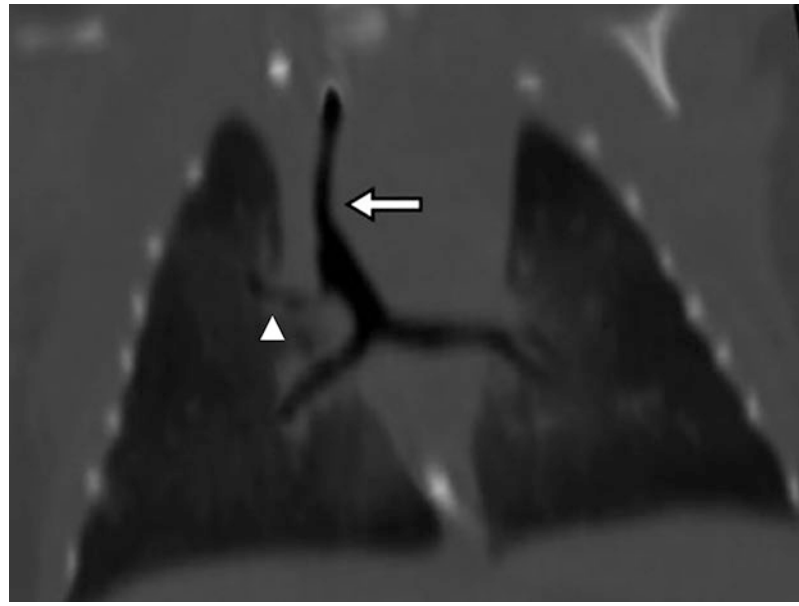

Fig. 23.44 Tracheal stenosis and accessory tracheal bronchus. Reconstructed coronal CT image shows a long segment area of tracheal narrowing (arrow) and an accessory right bronchus (arrowhead) arising from the trachea

5. Tracheobronchomalacia can be diagnosed with fluoroscopy (Fig. 23.45) or expiratory/inspiratory CT. CT can also be performed to determine the optimal PEEP value for tracheostomy patients using serial low-dose CT images of the airway (Fig. 23.46).

I. Assessment of Tubes and Catheters (Fig. 23.47)
   1. ETT
      (a) ETT 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 (toward the carina), with neck flexion and cephalad (toward the glottis) with neck extension and lateral rotation.
      (c) Unintentional right main bronchus intubation is a common radiographic finding and usually associated with atelectasis of the ipsilateral lung (Fig. 23.13).
   2. Vascular Catheters, Gastric Tubes, Surgical Drains
      (a) Placement of vascular catheters, gastric drainage, and chest tubes may require additional imaging to assess correct position.
      (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 including the liver can be very challenging (Fig. 23.48).
      (c) Umbilical arterial catheters (UAC). A high position tip is usually located at the T6–T10 vertebral level. A low position tip is ideally located at the L3–L5 vertebral body interspace.
      (d) US can be used to guide peripherally inserted central catheters (PICC) and umbilical catheter placement and monitor possible complications (Fig. 23.49).
   3. Extracorporeal Membrane Oxygenation (ECMO) Cannulas
      (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, although part of the catheter may be radiolucent, with a punctate radiodense focus representing the tip. The tip of the arterial cannula should be within the aortic arch at the expected location of the origin of the innominate artery (Fig. 23.48).

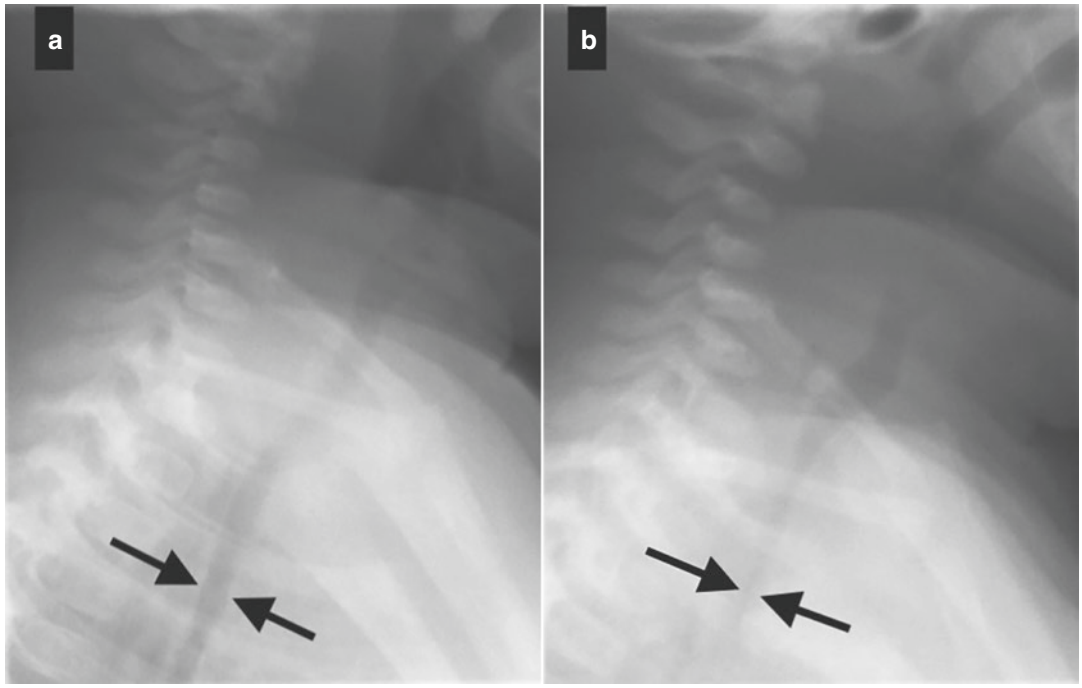

Fig. 23.45 Tracheomalacia. (**a**) Fluoroscopic lateral image during inspiration shows a normal caliber trachea (arrows). (**b**) Fluoroscopic lateral image during expiration shows more than 50% caliber collapse of the trachea (arrows)

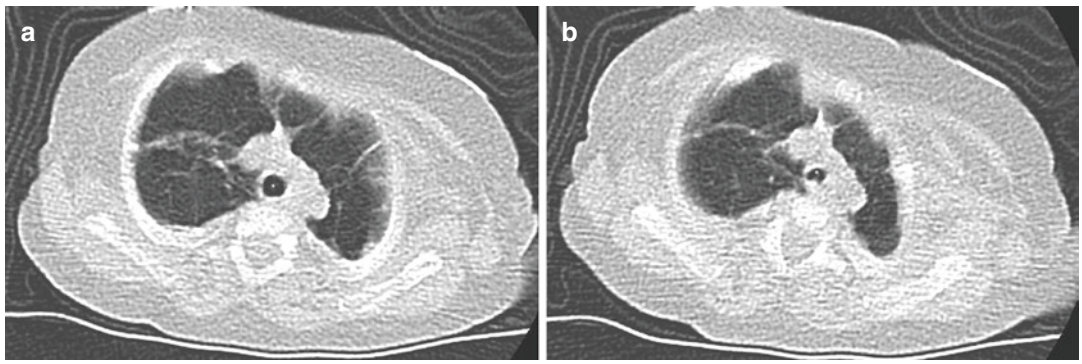

Fig. 23.46 PEEP study. (**a**) Axial low-dose limited CT in a tracheostomy patient with BPD shows a patent trachea (*). (**b**) After lowering the PEEP settings, there is significant flattening of the trachea (*)

(c) After bypass, a whiteout of the lungs is a common radiologic finding.
(d) A rapidly increasing pleural effusion is suggestive of anticoagulation-associated hemothorax.

J. Chest Wall Deformities Causing Respiratory Distress

1. Neuromuscular disease, skeletal dysplasia, and congenital osseous anomalies may be responsible for restrictive lung disease (Fig. 23.50a). Lung hypoplasia, atelectasis, and aspiration 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. 23.50b).

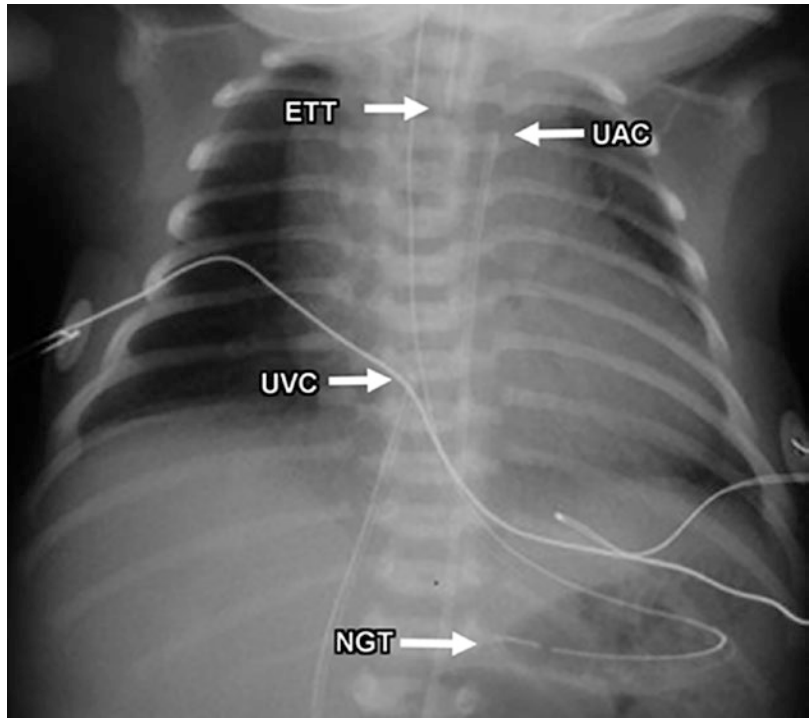

Fig. 23.47 Catheters and tubes. Neonate with RDS. Note the tip of the ETT, UVC, UAC, and NGT

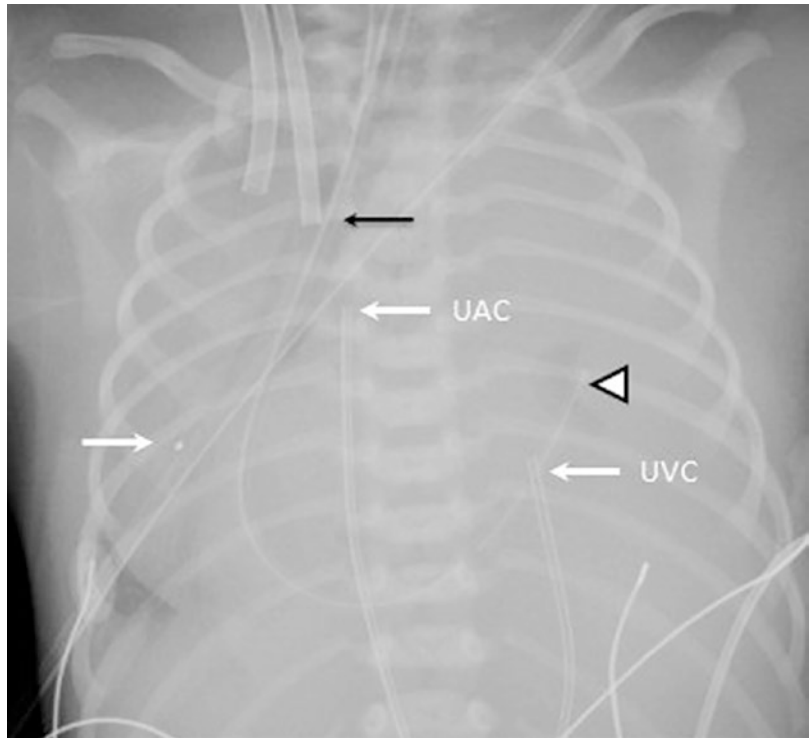

Fig. 23.48 ECMO cannulas. Chest radiograph in a neonate with left CHD on ECMO. The venous cannula tip (white arrow) is located at the expected location of the right atrium. The arterial cannula tip (black arrow) is located at the innominate artery/aorta junction. Note the tip of the NG tube (arrowhead) in the herniated stomach. UAC is noted. UVC projects over the contralateral chest with tip likely in the left portal vein of the herniated liver

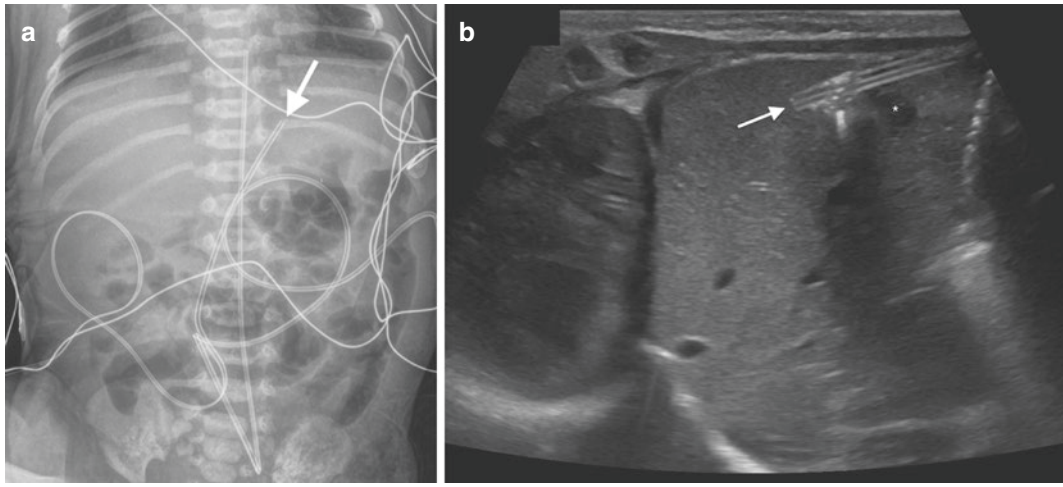

Fig. 23.49 Malpositioned UVC. (**a**) Chest radiograph demonstrates a UVC with tip overlying the left hepatic lobe (arrow). (**b**) US image shows the UVC catheter within the liver parenchyma (arrow). Note the small adjacent fluid collection (*)

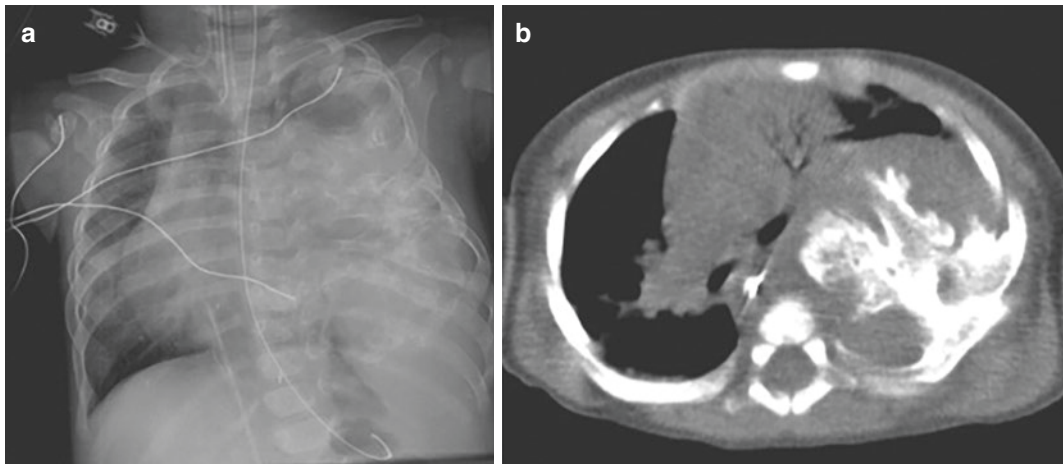

Fig. 23.50 Chest wall deformity. (**a**) Chest radiograph in a newborn with "chest mass" seen on prenatal US shows a large dense left lung opacity with involvement of multiple left ribs. (**b**) Axial CT chest image shows a soft tissue mass containing ossified elements arising from multiple left-sided ribs. Pathology was consistent with mesenchymal hamartoma

X. US of the Lung Parenchyma
   A. Technique
      1. Requires expertise to perform and interpret
      2. Requires high-frequency linear probe
      3. No need to mobilize or manipulate patient
      4. Assessment of anterior and lateral chest
      5. Requires physical contact and therefore increased infection risk
      6. Longer acquisition time compared to chest radiograph

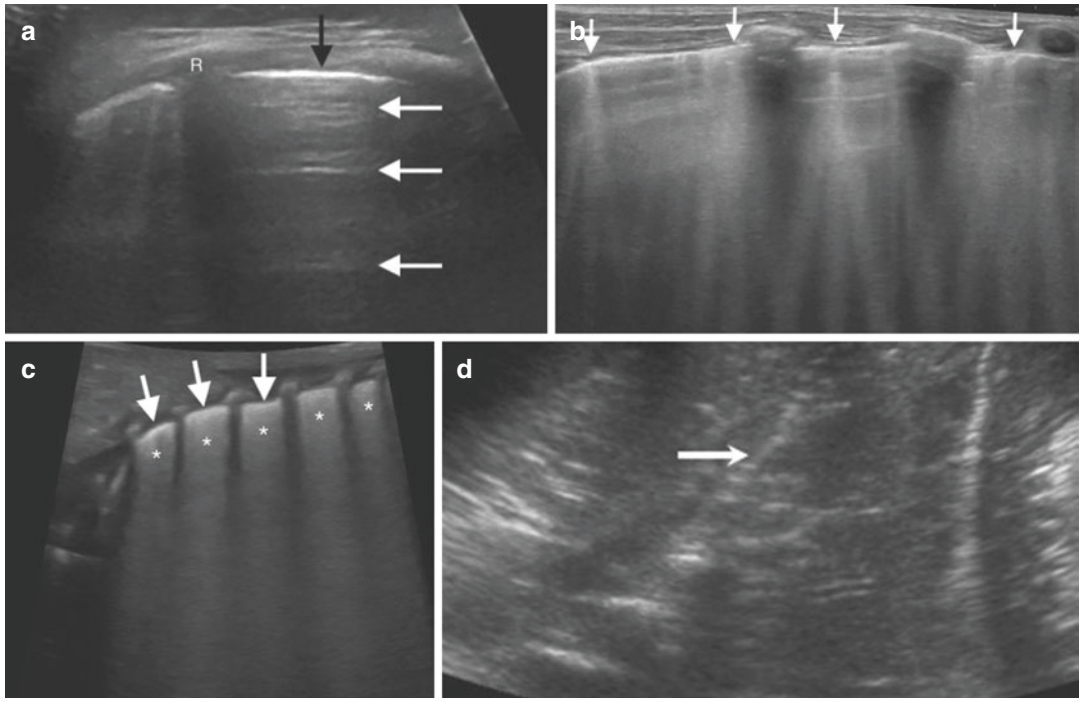

Fig. 23.51 Lung US. (**a**) Normal. The pleural line is a thin continuous echogenic line (black arrow). Parallel echogenic lines represent normal A lines (white arrows). Note the shadowing from the overlying rib (R). (**b**) B lines. Vertically oriented echogenic lines represent B lines (arrows). When short, B lines can be physiologic as opposed to this case where the B lines extend inferiorly in this patient with interstitial edema. (**c**) White lung. Thickened echogenic pleural line (arrows) with the appearance of "white lung" characterized by numerous coalescent B-lines (*). This imaging appearance is a nonspecific sign of increased pulmonary density. (**d**) Pneumonia. "Hepatization" of the lung parenchyma with air bronchograms (arrow)

B. Normal Imaging Appearance
   1. Pleural line: Thin (<0.5 mm) continuous hyperechogenic line which represents the interface between normal aerated lung and chest wall (Fig. 23.51a).
   2. Pleural sliding: Normal sliding of the parietal and visceral pleura observed during dynamic synchronous respiratory motion which disappears with pneumothorax, pleural effusion, and parenchymal consolidation.
   3. A lines: Parallel oriented and equidistant echogenic lines under the pleural line which represent reverberation artifacts by the pleural line (Fig. 23.51a).
   4. B lines: Vertical oriented echogenic lines originating from the pleural line which also correspond to reverberation artifacts by the pleural line (Fig. 23.51b).
      (a) B lines are considered physiological if single, scattered, and short, without extension to deep inferior aspect of image.
      (b) Coalescent, confluent B lines (compact B lines or white lung) are always abnormal and indicative of lung pathology (Fig. 23.51c).
   5. Lung consolidation: Subpleural lung parenchyma hepatization with or without internal branching echogenic lines (air bronchograms) are always pathologic (Fig. 23.51d).

Suggested Reading

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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 is 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 and covering with cellophane.
  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, the extent of visible light corona around probe tip is 2–3 cm; the 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

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F. Pneumothorax (Fig. 24.2)
   1. Generally expands uniformly in anterior direction
   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 midclavicular 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.

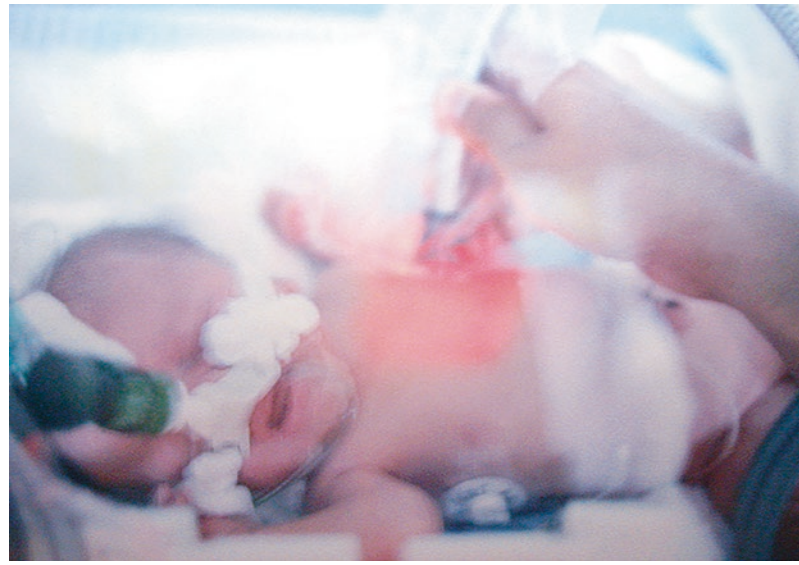

Fig. 24.1 Transillumination diagnosis of a pneumomediastinum

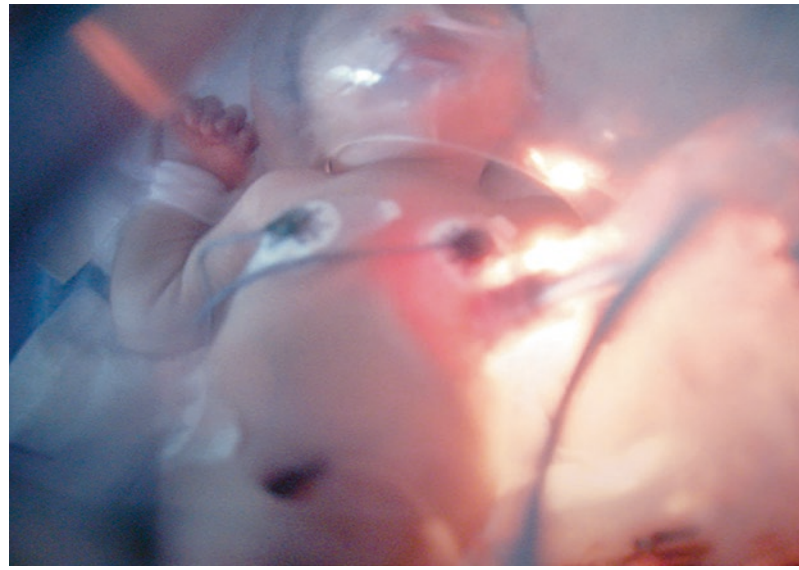

Fig. 24.2 Transillumination diagnosis of a pneumothorax

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. False negatives may occur if the volume of air is small or if the room is not dark enough. This occurs more frequently in larger, term babies.
   C. Cross-contamination of patients is avoided by covering light with cellophane and disinfecting after use.

Suggested Reading

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Echocardiography

25

Prashant Mallya and Jonathan Wyllie

I. Background

Cardiovascular assessment by clinical examination along with routine clinical observations such as heart rate (HR), blood pressure, and blood gas parameters often forms the basis for clinical intervention. This may be a fluid bolus or use of agents to modify blood pressure or cardiac contractility. Although each parameter on its own has limited correlation with the clinical situation, together they provide the attending clinician a sense of the patient's status and enable formulation of logical clinical intervention. Echocardiography is able to provide valuable additional information on clinicopathologic correlation and is able to guide the clinician toward the most appropriate treatment plan.

The requirement for this expertise has arisen from certain unique characteristics of neonatal medicine:

A. Despite routine antenatal sonography, babies are born with unidentified congenital heart defects.

B. There is a dynamic interplay in the newborn cardiovascular adaptation. The key difference is the fact that in utero placental circulation is a low-pressure, high-pulmonary-resistance circuit. The presence of fetal connections (PFO and PDA) helps to maintain systemic circulation. There are synchronous changes which lead to reversal of fetal circulation, initiated by a drop in pulmonary resistance, increase in the systemic blood pressure, and subsequently closure of fetal channels. There are numerous factors that interfere with this adaptation and include antenatal factors such as maternal conditions affecting fetal growth, placental function, and its circulation, with significant impact on the fetus, complications of labor, preterm delivery, and related surfactant deficiency.

C. In infants with cardiorespiratory maladaptation, the effect of respiratory support from any form of positive pressure ventilation must also be considered, as this increases intrathoracic pressure and impacts cardiac output from decreased venous return. Thus, respiratory status must be included when assessing the newborn hemodynamics.

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II. Neonatal Echocardiography
   A. 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, including functional echocardiography, point-of-care echocardiography, point-of-care ultrasound (POCUS), targeted neonatal echocardiography, clinician-performed cardiac ultrasound, and neonatologist-performed cardiac ultrasound.
   B. There are now a number of governing bodies, such as the American Society of Echocardiography (ASE), the Association for European Paediatric Cardiologists (AEPC), the British Congenital Cardiac Association (BCCA), and the European Society for Paediatric Research (ESPR)/European Society for Neonatology (ESN), that have issued guidance notes with local implications. Where neonatologists are performing structural assessment, they must work in close liaison with their local cardiac referral center. As there is no formal accreditation, a word of caution is needed regarding training and for practitioners to work within their own limitations.

III. Influences on Newborn Cardiovascular Adaptation
   A. Preterm delivery
   B. Surfactant deficiency
   C. Ventilation
   D. Hypoxia
   E. Acidosis

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
      1. Cross-sectional echocardiography is used to assess anatomy; to allow accurate positioning of an M-mode, continuous wave Doppler, or pulsed wave Doppler beam; and to give a subjective impression of function.
      2. Views used include:
         (a) Long-axis parasternal (Fig. 25.1)
         (b) Short-axis parasternal mitral (Fig. 25.2)
         (c) Short-axis parasternal pulmonary (Fig. 25.3)
         (d) Apical four chamber (Fig. 25.4)
         (e) Subcostal
         (f) Suprasternal view of aortic arch or ductal arch
         (g) Subcostal short axis (Fig. 25.5). Useful if lungs overdistended
         (h) Subcostal caudal view of mesenteric vessels and IVC

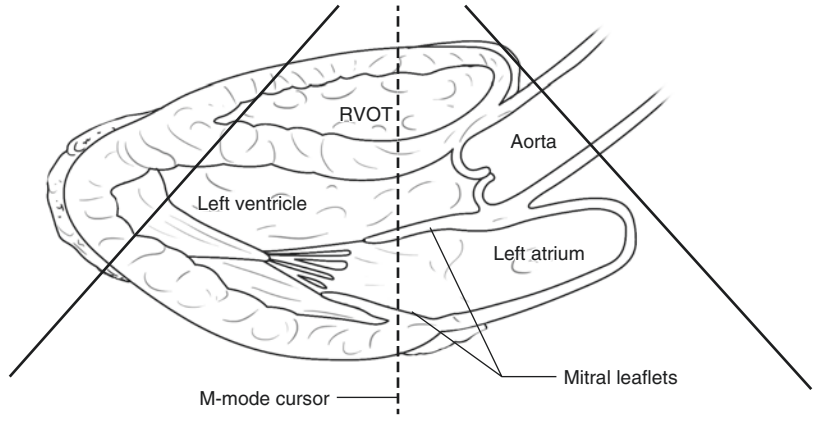


Fig. 25.1 Long-axis parasternal view. Positioning of M-mode cursor for left ventricular measurements is shown. RVOT right ventricular outflow tract

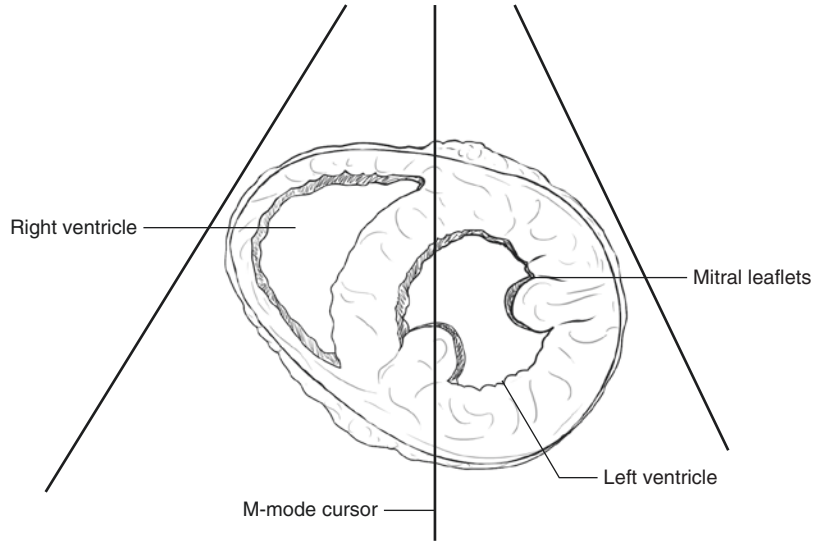


Fig. 25.2 Short-axis parasternal mitral view. Positioning of M-mode cursor for left ventricular measurements is shown

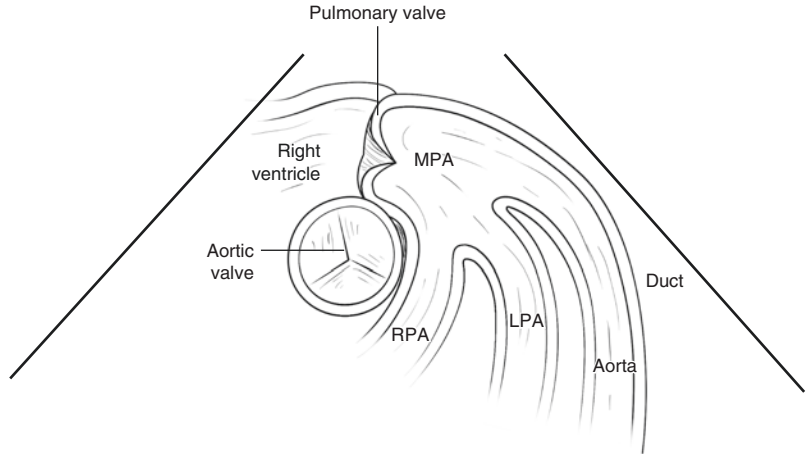


Fig. 25.3 Short-axis parasternal pulmonary view. MPA main pulmonary artery, RPA right pulmonary artery, LPA left pulmonary artery

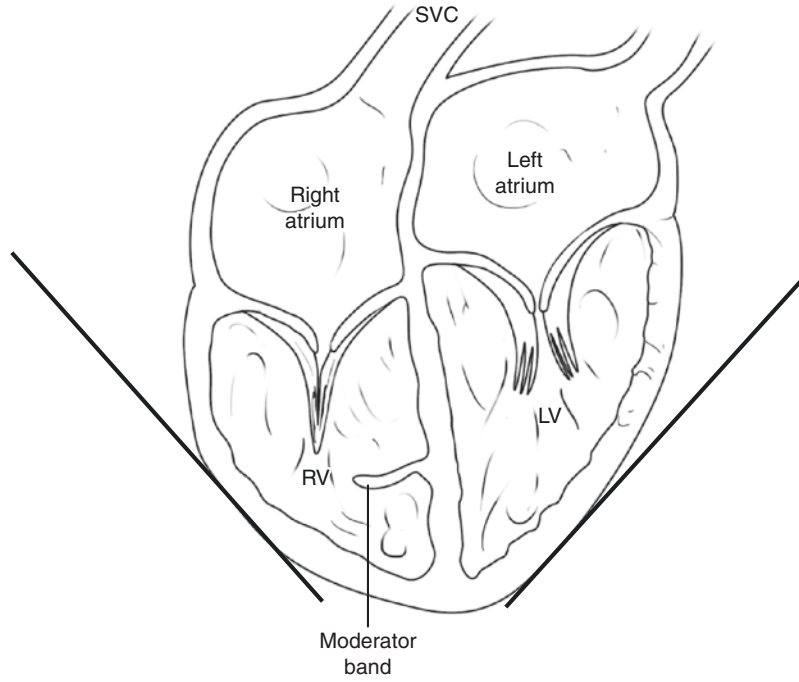


Fig. 25.4 Four-chamber apical view. Offset of tricuspid and mitral valves is seen. SVC superior vena cava, RV right ventricle, LV left ventricle

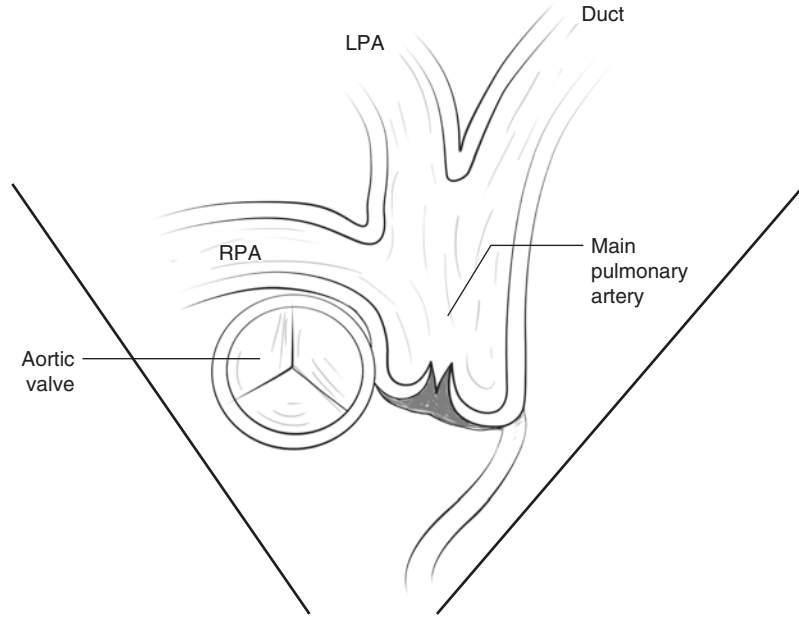


Fig. 25.5 Subcostal short-axis pulmonary view. RPA right pulmonary artery, LPA left pulmonary artery

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 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).

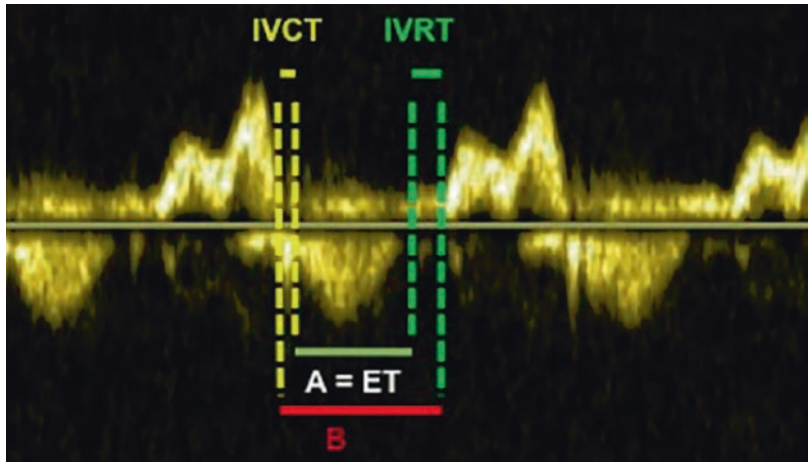
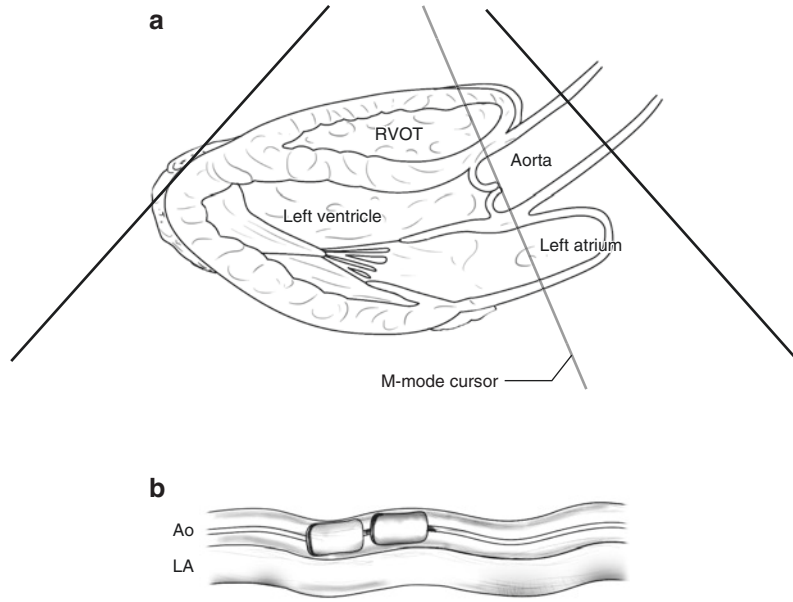


Fig. 25.6 The advantages include values that are independent of HR and blood pressure. MPI has an advantage that it is also not affected but the geometric interference as seen in other measurements. Normal values range from 0.25 to 0.38. The drawback is an abnormal value (more than 0.38) that does not differentiate between systolic and diastolic dysfunction. "B" represents duration in milliseconds from atrioventricular valve closure to opening for either the tricuspid or the mitral valve. "A" represents the ventricular ejection time in milliseconds for either the right or the left ventricular valve. ICT isovolumetric contraction time, IRT isovolumetric relaxation time, ET ejection time. Therefore, MPI equals (B–A)/A equals (ICT + IRT)/ET

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



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 (SVC), aortic arch, and celiac axis.

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).

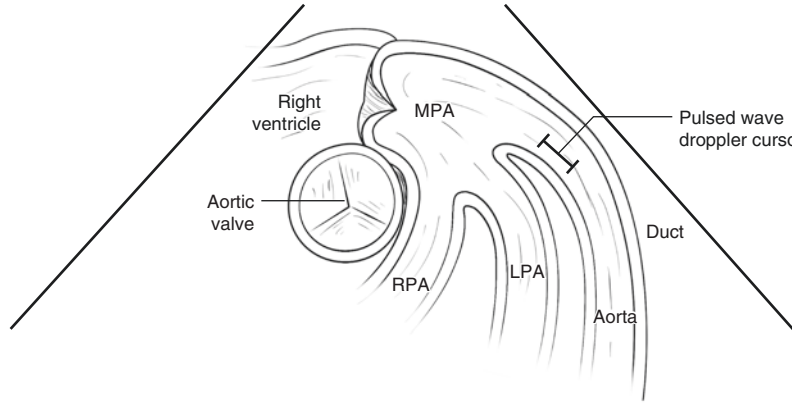


Fig. 25.8 Short-axis parasternal pulmonary view showing the position of the pulsed-wave Doppler cursor for sampling ductal flow velocity

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.

These 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 × 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.

VII. Indications for Echocardiographic Assessment
- A. Suspected congenital heart disease
- B. Suspected persistent pulmonary hypertension (PPHN)
- C. Suspected patent ductus arteriosus (60% patency <28 weeks' gestation)
- D. Hypotension or shock
- E. Asphyxia
- F. Suspected cardiac dysfunction or pericardial effusion
- G. Use of high PEEP/intrathoracic pressure
- H. High-frequency oscillatory ventilation
- I. Suspected pulmonary hypertension in bronchopulmonary dysplasia

VIII. Cardiac Function

Depressed ventricular function may occur in neonatal disease processes such as hypoxia, sepsis, hemolytic disease, RDS, PPHN, and transient tachypnea. Half of premature babies who develop hypotension have cardiac dysfunction in the first 24 hours of life. A dysfunctional heart may display tachycardia and bradycardia 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 obfuscate 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 functions. This can be appreciated without taking the above measurements. 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:

$$\text{Fractional shortening}(\%) = \frac{\text{LVIDD} - \text{LVIDS}}{\text{LVIDD}} \times 100\%$$

$$\begin{aligned} \text{Normal ranges:} \quad & 25-45\% \text{adults} \\ & 25-41\% \text{term babies} \\ & 23-40\% \text{preterm babies} \end{aligned}$$

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 (SV)

(a) SV 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 SV can be calculated as:

$$\text{SV} = \text{LVIDD}^3 - \text{LVIDS}^3$$

(b) Similarly, a proportion of ventricular contents or ejection fraction (EF) can be calculated as:

$$\text{EF} = \text{Stroke volume / end diastolic volume} = \left(\text{LVIDD}^3 - \text{LVIDS}^3\right) / \text{LVIDD}^3$$

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 result from poor contractility in a normovolemic neonate.

X. Doppler Assessment of Systolic Function

A. SV

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:

$$SV = VTI \times pi\left(\text{aortic diameter} / 2\right)^2$$

B. Cardiac Output

1. Left Ventricular Output

Multiplying SV by the HR produces the LVO:

$$LVO = VTI \times pi\left(\text{aortic diameter} / 2\right)^2 \times HR$$

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. RVO

In a similar way, RVO 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

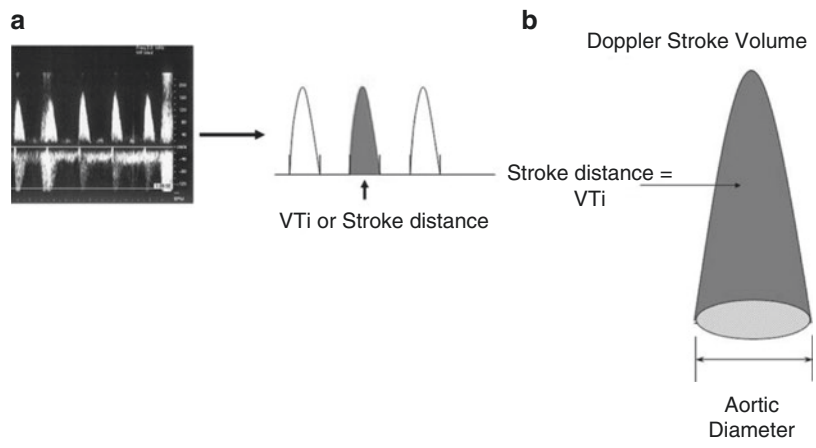


Fig. 25.9 (**a**) Aortic Doppler trace showing the measurement of the integral of the velocity time curve (VTi) or stroke distance. (**b**) Calculating SV using the aortic diameter calculated from the diameter

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).

$$RVO = VTI \times pi\left(\text{pulmonary diameter} / 2\right)^2 \times HR$$

A useful screening measurement which can give an indication of RVO in the first 48 hours is the maximum pulmonary velocity taken as above:

$$< 0.35\,\text{mps} = \text{RVO likely to be less than}\,150\,\text{mL} / \text{kg} / \text{min}$$

C. 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:

$$SVC\left(\text{cardiac output}\right) = VTI \times pi\left(SVC\,\text{diameter} / 2\right)^2 \times HR$$

A measurement of less than 40 mL/kg/min in the first 24 hours 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 interventricular 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 interrogating 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 suggests 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.

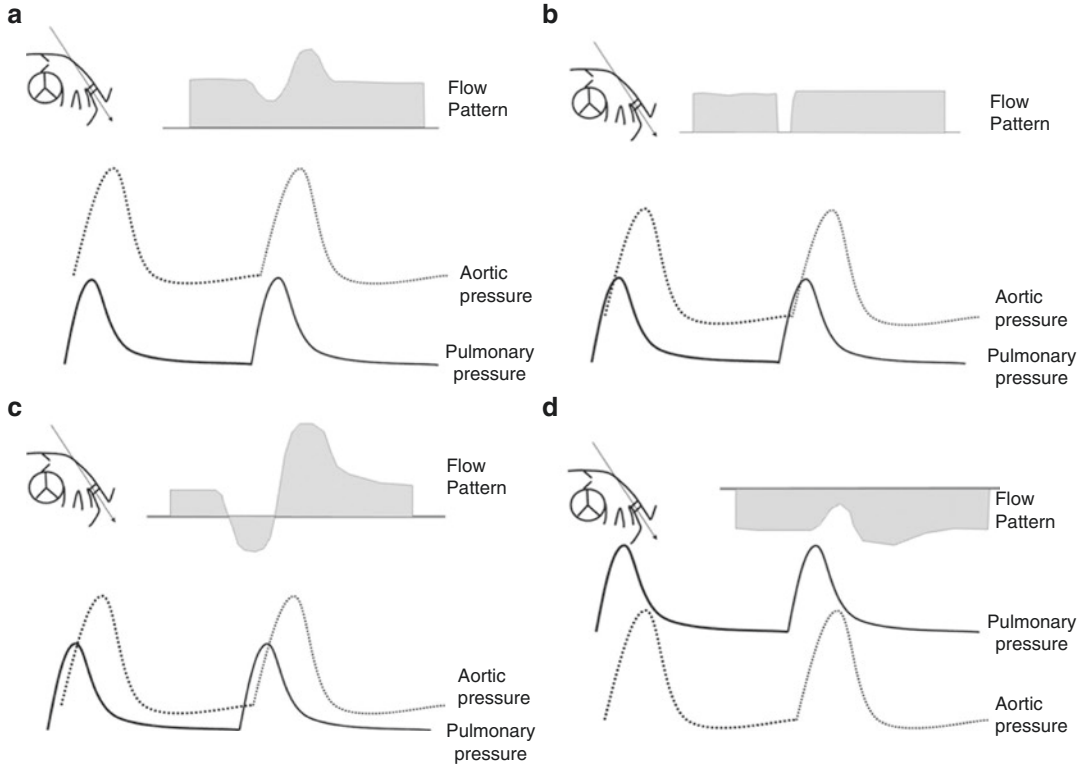


Fig. 25.10 Ductal flow patterns associated with differing systemic and pulmonary pressures: (**a**) Aortic > pulmonary pressure, (**b**) pulmonary = aortic pressure in early systole, (**c**) bidirectional flow with pulmonary > aortic pressure in early systole, (**d**) pulmonary > aortic pressure

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 PEEP and HFOV.

XIII. Assessment of the Patent Ductus Arteriosus (Chap. 82)

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 flow and the velocity profile. Velocity depends on 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, optimize the color gain, and measure. In some units, this is used to predict which ducts are likely to be significant

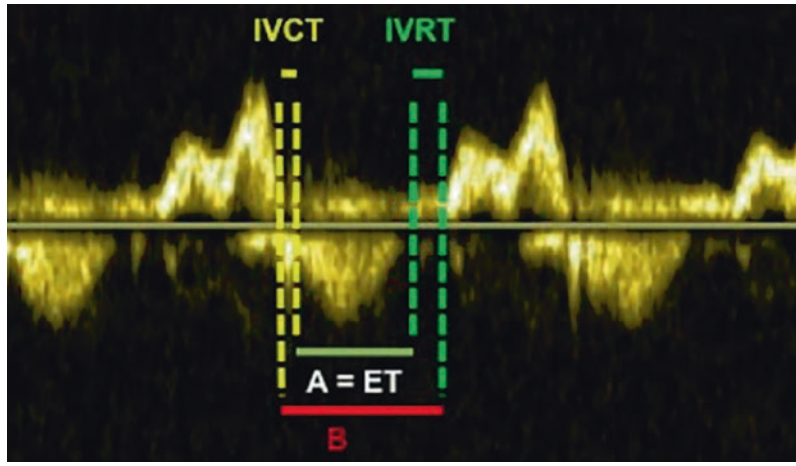


Fig. 25.11 "B" represents duration in milliseconds from atrioventricular valve closure to opening for either the tricuspid or the mitral valve. "A" represents the ventricular ejection time in milliseconds for either the right or the left ventricular valve. *ICT* Isovolumetric contraction time, *IRT* Isovolumetric relaxation time, *ET* ejection time. Therefore, MPI equals (B-A)/A equals (ICT + IRT)/ET. The advantages include values that are independent of heart rate and blood pressure. MPI has an advantage that it is also not affected but the geometric interference as seen in other measurements. Normal values range from 0.25 to 0.38. The drawback is an abnormal value (more than 0.38) does not differentiate between systolic or diastolic dysfunction

and require treatment. Diameter >1.5 mm in the first 30 hours has 83% sensitivity and 90% specificity for 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 a sensitivity of 88% and a specificity 95%.

D. 60% increase in LVO predicts the development of a significant ductal shunt.

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). The respiratory variations in IVC diameter in a mechanically ventilated patient are only observed when right atrial pressure is normal or low.

XV. Assessment of LV Diastolic or Combined Function (Fig. 25.11)
   A. Diastolic function is more difficult to assess by echocardiography especially in neonates with high HR. Mitral flow patterns are commonly used for diastolic function assessment. In the younger pattern, there is greater dependence upon atrial contraction (A wave), and this progresses toward a more mature filling pattern with higher early filling (E wave) with a greater E/A ratio.
   B. In preterm infants with an even higher HR, this assessment is difficult, as the E and A waves are fused making the calculation of the E/A wave ratio used in pediatrics (A wave reflecting

fetal filling type during atrial contraction and E wave the more mature filling pattern of the ventricle) difficult or impossible. The presence of a PDA further compounds the preload conditions with higher erroneous E waves secondary to higher left atrial pressures.

C. IVC collapsibility and measurement of LV end diastolic dimension have been suggested to reflect preload. This can also be useful to assess the impact of fluid replacement when assessing infants with high HR. This needs to be carefully interpreted when infants are receiving positive pressure respiratory support.

D. LV chamber dimension measurement is also compounded by a higher HR. In the presence of higher RV pressure, right bowing of the interventricular septum is noted during transitional circulation. This leads to a lower estimation of LV dimensions and impacts LV function assessment.

E. There are other measures such as myocardial performance index (MPI) also called Tei index. This is a summative systolic and diastolic performance of the heart. MPI uses isovolumetric relaxation and contraction times, corrected for the ejection time. This could be used for assessing either left or right ventricular performance index (Fig. 25.6). Pulse wave Doppler from the apical four-chamber view is used to obtain either mitral or tricuspid inflow. Parasternal short-axis view is used to obtain the right ventricular ejection time.

XVI. 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% underestimation of flow.

XVII. Best Practices in Neonatal Echocardiography

A. Infection control measures: use manufacturer recommended/compatible wipes for cleaning the probes prior to patient contact. This is also important as the use of silica-based wipes could damage the probes. Single patient use sterile gel sachets are available.

B. Ensure thermal control.

C. Minimize skin damage when removing ECG electrodes.

D. Continuous monitoring of oxygen saturation and blood pressure in the extremely premature infant to identify any significant instability.

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Bronchoscopy

26

Neil N. Finer and Anup Katheria

I. Fiber-optic bronchoscopy has remained a useful bedside tool for evaluating neonatal airways.
   A. Evaluate respiratory morbidities:
      1. Subglottic stenosis
      2. Airway edema
      3. Laryngomalacia
   B. Provide immediate, bedside information to providers:
      1. Neonatologists (fewer with skills due to less opportunity for training).
      2. Pediatric pulmonologists, intensivists, otolaryngologists, and adult providers may be an alternative.

II. Equipment
   A. Flexible 2.2 mm 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 less experienced 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

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https://doi.org/10.1007/978-3-030-93997-7_26

1. Atropine (0.01 mg/kg) can be used to decrease secretions and block vagal-mediated bradycardia.
2. Morphine (0.05 to 0.1 mg/kg) or other analgesic may be given for analgesia at least 10–15 min prior to procedure.
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.
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 minutes 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 esophagus. First check with $ETCO_2$ device!
4. Check ETT position after intubation if infant is 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 and 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, and 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, and rule out plug, tracheal narrowing, and tracheomalacia.
B. Persistent or recurrent atelectasis or wheezing in an intubated patient.
C. Evaluation of known or suspected tracheoesophageal fistula preoperatively.

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 trachea-esophageal fistula.

VI. Indications: Non-intubated Patient
   A. Evaluation of stridor, noisy breathing.
   B. Evaluation for evidence of reflux – inflammation around upper airway.

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, findings can be shared with parents and consultants avoiding 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, and tracheal tear – requires moving patient.
   B. Video laryngoscopy
      1. Most useful as teaching tool.
      2. Can be used to show inexperienced operators larynx during intubation attempts and guide them during attempt – optimal with premedication.
      3. Not recommended an as option to examine upper airway without adequate premedication – best done in operating theater.

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, and 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

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Part V

Noninvasive Ventilatory Techniques

Nasal Interfaces for Noninvasive Ventilation

27

Sherry Courtney

I. Overview

The American Association for Respiratory Care Clinical Practice Guideline on application of nasal continuous positive airway pressure (NCPAP) was updated in 2004 and is still in effect. 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 pressure 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 this single prong interface is not as effective for NCPAP delivery as are binasal prongs.

V. *Nasal masks* can be used with some NCPAP devices, most often the variable-flow devices such as Infant Flow© or SiPAP© in the US 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 perhaps the most effective way of providing NCPAP.
   A. Babies are obligate nasal 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 nurses 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 and most reliable for NCPAP delivery are binasal prongs or nasal mask.
   1. The RAM© cannula is approved only for high-flow nasal cannula use. It cannot be used with bubble NCPAP as it does not have an expiratory limb.
   2. With the RAM, expiration occurs through the leaks at the nose and mouth. NCPAP delivery is less than the set value.

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.

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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 noninvasive, positive pressure respiratory support.
   A. Continuous positive airway pressure (CPAP) provides noninvasive positive pressure respiratory support in spontaneously breathing infants with a goal of preventing alveolar collapse and allowing sufficient gas exchange.
      1. In neonates, avoidance of intubation and use of nasal CPAP is an effective strategy for treating respiratory distress and apnea.
      2. Early use of nasal CPAP has been associated with a decreased incidence of chronic lung disease in premature infants.
   B. Multiple devices are available through which CPAP can be delivered.
      1. Nasal cannulas are a common means of providing supplemental oxygen to neonates. However, recent investigations have shown the potential for positive distending pressure delivery via nasal cannulas, with utilization of higher gas flow rates and larger diameter cannulas, to be safe and efficacious.
         (a) Pressure = flow × resistance
         (b) The term "high-flow" nasal cannula relates to the use of >1 liter per minute of gas flow, most commonly 2–8 L/min in the neonatal population. Commercially available humidified HFNC systems (i.e., Vapotherm, Fisher & Paykel, Teleflex) are available to deliver heated, humidified air as well as positive distending pressure (Chap. 29). 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 gas flow parameters and internal pressure limits vary among systems.
         (c) Closure of the infant's mouth allows more optimal delivery of positive distending pressure, but leak around the nares is still present, thus making pressure delivery variable.

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2. Proposed mechanisms of action of heated, humidified HFNC
   (a) Flushing of dead space in the nasopharyngeal cavity leading to improved alveolar ventilation and carbon dioxide removal.
   (b) Adequate gas flow reduces inspiratory resistance in the nasopharynx and reduces work of breathing.
   (c) Heated and humidified air improves pulmonary mechanics, decreases mucosal injury, and prevents airway water loss and cooling.
   (d) Delivery of positive distending pressure, although not specifically set nor able to be reliably measured
      1. Pressure delivery is variable as HFNC is not intended to be occlusive in the nares and pressure delivery is not directly measured.
      2. Pressure delivery typically increases with increasing flow rates.
      3. Pressure delivery typically increases with decreasing infant weight.
3. 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. Respiratory mechanics and assessments of work of breathing are comparable to nasal CPAP.
      4. Easy to administer and well tolerated by patients due to simpler nasal interface as compared to nasal CPAP.
      5. Allows the care provider and patient families easier interaction for holding, neurodevelopmental cares, oral feeding, and sleep positioning of the baby with minimal impediments related to the device.
      6. Lower device cost than nasal CPAP.
   B. Limitations and Risks
      1. Inability to consistently predict actual level of positive distending pressure support delivered to the patient as it is an open system
         (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) Data trying to assess actual pressure delivery is conflicting, even when assessing on same flow rates:
            1. Significant intra-patient and inter-patient variability in physiology.
            2. Variable leaks around the nares and mouth and differences in patient anatomy.
            3. Differences between commercially available HFNC systems' internal diameter of nasal cannulas and pressure delivery at a given flow rate.
            4. Different sites of pressure measurement could explain some of the differences.
         (d) Necessitates the calculation of effective FiO_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 an open system with nasal cannula prongs occupying approximately 50% of the naris diameter.
   (b) Variable levels of positive distending pressure delivered with concern for potential excessive pressure causing lung overdistention, gastric distention, and air leak syndromes. Subcutaneous scalp emphysema, pneumo-orbitis, pneumocephalus, and pneumothorax have been reported with the use of humidified HFNCs. Recent literature does not suggest increased risk of air-leak syndromes compared to nasal CPAP.
   (c) Commercially available HFNC systems typically have pressure-limiting controls to minimize excessive pressures being delivered to the patient; 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) Handmade high-flow systems (those not commercially produced) should be used with extreme caution as they 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. However, recent literature does not suggest increased rates of infection.
4. Literature on HFNC in neonates is limited and difficult to compare because of wide variations in HFNC application, trial methodology, and clinical scenarios:
   (a) Paucity of data for use of HFNC in extremely low gestational age infants (ELGA; <28 weeks' gestational age)
   (b) Population heterogeneity makes interpretation of data difficult as few large 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 specific type of HFNC system that was used, variable treatment algorithms, variability in pretreatment surfactant administration, and variable clinical outcomes analyzed as primary endpoint.
5. No studies to date with adequate power to assess long-term major clinical morbidities and neurodevelopmental outcomes after discharge.

II. Assessment of Potential Clinical Applications for HFNC in Neonates
   A. HFNC as primary respiratory support for neonates with mild to moderate respiratory distress
      (a) Majority of evidence suggests that HFNC is inferior to nasal CPAP as a primary treatment in neonates with early respiratory distress after birth who have not received exogenous surfactant.
      (b) No trials to date have included ELGA infants.
      (c) No trials to date have included infants with severe respiratory distress.
   B. A selection of relevant randomized controlled trials
      (a) Manley et al. [16] in the multicenter HUNTER trial compared rates of treatment failure in 754 infants randomized to HFNC or nasal CPAP to treat early respiratory distress in patients who had *not* received exogenous surfactant prior to enrollment (<24 hours of age; gestational age >31 weeks):

(a) Infants were randomized to either bubble nasal CPAP or HFNC (Fisher & Paykel Optiflow) with predefined treatment failure criteria assessed over subsequent 72 hours.
(b) CPAP was superior to HFNC in reducing treatment failure, with 20.5% of infants on HFNC failing treatment versus 10.2% of infants on bubble CPAP.
(c) Infants randomized to HFNC, who subsequently failed therapy, could receive bubble CPAP as rescue therapy before proceeding to intubation and mechanical ventilation.

When used, rescue CPAP therapy resulted in success for more than half of the patients and avoided mechanical ventilation.

(b) Roberts et al. [19] in the multicenter HIPSTER trial compared rates of treatment failure in 564 infants randomized to HFNC or nasal CPAP to treat early respiratory distress in preterm infants who had *not* received exogenous surfactant prior to enrollment (<24 hours of age; gestational age >28 weeks) who were randomized to either bubble CPAP or HFNC to treat respiratory distress.
(a) Infants were randomized to either nasal CPAP or HFNC (using either Vapotherm Precision Flow or Fisher & Paykel Optiflow) within the first day of life. Predefined treatment failure criteria assessed over the first 72 hours after randomization.
(b) CPAP was superior to HFNC in reducing treatment failure.

The study was terminated early when interim safety analysis at 75% of enrollment goal showed significantly higher treatment failure in the HFNC group (25.5%) compared to the nasal CPAP group (13.3%).

(c) Infants in the HFNC arm who met treatment failure criteria could receive rescue CPAP therapy before proceeding to intubation if deemed clinically appropriate by care team.

Intubation rates did not differ significantly between the groups likely because CPAP was successfully used as a rescue therapy for babies who failed HFNC.

(c) Murki et al. [18] compared rates of treatment failure in 272 infants randomized to HFNC or nasal CPAP as primary respiratory support in preterm infants with respiratory distress who had *not* received exogenous surfactant prior to enrollment (<24 hours of age; gestational age >28 weeks and birth weight >1000 g):
(a) Infants were randomized to either nasal CPAP or HFNC within the first day of life. Predefined treatment failure criteria assessed over the first 72 hours after randomization.
(b) CPAP was superior to HFNC in reducing treatment failure

The study was terminated early when interim safety analysis showed significantly higher treatment failure in HFNC group (26.3%) compared to the nasal CPAP group (7.9%).

(c) Infants in the HFNC arm who met treatment failure criteria could receive rescue CPAP therapy before proceeding to intubation if deemed clinically appropriate by care team. Intubation rates did not differ significantly between the groups likely because CPAP was successfully used as a rescue therapy for babies who failed HFNC.

(d) Shin et al. [22] compared rates of treatment failure using HFNC versus CPAP in 87 infants at a single center who had early respiratory distress and had *not* received exogenous surfactant prior to enrollment (<24 hours of age; gestational age 30–35 weeks, birth weight >1250 grams):
(a) Infants were randomized to either nasal CPAP or HFNC within the first day of life. Pre-defined treatment failure criteria. Non-inferiority margin 20%, notably higher than other studies that were set at 10%.
(b) Concluded that it is not certain if HFNC is non-inferior to nasal CPAP as initial respiratory support. However, this study did not show significantly higher treatment failure in the HFNC group (38.1%) compared to the nasal CPAP group (20.9%, $p = 0.09$).

(e) Lavizzari et al. [14] compared rates of treatment failure using HFNC versus CPAP in 316 infants at a single center who had early respiratory distress (<24 hours of age; gestational age 29–36 6/7 weeks):
  (a) Infants were randomized to either nasal CPAP or HFNC. Predefined treatment failure criteria requiring intubation were noted and no allowance of "rescue" CPAP for HFNC group. Patients in both treatment groups could receive exogenous surfactant via INSURE technique during the study if FiO_2 >0.35.
  (b) Concluded that the use of HFNC was non-inferior to nasal CPAP in minimizing treatment failure (HFNC 10.8% vs. CPAP 9.5%). Equivalent administration of exogenous surfactant to neonates in both treatment arms (HFNC 44%, CPAP 46%).

C. HFNC as noninvasive respiratory support after extubation from mechanical ventilation
  (a) Majority of evidence suggests that HFNC is as efficacious as conventional nasal CPAP for preventing extubation failure.
    (a) Individual trial data vary with regard to study design and failure criteria, the use of different HFNC devices and settings, and varying severity of patient respiratory status at time of extubation.
    (b) Use of "rescue" CPAP in HFNC groups may play a role in HFNC efficacy.
  (b) A selection of relevant randomized controlled trials
    (a) Soonsawad et al. [24] compared rates of extubation failure within 72 hours in 49 preterm infants, born at <32 weeks or weighing <1500 grams at birth, who were randomized to post-extubation support of either HFNC 4–6 LPM (Fisher & Paykel) or nasal CPAP.
      1. Predefined extubation failure criteria for all infants. Infants in HFNC group could receive "rescue" CPAP or bi-level CPAP. Infants in CPAP group could receive "rescue" bi-level CPAP.
      2. No differences in extubation failure rates within 72 hours of extubation between groups. Less nasal trauma in HFNC group compared to CPAP group.
    (b) Collins et al. [3] compared rates of extubation failure within 7 days in 132 preterm infants, born at <32 weeks' gestational age, who were randomized to post-extubation support of either nasal CPAP of 7–8 cm H_2O or Vapotherm® heated, humidified HFNC at 8 LPM.
      1. Predefined extubation failure criteria of apnea (>20 seconds) with more than six episodes in 6 hours or 1 requiring intermittent positive pressure ventilation, acidosis (pH <7.25, PCO_2 >66), and >15% sustained increase in FiO_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
    (c) In their multicenter non-inferiority study, Manley et al. [15] compared rates of extubation failure in 303 preterm infants, born at <32 weeks' gestational age, who were randomized to post-extubation support of either Fisher & Paykel® HFNC at 5–6 LPM or nasal CPAP 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 based on initial assignment; however, HFNC group could receive "rescue" nasal CPAP to prevent reintubation.
      3. Less nasal trauma in HFNC group compared to nasal CPAP group.

(d) Yoder et al. [29] compared early (<72 hours) support failure in a multicenter study of 432 infants, born >28 weeks' gestational age, managed on HFNC (3–5 LPM) versus nasal CPAP 5–6 cm H_2O either after extubation or as primary respiratory support:
1. Study population was mixed with more randomized post-extubation (~66%) than as primary support method (34%), and a variety of CPAP and HFNC devices were used across the various centers.
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 or rates of chronic lung disease.

D. HFNC to prevent apnea of prematurity and increased work of breathing
(a) Sreenan et al. [25] 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.
(b) Saslow et al. [20] 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.

E. HFNC as a weaning mode from nasal CPAP
1. Limited prospective, randomized trials evaluating utility of HFNC as a weaning mode from CPAP. Single site or retrospective studies with different HFNC systems and weaning protocols make it difficult to generalize findings into clinical practice.
2. Soonsawad et al. [24] randomized 101 preterm infants <32 weeks' gestation to wean off CPAP directly versus wean by using HFNC. All infants were stable on CPAP 6 cm H_2O pressure and FiO_2 ≤30% at entry. The CPAP group weaned every 24 hours until stable on CPAP 4 cm H_2O pressure and then discontinued. The HFNC group weaned to HFNC and weaned by 1 LPM every 24 hours until stable on HFNC at 2–3 LPM and then discontinued.
(a) There were no differences in time to successfully wean off support between the two groups.
(b) There was less nasal trauma in the HFNC group.
3. Abdel-Hady et al. [1] evaluated two approaches to weaning 60 preterm infants >28 weeks' gestation from CPAP. All infants were stable on CPAP at FiO_2 ≤30% at entry. At randomization, the first group was maintained on CPAP until in F_iO_2 21% for 24 hours and then weaned directly to room air. The second group weaned from initial CPAP to HFNC 2 LPM and maintained on HFNC until in F_iO_2 21% for 24 hours 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.
4. Fernandez-Alvarez et al. [6] conducted a retrospective pair-matched cohort analysis of two approaches to weaning from CPAP in preterm infants ≤28 weeks' gestation and <1250 grams. All infants were stable on CPAP at FiO_2 <40% at time of transition from CPAP. The first cohort of 39 patients was managed on Vapotherm HFNC 8 LPM and weaned to 2 LPM

before transitioning to a low-flow nasal cannula (LFNC). The second cohort of 40 patients was weaned from CPAP to a LFNC <0.3 LPM. All infants were taken off nasal cannula support once they had been in room air for over 24 hours.

(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

5. Taha et al. [25] retrospectively analyzed a database with information on the respiratory outcomes of 2847 very low birth weight infants treated with HFNC versus CPAP versus CPAP+HFNC over a 5-year timeframe across 466 NICUs in the USA. Infants who received a combination of CPAP and HFNC or HFNC alone were on oxygen for longer and in the hospital for longer than infants treated with CPAP alone.
6. Heath Jeffery et al. [9] prospectively analyzed 72 preterm babies who were treated with CPAP versus CPAP + HFNC during their NICU course.

   Infants who received CPAP + HFNC had greater oxygen requirements and longer time on respiratory support as compared to those treated with CPAP alone.

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Continuous Distending Pressure

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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 discussed further.
   B. High-flow nasal cannula (HFNC) use is increasingly common in preterm 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. However, this chapter does not specifically discuss HFNC.
   C. CPAP is a positive pressure applied to the airways of spontaneously breathing infants. We use the term to describe noninvasive CDP.
   D. PEEP is a pressure applied to the airways through an endotracheal tube (ETT) during invasive positive pressure mechanical ventilation.

II. The Pathophysiology Treated by CDP
   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 results in inadequate oxygenation through a reduction in the area available for gas diffusion as well as increased ventilation/perfusion mismatch

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and intrapulmonary shunt. While carbon dioxide diffuses more readily across the alveolar-capillary membrane, it can also be eventually compromised by low lung volumes and atelectasis.

3. The chest wall of the premature infant retracts with the negative pressure generated by diaphragmatic contractions and further exacerbates a tendency for atelectasis and increases the work of breathing. This is seen in the "paradoxical" movements of the thorax and abdomen.

B. Mechanisms Contributing to Disease

1. Inadequate fetal lung fluid clearance: The alveolar epithelium secretes fluid into the lungs during fetal life. In a healthy term infant, labor-induced adrenergic hormones and fetal postural changes initiate the process of fluid absorption. While the initial absorption of lung fluid is predominantly driven by the osmotic gradient resulting from active transport of sodium from the lumen to the interstitial space after birth, the transepithelial pressure gradient produced with the infant's first breaths (which generate negative pressures of up to −80 cm H_2O) has a large impact. Aeration of the lungs moves the fluid out of the air-spaces into the surrounding interstitium, where over time it is removed by lymphatics and blood vessels. After preterm birth, the infant's inability to generate large negative pressures during initial breaths contributes to the slower clearance of fetal lung fluid. Additional contributory mechanisms include elective cesarean delivery, continued secretion of fluid into alveolar lumen, elevated left atrial pressure, and low plasma protein concentration.
2. Low lung volume: 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 equilibrium between the tendencies of outward chest wall recoil and inward lung recoil. The flexible chest wall of the premature infant falls with the negative intrathoracic pressure generated by diaphragmatic contractions and is unable to maintain lung volume during excessive inspiratory efforts. A highly compliant chest wall combined with the low compliance of lungs in surfactant-deficient preterm infants shifts the balance of forces in the newborn's lungs toward a low FRC close to airway closing volume.
3. Anatomy of the chest wall and diaphragm: The horizontal ribs and round shape of the preterm infant's chest wall reduce the potential for lung expansion. The diaphragm's relatively flat shape and attachment to the rib cage contribute to inefficient mechanics. The preterm infant's diaphragm has fewer endurance fibers, and its contractility may be impaired by reduced oxygen availability.
4. Upper airway narrowing: 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.
5. Inability to generate/maintain "intrinsic PEEP": A term infant maintains a low level of PEEP in the airways after birth by adduction of the larynx during expiration. A newborn with lung disease has two mechanisms to maintain FRC. The first is to breathe rapidly and shorten the expiratory time to prevent the lung from losing volume. The second is to "grunt" during expiration. During these breaths, the baby quickly inspires, and then the larynx closes 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 ETT.

6. Inadequate lung architectural support: The preterm infant lacks the supportive internal lung architecture and collateral ventilation channels that help stabilize and maintain open air spaces.
7. Lack of surfactant: Surfactant has two important functions in healthy newborn lungs. First, it lowers surface tension of the lung fluid and facilitates lung aeration and the formation of an FRC at birth. Second, during expiration, it becomes compressed and semisolid, helping maintain the alveoli open. Surfactant quantity and quality are decreased in preterm infants, as well as in conditions such as meconium aspiration syndrome and pneumonia. The resulting alveolar collapse may result in edema, which further reduces the efficacy of surfactant.
8. Risk of atelectotrauma: 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 pathology of RDS.
9. Alveolar anatomy: The immature lung has thicker and fewer alveolar septae, further limiting diffusion and the surface area available for gas exchange.
10. Patent ductus arteriosus (PDA): Premature infants often have a PDA. As the pulmonary artery pressure falls after birth, blood is shunted from the aorta through the PDA to the pulmonary arteries and lungs. This may increase fluid in the lungs, predisposing to pulmonary edema, which in turn may impair gas exchange and surfactant function, and decrease lung compliance. However, whether and when to intervene for a PDA remains controversial.

C. How CDP 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 mechanical splinting. In infants receiving PEEP, the ETT bypasses the upper airway and stops the ability of laryngeal adduction to help maintain lung volume.
3. CDP decreases the "opening" pressures throughout the lung resulting in greater homogeneity, enabling gas flow into different areas of the lung, and reduces variation in delivered tidal ventilation within the lung.
4. CDP helps stabilize a 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 lung compliance. CDP 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 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 overdistension and may contribute to pneumothoraces or pulmonary interstitial emphysema.
   B. Overdistention with excessive CDP can induce lung injury as well as 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. Overdistension may increase intrathoracic pressures. This could diminish venous blood return and decrease cardiac output. The transmission of pressure to the thorax and its effect on pulmonary hemodynamics is proportional to the relative compliance of the lungs and the chest wall. However, such side effects are less when the infant is sickest (i.e., has the "stiffest" lungs).
   D. Overdistension may increase pulmonary vascular resistance. Along with a decrease in cardiac output, this may increase V/Q mismatch. An elevated pulmonary vascular resistance also promotes extrapulmonary shunting of deoxygenated blood from the pulmonary to systemic circulation via the patent foramen ovale or PDA. Both V/Q mismatch and extrapulmonary right-to-left shunting decrease oxygenation.
   E. Dislodgement of 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 and alternating between different types of devices.
   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 "braking" during expiration plays an important role in lung recruitment and maintaining FRC 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 VIII apply specifically to the use of noninvasive CPAP in spontaneously breathing infants.

IV. Indications
   A. Very preterm 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, particularly oxygenation. Assessment for and implementation of initial resuscitative steps should follow existing guidelines. Early application of CPAP need not interfere with other aspects of resuscitation.
   B. Very preterm infants can be successfully started on nasal CPAP from birth and do not necessarily need to be intubated. Recent meta-analyses of randomized trials conclude that strategies favoring the use of noninvasive CPAP over mechanical 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). More recently, less invasive surfactant administration (LISA) by a catheter may allow for delivery of surfactant, while a baby is receiving CPAP without need for intubation. Increasing evidence at the time of writing supports this strategy but requires experienced clinicians with technical expertise in the procedure.

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 could 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 nasal CPAP immediately post-extubation. Inadequate laryngeal function following extubation, the impact of which is mitigated by CPAP, may explain some of this benefit.
E. The use of CPAP in late preterm or term infants should be based on observation of clinical signs 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. CPAP Interfaces
A. The following interfaces may be used to deliver CPAP to newborns: face mask, single nasal prong, long nasopharyngeal prongs, nasal mask, and short binasal prongs. A head box with a neck seal (Gregory box) is rarely used.
1. Face mask: has the benefit of not losing pressure through the mouth and nose. It is most commonly used for administering CPAP immediately after birth. Difficulty maintaining an adequate seal and the need to remove the mask to access the nose or mouth limit its long-term use.
2. A single nasal prong: the drawbacks are higher resistance and loss of pressure through the other nostril compared to binasal prongs. A single prong can be short, inserted into a nostril about 1.5 cm, or inserted into the pharynx. An ETT cut to about 5 cm can be used. We do not recommend this (see item B below).
3. Long nasopharyngeal prongs: compared to short prongs, resistance is higher, and the risk of obstruction with secretions is higher. We do not recommend this.
4. Short binasal prongs: are among the most commonly used devices and are recommended in Cochrane reviews over single or nasopharyngeal prongs. They are inserted into the nostrils and attached to a pressure source for delivering CPAP. In recent years, a specific type of cannula with long and narrow tubing (RAM cannula, NeoTech, USA) has gained popularity because of ease of use. However, available evidence suggests that this interface results in more attenuation of delivered pressure compared to traditional short binasal prongs.
5. Nasal mask. This is a commonly used interface which surrounds the infant's nose.

B. A systematic review of trials comparing devices concluded that binasal prongs are more effective than short or long single prongs in preventing reintubation in premature infants.
C. In recent years, meta-analyses of randomized trials comparing nasal masks vs. prongs suggest that masks may lead to a lower risk of CPAP failure within 72 hours. However, the quality of evidence is low to moderate.
D. More than one device (e.g., short binasal prongs and nasal mask) can be alternated to reduce skin, nasal, and septal breakdown associated with sustained pressure to specific areas. Prevention of injury is the key – with a combination of appropriate positioning, taping of the device, choice of device, barrier gel protection, alternation of devices, and correct sizing.

VI. CPAP Devices
A. Various types of devices may be used to deliver CPAP to neonates. The basic components of any CPAP delivery setup consist of a gas flow source (preferably with blended oxygen), a heater and humidifier, a ventilator circuit for gas to flow to and from the baby, a nasal interface, and a mechanism to generate pressure.

B. CPAP delivery devices can be broadly categorized into constant flow and variable flow devices. Constant flow devices can be further subcategorized into ventilator-based CPAP and bubble CPAP devices.
C. Variable flow devices provide a jet of gas into the interface chamber (where the velocity decreases with a concomitant pressure increase, in accordance with Bernoulli's principle), maintaining a constant pressure at the interface level. These devices are believed to result in a "fluidic flip" of gas flow toward the exhalation tubing (Coanda effect) during the expiratory phase, although there are limited data supporting the occurrence of this phenomenon during nasal CPAP. Compared to other CPAP systems, some studies have shown decreased work of breathing with these devices. However, trials to date have not shown evidence of benefit with respect to any other clinical outcomes.
D. Bubble CPAP has generated considerable enthusiasm over the years, partly because of the simplicity of its design, and also from the oscillations generated by the bubbling effect, which is believed to improve gas exchange based on limited data. A recent meta-analysis of trials comparing bubble to all other forms of CPAP demonstrated less likelihood of CPAP failure with its use.

VII. How to Determine CPAP Level
A. The CPAP level should be individualized to each infant's underlying pathophysiology and distending pressure need (see F and G, below). Using the same pressure for all infants is common but not appropriate.
B. There is limited evidence to help guide the selection of the most appropriate CPAP level in individual clinical scenarios. An optimal CPAP level maximizes the benefits of achieving and maintaining appropriate lung volumes while minimizing potential harms associated with overdistension (Sections II and III). At this time, clinical assessment, oxygenation requirement, and chest radiographs remain the practical and readily available surrogates for these principles at the bedside.
C. An infant may require different CPAP levels as he or she progresses through the neonatal course.
D. Immediately after birth, CPAP between 4 and 8 cm H_2O are commonly used. Infants with poorly compliant lungs or with severe evolving chronic lung disease may benefit from higher pressures.
E. Trials demonstrate that pressures between 4 and 8 cm H_2O do not typically affect hemodynamics (heart rate and blood pressure) in stable premature infants with lung disease. Trial data also suggest initial uniform starting CPAP levels of 8 cm H_2O may be associated with air leaks. However, in selected patients outside the delivery room (e.g., with rising oxygen needs), emerging data suggest CPAP levels of >8 cm H_2O might be well tolerated, but this requires further research.
F. Signs that an infant may require more distending pressure include poor oxygenation with FiO_2 needs rising, 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 overinflated 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 5–7 cm H_2O and gradually adjusting pressures while monitoring for the signs described above is a reasonable empiric approach. Data from one randomized controlled trial involving preterm neonates extubated around 2 weeks' chronological age suggests that high CPAP (7–9 cm H_2O) may result in lower extubation failure rate compared to standard CPAP (4–6 cm H_2O).

I. Initial CPAP levels in a baby with RDS may affect surfactant treatment criteria. Applying a higher CPAP level will lower FiO_2, and if the latter is used as the surfactant criterion, this may result in postponing surfactant treatment. Clinicians should be aware of this.

VIII. Duration and Weaning of CPAP Therapy

A. CPAP should be discontinued when its use no longer improves gas exchange, including prevention of apnea, or when 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. When a baby is ready to trial off CPAP, one approach is to simply discontinue and remove CPAP. Alternative approaches include (I) gradually wean the pressure, (II) a "step-down" transition to a different support strategy such as HFNC, or (III) a "cycling" method of 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.

E. The best approach has not been firmly established by trials. A recent systematic review of these strategies concluded that compared to direct discontinuation to room air, gradual weaning improved chances of initial successful weaning but resulted in longer time on CPAP. On the other hand, the step-down method resulted in shorter time on CPAP but longer oxygen supplementation. Neither of these methods resulted in differences in BPD or length of hospitalization. Finally, cycling off CPAP did not confer any advantages and in one trial not included in this systematic review, direct trial off CPAP resulted in shorter time on CPAP, less BPD, and shorter length of stay.

F. 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 across studies, and the duration of CPAP therapy should be individualized for each infant.

G. One recent trial demonstrated an improved FRC in preterm neonates randomized to CPAP extended (by 2 weeks), compared to discontinuation of CPAP at 32 weeks' postmenstrual age. This improvement was sustained until term. However, the mean GA of included infants was ~29 weeks, and whether this is advantageous for smaller preterm neonates with more severe lung disease is unknown.

H. 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.

I. Infants born at a lower gestational age typically require CPAP support to a later age.

PEEP

Sections IX to XII apply specifically to the use of PEEP in mechanically ventilated infants.

IX. 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 noninvasive 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 mm Hg (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 episode requiring bag mask ventilation within a 1-hour period.
4. Severe tachypnea, retractions, and breathing asynchronously with the ventilator.
5. Mean blood pressure (in mm Hg) below the infant's gestational age, poor perfusion on physical exam, or progressive metabolic acidosis.

X. How to Administer PEEP
   A. The ventilator delivers PEEP by closing an exhalation valve on the ventilator at the preset pressure.
   B. Ventilators measure PEEP in two phases; the starting value of the measurement corresponds to the set PEEP on the ventilator and the ending 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, with a gas leak from the ETT and longer expiratory times, the PEEP will decrease. This depends on ventilator parameters, such as the inflation/expiratory time ratio and respiratory rate, as well as properties of the lung, such as thoracic compliance, airway, and ETT resistance (the product of which is the "time constant"). When time for expiration is insufficient, gas trapping and intrinsic (or "inadvertent") PEEP can occur. Infants at risk for air trapping (e.g., meconium aspiration) or with heterogenous lung disease (severe BPD) are at risk for intrinsic PEEP. It can be appreciated by flow-time curves displayed on the ventilator monitoring when the flow during expiration does not reach zero before the next inflation starts.

XI. How to Determine the PEEP Level
   A. At zero end expiratory pressure (ZEEP) in a mechanically ventilated infant with low lung compliance, 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 (see H and I, below). Using the same pressure for all infants is common but not appropriate.
   C. There is limited evidence to guide the selection of optimal and individualized PEEP levels. An ideal PEEP level maximizes the benefits of achieving and maintaining appropriate lung volumes while minimizing potential harms associated with overdistension (Sections II and III). As is the case with use of CPAP, clinical assessment, oxygen requirement, and chest radiographs are surrogates for these principles available to the bedside clinician.
   D. An infant may require different PEEP levels as he or she progresses through the neonatal 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. The most recent Cochrane review on this topic identified four trials in patients with respiratory distress syndrome (RDS). Two cross-over trials of 28 patients compared various PEEP levels with no difference in short-term physiologic gas exchange parameters. Two other trials in 44 patients evaluated a lung recruitment maneuver strategy to determine optimal PEEP, compared to routine care, and showed a reduction in the duration of mechanical ventilation and oxygen support compared to routine care. No studies were found in patients with established BPD. These strategies will require further study.

G. A few other 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. Signs that an infant may require higher PEEP include poor gas exchange (in particular oxygenation), low lung volumes or atelectasis on chest radiography, chest wall retractions, or tachypnea.
I. Signs that an infant may require less PEEP include overinflated lungs, a flat diaphragm and a small cardiac shadow on chest radiography, worsening gas exchange (in particular increased carbon dioxide), and increasing heart rate and decreasing blood pressure.
J. The availability of pressure-volume (PV) information on modern ventilators theoretically provides additional information in intubated infants. It has been 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 to maximize dynamic compliance are suitable approaches 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 in a spontaneous breathing baby and with large ETT leaks.
K. 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.

XII. Duration of PEEP Therapy
A. Mechanical ventilation should be discontinued as soon as it is no longer needed. CDP 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.

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Sustained Inflations

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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. The term infant usually takes a few deep breaths to aerate the lungs resulting in transport of fluid within the airways down to the alveoli and from the alveoli to the surrounding interstitial tissue, where it transiently increases interstitial pressure and may reenter into the alveoli in the absence of sufficient distending pressure. From the interstitial space, it is cleared within 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. Healthy term infants with strong respiratory effort may clear amniotic fluid from the airways with a few breaths within a few 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 to ensure adequate gas exchange for survival.
      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 using 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 allowing gas to enter the alveolar system. This hydrostatic pressure gradient may be very large (>50–100 cm H_2O) in normal newborn infants to overcome the high resistive forces imposed by the high viscosity of fluid present in the airways. This results in a long time constant. In asphyxiated term neonates requiring respiratory support, sev-

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eral breaths with a large pressure gradient have been used to establish functional residual capacity (FRC).

2. To avoid large trans-pulmonary pressures, longer inflation times have been implicated for asphyxiated term neonates to move the amniotic fluid distally without the need for large trans-pulmonary airway pressure gradients. Therefore, the use of a prolonged inflation time of 15–20 sec maintaining the peak inflation pressure, called "sustained inflation" (SI), may allow clearance of lung fluid from the airways without the need for large trans-pulmonary pressures.

II. History

A. Boon et al. studied the formation of tidal volume and FRC 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., however, 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-sec duration) in the resuscitation in term newborns with asphyxia. They were able to show that *time*, rather than *pressure*, was needed to move air from the airways to the alveoli and to create the FRC. This approach, however, has never been tested clinically in a controlled study in a significant number of infants with clinical or long-term outcomes other than physiologic variables.

B. More recently, new data from important studies in very preterm infants became available, which require a change to the recommendations given in the previous edition of this book. Furthermore, studies in term infants with SIs as a mode of lung aeration during cardiac compressions in severely asphyxiated neonates are currently under investigation.

III. Technical Issues

A. Sustained inflations are given with a pressure generating device with the airway pressure of 20–30 cm H_2O often maintained for 15–30 seconds. Usually a face mask, or sometimes nasal prongs, or nasal tubes are used as interfaces.

B. The use of almost all pressure delivery devices and interfaces is associated with leaks, which may be substantial in size and need compensation during the prolonged "inspiratory time" of SIs. Leak compensation over 15–30 seconds is difficult when using a self-inflating bag with or without a PEEP valve. Although anesthesia bags may compensate for larger leaks, most neonatologists are not familiar with these devices. It is therefore not surprising that most clinical studies with SIs were undertaken using a T-piece, or sometimes ventilator systems, which have in common that they can easier compensate for leaks.

IV. Selected Experimental Studies

A. Te Pas et al. [29, 30] showed that PEEP is important to form FRC in newborn rabbits, that SIs were particularly useful to aerate the lungs within seconds, and that the combination of PEEP and SIs was most effective. In another experiment, the same authors showed that longer SIs (up to 20 s) are useful to fully aerate the lungs and to obtain a more uniform aeration of the lungs.

B. Sobotka et al. [37] demonstrated that a single SI improved lung function in preterm lambs after birth without adverse circulatory effects. In asphyxiated lambs, however, the same researchers found evidence for a disruption of the blood-brain barrier, which may exacerbate brain injury.

C. Hillman et al. [12] 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. Crawshaw et al. [5] studied laryngeal function using phase contrast radiography in spontaneously breathing preterm rabbits immediately after birth and found that the larynx and the epiglottis were open mostly during spontaneous breathing but not during unstable breathing patterns including apnea. The upper airway was open with aerated lungs and a stable breathing pattern. These findings provide an explanation of the clinical observation that noninvasive (bag/mask) ventilation is often not effective in aerating and ventilating the neonatal lungs.

E. Katira et al. [18] exposed rats to mechanical ventilation (V_t 6 mL/kg) using gradually increasing PEEP (from 3 to 11 cm H_2O) vs. a moderate PEEP (3 cm H_2O) strategy over 70 minutes. Thereafter, the high PEEP group was abruptly exposed to 0 cm H_2O PEEP. The investigators found evidence for acute lung dysfunction with a lower compliance, increased vascular leak, a sharp increase in systemic blood pressure, and acute left ventricular decompensation, suggesting that abrupt deflation to low levels of PEEP may cause severe lung injury. It remains unclear whether SIs with high pressures causing overdistension for 15–30 s with a sudden decrease to "low" levels of PEEP may cause similar lung injury.

F. 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. However, a major difference from clinical studies lies in the fact that the upper airway was bypassed in most experimental studies with tracheostomy/endotracheal tubes, whereas initial respiratory support in neonates is usually performed using noninvasive ventilation.

V. Clinical Studies

A. Cohort Studies

1. Lindner et al. [24] reported on 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 15s) compared to an approach based on conventional IPPV, the rate of intubation and mechanical ventilation in the delivery room and the rate of BPD and IVH grades 3–4 was reduced.
2. Lista et al. [26] studied 89 preterm infants up to 2 SIs (25 cm H_2O for 15s) compared to a historical control group supported with conventional IPPV and found a decreased need for mechanical ventilation and a significantly lower rate of BPD.
3. Grasso et al. [10] 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, and there were no differences in mortality and morbidity. The authors reported a trend towards a higher rate of IVH (23% vs. 14%, $P = 0.15$).
4. Van Vonderen et al. [43] 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 was extremely important, as positive pressure inflations given to support newborn infants with apnea have been reported to be obstructed in clinical circumstances, whereas in most experimental animal models the upper airway is bypassed.
5. Fuchs et al. [8] studied preductal arterial oxygen saturation using pulse oximetry and cerebral tissue oxygenation using near-infrared spectroscopy (NIRS) immediately after birth in 51 preterm infants exposed to SIs. Cerebral tissue saturation increased almost as fast compared to 10 vigorous preterm infants requiring only CPAP, suggesting that gas exchange and brain perfusion is not impaired by the increased intrathoracic pressure imposed by SI.

6. One retrospective study suggested that the use of SIs with 30 cm H_2O may be associated with a higher risk for air leaks. A higher incidence of air leaks was found in one randomized clinical trial. However, most other randomized trials did not report a higher rate of air leaks in SI groups.

B. Randomized Trials

1. Lindner et al. [23] randomized 61 preterm infants requiring respiratory support immediately after birth as judged by the caretakers to SIs vs. conventional IPPV using a nasopharyngeal tube. Up to 3 SIs (PIP increased stepwise 20, 25, and 30 cm H_2O) were given in the experimental group according to the infants' responses. Primary outcome was treatment failure (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, or other morbidities, although the study lacked power because of early closure secondary to slow recruitment.
2. Harling et al. [11] randomized 51 preterm infants to SIs (25–30 cm H_2O for 5-sec duration) vs. conventional IPPV. Primary outcome measures were cytokine concentrations in bronchoalveolar lavage fluid collected immediately after intubation and again at 12 hours of age. There were no differences in cytokine levels as well as mortality and other clinically relevant variables between groups.
3. Te Pas et al. [31] randomized 207 preterm infants to SIs (20 cm H_2O for 10 sec, with 25 cm H_2O/10 sec for the second SI depending on the infants' response) and conventional IPPV using nasopharyngeal tubes vs. face masks (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 in this study was part of an intervention package including CPAP 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 another study published by Lista et al. [25], 291 infants were randomized to SIs (25 cm H_2O for 15 sec up to two times), by face mask or conventional IPPV in a prophylactic approach, regardless of their own respiratory effort. The authors found a lower rate of intubation and mechanical ventilation in the first 72 h of life with no differences in mortality and in the rates of BPD or IVH and a trend for more air leaks in the SI group.
5. In a randomized trial, Schwaberger et al. [35] studied the effect of SI (1–3 x 30 cm H_2O for 15 sec) vs. standard IPPV on cerebral blood volume (CBV) using NIRS in 40 preterm infants 28 + 0 to 33 + 6 w GA. Whereas CBV showed a significant decrease from minutes 3 to 15 in the control group, CBV basically remained unchanged in SI group. The authors speculated that decreased venous return from the high intrathoracic pressure in SI infants may have caused these findings, although the clinical implications are currently unclear as cerebral tissue oxygenation index was similar in both groups.
6. Mercadante et al. [27] randomized 185 infants 34 + 0 to 36 + 6 w GA to SI (25 cm H_2O for 15 sec) followed by CPAP or standard IPPV and did not find a difference in the primary outcome (need for any type of respiratory support [10.6% vs. 8.7%, SI vs. control]).
7. Jiravisitkul et al. [16] randomized 81 preterm infants 25–32 w GA to SI (25 cm H_2O for 15 sec) or standard IPPV to assess HR, SpO_2, FiO_2, and intubation rate. Mean FiO_2 was lower 10 min after birth in the SI group with a lower intubation rate in infants ≤28 w GA, but there were no differences in other clinical outcomes.

8. Hunt et al. [15] randomized 60 preterm infants <34 w GA to a 15-sec SI vs. five conventional inflations (2–3 sec) to study its effects on minute ventilation and maximal end-tidal CO_2 in the first minute after the intervention and found no differences between groups. Infants allocated to the SI group had earlier spontaneous breathing (3.5 [0.2–59] vs. 12.8 [0.4–119] sec) and were exposed to mechanical ventilation for less time during the first 48 h (17 [0–48] vs. 32.5 [0–48] h).
9. Abuel Hamd et al. [1] randomized 160 preterm infants with GA ≥27 to ≤32 weeks to SI using a pressure of 20 cm H_2O for 15 sec followed by CPAP (5 cm H_2O) vs. nasal CPAP alone. They did not find a difference in the primary outcome (need for mechanical ventilation within the first 72 h of life) or in any secondary outcome.
10. In the largest trial published so far, 460 preterm infants with a GA of 23–26 weeks were randomized to either up to two SIs at a maximal peak pressure of 25 cm H_2O for 15 sec or standard resuscitation with intermittent pressure ventilation with the primary outcome of BPD or death [19]. The study was closed early because death at <48 hours of age occurred in 16 infants (7.4%) in the SI group vs. three infants (1.4%) in the standard resuscitation group (adjusted RD, 5.6% [95% CI, 2.1% to 9.1%]; $P = 0.002$). BPD or death occurred in 137 infants (63.7%) in the SI group vs. 125 infants (59.2%) in the standard resuscitation group (adjusted RD, 4.7% [95% CI, −3.8% to 13.1%]; $p = 0.29$).
11. Three systematic reviews and meta-analyses on SIs vs. conventional respiratory support after birth in preterm infants were published recently:
    A. The analysis from Foglia et al. [7] included nine trials and 1406 preterm newborns. Primary outcome was death before hospital discharge, which occurred in 11.5% vs. 9.3% infants; SI vs. standard respiratory support; and risk difference of 3.6% (95% CI, −0.7% to 7.9%). There was marked heterogeneity in study methods. SI was associated with increased risk of death in the first 2 days after birth (risk difference, 3.1%; 95% CI, 0.9–5.3%). No differences in the risk of other secondary outcomes were identified. There was no evidence of efficacy for sustained inflation to prevent secondary outcomes. The authors conclude that these findings do not support the routine use of SI for preterm infants after birth.
    B. The Cochrane Analysis from Bruschettini et al. [4] assessed benefits and harms of an initial SI (>1 sec) vs. standard inflations (≤1 sec) in newborn infants receiving resuscitation with intermittent PPV in ten trials enrolling 1467 infants. There was no significant difference in mortality in the delivery room or during hospitalization or in any meaningful morbidity. However, the authors cite the single largest study, which was well conducted and was stopped early for a higher mortality rate 2 days after birth in the SI group. The authors do not see any evidence to support the use of SI for neonatal stabilization.
    C. Kapadia et al. [17] undertook another systematic review including ten trials enrolling 1502 preterm newborns and found no differences between SI (duration >5 sec) and control groups for death before discharge or other relevant morbidities. However, the risk for death within the first 2 days was elevated with SI, with a risk ratio of 2.42 (95% CI = 1.15–5.09). In a subgroup analysis of preterm infants ≤28 weeks' gestation, the risk ratio for death before discharge was 1.38 (95% CI = 1.00–1.91). The authors conclude that there is potential harm for SI, especially for preterm infants ≤28 weeks' gestation, and the absence of any benefit.

12. In *summary*, although SIs seem to work in carefully controlled animal experiments, in randomized human clinical trials, SIs seem to have limited efficacy when used in preterm infants immediately after birth. This may be related to the fact that the upper airway was bypassed in most experimental studies with tracheostomy/endotracheal tubes, whereas initial respiratory support in neonates is usually performed using noninvasive ventilation. The evidence based on the available meta-analyses of randomized controlled trials does not show any clinical benefit of SIs when used for delivery room stabilization in preterm infants. Moreover, there seems to be potential harm in the most immature infants.

VI. Cardiopulmonary Resuscitation During Sustained Inflations

A. Experimental evidence:

1. A 30-sec SI was compared to conventional ventilation by Klingenberg et al. [20] in late preterm asphyxiated lambs (without asystole, but severe arterial hypotension) and was associated with a faster recovery of the heart rate and carotid arterial pressure [20].
2. Schmölzer et al. [34] compared continued chest compressions (120/min) combined with a 30-sec SI (30 cm H_2O) with standard neonatal resuscitation (three compressions/one inflation) in a piglet model of asphyxia and were able to show earlier return of spontaneous circulation (ROSC) in the SI group. In a similar study, the compression rate was matched in both groups (SI + CC vs. standard three compressions/one inflation) to 90/mins resulting again in a shorter time to ROSC in the SI group. In another experiment of the same group of investigators, different SI durations (20 sec and 60 sec) were compared with standard 3:1 resuscitation, and both SI groups experienced ROSC earlier than the standard group with no difference between SI groups. Shim et al. studied different SI pressures (10, 20, and 30 cm H_2O) in the same model and found similar time to ROSC, but PIP at 30 cm H_2O showed a larger V_t delivery, lower exhaled CO_2, and increased tissue inflammatory markers in the brain.
3. Vali et al. [42] compared a group of asphyxiated neonatal lambs given up to two SIs (35 cmH_2O for 30 s) + 120 chest compressions/min to a group of lambs undergoing standard neonatal resuscitation (three compressions/one inflation). There was no difference in median time to ROSC (390 [225–405] vs. 345 [204–465] sec) or the need for epinephrine. These results are contradictory to those mentioned in the piglet model above, which may be related to the lamb model being a transitional model, whereas the piglet model is post-transitional.

B. Clinical evidence:

In a small feasibility study, Schmölzer et al. randomized nine preterm infants <32 w GA and found a shorter mean time to ROSC in the SI group vs. the group undergoing conventional resuscitation (31 ± 9 vs. 138 ± 72 sec, $p < 0.05$). There were no differences in short-term outcomes, although mortality was 2/5 vs. 0/4.

VII. Recommendations

A. The currently available evidence suggests that the clinical use of SIs to aerate the lungs and support gas exchange immediately after birth may reduce the rate of intubation and mechanical ventilation but does not convey any other relevant clinical benefits. There seems to be potential harm in the most immature preterm infants, as mortality within the first 48 h seems to be significantly higher when using SIs compared to standard IPPV in the delivery room. The topic "sustained inflations" was reviewed for the latest 2020 international consensus on cardiopulmonary resuscitation for neonatal life support. It recommends *against the routine use of SIs longer than 5 sec in preterm infants* and that SIs may be considered in research settings in this population.

B. For term or late preterm infants, there are no published randomized trials available, and therefore no recommendations for any specific duration for initial inflations can be given at this time.
C. More research is needed on the optimal duration and optimal pressure for both preterm infants with different gestational age categories and term infants. Future studies should look at the effect of SIs on the newborn infants' own respiratory effort. A gradual increase in aeration after birth as an alternate lung recruitment strategy may be more beneficial than SI to recruit lung volume and deserves investigation. Furthermore, the role of SIs during cardiac compressions needs to be studied.
D. In *summary*, at this time, the routine use of SIs to support neonatal transition cannot be recommended outside of carefully designed research trials. The use of SIs during neonatal resuscitation along with chest compressions cannot be recommended at this time as not enough data are available.

Suggested Reading

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Noninvasive Ventilation: An Overview

31

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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 noninvasive ventilation can be confusing. When noninvasive 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 inflation. 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).

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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 by a ventilator. Patients can breathe at both levels of pressure:
   1. Bi-level will be used here to refer to noninvasive ventilation delivered by such a device.
   2. BiPAP (bi-level positive airway pressure).
   3. These biphasic devices are often 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 (HFO) decreases alveolar damage, showing improved histologic appearance compared to intubated and ventilated animals. Nasal 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. Nasal HFO has been compared to nCPAP in four single-center randomized trials. Three trials compared nasal HFO to nCPAP as a primary mode of support. One trial showed a reduced incidence of subsequent intubation in those randomized to nasal HFO. The fourth trial enrolled preterm infants ready for extubation and reported a lower reintubation rate in those randomized to nasal HFO. Nasal HFOV modes have potential but will not be discussed further because of the limited randomized 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 reduction in 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 NV also provide additional positive pressure breaths. These provide slightly higher mean airway pressure and possibly higher tidal volumes. Whether synchronized or not, they reduce thoracoabdominal asynchrony and improve chest wall stabilization, resulting in decreased work of breathing. These effects have been shown particularly with synchronized NV.

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 most recent Cochrane reviews. Although those data suggest benefit in prevention of extubation failure or need for intubation, 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 bi-level and synchronized NIPPV); no difference was observed in short-term outcomes (see below).

E. The largest pragmatic randomized controlled trial enrolled 1009 infants <1000 g and randomized them to NV (via a ventilator or bi-level) or nCPAP, either as a primary mode or 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 was the inability to assess whether synchronization might improve these effects, since the majority of infants were on non-synchronized NIPPV. Babies in the intervention group also received either NIPPV or bi-level, which may have reduced efficacy.

IV. How Can Noninvasive 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 on 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 there is appropriate fit to the nares.

B. A recent RCT comparing synchronized CMV-NIPPV with unsynchronized 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 noninvasive respiratory support) between the two groups.

C. Synchronized NV 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 neutrally assisted ventilatory assist (NAVA) (Chap. 48) 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 transdiaphragmatic potential. This enables triggering of a ventilator breath with a tidal volume proportional to the magnitude of the transdiaphragmatic potential. Efficacy in reducing clinically relevant outcomes is as yet undetermined by randomized trials.

V. Indications for Use

A. Post-extubation: As of 2021, 12 randomized controlled trials have compared NV to CPAP after extubation in premature infants. A meta-analysis of these trials demonstrated a reduction in extubation failure (RR 0.60, 95% CI 0.45–0.81; RD 0.15, 95% CI 0.23–0.08, NNT = 7). However, the time up to which this was assessed varied, and the longest was 1 week post-extubation. Nine trials used NIPPV generated by a ventilator (five used synchronized devices and four used a non-synchronized device); a reduction in extubation failure was demonstrated for both types of devices. Two trials used bi-level CPAP and did not show a reduction in post-extubation failure.

B. Apnea of prematurity: Three studies compared CPAP with NV (non-synchronized) for the treatment of apnea of prematurity. Trials were 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. A recent systematic review and

meta-analysis reported high risk of bias in trials examining this question and no decrease in the frequency of apnea of prematurity with NIPPV.

C. Primary mode of ventilation for respiratory distress syndrome: 16 randomized controlled trials, with 2014 patients, examined this question. Seven used non-synchronized NV delivered by a ventilator, while four used synchronized NIPPV. Four 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 noninvasive respiratory support with need for intubation (4 h to 1 week). Pooled data from all trials showed that the incidence of respiratory failure was reduced significantly by NIPPV (RR 0.55, 95% CI 0.46–0.65; RD 0.12, 95% CI 0.16–0.09, NNT = 8). This was observed in both synchronized and non-synchronized NIPPV and bi-level.

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 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 4–6 cm H_2O, and rates 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 ventilator-generated NIPPV, synchronized and non-synchronized.
B. Reduction in post-extubation apnea has not been convincingly shown.
C. Prevention of intubation in RDS, when used as the primary mode of respiratory support.
D. Reduction in BPD, in primary mode trials but not in post-extubation 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 by 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 is crucial.

Suggested Reading

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Nasal Intermittent Positive Pressure Ventilation (NIPPV)

32

Vineet Bhandari

I. Introduction
   A. Nomenclature
      1. Nasal intermittent positive pressure ventilation (NIPPV) is providing of nasal continuous positive airway pressure (NCPAP) in the intermittent mandatory ventilation (IMV) mode.
      2. When synchronized with the infant's respiratory efforts, 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 hours) of endotracheal intubation or less invasive mode for surfactant administration, prior to extubation to NIPPV.
      4. Secondary mode: refers to its use after a longer period (>2 hours 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 modes.
      3. SNIPPV: Infant Star with Star Sync® (used a Graseby capsule for synchronization; discontinued in the USA); Giulia ventilator (uses flow synchronization; Ginevri, Italy); and Servo-i® (uses neutrally adjusted ventilator assist or NAVA; Maquet, Getinge group, Germany).
      4. Not considered SNIPPV: Infant Flow®Si-PAP™ (Care Fusion, BD 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 time (Ti) is typically prolonged, even up to 1.0 second.

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C. Mechanism of Action (Mostly in Reference to SNIPPV)
   1. Decreased thoracoabdominal motion asynchrony and flow resistance; improved stability of the chest wall and pulmonary mechanics.
   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, thereby washing out carbon dioxide and thus reducing anatomical dead space.
   3. Increased tidal and minute volumes shown in a few studies.
   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 tracheoesophageal 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® for skin protection
   E. Oro-gastric tube (8 or 9 Fr)
   F. Suction catheter

IV. Procedure (Note: This May Be Unit Specific)
   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 would 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 oro-gastric tube; connect the other end of the tube to a 10 cc syringe, remove plunger, place it higher than the infant, and open to the atmosphere.
   F. Connect the nasal interface setup to the ventilator.

V. Primary Mode: Initial Settings
   A. Frequency (rate): ~40/minute
   B. PIP: 4 cm H_2O > than the PIP required for manual ventilation; adjust PIP based on chest rise and aeration on auscultation. Some clinicians prefer a lower starting pressure with gradual titration upward.
   C. PEEP: 4–6 cm H_2O
   D. Ti: ~0.45 seconds
   E. Fraction of inspired oxygen (FiO_2): adjusted to keep saturations 89–94%
   F. Flow: 8–10 L/minute
   G. Caffeine: give a loading dose prior to placing on NIPPV
   H. Hematocrit: ≥35%

VI. Primary mode: Monitoring and Maximal Support
  A. Monitor: SpO_2, heart rate, and respiratory rate
  B. Obtain blood gas in 15–30 minutes
  C. Adjust ventilator settings to maintain blood gas parameters within range
  D. Suction mouth and pharynx, as necessary
  E. Maximal support recommendations
    1. 1000 g – mean airway pressure (MAP) 16 cm H_2O
    2. ≤1000 g – MAP 14 cm H_2O

VII. Extubation Criteria: While on Conventional Ventilation, Prior to Placing on Secondary Mode NIPPV
  A. Frequency (rate): 15–25/minute
  B. PIP: ≤16 cm H_2O
  C. PEEP: ≤5 cm H_2O
  D. Ti: ~0.45 seconds
  E. FiO_2: ≤0.35
  F. Caffeine: targeted levels, 15–25 μgm/mL
  G. Hematocrit: ≥35%

VIII. Secondary Mode: Initial Settings
  A. Frequency (rate): 15–25/minute
  B. PIP: 2–4 cm H_2O > than the PIP on conventional ventilation settings; adjust PIP based on chest rise and aeration on auscultation.
  C. PEEP: ≤5 cm H_2O
  D. Ti: ~0.45 seconds
  E. FiO_2: adjusted to keep saturations 87–93%
  F. Flow: 8–10 L/minute
  G. Caffeine: give a loading dose at least 1 hour prior to placing on NIPPV (targeted levels: 15–25 μgm/mL)
  H. Hematocrit: ≥35%

IX. Secondary Mode: Monitoring and Maximal Support
  A. Monitor: SpO_2, HR, and RR.
  B. Obtain blood gas in 60 minutes.
  C. Adjust ventilator settings to maintain blood gas parameters within range.
  D. Suction mouth and pharynx, as necessary.
  E. Maximal support recommendations:
    1. 1000 g – MAP 16 cm H_2O
    2. ≤1000 g – MAP 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/mean Paw within 4/2 cm H_2O of the targeted value.
  C. The oro-gastric (large bore) decompression tube:
    1. Connect to an empty 10 mL syringe, with the plunger removed, open to the atmosphere.
    2. Needs to be kept at a higher level than the infant to decrease abdominal distension.
    3. Can be used for feeding via "gravity-drip" method.
  D. If requiring continuous feeds, a 6 Fr 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 $PaCO_2$ ≥60 mmHg (8 kPa)
  B. Severe apnea: any episode requiring bag and mask resuscitation
  C. Frequent (>two to three episodes/hour) apnea/bradycardia (cessation of respiration for >20 seconds associated with a HR <100/minute) not responding to methylxanthines
  D. Frequent desaturations (≤85%): ≥ three episodes/hour, not responding to increased ventilator settings

XII. NIPPV Failures
  A. Group 1
    1. Get intubated usually within a few hours of extubation.
    2. Infants tend to be <750 g weight.
    3. Chest X-ray shows significant areas of collapse.
    4. After re-intubation, minimize endotracheal tube ventilation settings.
    5. Attempt re-extubation usually after 7 days and/or when infants have gained another ~100 g weight.
  B. Group 2
    1. Get intubated usually after 3 days or so being managed with NIPPV.
    2. Over the 3 days, the infant starts developing micro-atelectasis and, when a significant portion of the lung is involved, fails NIPPV and gets intubated. Hence, to prevent this:
      (a) Keep caffeine at higher end of the therapeutic range.
      (b) Give a blood transfusion if hematocrit is <35% with a FiO_2 requirement of >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 and get re-intubated at any time.
    2. Usually the cardiorespiratory compromise secondary to sepsis is the inciting event leading to NIPPV failure.
    3. Do not attempt extubation of such infants to NIPPV until clinical manifestations of the sepsis syndrome have resolved.

XIII. Weaning NIPPV: Consider Weaning to Nasal Cannula at These NIPPV Settings
  A. Frequency (rate): <20/min
  B. PIP: ≤14 cm H_2O
  C. PEEP: ≤4 cm H_2O
  D. FiO_2: ≤0.3
  E. Flow: 8–10 L/minute
  F. Blood gases: within normal limits

XIV. Wean NIPPV to -
  A. Nasal cannula: adjust flow to 1–2 L/minute and FiO_2 to maintain SpO_2 89–94%.
  B. Oxyhood: adjust FiO_2 to maintain SpO_2 89–94%.
  C. Some prefer nasal CPAP, then high-flow nasal cannula, and then low-flow nasal cannula as a weaning strategy.

XV. NIPPV: Potential Hazards/Complications
  A. Obstruction of prongs due to mucus plugging.
  B. Feeding intolerance.
  C. Abdominal distension.
  D. Abdominal perforation.

E. Ventilator-induced lung injury.
F. Hypoventilation.
G. Infection.
H. Nose bleed/irritation.
I. Drying of mucus deep in the oropharynx caused by the application of high flows. This can obstruct breathing. Nurses need to perform deep suctioning in these babies and sometimes laryngoscopy.
J. Skin irritation and pressure necrosis.

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Practical Applications of Nasal High-Flow Therapy

33

Kate Hodgson and Brett J. Manley

I. Nasal high-flow therapy (nHF) is a form of noninvasive respiratory support for neonates, which provides heated and humidified air and oxygen via two small nasal prongs.
   A. Neonatal nHF flow rates are generally 2–8 L/min.
   B. Nasal HF prongs are designed to not occlude the nares; leak around the prongs avoids generation of excessive pressure.
   C. Compared with continuous positive airway pressure (CPAP), nHF may be preferred by nursing staff and parents due to perceived comfort and ease of use.

II. Nasal HF is used in several settings in neonates:
   A. Primary support of preterm infants with respiratory distress
   B. Post-extubation support of preterm infants following a period of mechanical ventilation and/or exogenous surfactant treatment
   C. Respiratory support in preterm infants with evolving or established bronchopulmonary dysplasia (BPD)
   D. Short-term support for neonates with a respiratory tract infection, e.g. bronchiolitis. Only indications A and B are covered in this chapter.

III. Primary Support
   A. Nasal HF may be used soon after birth for primary support of preterm infants with respiratory distress syndrome:
      1. Randomised controlled trial evidence suggests that nHF is associated with a higher rate of treatment failure when used for primary support in preterm infants, compared with CPAP.
      2. Despite this, rates of mechanical ventilation are similar.
      3. The approach to the use of 'rescue' CPAP in the event of nHF failure, and to surfactant use differs in randomised controlled trials and in the clinical setting.

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4. Rates of nasal trauma are lower with nHF use.
5. Total duration of respiratory support may be slightly longer with nHF use.
6. There is very little evidence available for the efficacy or safety of nHF for extremely preterm infants born <28 weeks' gestation.
7. Some centres and clinicians report good outcomes using nHF for primary support in preterm infants, without the need for rescue CPAP.

B. Therefore, choice by clinicians between nHF and CPAP for this indication should consider:
1. The value placed on the benefits of nHF
2. The approach to 'rescue' CPAP and surfactant use

IV. Post-extubation and/or Post-surfactant Respiratory Support

A. Nasal HF may be used in preterm infants following a period of mechanical ventilation or following exogenous surfactant treatment.
1. Randomised controlled trial evidence suggests that nHF is non-inferior to CPAP for post-extubation support of preterm infants born >28 weeks' gestation.
2. The availability of 'rescue' CPAP is important to prevent higher rates of endotracheal intubation and mechanical ventilation in those infants in whom nHF treatment fails.
3. Limited evidence is available, but CPAP may be superior to nHF for post-extubation support of extremely preterm infants born <28 weeks' gestation.

B. Nasal HF may be considered an alternative to CPAP for post-extubation or post-surfactant respiratory support in preterm or term infants born >28 weeks' gestation, but CPAP is currently recommended for extremely preterm infants.

V. Nasal HF Devices and Equipment

A. The two most commonly used commercial devices for delivering nHF in neonates are Optiflow Junior (Fisher and Paykel Healthcare, Auckland, New Zealand) and Precision Flow (Vapotherm, Exeter, New Hampshire, USA).
1. There are a variety of other devices used to deliver nHF, which will not be covered in this chapter.
2. Randomised trials of nHF in neonates have used both devices, although predominantly the Fisher and Paykel device.
3. Whilst there is little evidence from randomised trials to suggest one device is superior to the other for any clinical indication, some centres prefer one device over the other and report good clinical outcomes.

B. Both devices require:
1. A power source
2. Air and oxygen gas sources
3. Source of humidification
4. A disposable patient circuit
5. Nasal prongs (cannulae)

C. Both devices can adjust fraction of inspired oxygen (FiO_2) and flow rate to the delivered to the patient.

D. According to the manufacturers, the nasal prong size chosen should aim to occlude less than 50% of the nares, to avoid excessive pressure generation and enable optimal dead space washout, although this may be difficult to achieve in very small preterm infants
1. For Optiflow Junior (Fisher & Paykel, Fig. 33.1)
2. For Precision Flow (Vapotherm, Fig. 33.2)

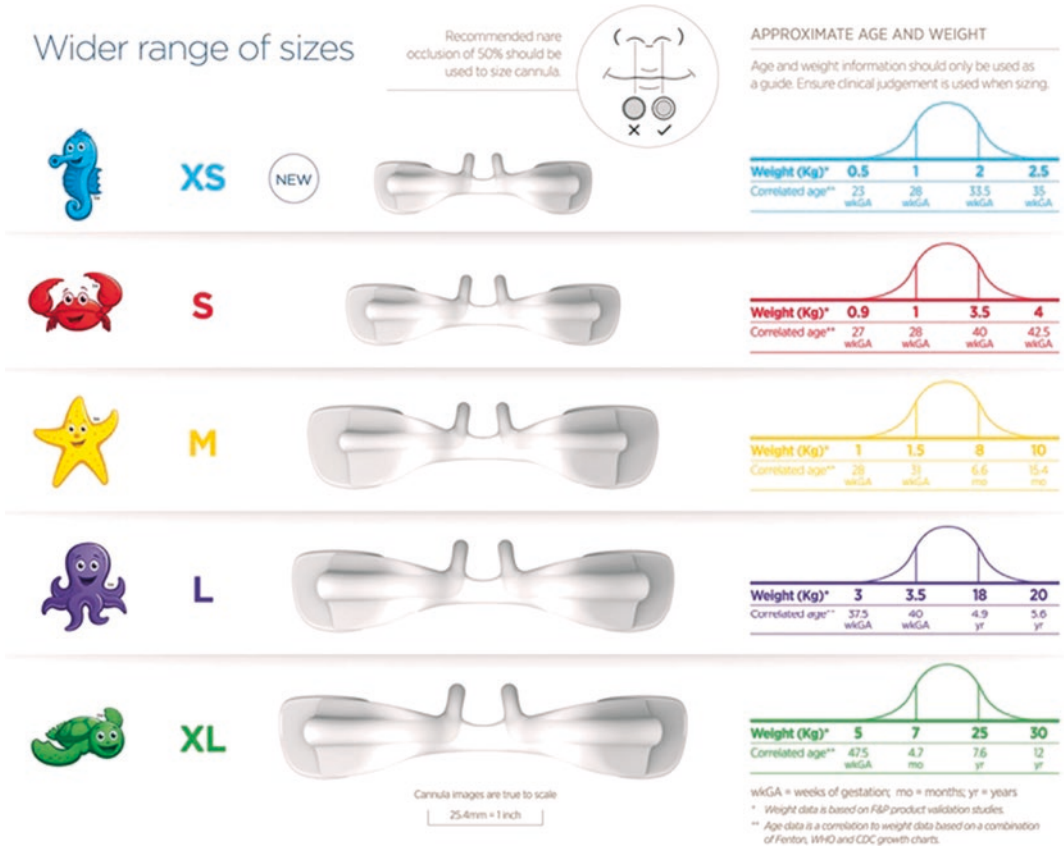

Fig. 33.1 Optiflow Junior 2 prong sizes (https://www.fphcare.com/au/products/optiflow-junior-2/)

Fig. 33.2 Vapotherm Precision Flow prongs (https://vapotherm.com/neonatal-guidelines-best-practices/)

Cannula Sizes	Weight	Tip OD
Premature	<700g	1.5 mm
Neonatal	<1100g	1.5 mm
Infant	<1100g	1.9 mm
SOLO (P,N,I)	700-1100g	1.9 mm
Intermediate Infant	>1100g	1.9 mm

VI. Initial Gas Flow Settings
   A. Trial evidence and clinical practice varies widely, and choice of starting gas flow in neonates should consider the infant's:
      1. Gestational age
      2. Underlying disease pathophysiology
      3. Current clinical status: respiratory distress, oxygen requirement and acid-base balance
   B. Flow rates are generally in the range of 2–8 L/min for primary and post-extubation support of preterm infants.
   C. In neonates, flow rates are usually prescribed like this, rather than per kilogram of body weight.

D. An appropriate recommended starting point for nHF in preterm neonates is:
   1. Flow rate 6 L/min
   2. Fraction of inspired oxygen to maintain peripheral oxygen saturation (SpO_2) within unit-specific target range

E. These settings are consistent with large clinical trials and authors' clinical experience.

VII. Adjustment of Gas Flow and Fraction of Inspired Oxygen

A. Supplemental oxygen is generally increased to maintain SpO_2 in the target range prior to increasing the gas flow.

B. Gas flow is generally increased in increments of at least 1 L/min in the event of:
   1. Increased supplemental oxygen requirement
   2. Respiratory acidosis on blood gas analysis
   3. Increasing frequency or severity of apnoea
   4. Increased respiratory distress (tachypnoea or use of accessory muscles).

C. The maximum gas flow currently recommended for neonatal use is 8 L/min.

D. At the commencement of nHF support, or in the event of clinical deterioration, the patient may require regular review and adjustment of the set gas flow and/or FiO_2 according to clinical condition.

E. In the event of clinical deterioration despite nHF of 8 L/min, consideration should be given to:
   1. Commencement of CPAP (usually at a pressure of 7–8 cm H_2O) (see Chap. 29)
   2. Surfactant administration via less invasive surfactant administration (LISA) (see Chap. 58)
   3. Endotracheal intubation and mechanical ventilation

VIII. Monitoring of Infants Receiving nHF

A. Monitoring should involve:
   1. Cardiorespiratory monitoring
   2. Clinical observation of severity of respiratory distress
   3. Clinical inspection of the nares for signs of nasal trauma
   4. Chest X-ray (as clinically indicated, not routine)
   5. Blood gas analysis (as clinically indicated)
   6. Documentation of frequency and severity of any desaturation and/or apnoeic events

IX. Weaning of nHF

A. Supplemental oxygen is generally weaned prior to gas flow in preterm infants receiving nHF. The exception is preterm infants with evolving or established BPD who may have the gas flow weaned whilst still requiring higher FiO_2.

B. Weaning strategies vary significantly, and there is little evidence to guide practice.

C. Pragmatically, gas flow should be reduced by increments of at least 1 L/min in the event of clinical improvement of the infant:
   1. Weaning may be able to occur rapidly in late preterm infants or those with mild respiratory distress. Consider reducing gas flow by 1 L/min every 6–12 hours if FiO_2 <0.30.
   2. Weaning may need to be more cautious in extremely preterm infants born <28 weeks' gestation or in those infants with more severe disease pathophysiology:
      (a) These infants may deteriorate in the event of rapid weaning and therefore benefit from more prolonged nHF support and slower weaning of gas flow.
      (b) When improving, consider reducing gas flow by 1 L/min every 24–48 hours if FiO_2 <0.30.
   3. It may be necessary to re-escalate nHF support if there is a deterioration during weaning.

D. Ceasing nHF will depend on clinical circumstances:
   1. Pragmatically, nHF can often be ceased entirely from 4 L/min with FiO_2 <0.3.
   2. 'Low flow' or ambient oxygen may still be required.
   3. In some infants, for example, infants with evolving or established BPD, lower gas flows (2–4 L/min) or longer durations of respiratory support may be indicated.

X. Future Research
   A. Future research questions for nHF include:
      1. Comparison of precision flow (Vapotherm) and Optiflow Junior (Fisher and Paykel) devices
      2. Use of gas flows higher than 8 L/min
      3. Use in novel settings (e.g. during delivery room stabilisation, neonatal endotracheal intubation)

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Part VI

Ventilatory Modes and Modalities

34 Intermittent Mandatory Ventilation

Steven M. Donn

I. General Comments
   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.

II. 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 ventilator rate (BR). Total cycle time is the BR (bpm) divided by 60 seconds/min.
      2. With pressure-targeting, the mandatory tidal volume (V_T) is determined by the preset pressure limit (PL) above the baseline (PEEP), 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.

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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.

C. Indications (Relative)
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 peak inspiratory pressure (PIP) 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 skeletal muscle relaxants if synchronized ventilation is not available and the baby is struggling against the ventilator.
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 on 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

III. Controls, Monitors, and Alarms
  A. Controls
    1. Ventilator Rate (BR)
      (a) BR adjusts the number of mandatory (i.e., ventilator-controlled inflations) delivered each minute.
      (b) Conventional ventilators typically have a range of zero (CPAP) to 150 breaths per minute (BPM).
      (c) Initial BR will generally be between 30 and 60 BPM; however, rates ≥60 BPM may be necessary.
    2. PIP
      (a) During pressure-targeted ventilation, IP adjusts the PIP applied to the airway during the inspiratory phase. It is the primary determinant of the delivered V_T (i.e., the depth of inspiration).
      (b) Typically, the adjustable range will be 3–80 cm H_2O.
      (c) The PIP 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.
      (d) If the ventilator system in use has a V_T monitor, PIP 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.
    3. Inspiratory Time (T_I)
      (a) T_I adjusts the length of time pressure is applied to the airway during inspiration (i.e., the length of the inspiratory phase).
      (b) The adjustable range is typically 0.1–3.0 seconds.
      (c) Initial T_I generally ranges from 0.3 to 0.5 seconds. A shorter T_I may be required if BR >60 BPM.
    4. Flow Rate
      (a) This control generally has a dual purpose. First, it adjusts the magnitude of flow directed to the airway during the inspiratory phase of each inflation. 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.
      (b) The range of flow varies among ventilators. The low end is usually 2–3 liters per minute (LPM) with the high end 20–30 LPM and, in some cases, up to 40 LPM.
      (c) 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.

IV. 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 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 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 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 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 seconds but may be adjustable from 10 seconds to 2 minutes 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 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-minute 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.

V. Patient Management
   A. Ventilation
      1. The primary controls which adjust the level of ventilation are the amplitude (ΔP = IP-PEEP) and BR (frequency).
      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. However, institutional practices will vary.
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.

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Synchronized Intermittent Mandatory Ventilation

35

Steven M. Donn

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 preset time.
   B. Flow: Inspiration ends when flow decreases to a chosen percentage of the peak inspiratory flow rate.
   C. Volume: Inspiration ends when the preset volume is delivered. Not practical with an uncuffed endotracheal tube because of leaks.
III. Trigger Mechanisms
   A. Airway flow change
      1. Heated wire anemometer
      2. Differential pressure transducer
   B. Airway pressure change
   C. Diaphragmatic EMG signal (see Chaps. 48 and 49)
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 SIMV with pressure support.
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 unless pressure support (Chap. 37) is added to help unload respiratory musculature.
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 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.

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Assist/Control Ventilation

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Steven M. Donn

I. Description
   A. Ventilatory mode in which mechanical breaths are either patient (assist) or ventilator (control) initiated.
   B. Another form of patient-triggered ventilation (PTV)
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 (Chap. 48)
IV. Assist Breath
   A. If patient effort exceeds trigger threshold, 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)
      2. Tidal volume delivery (if volume-targeted)
      3. Inspiratory time (if time-cycled)

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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 phases).
3. Prevents inversion of inspiratory/expiratory ratio and minimizes risk of gas trapping.
4. May occasionally result in insufficient inspiratory time and tidal volume delivery.

V. Control Breath
A. Essentially a safety net, providing backup 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 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 eliminate or 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. Since the patient initiates and controls tidal volume delivery, the preferred strategy in volume-targeted ventilation is to reduce tidal volume to a minimum acceptable physiologic level and allow the patient to "autowean." When the required ventilator pressure to deliver the set volume no longer falls with time, extubate.
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. However, check for signs of autocycling as this will also produce hyperventilation. Generally, if the measured respiratory rate is >60, this should be considered.
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. 77).
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.

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Pressure Support Ventilation

37

Steven M. Donn

I. Description
   A. Ventilatory mode in which spontaneous breaths are partially or fully supported by an inspiratory pressure assists 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 (PTV) 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 inspiration 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). This is easier to trigger.

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 accelerates, peaks, and 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 on 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 semiquantitative 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 a 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 (VAPS)
      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 (MMV)
      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.

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Volume-Targeted Ventilation

38

Martin Keszler and Steven M. Donn

Section 1: Volume-Controlled Ventilation (VCV)

I. Description
   A. A form of mechanical ventilation where tidal volume is the primary control variable and pressure is permitted to fluctuate to deliver this volume.
   B. Although tidal volume is sometimes monitored at the ventilator, measurement at the proximal airway is more accurate and safer for the neonatal patient.
   C. Because cuffed endotracheal tubes are seldom 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.
   D. Many authors prefer to distinguish VCV as originally used in adult ventilation, now adapted for use in infants, and volume-targeted ventilation (VTV) that has been specifically developed for the needs of newborn infants.
   E. VCV delivers a set volume into the ventilator circuit (referred to as V_{del}) with pressure rising passively, in inverse proportion to lung compliance as the lungs fill. The lung pressure and volume reach maximum just before exhalation.
   F. VTV, on the other hand, is pressure-controlled ventilation with volume targeting. The flow pattern is that of pressure-controlled ventilation, but the inflation pressure is adjusted by the ventilator breath to breath to maintain a user-selected exhaled tidal volume. Examples of VTV include volume guarantee (VG), pressure regulated volume control, and adaptive pressure ventilation. Volume assured pressure support is a hybrid mode with features of both VTV and VCV.

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II. VCV can be used in synchronized intermittent mandatory ventilation (VC-SIMV), SIMV with pressure support (VC-SIMV+PS), or assist/control (VC-AC).
III. Characteristics of Volume-Controlled Breaths.
  A. Continuous inspiratory flow produces a characteristic "square" flow waveform.
    1. This results in gradual ramping of pressure, with peak pressure and volume delivery occurring at the end of inspiration.
    2. This differs from pressure-controlled 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-controlled 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-controlled 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.
    4. Spontaneous breathing will also lower the pressure level.
  E. Delivered volume is "assured."
  F. Maximum alveolar distension depends on end alveolar pressure.
IV. Advantages of VCV.
  A. Consistent volume delivery even in the face of changing compliance.
  B. Volume-limited breaths; avoidance of volutrauma.
  C. Can be combined 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 the same volume if compliance decreases.
V. Clinical Limitations.
  A. Minimal tidal volume delivery.
    1. Must know smallest delivered volume machine is capable of providing.
    2. Should not exceed patient's physiologic tidal volume measured at the airway opening.
      (a) <1000 g: 4–7 mL/kg
      (b) >1000 g: 5–8 mL/kg.
    3. Ventilator circuit should be of reasonable rigidity (compliance) and minimal internal volume, so as not to cause excessive tidal volume loss in circuit if pulmonary compliance is low. The smaller the infant, the greater proportion of volume delivered into the circuit will be lost to compression.

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-controlled ventilation but do not cause a loss of tidal volume delivery because extra gas flow is able to compensate and delivered volume is a function of pressure and lung compliance (ability to ventilate effectively despite large leak was the main reason for the popularity of pressure-controlled ventilation).

VI. Clinical Indications
   A. Respiratory failure. Virtually all forms of neonatal respiratory failure have been shown to be amenable to VCV.
   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 recommended for acute illness.
      2. SIMV, preferably with PSV, may be used 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.
      4. Tidal volume waveform.
      5. Pressure-volume loop.
   C. Some ventilators do not provide exhaled tidal volume monitoring. The volume delivered to the baby's lungs may be much less than the set volume. Clinical assessment of adequacy of ventilation is therefore essential.
   D. Set flow rate to achieve desired inspiratory time. This can be modified by adding an inspiratory hold to avoid using a flow rate that is inadequate and results in a short inspiratory time at higher flow rates. Make sure there is sufficient hysteresis on the pressure-volume loop.
   E. Set mechanical ventilatory rate.
   F. Set trigger sensitivity if using patient-triggered mode.
      1. Generally use minimal setting unless auto-cycling.
      2. Assure patient is able to trigger ventilator.
   G. 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.
   H. Some ventilators have a leak compensation system. While beneficial in maintaining stable baseline in the presence of a leak, it may increase the work of breathing and possibly increase expiratory resistance.
   I. 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 VCV.
- A. As pulmonary compliance improves, inspiratory pressure will be automatically decreased to maintain desired volume delivery.
- B. Adjustments in delivered volume should be made to maintain desired tidal volume delivery within the physiologic range.
- C. Adjustment 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-controlled ventilation, volume-targeting used for the treatment of RDS 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.

Section 2: VTV

I. *Description*
- A. VTV combines advantages of pressure-controlled (PC) ventilation with the ability to deliver a more consistent tidal volume (V_T) in small infants.
- B. VTV is a pressure-controlled, volume-targeted, and time- or flow-cycled form of ventilation that automatically adjusts inflation pressure to deliver a user-selected V_T.
- C. The gas flow pattern is that of PC ventilation; therefore, the lungs fill earlier in the respiratory cycle with increased dwell time to facilitate intrapulmonary gas distribution.
- D. Lung compliance (and to a lesser extent resistance) determines how much pressure is needed to generate a set V_T. The relationship between peak pressure, lung compliance, and V_T is the same as with standard PC ventilation, but instead of manual intermittent pressure adjustment, this occurs automatically in real time.
- E. Exhaled V_T of the previous breath is used to minimize the effect of endotracheal tube leaks.

F. VG is a specific modality on the Draeger Babylog VN500 and new VN800 (Draeger Medical, Telford, PA). More recently, Vyaire Medical (Mettawa, IL) and Hamilton Medical (Reno, Nevada) implemented a version of this modality on their ventilators.
G. Therefore, VG is now increasingly used as a generic term to describe VTV.
H. 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 lung strategy to ensure even distribution of the tidal volume into a well-recruited ("open") lung.

II. *Benefits Common to Both VCV and VTV*
A. Avoidance of excessive tidal volume: VTV reduces the number of excessively large tidal volume inflations, rate of air leak, and the incidence of bronchopulmonary dysplasia.
B. Excessive 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, does not lead to lung injury.
C. Avoidance of hypocapnia: Hyperventilation is associated with increased risk of periventricular leukomalacia (PVL) and severe intraventricular hemorrhage (IVH). VTV/VCV reduces the incidence of hypocapnia, IVH, and PVL, compared to PC ventilation.
D. Faster weaning from mechanical ventilation: When lung compliance and patient respiratory effort improves, VTV/VCV lowers inflation pressure in real time. Weaning occurs throughout the day, not just during rounds or when a blood gas is obtained, resulting in a shorter duration of ventilation.
E. Fewer blood gas measurements: With stable minute ventilation ensured by VTV/VCV, and pulse oximetry monitoring, only 1–2 invasive blood gas measurements/day are needed once the appropriate settings are confirmed.

III. *Benefits Unique to VTV*
A. VG is designed with the needs of small preterm infants with uncuffed endotracheal tubes and immature respiratory control with tidal volume regulation based on exhaled tidal volume measurement at the airway opening.
B. Effective leak compensation and adaptation minimizes the impact of endotracheal tube leaks on tidal volume measurement, breath triggering, and breath termination during PSV.
C. VTV compensates for the highly variable respiratory drive of an extremely low gestational age newborn with immature respiratory control.
D. 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.

IV. *Controls/Displays/Alarms*
A. Controls
1. Basic ventilator mode. VG can be combined with any of the standard synchronized modes.
2. VG functions best when combined with assist/control (AC) or pressure support (PSV). When used with SIMV + PS, only the SIMV inflations are subject to VG.
3. Control variables specific to each mode must be selected first (rate, T_I, etc.).
4. Target tidal volume is the most critical setting. One size does not fit all. See Sect. IV D.
5. Pressure limit. The microprocessor will adjust inflation pressure up to the limit set by the operator. Set the PIP ~5 cm H_2O above current inflation pressure for optimal safety.
6. With the VN500/800 ventilator, effective leak compensation is available; a calculated estimate of true tidal volume entering the lungs is used for regulation of PIP. The clinician must choose whether or not to use the leak compensation, which is set as a default in the ventilator setup.

7. Use of leak compensation is strongly recommended, because it allows accurate V_T control even with a leak of up to ~70%.

B. Displays
1. Most ventilator screens are configurable to user preference. Key variables are:
   (a) Measured exhaled tidal volume.
   (b) Calculated tidal volume when using leak compensation.
   (c) Tidal volume target.
   (d) Measured PIP.
   (e) PIP limit.
   (f) % ETT leak
   (g) Scalar waveforms for pressure, flow, and volume (N.B., with leak compensation, 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. An additional alarm is the low tidal volume alarm. This is activated when the tidal volume cannot be reached with the set pressure limit.
3. This prompts the user to evaluate the patient status before serious clinical deterioration occurs. See Sect. VII Troubleshooting.

V. *Initiating VG*

A. Use VG as soon as possible after initiation of mechanical ventilation, because this is when lung compliance changes most rapidly.

B. Choose a basic mode of synchronized ventilation: AC or PSV are preferred.

C. Select PEEP, Ti, and ventilator/control rate appropriate for patient size and underlying disease process, typically 40/min in preterm, 30–35 in term infant.

D. Select target V_T based on disease process, patient size, and age:
   (a) 4–5 mL/kg for typical preterm with RDS
   (b) 4 mL/kg for larger preterm with RDS/pneumonia
   (c) 4 mL/kg for infant with congenital diaphragmatic hernia
   (d) 5.5 to 6 mL/kg if <700 g
   (e) 5.5 to 6 mL/kg if MAS, air-trapping
   (f) 6 mL/kg if >1–2 wks of age, BPD
   (g) As much as 8–12 mL/kg for severe 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 cmH_2O above current PIP or anticipated PIP need.

G. If unable to reach target V_T, verify ETT position and ETT leak, and reassess target V_T.

H. Attempt to optimize lung recruitment to improve compliance and oxygenation and to ensure that the VT will be evenly distributed into an open lung.

VI. *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 analysis.

D. Tachypnea, retractions, low measured PIP, 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 the flow sensor is relatively large.

2. Increased alveolar dead space – overexpansion, gas trapping.
3. Metabolic acidosis, to which the baby is trying to compensate (pH, not PCO_2, is the primary respiratory driver).

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 mm Hg.
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. Don't forget to increase V_T target as the baby grows.
J. Anticipate need to increase V_T with advancing age because of increasing alveolar dead space and stretching of upper airway as well as changing pulmonary mechanics..
K. Anticipate increasing ETT leak as larynx stretches over time. Except with the VN500/800 where large leaks can be compensated effectively, at leaks >40%, the V_T measurement is no longer accurate. When the measured value underestimates true V_T, the ventilator will increase PIP, potentially leading to overventilation.

VII. *Weaning from VG*

A. VG is a self-weaning modality. 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 need a larger V_T, even 4 mL/kg may be too low.
D. When measured PIP is sufficiently low (<12–16 cm H_2O), the infant is breathing comfortably without tachypnea, and the FiO2 is <0.30–0.35, extubation should be attempted.

VIII. *Troubleshooting*

A. Low V_T alarm.
1. VG modes generate alarms not encountered with simple PC; these can become annoying when excessive.
2. They are there to provide feedback regarding adequacy of ventilator support and should not be ignored.
3. Low V_T alarm is activated when the tidal volume cannot be reached with the set pressure limit. This may result from:
   (a) PIP limit is set too close to actual PIP.
   (b) Worsening lung compliance (e.g. atelectasis, pneumothorax, abdominal distention).
   (c) Decreased patient effort (e.g. baby is septic, 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.
4. 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.

5. 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 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 (gas trapping, BPD).
3. Relatively increased instrumental dead space (tiny baby).
4. Inadequate respiratory rate (e.g. narcotic respiratory depression, sepsis).
5. Increased CO_2 production (e.g. fever, sepsis, 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 excess 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.

IX. *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 VN500/800.

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 VN500/800 eliminates this risk because it uses the last PIP generated before the disconnection or manual inflation.

E. When the target V_T is too low, the infant may be able to generate sufficient V_T and maintain adequate gas exchange on his/her own, but the 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 avoidable by appropriate V_T settings.
F. Worsening respiratory status may develop if the operator fails to appropriately increase the target V_T with growth and advancing postnatal age.

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Pressure Control Ventilation

39

Steven M. Donn

I. Description
   A. Pressure control (PC) was developed in the 1980s for the treatment of ARDS. It is now included in most neonatal ventilators.
   B. Mechanical breaths are delivered at a preset peak inspiratory pressure, with a fixed or variable inspiratory time and variable inspiratory flow, which distinguishes PC from traditional time-cycled, pressure-limited ventilation (TCPL), 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. Accelerating-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.
   F. If slope is inadequate, there may be poor hysteresis on the pressure-volume loop with minimal separation of the inflation and deflation limbs. Severe flow starvation results in a "figure 8" appearance of the loop.
   G. High flow rapidly pressurizes ventilator circuit resulting in rapid gas delivery and alveolar filling.

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Table 39.1 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

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)
  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
  G. May overcome increased resistance by rapid flow
VI. Disadvantages
  A. Delivered tidal volume is variable and depends on 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 39.1)

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Part VII

High-Frequency Ventilation

High-Frequency Ventilation: General Concepts

40

J. Bert Bunnell

I. High-Frequency Ventilation (HFV) Is the Safest Way to Facilitate Gas Exchange in Newborn Infants
   A. Preterm baby lungs are extraordinarily vulnerable due to lack of surfactant and incomplete structural and functional lung development.
   B. Instituting conventional mechanical ventilation (CMV) causes lung injury.
      1. Distribution of conventional ventilation within the lungs is primarily determined by regional lung compliance; thus, relatively healthy parts of the lung become overexpanded, while atelectatic areas remain unventilated.
      2. Attempts to improve ventilation by using higher pressure and larger tidal volumes trigger inflammation.
         (a) Inflammation reduces airway patency, increasing airway resistance.
         (b) Higher pressure and larger tidal volumes may be able to penetrate narrowed airways on inhalation, but exhalation will likely be incomplete, leading to gas trapping and disruption of the more compliant areas of the lungs, typically terminal bronchioles.

II. HFV Either Prevents or Reduces Lung Injury
   A. *Barotrauma*
      1. HFV uses lower transpulmonary pressure than any other mode of assisted ventilation, including the iron lung.
      2. HFV pressure waveforms quickly attenuate as they advance toward the alveoli.
      3. Thus, pressure amplitude at terminal airways and alveoli is very small.
   B. *Volutrauma*: HFV uses tidal volumes that are smaller than any other mode of assisted ventilation (1/2–1/10 of those used during CMV).

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C. *Atelectrauma* (alveolar damage resulting from transient and repeated closure and reopening)
   1. The only type of lung injury *not* inherently lessened by HFV.
   2. Caused by using too little PEEP (positive end-expiratory pressure) or Pāw (mean airway pressure), which are nearly equivalent in their physiologic effect (allowing alveoli to collapse, remain collapsed, or open and collapse with every breath).
   3. One must properly manage PEEP/Pāw during HFV to achieve and maintain optimal lung volume.
      (a) 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.)
      (b) Raising PEEP/Pāw too high interferes with pulmonary blood flow and cardiac output.
      (c) Optimizing PEEP/Pāw improves pulmonary blood flow and maximizes potential gas exchange.

D. *Rheotrauma* (airway injury caused by the shear forces of high gas flow rates)
   1. HFJV (high-frequency jet ventilation) uses highly accelerated inspirations that were suspected of causing tracheal injury in the past, but no evidence of such injury arose in numerous randomized controlled trials with either HFJV or HFOV (high-frequency oscillatory ventilation).
   2. HFJV uses very low overall gas flow rates (<1 Lpm when ventilating preterm infants).
   3. HFOV uses much higher overall gas flow rates, but most of the gas bypasses the patient.

E. *Biotrauma*
   1. All forms of mechanical ventilation trigger biochemical and biophysical injury caused by release of inflammatory mediators and cells, but the parameters and mechanisms for this type of lung injury have yet to be fully explored.
   2. Animal studies have demonstrated less biotrauma with more gentle forms of assisted breathing such as CPAP (continuous positive airway pressure), and HFV is the closest thing to CPAP in mechanical ventilation.

III. If HFV Is So Inherently Lung Protective, Why Are Not All Patients Treated with HFV?

A. It takes education and experience to understand and realize the benefits of HFV.

B. HFV is a "disruptive" technology.
   1. Disruptive technologies are not "normal"; they change the way people normally do things, and people are resistant to change.
   2. HFV, unlike CMV, does not try to mimic normal ventilation.
      (a) HFV rates are many times higher than normal breathing rates, although comparable rates and examples of enhanced pulmonary gas exchange do occur in nature.
      (b) HFV tidal volumes can be smaller than anatomic dead space volume, which may also be true in running and panting animals.
      (c) Intrapulmonary distribution of fresh gas during HFV is mostly determined by airway resistance rather than lung compliance as is the case with normal breathing and conventional ventilation.

C. No ventilator mode is totally safe, and there are three risks associated with HFV:
   1. Hyperventilation and related cerebral injury.
   2. Atelectrauma due to improper management of lung volume via positive end-expiratory pressure (PEEP) and mean airway pressure (Pāw).

3. Lung hyperinflation due to gas trapping.

IV. How Does HFV Work?
   A. Enhanced diffusion
      1. Abundant fresh gas of high-frequency inspiration washes expired gas from upper airways.
      2. This increased washout 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 lower 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, with higher frequencies in babies (up to 40 Hz).
      2. Impediments to gas moving in and out of the lungs (i.e., impedance) include compliance, airway resistance, and inertance, which is related to momentum.
      3. At resonance:
         (a) Minimum energy is needed to move gas in and out of the lungs, because of the following:
            (1) The momentum of inspired gas (i.e., the inertance) supplies energy sufficient to overcome lung compliance, effectively changing kinetic energy into potential energy at the end of inspiration.
            (2) That potential energy is manifested in the elastic expansion of the lungs, which upon recoil supplies energy sufficient overcome exhalation inertance and send expired gas back out of the lungs.
         (b) Airway resistance is thereby the only element of impedance left, and it must be overcome during both inspiration and expiration.
            (1) High-frequency ventilators supply the energy to overcome airway resistance when they push gas into the lungs.
            (2) Lung recoil (aka, passive exhalation) provides the energy to move gas back out in the case of HFJV, which may become trapped if the time allotted for exhalation is insufficient.
            (3) HFOV actively pulls gas back out of the airways, which can promote gas trapping by creating "choke points" when pressure inside an airway is lowered too much. (More on that topic later.)
   C. Oscillatory flow-streaming (HFOV)
      1. In HFOV, inspiratory flow is laminar, which creates a parabolic (i.e., bullet-shaped) velocity profile of fresh gas entering the airways (Fig. 40.1).
      2. "Active" HFOV expirations accelerate at every bifurcation because gas from two airways is sucked into one more proximal airway, causing 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, which essentially reduces physiologic dead space volume.
   D. HFJV flow-streaming
      1. HFJV produces a more exaggerated form of flow streaming compared to HFOV.
      2. High-velocity jetted 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.

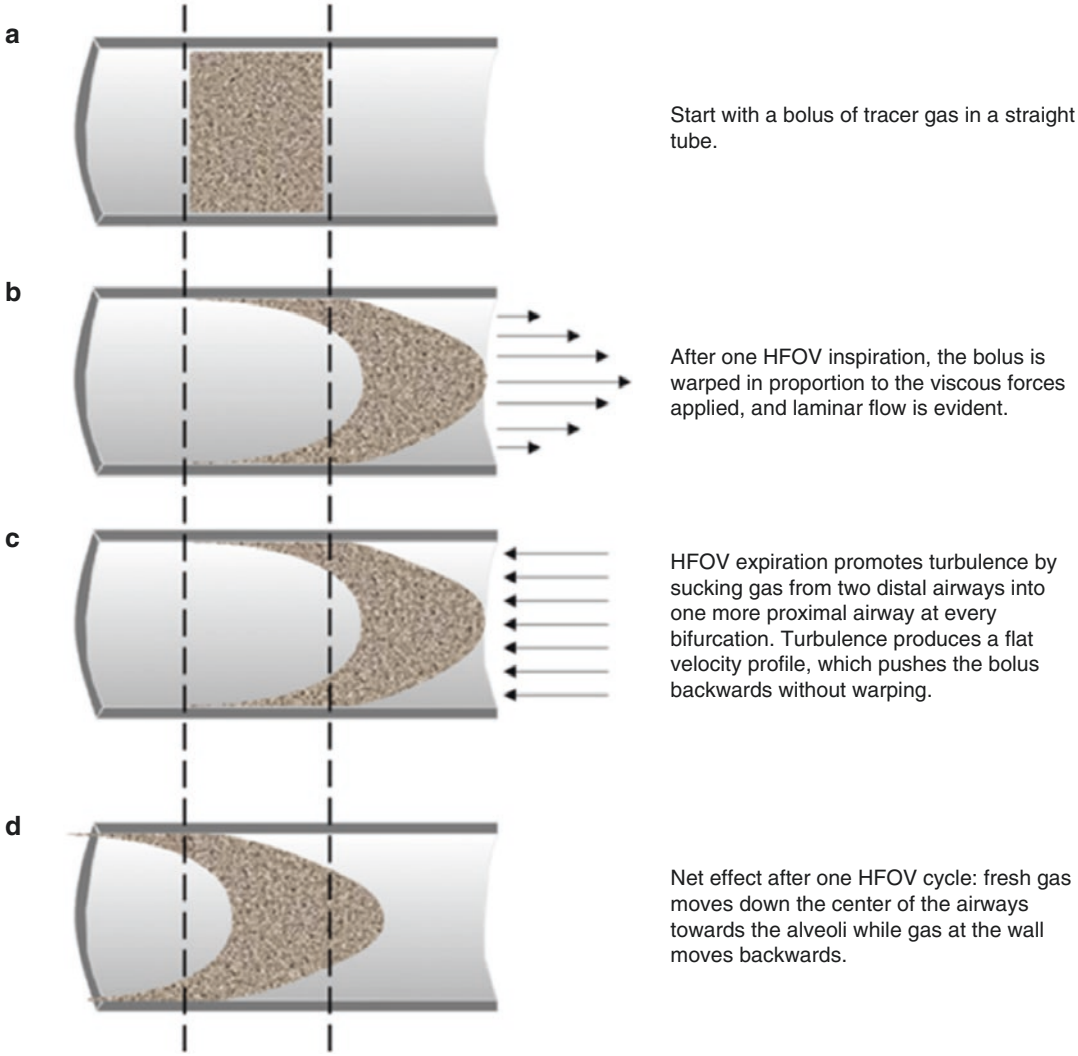

Fig. 40.1 Viscous shear and airway velocity profiles associated with HFOV. (Modified with permission from Haselton FR, Scherer PW. Bronchial bifurcations and respiratory mass transport. Science. 1980;208(4439):69. Reprinted with permission from AAAS)

(a) Although 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. (If inspiration lasts too long, turbulence develops, and gas flows in with a flat velocity profile.)
(b) Thus, "transitional" flow (transitional between laminar and turbulent) is 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.
(c) The higher the velocity, the sharper the point on the parabolic velocity profile of the in-rushing gas (Fig. 40.2).
(d) Since only portions of the anatomic dead space are used, HFJV tidal volumes dramatically reduce physiologic dead space.

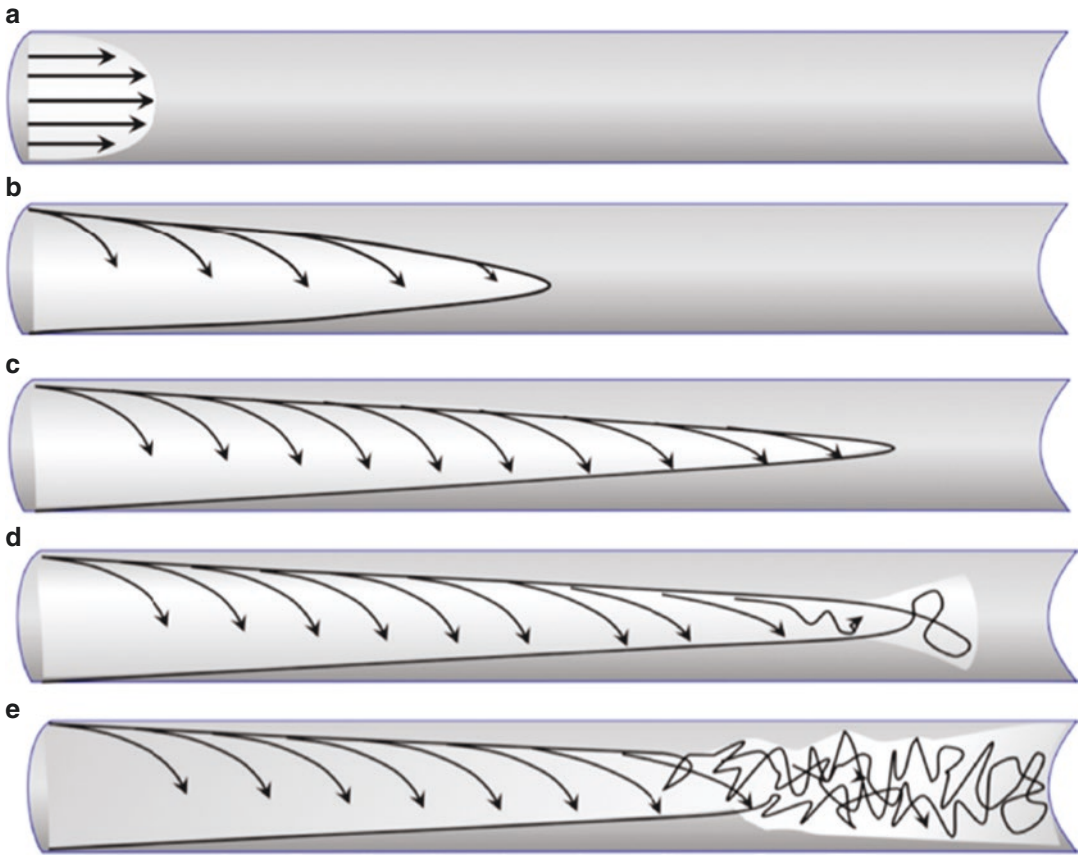

Fig. 40.2 When fluid (liquid or gas) flows into a tube, the velocity profile of the flow is determined by energy and time. (**a**) When energy is low, overall flow is relatively slow and laminar with molecules in the center of the tube moving faster than those at the wall, creating a parabolic velocity 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 flow 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 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 uniform (i.e., flat) across the diameter of the tube. (Used with permission. © 2011, Bunnell Inc.)

E. Brief, high-velocity inspirations reduce physiologic dead space volume via flow streaming.
   1. Tidal volume must be greater than physiologic dead space volume for gas exchange to take place.
   2. Typical anatomic dead space of mammalian lungs is 2 mL/kg body mass, but tidal volumes sufficient to achieve normal gas exchange <1 mL/kg have been measured in animal studies with HFJV.

V. HFV Choices
   A. HFV devices offer the promise of using smaller tidal volumes within the limits of their designs.
   B. Clinicians must learn individual device controls that enable management of ventilation and oxygenation, increasing or decreasing Pāw when appropriate, and how to effectively use concomitant CMV breaths, if available, for alveolar recruitment.
   C. Available modalities
      1. High-frequency jet ventilation (HFJV)

(a) HFJV in the USA and Canada is provided by the Life Pulse® Ventilator (Bunnell Inc., Salt Lake City, UT) as time-cycled, pressure-limited, servo-controlled ventilation with the following:
(1) Frequency range: 240–660 bpm or 4–11 Hz
(2) Peak inspiratory pressure (PIP) = 8–50 cm H_2O
(3) Inspiratory time (I-time, or T_I) = 0.020–0.034 s
(4) I:E from 1:1.6 to 1:12.
(b) Inspired gas is shot into a patient's endotracheal tube (ETT) through a jet nozzle, which is built into a special 15-mm ETT adapter ("LifePort®" ETT adapter, Bunnell Inc.) with two side ports for the following:
(1) Introduction of injected gas
(2) Monitoring airway pressure at the distal end of the adapter
(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, where it can provide three things:
(1) Gas flow for the patient's spontaneous breathing through the main lumen of the adapter
(2) Delivery of normal-size tidal volumes for recruitment of atelectatic alveoli
(3) Positive end-expiratory pressure (PEEP), which accounts for most of the Pāw during HFJV since all exhaled gas exits via the CMV's exhalation tubing and its PEEP valve
(e) HFJV may be used without a conventional ventilator in cases where the above mentioned three elements of CMV can be provided by means such as CPAP circuits with a T-piece resuscitator. (This off-label configuration was developed for hospitals that may have been faced with inadequate numbers of conventional ventilators during the COVID-19 pandemic.)

2. High-frequency oscillatory ventilation (HFOV)
(a) HFOV in the USA is provided by the 3100A® (CareFusion, San Diego, CA) using a sinusoidal, push-pull, pneumatic piston with settings to control ventilation and mean lung volume, which are fine-tuned with a piston-centering adjustment and with the following:
(1) Frequency range: 3–15 Hz (i.e., 180–900 bpm)
(2) % I-time adjustable from 30% to 50%, producing I:E from 1:2.3 to 1:1
(3) Adjustable pressure amplitude and mean airway pressure
(4) "Bias flow," which is adjustable from 0 to 40 Lpm

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., Babylog® VN500 Ventilator, Dräger Medical GmbH, Lübeck, Germany).

D. Device similarities
1. All HFV devices produce a train of gas pulses that penetrate through the dead space of the airways without pushing resident dead space gas ahead of the fresh gas as happens when we breathe normally or are ventilated conventionally.

2. All HFVs provide the means to adjust the pressure amplitude and/or tidal volume of the inspired gas, which is the primary means of controlling the patient's $PaCO_2$.
   (a) Ventilation (CO_2 elimination) is proportional to the square of HFV tidal volumes.
   (b) $V_{CO2} \cong f V_T^2$, where f = frequency and V_T = tidal volume.
3. Airway pressures that HFVs generate attenuate as inspired gases approach the alveoli.

E. Pressure waveforms and inspiratory to expiratory ratios (I:E)
1. HFJV inspiratory airway pressure rises sharply from PEEP and ends abruptly at the end of its set T_I, which is usually 0.020 s. (It is "spiky.") (See Fig. 40.3.)
2. HFJV expiration is passive, so the expiratory pressure waveform is a classic natural exponential decay, and expiratory time (T_E) is determined by set rate and T_I.
3. HFOV produces a sinusoidal waveform, with inspiratory airway pressure rising and returning to its Pāw within the inspiratory portion of the breath cycle and falling and returning to its Pāw within the expiratory portion; so, it is rounded at its peaks and valleys.
4. HFOV duty cycle (i.e., I:E) may be set by "% inspiration time," which is typically 33–50% or I:E = 1:2–1:1. (HFOV T_I is only as brief as that of HFJV at 15 Hz where T_I = 0.022 s.)

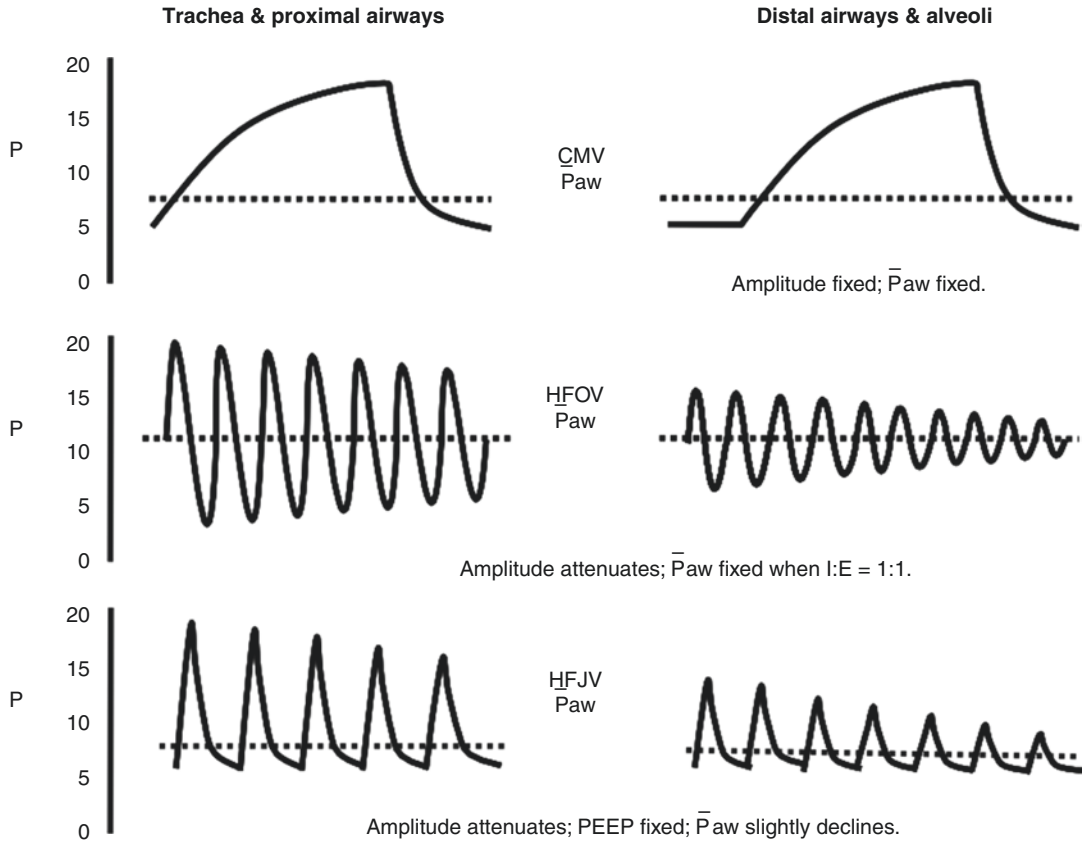

Fig. 40.3 CMV and HFV airway pressure waveforms, showing how HFV pressure amplitude is dampened as inspired gas approaches the alveoli, whereas airway pressure from CMV has enough time and volume to equilibrate throughout the lungs, producing pressure in the alveoli that is close to that introduced in the trachea. (Used with permission. © 2003, Bunnell Inc.)

(a) The greater the HFOV pressure amplitude, the higher the peak and the lower the minimum pressure excursions, which can go low enough to cause airway collapse and gas trapping via "choke points."
(b) Raising Pāw, usually alleviates this type of gas trapping with HFOV.

F. Intrapulmonary gas distribution
1. Airway resistance determines intrapulmonary distribution of HFV because the pressure necessary to produce flow through the airways is proportional to the square of their cross-sectional area (i.e., the radii of the airways raised to the fourth power).
2. The high velocity of HFV inspirations increases the inertance of incoming gas, which overcomes the elasticity of the lungs (i.e., lung compliance).
3. Therefore, the faster the inspiration, the less gas will penetrate inflamed and restricted peripheral airways like those found in pulmonary interstitial emphysema (PIE) .
4. This concept helps explain why HFJV works so well for treating PIE.
(a) It automatically reduces ventilation of injured areas (i.e., those with inflamed and narrowed airways) in favor of healthier areas of the lungs.
(b) Ventilation of injured parts of the lungs is counterproductive, because it only increases rheotrauma injury in areas that are not capable of participating in gas exchange due to inflammation and lack of perfusion.

G. HFV 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 back out, although higher frequencies may not be optimal. (See "Corner Frequency" below.)
(a) Tidal volume decreases with increasing HFOV frequency, because I:E is set (typically at 1:2), and increasing frequency automatically decreases the time allotted for inspiration.
(b) Because ventilation is proportional to the square of tidal volume (V_T^2) during HFV, CO_2 elimination paradoxically decreases with increasing HFOV frequency.
(c) Raising HFOV frequency may therefore require an increase in pressure amplitude to maintain appropriate ventilation.
2. Lowering HFOV frequency increases delivered tidal volume, because of the increase in inspiratory time.
(a) Again paradoxically, ventilation may improve, because of the V_T^2 relationship.
(b) Thus, lowering HFOV rate may enable a reduction in pressure amplitude and alleviation of gas trapping if frequency does not go too far below the corner frequency. (See below.)
3. HFJV rates are generally lower than HFOV frequencies to accommodate passive exhalation.
(a) Tidal volume is independent of frequency if I-time is kept constant and there is sufficient exhalation time to avoid gas trapping.
(b) With T_I 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 1:12 at 240 bpm.
(d) HFJV is therefore like CMV: the faster you go, the more CO_2 you eliminate, if rate is not so high as to cause gas trapping.
(e) Lowering HFJV frequency decreases minute volume, but it may improve gas exchange if it alleviates gas trapping by extending the time for expiration and thereby increasing tidal volume; otherwise, it may require an increase in pressure amplitude (ergo tidal volume) to provide adequate ventilation.

4. Gas trapping can occur with any ventilator, but the mechanism for trapping with HFJV is the same as CMV because of passive expiration, whereas gas trapping during HFOV can occur because active expiration can create "choke points." (See Potential for Gas Trapping" below.)
5. HFOV devices provide the means to manage PEEP/Pāw for optimal lung volume, whereas HFJV only shoots gas into the lungs, and exhaled gas exits via a CMV or CPAP circuit used in tandem.
   (a) HFV pressure amplitude and/or peak inspiratory pressure (PIP) adds little to mean airway pressure.
   (b) The mechanisms for controlling Pāw during HFJV and HFOV are quite similar: exhalation valves that elevate end-expiratory pressure.
6. HFJV tidal volumes are typically smaller and delivered faster compared to those of HFOV.
   (a) HFJV inspirations are best generated in a component located close to the patient, which minimizes compressible dead space volume and enhances inspiratory penetration.
      (1) Bunnell Inc.'s Life Pulse Ventilator uses a "Patient Box" to house a pinch valve to control inspirations, and it is placed near the patient's head in the incubator, on a warming table, or pinned to the gown of a parent holding their infant during "Kangaroo" care.
      (2) Percussionaire® combined CMV + HFOV ventilators similarly generate inspirations close to the patient's ETT with their pneumatic clutch assembly, the Phasitron®.
   (b) Overall gas flow during HFJV is conservative, requiring 1–8 L/min for infants and small children compared to HFOV where up to 20 L/min may be utilized.
7. Peak flow rates of 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 toward the alveoli faster than gas near airway walls.
8. Combined CMV + HFOV performance is positively and negatively affected by inherent design features.
   (a) Ease of use of CMV + HFOV ventilators provide alveolar recruitment techniques more easily 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 and made less effective by the compressible volume in the tubing and humidifier between where HFOV is created and where it is delivered to the patient's ETT.
9. Expiration
   (a) In HFJV, exhaled gas exits passively with lung recoil by spiraling out around the gas coming in, seeking the path of least resistance in the annular space around the highly accelerated inspired gas as illustrated in Fig. 40.4.
   (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 reduce the threat of creating choke points. (See "Potential for Gas Trapping" below.)
   (c) Net effects of passive versus active expiration are as follows:
      (1) HFJV is usually operated at frequencies lower than those used with HFOV, which lengthens exhalation time and enables complete exhalation.

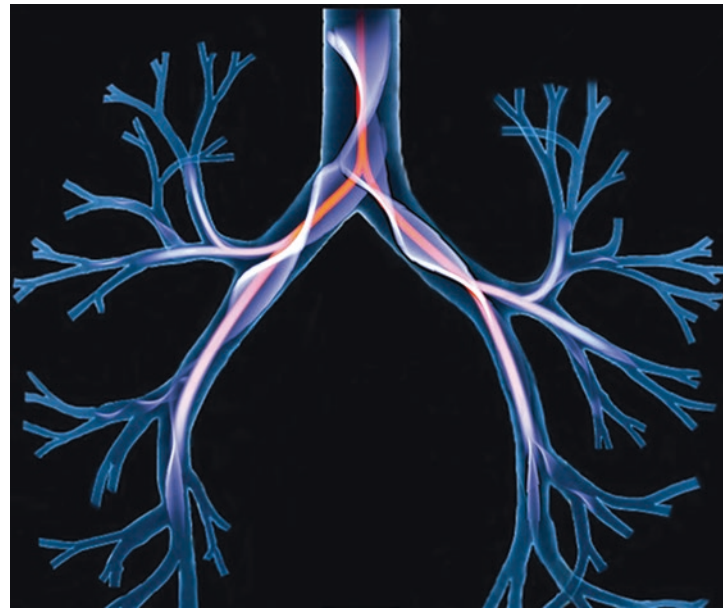

Fig. 40.4 Exhaled gas (colored violet) exits passively with lung recoil during HFJV, spiraling out around the high-velocity inspired gas (colored orange) that spirals down the central core of the airways. (Used with permission. © 2015, Bunnell Inc.)

(2) HFOV is usually operated at higher Pāw compared to HFJV to counteract the low-pressure excursion of airway pressure during active exhalation.

10. 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 PIP or airway pressure amplitude.
    (b) Gas trapping may occur during all forms of ventilation by various mechanisms.
    (c) The primary cause of gas trapping during CMV and HFJV is not allowing enough time for passive exhalation before subsequent inspirations.
    (d) An inherent cause of gas trapping during active exhalation with HFOV is "choking," which occurs when pressure outside an airway exceeds its inside pressure, overcoming its structural strength, and causing airway collapse.
11. Spontaneous breathing during HFV
    (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) Spontaneous breathing during HFOV is more difficult, especially in larger patients, but high bias flow rates have been shown to reduce the imposed work of breathing.

H. Who HFV may help, how, and why
1. 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 applications of HFV occur after lung injury has occurred.
4. HFJV has proven effective in treating nonhomogeneous lung injury and air leaks such as PIE.
   (a) Inflammation and high airway resistance keep high-velocity inspirations away from injured areas of the lungs, which improves ventilation/perfusion matching.
   (b) Deflation of injured, hyperexpanded areas of the lungs can be achieved by lowering HFJV rate while keeping I-time at its shortest setting (0.020 s), which lengthens HFJV exhalation time, producing I:Es as long as 1:12.
   (c) HFJV can be used successfully with lower mean airway pressure, 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 effectively ventilate any other way, such as:
   (a) Severe congenital diaphragmatic hernia patients, where small V_T s and high Pāw can preserve what little lung is available for ventilation
   (b) Upper airway leaks and fistulas where HFJV shoots inspired gas right past disruptions, enabling downstream ventilation and airway injuries to heal
   (c) HFJV is well suited for cardiac surgery patients, because
      (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, because HFJV can effectively ventilate, even hyperventilate, at relatively low mean airway pressures.
   (d) Obstructive lung disorders, such as meconium aspiration syndrome (MAS) , where HFJV may facilitate removal of excess secretions and improve ventilation/perfusion matching.
   (e) Patients with conditions where HFV may facilitate delivery or improve the benefits of using specialty gases such as nitric oxide and helium (e.g., PPHN and status asthmaticus).
   (f) BPD (bronchopulmonary dysplasia), where small VTs and lower rates with longer exhalation times facilitate healing and degassing of hyperinflated lungs.

VI. How to Maximize the Benefits and Minimize the Risks of HFV
   A. Begin HFV as soon as exogenous surfactant is administered and/or nasal CPAP/CMV appears to be inadequate, although early use is controversial because of a higher incidence of cerebral injury (IVH, PVL) in studies where ill-advised management strategies were used.
      1. Strategies of implementation are key to avoiding cerebral injuries.
         (a) Most important: avoid hyperventilation by carefully monitoring $PaCO_2$. (Transcutaneous continuous monitoring is highly recommended.)
         (b) Full lung recruitment and maintenance of appropriate lung volume is essential.

2. HFV is more like CPAP compared to CMV.

B. Match ventilator strategy to pathophysiology and the availability of an appropriate ventilator.
   1. Tailor ventilator strategies for specific lung disorders.
   2. Learn the limitations of the devices available to you.
   3. 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.
      (b) Use of tandem CMV can be overdone.
         (1) CMV should be used to aid alveolar recruitment, not to assist ventilation.
         (2) Follow instructions for finding optimal PEEP (see below) and use minimal CMV settings unless you are actively recruiting lung volume.
         (3) If patient's 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 to this advice. Increasing PEEP may be contraindicated for some cardiac patients, and a CMV rate of 5–10 bpm can help maintain their oxygenation.)
      (c) HFJV may unexpectedly mobilize secretions.
         (1) Be ready to suction right after initiation of HFJV.
         (2) Only suction when indicated to avoid unnecessarily collapsing alveoli.
   4. HFOV limitations
      (a) Active exhalation
         (1) May require increased Pāw to avoid gas trapping.
         (2) Therefore, it is important to select HFOV patients who will tolerate or even benefit from higher Pāw (e.g., RDS).
      (b) May not work well with nonhomogeneous lung disorders due to limited exhalation time.
      (c) Watch out for mucus impaction.
   5. Limitations of conventional ventilators with built-in HFV
      (a) Compressible volume of conventional-style patient circuits and humidifier limit 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 frequency to provide adequate ventilation with the lowest ΔP (pressure amplitude), smallest VT, and no gas trapping.
   1. Set rate and duty cycle (I:E) that are compatible with the patient's pulmonary time constants. (One pulmonary time constant = the time it takes to get 63% of a tidal volume in or out of the lungs.)
      (a) Time constants are calculated as: $T_C = C \times R$, where T_C = one time constant, C = lung compliance, and R = airway resistance.
      (b) The primary determinant of time constants and optimal frequency = patient size, because compliance increases in proportion to size.
      (c) 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.

(d) Rates as low as 240 bpm (4 Hz) where I:E = 1:12 can be used for lung diseases characterized by long exhalation time constants such as pulmonary interstitial emphysema (PIE), bronchopulmonary dysplasia (BPD), and meconium aspiration syndrome (MAS).

2. Venegas and Fredberg developed a formula for calculating optimal frequency using time constants, which they called the "corner frequency":

$$f_c = 1/(2\pi CR), \text{where } f_c = \text{corner frequency.}$$

(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. 40.5).
   (1) Peak pressure falls rapidly with increasing frequency until it reaches a "corner" where pressure either flattens or begins to rise.
   (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 lungs results in unnecessarily large pressure amplitudes in the proximal airways.

(b) In general, when lung compliance decreases, corner frequency goes up; and, when airway resistance increases, corner frequency goes down.

(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 if you look at the curve for such patients in Fig. 40.5, it is not terribly clear where that "corner" is.

(d) As compliance improves (i.e., increases), 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 post-term baby with meconium aspiration syndrome (MAS) might have a compliance of 0.4 mL/cm H_2O and airway resistance of 100 cm H_2O/L/s.
   (2) Corner frequency for such a baby, $f_c = 1/(2\pi CR) = 4$ Hz or 240 bpm.

(f) As airway resistance improves (i.e., decreases), 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, $f_c = 1/(2\pi CR) = 6$ Hz or 360 bpm.

(g) As illustrated in Fig. 40.5, using lower frequencies when airway resistance is problematic is essential, whereas peak pressure necessary to ventilate at higher frequencies flattens out 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 you are switching from HFOV to HFJV.

(a) If starting from CMV, you must raise PEEP by ~2 cm H_2O to maintain Pāw.
(b) If starting from HFOV, use CMV PEEP setting to 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; adjust settings that create tidal volume.
   (a) Adjust ΔP and Power on HFOV.
   (b) Adjust PIP on HFJV, which alters tidal volume, as ΔP = PIP − PEEP.
3. Avoid hyperinflation.
   (a) *HFOV*: if you will find you cannot adequately ventilate without changing rate, delivered tidal volumes 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 help bring ventilation under control, you may need to switch to HFJV to achieve longer exhalation times.
   (b) *HFJV*: if monitored PEEP > set PEEP, it indicates inadvertent PEEP caused by gas trapping.
      (1) Lowering rate will increase exhalation time but decrease minute volume.
      (2) You may need to increase PIP to maintain adequate ventilation, although alleviating gas trapping will increase effective tidal volume.

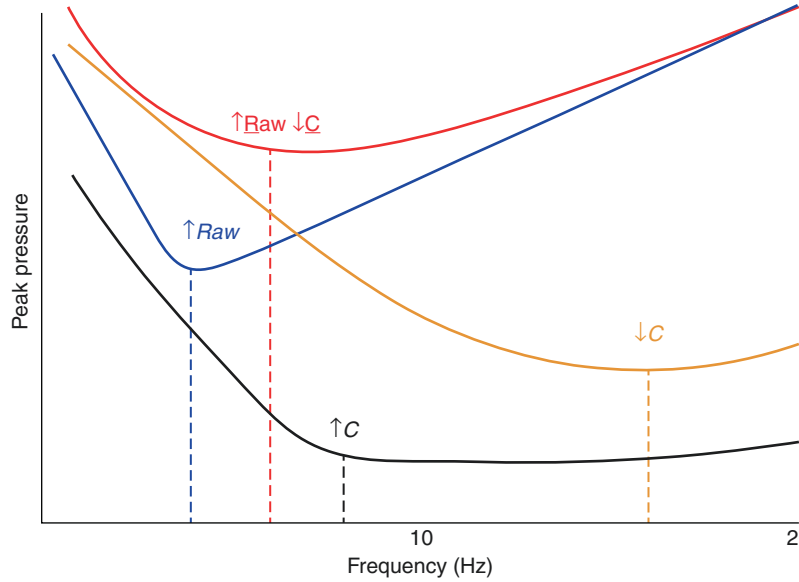

Fig. 40.5 Optimal HFV rates enable adequate ventilation with the lowest airway pressure, and pulmonary time constants (compliance and airway resistance) determine them. Decreased compliance increases the optimal frequency, and increased airway resistance decreases it. Lungs with poor airway resistance and hyperinflated by trapped gas, as happens in infants with BPD, have a sharply lower optimal frequency as indicated by the blue curve above. Note how infants with RDS (represented by the gold curve) 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.)

(3) If increasing PIP does not reduce $PaCO_2$, try increasing I-time to allow more time for tidal volume delivery. (Start by increasing I-time from 0.020 to 0.026 and use the maximum of 0.034 s if necessary.)

4. Avoid hyperventilation by vigilant CO_2 monitoring (transcutaneous CO_2 monitoring is strongly recommended).
5. Permissive hypercapnia is not recommended during HFV, because typical HFV tidal volumes do not cause volutrauma.

F. Optimize PEEP/Pāw and maintain appropriate lung volume for good oxygenation, which is 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) Assuming acceptable lung inflation during HFOV:
      (1) $F_IO_2 > 0.40$, increase Pāw in 1 cm H_2O increments until decreasing F_IO_2 is no longer indicated.
      (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 oxygenation begins to wane.
      (4) If F_IO_2 worsens by 0.2, evaluate lung inflation.
2. *HFJV*: use CMV to recruit collapsed alveoli and PEEP to stabilize the lungs.
   (a) Use CMV at 5 bpm with PIP set high enough to cause noticeable chest rise and adjust F_IO_2 so that oxygen saturation (SpO_2) is close to 90% and stable.
      (1) To determine if PEEP is adequate, switch from 5 bpm CMV to CPAP or minimal CMV rate, PIP, and T_I to avoid causing apnea alarms on the CMV.
      (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 back up ~90%.
   (b) Repeat switch to CPAP or minimal CMV with higher PEEP until HFJV can continue with SpO_2 near 90% with reduced F_IO_2 without CMV at 5 bpm.
   (c) If $F_IO_2 < 0.50$, weigh risks versus benefits of further alveolar recruitment.
3. *HFOV + CMV*: use an approach like 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. (Wean to nasal CPAP or other noninvasive mode.)
   (a) If you get an unacceptable blood gas, reassess, and adjust strategy.
   (b) If you get a normal or better blood gas, wean appropriately.
3. Strategy for treating hyperinflation with HFJV
   (a) Minimize CMV breaths.
   (b) PEEP sufficient to maintain airway patency (typically ≥8 cm H_2O).
   (c) Lower HFJV rate to prolong E-time (exhalation time) and enable diffusion of gas out of affected areas (e.g., 240 bpm with I:E = 1:12).
   (d) Be patient (average time to extubation was 7 days in a retrospective study of 10 severely hyperinflated patients treated with HFJV).
   (e) In extreme cases where patients with diffuse lung injury are suffering extraordinary hypercarbia despite optimizing rate and raising PIP:
      (1) Increase I-time from 0.020 s incrementally up to the maximum of 0.034 s.

(2) Increasing I-time can increase V_T delivery by as much as 70% while decreasing E-time by <10%.

H. Wean to nasal CPAP or other noninvasive mode.

VII. Conclusions

A. HFV can be extraordinarily beneficial if the appropriate device is used on the appropriate patient in the appropriate way at the appropriate time.
   1. Initiate HFV sooner rather later (prevention of lung injury is obviously better, albeit less dramatic, than rescuing infants in dire straits).
   2. Know the capabilities and limitations of the HFV devices you have available.
   3. Develop application strategies based on lung time constants and pathophysiology.

B. Be prepared to change strategy as conditions dictate.

C. Wean to nasal CPAP or other noninvasive mode of ventilation.

D. Let common sense and solid knowledge of pulmonary pathophysiology, lung mechanics, and HFV device characteristics be your guides.

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High-Frequency Jet Ventilation

41

Martin Keszler

I. Indications
   A. *Late rescue treatment:* Refractory respiratory failure unresponsive to conventional ventilation (CMV).
      1. Severe pulmonary interstitial emphysema (PIE)
      2. Large leaks through a bronchopleural fistula (intractable pneumothorax)
      3. Severe respiratory distress syndrome (RDS)
      4. Meconium aspiration syndrome (MAS)
      5. Pneumonia
   B. *Early rescue treatment:* Infants with complications of CMV, at high risk of complications, or who require high settings on CMV.
      1. Moderate RDS
      2. Pulmonary hypoplasia secondary to diaphragmatic hernia
      3. Pulmonary hypoplasia secondary to oligohydramnios
      4. Air leak syndrome:
         (a) PIE
         (b) Pneumothorax
         (c) Tracheoesophageal fistula
      5. Abdominal distention with poor chest wall compliance
      6. 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 remains relatively infrequent.

II. Benefits of HFJV
   A. Lower pressure amplitude (ΔPressure = peak inspiratory pressure (PIP) – positive end-expiratory pressure, PEEP), compared to conventional ventilation

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B. Very effective CO_2 elimination
C. Flexibility to use both low and high mean airway pressure (MAP) 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. Ability to selectively direct ventilation toward the better lung with unilateral PIE
K. Decreased risk of BPD

III. Possible Complications of HFJV
A. Mucosal damage to the trachea and large bronchi
1. Reported in some early studies when inadequate humidification was used.
2. No longer considered a problem with modern equipment.
3. All forms of mechanical ventilation can cause tracheal mucosal damage under some conditions (e.g., inadequate humidity, high MAP, and hypotension).
B. Increased incidence of periventricular leukomalacia and intraventricular hemorrhage (IVH) reported in one study
1. Shown to be related to inadvertent hyperventilation.
2. Similar findings were seen in some oscillatory ventilation studies and with conventional hyperventilation.
3. Risk of inadvertent hyperventilation can be minimized by using transcutaneous PCO_2 monitoring, especially when initiating HFJV.
C. Gas trapping
1. Occurs if inappropriately high ventilator rate is used, because HFJV relies on passive exhalation.
2. When time constants increase with advancing postnatal age, the ventilator rate must be lowered to allow for adequate expiratory time.

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 (see below).
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.
B. Basic control of gas exchange
1. Basic principles of gas exchange on HFJV are not different from conventional or oscillatory ventilation.
2. Similar to other modalities of ventilation, oxygenation is determined by FiO_2 and MAP; increased MAP = improved oxygenation (except when lungs are overexpanded).
3. MAP is determined by PIP, PEEP, and inspiratory time, with PEEP being by far the most important factor.
4. Because of the extremely short Ti, the MAP 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.
5. Ventilation (CO_2 elimination) is primarily controlled by pressure amplitude:

(ΔP = PIP–PEEP), which determines the delivered tidal volume (V_T). In all forms of HFV, including HFJV, CO_2 elimination is proportional to $V_T{}^{\sim 2}$. Therefore, even small changes in V_T can result in large swings in $PaCO_2$. Monitor closely.

6. 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 change.
7. Currently, we lack technology to measure V_T during HFJV, and thus we must rely on visual inspection of chest wall movement. Transcutaneous CO_2 monitoring is helpful in evaluating changes in ventilation.
8. When lung volume is optimized or surfactant is given, 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 $PaCO_2$. Transcutaneous CO_2 monitoring is recommended to minimize the risk of inadvertent hyperventilation.
9. Decreasing ΔP by lowering PIP also lowers MAP and thus may adversely affect oxygenation. This problem should be avoided by increasing PEEP to compensate.
10. Ventilator rate has a relatively small effect on $PaCO_2$. Usual range is 300–450 cycles/min, depending on size of baby and time constants. Time constants reflect how quickly gas gets in and out of the lungs: small stiff lungs have short time constants; large lungs with good compliance and low resistance = long time constants. A rate that is too fast will cause CO_2 to rise because of gas trapping. Larger babies and those with conditions that increase airway resistance (e.g., meconium aspiration, BPD, PIE) need lower rate to avoid air-trapping.
11. Unlike with HFOV, a change in ventilator rate does not change the V_T, unless the rate change eliminates or causes gas trapping.
12. With HFJV, exhalation is passive. T_I should almost always remain at the lowest possible value of 0.02 s to maximize expiratory time.
13. When using lower rates in large infants or when nearing the limit of PIP, slight increases in T_I may be appropriate to increase tidal volume (increments of 0.004 s to a maximum of 0.034). Care must be taken to avoid compromising expiratory time (I:E ratio should be at least 1:4, preferably 1:5, or above to avoid gas trapping).
14. Background conventional IMV rate of two to five inflations/minute may be superimposed on the HFJV pulses to recruit/maintain lung volume (periodic sigh). The PIP should be slightly lower than the HFJV PIP so as not to interrupt the jet ventilator. T_I of the sighs should be 0.4–0.5 s. Background IMV should be omitted in the presence of overexpansion or air leak.
15. Sighs recruit lung volume, but adequate MAP (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 two sighs/minute to maintain lung volume with lower MAP. This may also help to distribute surfactant.
16. Weaning from HFJV is accomplished primarily by decreasing PIP, leaving rate unchanged, except when there is a suspicion of gas trapping from increased airway resistance.

C. Practical aspects

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 and 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 bronchi.
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 in midline and slightly extended with a shoulder roll, in order 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.
5. A sudden loss of chest wall movement or large increase in $PaCO_2$ is usually secondary to a mechanical problem, such as ETT malposition or secretions in the airway disrupting the jet stream. These conditions should be promptly identified and corrected.
6. Monitoring Servo Pressure provides important clues regarding lung compliance and airway obstruction issues. Rising Servo Pressure generally indicates improving lung compliance, and falling Servo Pressure suggests worse compliance (e.g., atelectasis, pneumothorax) or airway obstruction (see Chap. 54 for details of Servo Pressure interpretation).
7. 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 dumped to 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.

D. Matching ventilator strategy to disease pathophysiology
1. Choosing 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 air leak in the early days of HFJV but is seldom used today. It may still occasionally be necessary when refractory air leak is a major problem (e.g., severe PIE with gross overexpansion, large bronchopleural fistula) and the imperative is to reduce peak and MAPs 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.

F. Treatment of PIE and other forms of air leak
1. Most cases of PIE can be treated with a modified low-pressure strategy that recognizes that air leak usually develops in atelectasis-prone lungs and thus atelectasis and PIE commonly coexist.

2. Gas escapes from airways primarily during peak inflation. Therefore, a moderate level of PEEP (6–8 cm H_2O) is indicated in most cases of air leak to avoid atelectasis, a strategy that is no longer a true "low-pressure" strategy.
3. PIP should be set 10–15% below current levels on CMV.
4. PEEP should be 6–8 cm H_2O, depending on severity of air leak and coexisting lung disease.
5. Remember that oxygenation is related to MAP and that it may deteriorate with the drop in PIP and short T_I. Marginal PaO_2 may have to be accepted, and higher FiO_2 is often needed until the air leak improves.
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. Severe PIE increases airway resistance. Therefore, a lower rate (300–340/min) should be used, and T_I should be kept at the minimum value of 0.02 s to maximize expiratory time.
9. Background IMV should be omitted.
10. If marginal oxygenation prevents further decrease in PIP but $PaCO_2$ is lower than desired, decrease the pressure amplitude by increasing PEEP to maintain oxygenation.
11. If diffuse atelectasis develops and oxygenation is inadequate, an increase in MAP (i.e., higher PEEP) is indicated, provided ventilation is adequate. Sighs to re-recruit lung volume should be avoided for some time after resolution of PIE for fear of recurrence of air leak.
12. If ventilation is also inadequate, PIP should be increased.
13. As air-trapping improves and atelectasis begins to develop, transition to the optimal volume strategy (see below).

G. Optimal volume strategy
1. 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.
2. This strategy, also known as the "open lung concept," has been emphasized with HFOV but is equally important with HFJV and even CMV.
3. The open lung strategy is appropriate in most situations, especially in RDS or any other condition that leads to diffuse atelectasis.
4. Optimizing lung volume and V/Q matching reduces exposure to high FiO_2, improves lung compliance, and thus reduces PIP and minimizes volutrauma from maldistribution of tidal volume.

H. Treatment of RDS and other atelectasis-prone conditions
1. When switching from CMV, a slight increase in MAP should be achieved by increasing PEEP.
2. 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
3. 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 generates adequate but not excessive chest wall movement.
4. 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.
5. 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 resis-

tance increases, the rate needs be lowered to avoid air trapping. Tiny infants intubated with a 2 mm endotracheal tube should be ventilated with a rate of 240–280 to allow adequate expiratory time, given the very high resistance of the 2 mm tubes.

6. 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, unless contraindicated by air leak or lung overexpansion.
7. 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. When oxygenation remains stable, the PEEP is adequate. If oxygenation deteriorates, return to a rate of 5/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 two sighs/min.
8. It is uncertain if background IMV is beneficial once stable lung volume is reached. However, note that the published randomized clinical trials were done using background sighs.
9. The background sigh rate or pressure should *not* be increased as a primary means of increasing MAP. Higher MAP 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.
10. 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 transcutaneous CO_2 monitoring if available.
11. The decreased PIP will lower MAP as well, which is appropriate, because the recruited lungs are now more compliant and require less distending pressure to maintain recruitment (think Laplace's law).
12. If the FiO_2 is ≤0.30, the MAP (PEEP) may need to be lowered further to avoid overexpansion.
13. If FiO_2 begins to rise, the MAP may have dropped too much and PEEP may need to be increased.
14. Periodic chest radiographs are helpful in verifying adequate lung expansion or detecting overexpansion. The goal is 8 1/2–9 1/2 rib expansion.

I. Treatment of MAS and persistent pulmonary hypertension of the newborn (PPHN).

1. MAS 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 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 surface.
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 from inadequate expiratory time. Remember: larger infants with airway obstruction have longer time constants and need slower rates. Typical range is 240–320 cycles/min.
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. With low rate and longer expiratory time, the MAP is not far above PEEP; thus, PEEP values ≥10 cm H_2O are often needed in infants with severe lung disease treated with low HFJV rate.

6. Although HFJV is an effective and relatively gentle means of achieving effective ventilation, respiratory alkalosis is no longer recommended as treatment or prevention of PPHN. Permissive hypercapnia is a reasonable strategy in the absence of PPHN, but low pH increases pulmonary vascular resistance and should be corrected as needed by improving ventilation.

J. 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 counterpressure on the diaphragm and maintain lung volume is advantageous. Babies with acute abdominal distention from necrotizing enterocolitis or similar conditions such as postoperative gastroschisis, diaphragmatic hernia, 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, transcutaneous CO_2, and blood gases closely.
   2. Infants with airway disruptions such as intractable pneumothorax with constant large flow through chest tubes, tracheoesophageal 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 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 conventional ventilation, 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 30 s before PPHN will respond to iNO. A relatively low-pressure strategy works best, but atelectasis must be avoided. 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 former 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.

K. Weaning from HFJV
   1. Weaning is accomplished by lowering FiO_2 first and PEEP second, once the FiO_2 is ≤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 MAP.
   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 ≤12–15 cm H_2O and PEEP ≤7 cm H_2O.
5. Older and larger infants can be extubated from higher settings.
6. Alternately, once the pressure is ≤16–20 cm H_2O and PEEP ≤7 cm H_2O, the infant can be switched to conventional ventilation. 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 MAP.

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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 which applies a constant distending pressure (mean airway pressure) with pressure oscillations around the mean pressure. The ventilatory rates range from 300 to 1500 cycles per minute. Gas exchange during conventional ventilation is primarily dependent on bulk convective flow, and delivered tidal volumes fill the anatomical dead space of the airways and distend and fill the volume of the alveolar compartment. During HFOV, 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 minimal. 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 maintain functional residual

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capacity (FRC is the 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 cause lung injury. This mechanism of injury explains the observation that recruitment of lung volume and normalization of FRC protects the lung against ventilator-induced lung injury (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 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
5.	Active expiratory phase	No	Yes

B. Advantages of HFOV

1. Improved alveolar ventilation while exposing the lung to lower pressures and volume swings.
2. It is a safer way of using "high" 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. It 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 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.
3. HFOV can produce ambient sound levels above the current recommended safety limits.

III. Types of HFOV

A. Diaphragm HFOV with variable fractional inspiratory time. The SensorMedics 3100A oscillatory ventilator (Chap. 55) is the only HFOV device currently 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.

C. An important distinguishing feature of different types of HFOV devices is frequency composition of the oscillatory waveform. Some oscillators generate sinusoidal waveforms, and some produce more complex waveforms comprising multiple frequencies. More complex waveforms may enhance gas mixing and regional ventilation homogeneity; however, the impact on the airway wall properties is unknown.

D. Another distinguishing feature is the ability to switch from conventional ventilation to HFOV, or even of combined conventional and HFO ventilation. Hybrid HFOV devices allow combined conventional and high-frequency modalities. Hybrid HFOV devices may have limited power than standalone oscillators. This limitations can be overcome by either switching to a lower oscillatory frequency or changing from a 1:2 to a 1:1 inspiratory-to-expiratory ratio (I:E).

E. The importance of incorporated tidal volume monitoring allows measurement of tidal volume and the diffusion coefficient that can be helpful in optimizing ventilation and prevention of VILI.

IV. Calculations of Minute Ventilation

A. For CMV 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 which increases the amplitude of the pressure oscillation.

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. Oscillation with simultaneous multiple frequencies may be a more efficient ventilator modality compared to 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 significantly injured and still has 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/Q 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. Clinical reports of uncontrolled trials of the use of HFOV as a rescue technique suggest HFOV is beneficial in several different clinical settings. 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, PIE)
      (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
      (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 PEEP during CMV.

F. Specific reports and summary of clinical trials
   1. 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. This study enrolled patients between March 1, 1986, and March 31, 1987, which was before surfactant was approved and 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, grade 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 (enrollment between March 1, 1985, and October 1, 1989), 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 grade 3 and 4 IVH in those infants treated with HFOV.
      (d) Gerstmann and coinvestigators did the first study in which all infants received surfactant. This study compared the hospital course and clinical outcome of preterm infants to 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 done after approval of surfactant showed 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 CMV. 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 CMV 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 to CMV showed survival was similar for both groups and these results were consistent across studies and in subgroup analyses. The risk of BPD in survivors at 36 to 37 weeks' PMA or at discharge was reduced with the use of HFOV, but this effect was inconsistent across studies (summary RR 0.86, 95% CI 0.78–0.96; summary RD −0.05, 95% CI −0.08 to −0.02; NNTB 20, 95% CI 12–50). 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 PIE, 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) In 2019, Iranpour et al. evaluated noninvasive use of HFOV (nHFOV) in infants with a gestational age between 30 and 36 weeks and 6/7 days who had RDS. Surfactant was administered if patients had FiO_2 >35% to maintain the desired oxygen saturation. A total of 68 neonates were randomly assigned to either the nasal CPAP ($n = 34$) or nHFOV ($n = 34$). The median (IQR) duration of noninvasive respiratory support was significantly shorter in the nHFOV group than that in the NCPAP group (20 [15–25.3] versus 26.5 [15–37.4] h, respectively; $p = 0.02$). The need for mechanical ventilation occurred in 4 of 34 (11.8%) neonates in the NCPAP group and in none of the neonates in the nHFOV group ($p = 0.03$).

(h) Current status

1. 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. CDH – Al-Jazaeri et al. and Migliazza et al. suggested that HFOV can be used to support infants with CDH and reduce lung injury. Snoek et al. conducted an international, multicenter study in prenatally diagnosed CDH infants ($n = 171$) born between November 2008 and December 2013. Ninety-one (53.2%) initially received CMV and 80 (46.8%) HFOV. Death or BPD occurred in 45.1% of patients randomized to CMV and in 53.8% treated with HFOV (unadjusted OR of 0.62, 95% confidence interval 0.25–1.55, $p = 0.31$). Patients assigned to initial treatment with CMV were ventilated for fewer days, less often needed extracorporeal membrane oxygenation (ECMO) support, inhaled nitric oxide, and sildenafil, as compared with infants initially ventilated by HFOV. Other clinical cohort studies show outcomes are similar in patients treated with HFOV and CMV.
5. 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 RDS and MAS.
   (d) Chen et al. investigated the clinical efficiency of HFOV combined with pulmonary surfactant (PS) for the treatment of MAS in 53 patients admitted for neonatal intensive care. Early use of HFOV and PS 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-h period following HFOV. Airway trauma associated with suctioning should be avoided by passing the suction catheter only one centimeter 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 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 the association between HFOV and poor neurologic outcome, but Cools et al. show these outcomes are 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. Use continuous monitoring where possible.
5. Greenough et al. reported long-term follow-up of infants at 11–14 years of age. Her study included extremely prematurely born infants entered into a randomized trial of HFOV versus CMV and demonstrated significant differences in lung function favoring HFOV. In addition, HFOV children did better in some school subjects. Follow-up at 16–19 years of age in the same study cohort showed HFOV in the neonatal period was not associated with superior respiratory or functional outcomes.
6. 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 limits the power of this observation, but it is reasonable to suggest that HFOV is not associated with a poorer neuromotor outcome.

H. 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. MAS
   (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.

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Part VIII

Commonly Used Neonatal Ventilators

Ventilator Mode Classification

43

Morgan Sorg and 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 four modes of ventilation (CPAP, assist, control, 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:

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

where Pvent(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 zero 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, e.g., 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.

C. Volume Control

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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.

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 machine triggered, *or* machine cycled (or both machine triggered and machine cycled), independent of what the patient does.

C. Sequences

Given the above definitions, there are only three possible breath sequences:

1. All breaths are spontaneous, called continuous spontaneous ventilation, CSV. Examples include pressure support, volume support, proportional assist ventilation, NAVA (Draeger version), and automatic tube compensation.
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. There are four types of IMV: (1) Mandatory breaths are always delivered at a set frequency and allow spontaneous breaths within a window between mandatory breaths (e.g., SIMV); (2) mandatory breaths are suppressed when the spontaneous breath rate is greater than the set mandatory rate (e.g., Automode on Maquet Servo-i and u); (3) mandatory breaths are suppressed when the spontaneous minute ventilation is greater than the set/target mandatory minute ventilation (e.g., Dräger Mandatory Minute Ventilation); and (4) mandatory breaths are suppressed when dual targeting switches inspiration from volume control to pressure control due to inspiratory effort. Specifically, this happens when a flow- or pressure-triggered inspiration becomes flow cycled (i.e., patient triggered and patient cycled, hence a spontaneous breath), for example, volume control with the flow adaptive setting activated on Maquet Servo-i ventilators. Compared to CMV, during IMV, the mandatory breath frequency will never be higher than the set rate, but it may be lower for IMV(2), IMV(3), and IMV(4). Whether or not the triggering 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 (s)

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 venti-

lator 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 (r)

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 United States).

C. Adaptive (a)

A targeting scheme that 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: *PC* (pressure), *VC* (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., lowercase letters separated by a comma; the first lowercase letter represents the mandatory breaths and the second one represents the spontaneous breaths). For some modes there may be more than one targeting scheme occurring at once. In this circumstance the targeting schemes would both be in lowercase letters and not have a comma separating them

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

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AVEA Ventilator

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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 on the neonatal applications.

II. Description. Both volume- and pressure-targeted ventilations 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 (AAC)
      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 (FCV) 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 measure accurate tidal volume delivery.

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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

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 Ppeak (cm H_2O)
G. High Ppeak (cm H_2O)
H. Low PEEP (cm H_2O)
I. Apnea interval (sec)

VI. Nomenclature
A. Pressure Versus Volume Control Ventilation
1. Pressure Control (PC) Ventilation
(a) The pressure is preset, and 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 preset.
(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 preset 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 preset 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 will 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 preset 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 VT. This sometimes results from an inspiratory flow setting that is too high, producing a very rapid increase in flow on inspiration. In this case, a change in rise time (see below) may be useful. If adjustment of this parameter is not helpful, 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) PC
   (c) PS
2. Time-Cycled, Pressure-Limited (TCPL)
   (a) Flow through the patient circuit is operator preset and continuous. However, this preset 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 and the spontaneous breathing effort of the infant.
3. PC
   (a) Peak inspiratory pressure (PIP) is preset 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. 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., due to a 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 preset 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 tidal volume is measured proximally at the patient's endotracheal tube. However, the delivered volume is measured at the connection of the ventilator circuit to the ventilator itself. 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 depending on the patient's lung compliance and airway resistance (and patient breathing 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 preset to get the desired target delivered volume.
4. The set volume, flow rate, and inspiratory pause parameters determine the inspiratory time.

C. Volume Guarantee (PC with Adaptive Targeting)
1. Overview
   (a) In pressure controlled ventilation with set-point targeting, V_T varies based on compliance and resistance (and patient breathing effort).
   (b) Rapidly changing lung mechanics can cause variable tidal volumes resulting in the risk of lung injury, progressive atelectasis, and suboptimal ventilation.
   (c) Volume guarantee automatically adjusts inspiratory pressure (IP) to deliver consistent average expiratory tidal volumes. This mode both measures and controls based on the tidal volumes measured at the ET tube, producing a more accurate way to target volumes for small babies.
   (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) This function provides an additional operator setting for target tidal volume.
   (g) The control pressure for mandatory breaths will then be adjusted by the ventilator to maintain the expired tidal volume close to the preset 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) IP – in VG, IP is no longer a primary control. The operator-set IP is an advanced control of volume and is used for test breaths. Rather than a fixed value, it is a maximum value set by the user. If it is inadequate to deliver the set tidal volume, a "volume guarantee pressure is limited" alarm will sound. It also acts as a backup pressure setting during certain alarm conditions.

(e) The IP 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: IP plus PEEP
2. Minimum: PEEP +2 cmH_2O
3. Maximum: High peak pressure –3 cmH_2O

(b) Delivered pressure will be limited when it reaches the high pressure limit setting of −3 cmH_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 44.1)

Note: the AVEA offers an unusually large number of modes, but they are not all 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 on 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 = (VT) × respiratory rate. Measured inspiratory tidal volumes should be 4–7 mL/Kg to avoid overinflation. The normal MV = 240–360 mL/Kg/min. This calculation is based on expiratory tidal volume (VTe) and will be affected by endotracheal tube leaks.

1. Pressure Modalities

(a) The VT is adjusted by setting the IP in TCPL/PC and PS 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, resistance, and spontaneous breathing effort will affect the delivered tidal volume.

Table 44.1 Mode Map

Mode name	Mode classification				
	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 airwag 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 air	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
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	Pressure	IMV	Adaptive	Set-point/servo	PC-IMVa,sr

Table 44.1 (continued)

Mode name	Mode classification				
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
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	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVar,ar
Pressure regulated volume control SIMV with flow cycle and artificial	Pressure	IMV	Adaptive/servo	Set-point/servo	PC-IMVar,sr
Time cycled pressure limited A/C with flow cycle and artificial airway	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

2. Volume-Targeted
   (a) The inspiratory tidal volume (VTi) delivered to the patient is determined by the set tidal volume minus the volume that is compressed in the ventilator circuit. This results in unreliable volume delivery in small babies and must be carefully watched.
   (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.

B. Oxygenation (PaO_2) correlates directly with mean airway pressure (Pāw) and FiO_2.
1. Increases in 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. However, it is important to remember that the best technique to adjust Pāw is usually PEEP, which prevents end-expiratory lung collapse.
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 breathe 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 VT 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 a bit difficult to accomplish in the volume assist-control mode but much easier when using VG. In this case, when the required pressure to deliver VTi is between 10 and 15 cm H_2O, the patient can be evaluated for extubation.
2. If volume control is being used, it is sometimes necessary to change to SIMV/PS prior to extubation.
(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 VT.
3. Once the PS IP has been weaned to a level which provides a 3–4 mL/kg VT, 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.
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http://www.carefusion.com/pdf/Respiratory/Ventilation/AVEA_brochur

Twinstream Ventilator

45

Raphael Ulreich

I. *Introduction*
   A. The Twinstream ventilator (Carl Reiner GMBH, Vienna, Austria) (Fig. 45.1) 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 bi-level 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 p-BLV, which can be used in critically ill infants and children with acute respiratory insufficiency.
   C. The technical information, which follows, is from the manufacturer's device information. The guidance on the use of p- BLV is based on the authors' center experience over many years. We use the Twinstream device mainly as a "rescue" treatment to enable ventilation in challenging situations (indications listed below). Basically, the combination of high-frequency and low-frequency jet ventilation enables us to maintain or improve oxygenation and ventilation while still using low driving pressures, low plateau pressure, and maintaining/establishing lung protective ventilation in selected cases.

II. *Technical Information*
   A. The p-BLV-converter consists of a Venturi body with one entrainment port (for low- and high-frequency entrainment), connected to the expiratory limb of the breathing tube system. A variable bias flow, warmed and humidified in the inspiratory limb of breathing circuit, reaches the wye piece connected to the endotracheal tube. The expiratory limb of the breathing circuit is connected with the p-BLV converter (Fig. 45.2), and the inspiratory bias flow will now be modified by two jet streams resulting in an oscillating gas column to the patient's airways. In addition, the p-BLV converter acts as a pneumatic-driven PEEP generator.
   B. The Twinstream ventilator in p-BLV mode can be used as a stand-alone device without the need of an adapter or additional conventional ventilator as in other jet ventilators.

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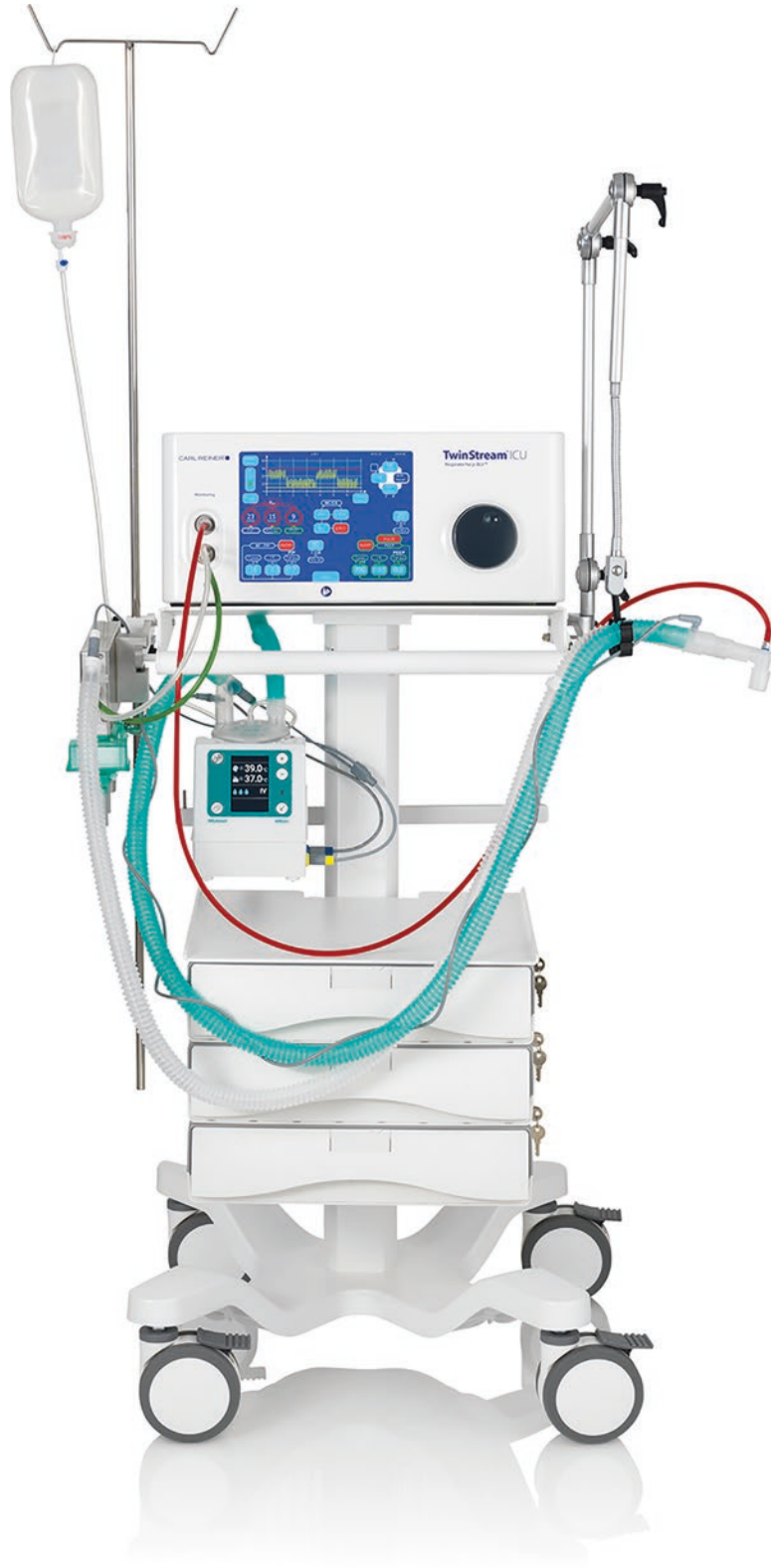

Fig. 45.1 Twinstream ventilator

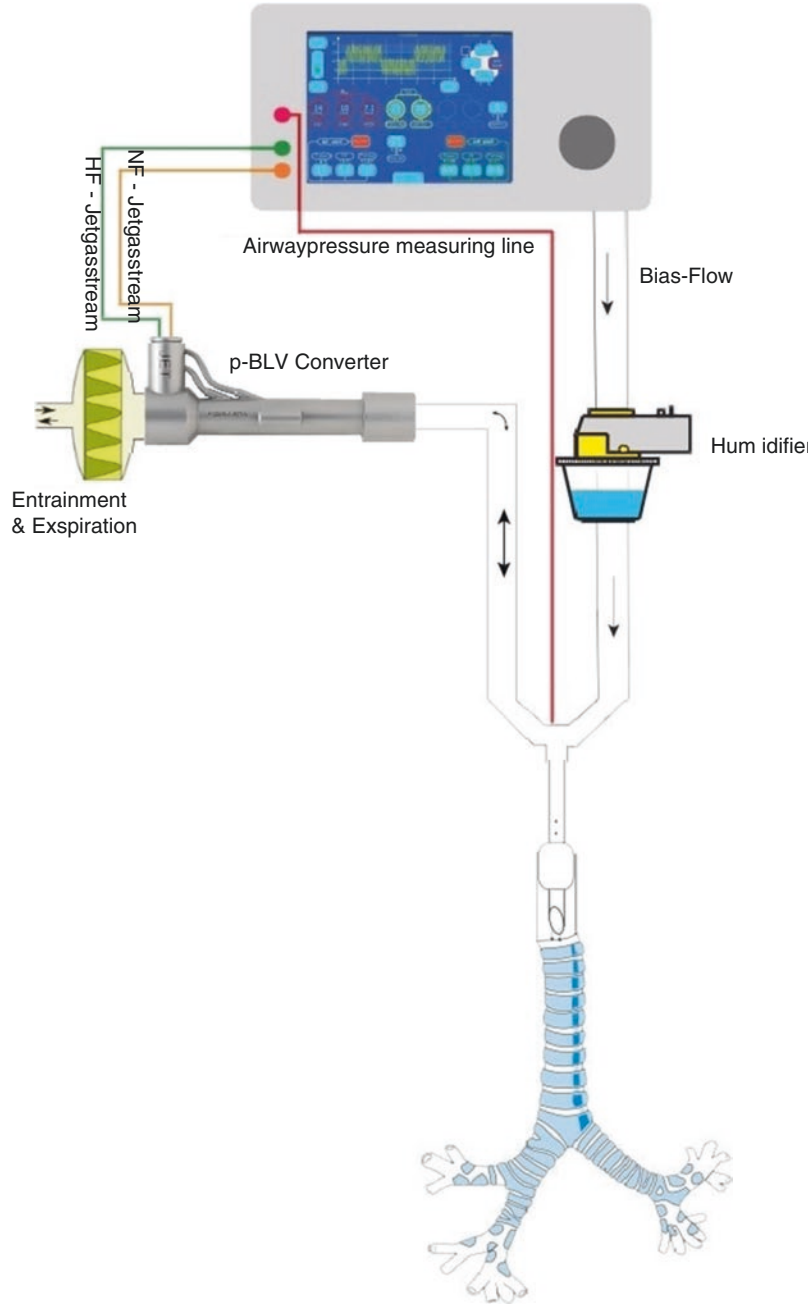

Fig. 45.2 Circuit and components of the Twinstream ventilator

C. During p-BLV, optimal gas conditioning (warming, humidification) with a standard heater is important. The inspiratory and expiratory limbs of the breathing circuit are heated, resulting in a correctly conditioned inspiratory gas.

III. *Relative Indications (Experientia)*

A. Pediatric/neonatal indications by disease

1. Air leak syndrome
2. Lung hypoplasia (congenital diaphragmatic hernia and other etiologies)
3. Meconium aspiration syndrome

4. Congenital lobar emphysema
5. Severe ARDS

B. Indication by ventilation situation (on conventional mechanical ventilation)
1. Plateau pressure >30 mbar
2. Mean airway pressure > 20 mbar
3. Excessive airway secretions
4. Recruitment of large atelectasis
5. Reduced chest wall compliance
6. Nebulized drug therapies interfering with a conventional flow sensor
7. Rescue treatment if ECMO criteria are met but ECMO not immediately available

IV. *Selection of Patients and p-BLV Converter*

A. Neonates, small infants, and children with a body weight from <1 kg up to 40 kg can be ventilated with the p-BLV converter pediatric. However, the author's team has never used it below 1 kg.

B. We use a separate p-BLV converter for body weight >40 kg up to 200 kg (Fig. 45.3).

V. *Monitoring*

A. Pressures are monitored near the wye piece of the ventilator. Pressure-time curve displays peak, mean, and end expiratory pressures.

B. Two oxygen cells can measure oxygen concentrations of the jet stream and the bias flow.

C. In contrast to high-frequency oscillatory ventilation (HFOV), p-BLV ventilation enables us to use end expiratory CO_2 monitoring. However, we recommend additional tcPCO_2 monitoring (Fig. 45.4).

VI. *Initial Settings*

A. Bias flow: Minimum 20 L/min (range 20/40/55 L/min)

B. FiO_2: According to FiO_2 on conventional mechanical ventilation (CMV) before transition to p-BLV

C. Low-frequency module:
1. Emitting pressure P_{NF} 0.5 bar (range 0.1–3.5 bar)
   Adapt in steps of 0.1 bar for the desired peak inspiratory pressure measured in mbar.
2. Ventilation rate: Start with 25% less than CMV before transition to p-BLV (range 1–100/min).
3. I:E ratio 1:2

D. High-frequency module:
1. Emitting pressure P_{HF} 0.5 bar (range 0.1–2.0 bar)
   Adjust in increments of 0.1 bar to achieve the desired PEEP measured in mbar.
2. Ventilatory rate: 360–600 bpm = 6–10 Hz (range 1–25 Hz)
   Adapt according to clinical needs and patients size or as you would for HFOV.
3. I:E ratio 1:2

VII. *Troubleshooting*

A. To optimize oxygenation and ventilation, the principles of CMV and HFOV apply.

B. Optimizing oxygenation:
1. Increase PEEP (mbar) by increasing P_{HF} on the high-frequency module (bar).
2. Increase FiO_2.
3. Increase rate of high-frequency module (bpm/Hz).

C. Optimizing ventilation
1. Increase frequency of low-frequency module (bpm).
2. Decrease frequency of the high-frequency module (bpm/Hz).
3. Increase P_{NF} to increase pressure amplitude of the low-frequency module (mbar).

Fig. 45.3 Jet converter

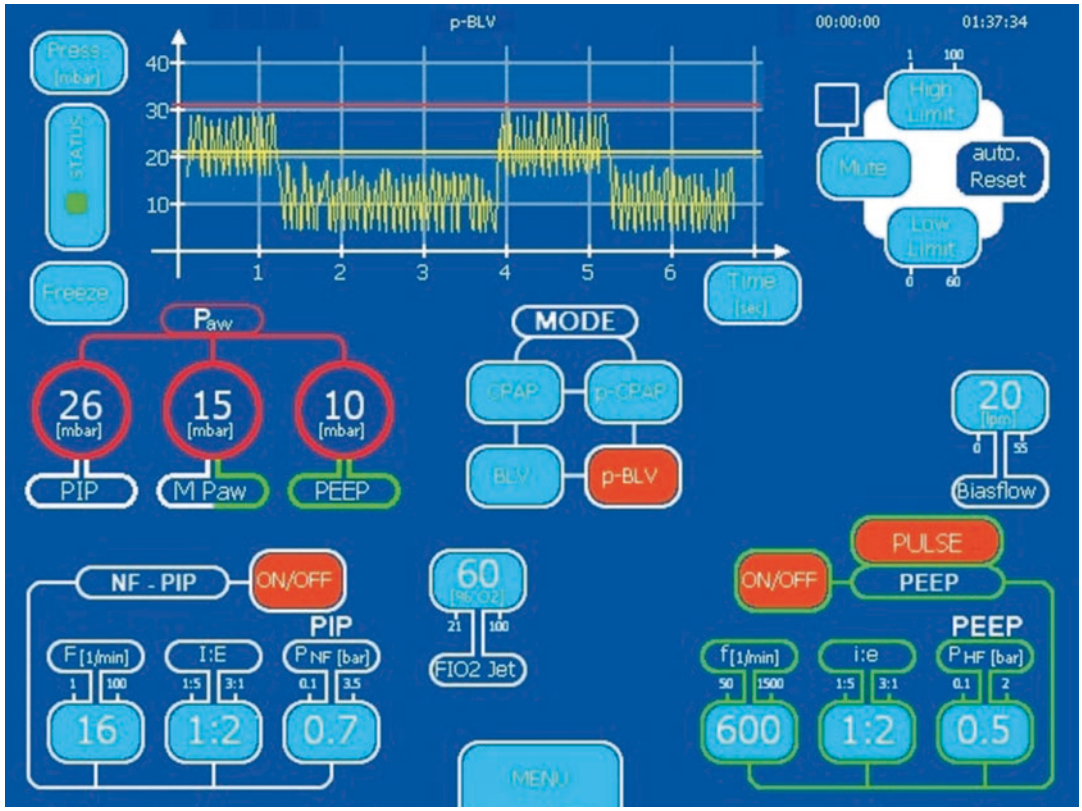

Fig. 45.4 Twinstream ventilator display
The pressure/time curve, in yellow, shows oscillations on two different pressure levels
The red line indicates the alarm set for upper pressure limit
Left lower angle: settings of low-frequency module/pressure – setting (P_{NF}) in bar
Right lower angle: settings of high-frequency module/pressure – setting (P_{HF}) in bar
Red circles indicate the measured pressures in mbar created by the abovementioned settings

Table 45.1 Modes for the Twinstream ventilator

Mode classification					
Mode name	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	Tag
Bi-level ventilation	Pressure	IMV	Set point	Set point	PC-IMVs,s
Pulsatile bi-level 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. *Non-ventilator Interventions Complementing p-BLV Ventilation*
- A. Adapters for nebulized drugs and inhaled nitric oxide can be integrated into the circuit before connection to the patient.
- B. We use prone positioning, if indicated, regardless of body weight. Tracheal mucosal injury has never been observed.
- C. Spontaneous breathing is possible.

IX. *Mode Map* (Table 45.1)

46 Puritan Bennett 840 and Puritan Bennett 980 Ventilators

Robert L. Chatburn and Cindy 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. 46.1).

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.

Fig. 46.1 Puritan Bennett 980 ventilator

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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.
    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. 43 as the breath sequence (i.e., CMV, IMV, 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's 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 (preset 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 (preset 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 (preset 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 (preset 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 (preset 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 ID, and tube type.
   3. Between-breath targets: none.

F. SIMV Pressure Control (With Pressure Support)
   1. Mandatory breaths: machine triggered (preset 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 (preset 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 (preset 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 (preset 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 ID, and tube type.
   3. Between-breath targets: none.

J. SIMV Volume Control Plus (With Pressure Support)
   1. Mandatory breaths: machine triggered (preset 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 (preset 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 ID, and tube type.
   (b) PAV+ adjusts pressure delivery to offload the operator 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 ID, 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. The mode names and classifications are shown in Table 46.1. Note that 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 data values.

Table 46.1 Modes on the Puritan Bennett 840 and Puritan Bennett 980 ventilators

Mode name	Mode classification				
	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
A/C 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
A/C 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

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 VN 800/600/500

47

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I. Introduction

Draeger Babylog VN800 and VN600: Both devices have similar characteristics; the main difference between VN/800 and VN/600 is the screen size.

Also, ventilation modes are similar to the prior version of the Babylog VN500, so similar content can be applied for the three models.

A. Overall benefits
   1. Complete and integrated solution that can be applied to most clinical situations.
   2. Single platform supports all respiratory needs, including noninvasive, 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, 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 VN800/600 offers a variety of conventional modes: mandatory ventilation modes (pressure controlled) and spontaneous and assisted modes, with different interfaces related to the model used.

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B. Invasive and noninvasive 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.
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 T_i 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 T_i.
      (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) T_i
         (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) T_I
         (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 T_i and number of mandatory breaths are determined by the operator.
      (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 rate.
   (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 T_i 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 x 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 preset 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 preset 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; T_i, 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 volumes are 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 V_T) 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) The apnea ventilation 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 (ATC)
    (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 VN800/600/500 are shown in Table 47.1.

Table 47.1 Mode map for the VN/800/600/500

Mode name	Mode classification				
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
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

(continued)

Table 47.1 (continued)

Mode name	Mode classification				
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
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
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

IV. Highlights

A. Conventional ventilation with focus on volume guarantee (Chap. 38)

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 targeted.

(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 in 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, lung fibrosis), the patient is more supported by increasing the pressure. However, it is still limited to the set Pmax.
(8) The Babylog VN800/600 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.
(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 VN800/600/500 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 limits V_T variation and over- or underventilation.
(2) High tidal volume injures the immature lung, so volume guarantee ventilation may limit 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 VN800/600/500 in HFOV works as oscillator providing 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 VN800/600/500, 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 VN800/600/500, different I:E ratio 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 the 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 modified up to the user-defined maximal amplitude to achieve the set VThf.
4. In this modality, variations in the tidal volume are limited, and a direct control on CO_2 clearance can be affected by adjustment in the tidal volume.
5. In this mode, the Babylog VN800/600/500 calculates the amplitudes required to reach the set VThf. The Ampl. Hf 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, use of the lower tidal volume is desirable, and the decrease of carbon dioxide elimination (DCO2) is $Vt^2 \times$ frequency and can be then compensated by increasing the frequency.

D. Noninvasive ventilation

1. Important principle: Noninvasive ventilation can be used mostly in the preterm infant with respiratory instability or 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 and postoperative respiratory failure
   (d) Decrease of nosocomial pneumonia

3. Noninvasive 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

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Neurally Adjusted Ventilatory Assist (NAVA) Ventilation

48

Howard Stein, Kimberly Firestone, and Jennifer Beck

I. Introduction
   A. Neurally adjusted ventilatory assist (NAVA) is a mode available on the Servo-i, Servo-n, and Servo-u ventilator systems (Maquet Critical Care AB, Solna, Sweden) and is intended for patients who are spontaneously breathing.
   B. Different from other modes of partial ventilatory assist, NAVA uses the electrical activity of the diaphragm (Edi) to control triggering, cycling, and the magnitude of assist (Fig. 48.1).
   C. Aside from the NAVA mode itself, the Edi waveform is available for monitoring in other conventional modes, and can be used to evaluate neural breathing pattern, central apnea, and patient-ventilator asynchrony.

II. Basic Principles and Physiology of Electrical Activity of the Diaphragm (Edi)
   A. NAVA uses the patient's neural respiratory drive, measured as the Edi, to control the timing and amount of assist.
   B. The Edi signal is measured with an array of small sensors embedded within the patient's feeding tube (Edi catheter), positioned at the level of the gastroesophageal junction (Fig. 48.1i). Sensors in this position pick up the Edi signals from the crural diaphragm, which forms a scarf-like structure around the lower esophageal sphincter. Appropriate positioning of the sensors is required to obtain a reliable Edi signal (see below section V on

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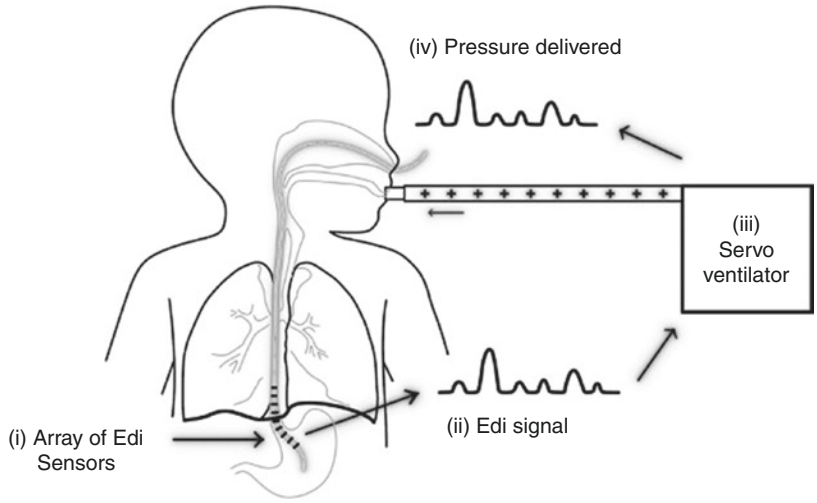

Fig. 48.1 Schematic representation of the NAVA mode. Electrical activity of the diaphragm (Edi) is recorded by an array of sensors placed on a naso−/orogastric feeding tube (i). The Edi signal (ii) is fed to a Servo ventilator (iii) to instruct delivery of positive pressure (iv). Hence, synchrony and prortionality to breathing are achieve

proper electrode positioning). A detailed description of the Edi signal acquisition and processing is beyond the scope of this chapter; however, it can be summarized as follows: raw Edi signals from all sensors on the array are processed to eliminate the ECG and motion artifacts, and continuously track the diaphragm, every 16 msec, resulting in an Edi waveform that can be reliably interpreted (Fig. 48.1ii).

C. The Edi signal represents the summation of electrical impulses arising from the activated diaphragm motor units. The more motor units that are recruited, and the higher the firing rate, the larger is the amplitude of the Edi signal. Factors which stimulate respiratory drive (increased loading, increased CO2) will increase diaphragm motor unit activation and, hence, will increase the Edi signal magnitude. Factors which decrease the respiratory drive (sedation, unloading by mechanical ventilation) will decrease the Edi signal amplitude.

D. The Edi waveform has a characteristic cyclic pattern, with varying peak and minimum values that can be used to interpret neural inspiratory effort (Edi peak) and postinspiratory activity (Edi min) (Fig. 48.2, bottom tracing). Monitoring the Edi waveform provides accurate information on respiratory metrics (neural breathing frequency), as well central apnea (flat Edi waveform). Because of the critical information it provides, the Edi waveform can be considered a respiratory vital sign, and monitoring its activity is often referred to as the "neural breathing pattern" to incorporate all the information (Edi peak, Edi min, neural respiratory rate, and central apnea). The Edi in combination with various other pneumatic variables (such as occlusion pressure or tidal volume) can provide indices of respiratory muscle function. Comparison of the Edi waveform (white tracing) to the ventilator pressure waveform (yellow tracing) allows detection of patient-ventilator asynchrony (Fig. 48.2, top tracings).

III. Basic Principles and Physiology of Neurally Adjusted Ventilatory Assist (NAVA) and Noninvasive NAVA (NIV NAVA)

Fig. 48.2 Screenshot from Servo-n ventilator demonstrating Edi and pressure waveforms during PRVC. Bottom tracing (purple) shows the Edi waveform, with Edi peak and Edi min noted. The top tracing shows the inspiratory pressure delivered by the ventilator (yellow) with superimposed tracing of the Edi signal (light gray)

A. In the NAVA mode, the Edi signal is used as the controller signal to trigger on the breath after an adjustable-threshold change in Edi is reached (default value 0.5 μV), then delivers assist (pressure) in proportion to the Edi, and cycles-off the breath after the Edi has reached its peak and decreases by 30%. PEEP and FIO_2 are fixed and set by the clinician.
B. The assist level must also be set by the clinician (so-called NAVA level; see section V), which determines the proportionality between the Edi and the ventilator pressure.
C. With respect to safety, upper pressure limits are in place, and backup ventilation is provided in the case of no Edi (central apnea or accidental catheter removal).
D. Figure 48.3 demonstrates the Edi and ventilator pressure waveforms during NIV NAVA and demonstrates the synchrony between the patient (Edi) and the ventilator (Pvent), both in terms of timing (vertical-dashed lines) and proportionality (thick short horizontal bars). During NIV NAVA, the synchrony and proportionality of the assist delivered are not affected by leaks.
E. Conceptually, the ventilator in the NAVA mode becomes a respiratory prosthesis, where the diaphragm and the ventilator share the load to support breathing, but in a synchronized and proportional fashion.
F. NAVA is available for both invasive and noninvasive ventilation, for adult, pediatric, and neonatal patients.

IV. Indications and Contraindications
A. Indications
1. NAVA is indicated in infants of all ages who require and qualify for partial ventilatory assist, and in whom spontaneous respiratory activity (phasic Edi) is present.
2. NAVA ventilation is a practical and effective mode used in neonates with respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), respiratory syncytial virus (RSV), congenital diaphragmatic hernia (CDH), and pulmonary interstitial emphysema (PIE) and patients undergoing surgery for congenital heart disease (CHD). It has been supportive in the diagnosis of central hypoventilation syndrome.
3. NAVA can be implemented with the methods described below for most neonatal respiratory conditions. Ventilating with NAVA allows the neonate to personalize their own ventilatory needs to accommodate their specific respiratory condition on an ongoing breath-to-breath basis.

Fig. 48.3 Screenshot from the Servo-n ventilator demonstrating Edi and pressure waveforms during NIV NAVA. Bottom tracing (purple) shows the Edi waveform, with Edi peak and Edi min noted. The top tracing shows the inspiratory pressure delivered by the ventilator (yellow). The Edi and ventilator pressure waveforms during NIV NAVA demonstrate the synchrony between the patient (Edi) and the ventilator (Pvent)

B. Contraindications
   1. A complete lack of respiratory drive and inability to place the NAVA nasogastric catheter are contraindications for the use of NAVA.
   2. Any condition that severely impairs respiratory drive such as hypoxic ischemic encephalopathy or stroke affecting the respiratory center in the brainstem, overwhelming sepsis, and oversedation or paralysis would result in the absence of Edi and the neonate ventilating exclusively in backup. In these cases, it is advisable to use conventional ventilation and to monitor the Edi. Once the Edi returns, even intermittently, NAVA can be initiated. When NAVA is used, the ventilator supports any breathing the neonate does synchronously but still provides the necessary backup ventilation when needed.
   3. The inability to place the NAVA catheter in conditions such as tracheal-esophageal fistula, recent upper airway surgery, esophageal perforation or surgery, abnormal esophagus, and known phrenic nerve lesions is another limitation to its use.
   4. The Edi catheter is not approved for use in the MRI environment, so it would need to be removed from the patient before entering the MRI area.

V. Adjustments at the Bedside
   A. Implementation of NAVA requires the appropriate equipment, namely, a ventilator with the NAVA option, module, and software, as well as an Edi catheter.
   B. Edi catheter positioning:
      1. The size of the Edi catheter is determined by patient height or weight as shown in Table 48.1.
      2. Correct placement of the Edi catheter is a critical part of NAVA management; it can be easily maintained and monitored through the catheter-positioning screen of the ventilator (Fig. 48.4).

Table 48.1 Edi catheter selection guide by weight or height

	6Fr/49 cm	6Fr/50 cm	8Fr/50 cm	8Fr/100 cm
Patient height	<55 cm	<55 cm	<55 cm	45-85 cm
	(<21.7 in.)	(<21.7 in.)	(<21.7 in.)	(17.7–33.5 in)
Patient weight	0.5–1.5 kg	1.0–2.0 kg	1.0–2.0 kg	–
	(1.1–3.3 lb)	(2.2–4.4 lb)	(2.2–4.4 lb)	–

Fig. 48.4 Screenshot from Servo-n ventilator demonstrating Edi catheter-positioning window. Catheter-positioning screen showing the signals obtained from the sensors of the Edi catheter. Note the presence of the retrocardial ECG. When the catheter is in an appropriate position (the diaphragm is located on the center of the array), the P waves are present on the most top leads (leads A/B) and progressively decline in amplitude more distally and may even disappear (lead D). The QRS progression is similar (from top to bottom, declining in amplitude, indicated by dashed oval). When the signals on the leads A-D turn purple, it indicates the presence of diaphragm activity, which in turn is translated into the Edi waveform (bottom tracing)

3. The screen is utilized to position the Edi catheter electrodes at the level of the crural diaphragm to detect the optimal Edi signal.
4. The initial insertion distance can be predicted by using the manufacturer's tool: open the calculation tool window, measure NEX of patient, select oral or nasal insertion, and enter the NEX value.
5. Appropriate final placement is accomplished when the retrocardiac ECG signal with large P and QRS complexes in the upper leads progressing to small or absent complexes in the lower leads.

6. The blue (Servo-i) or purple (Servo-u/Servo-n) tracings in the middle two leads represent the raw diaphragm EMG signal and the position of the diaphragm. The raw signal is then processed into the Edi waveform used to trigger and control the assist. As long as the ECG progression, as described above, is correct, the superimposed color on the leads can drift to the upper and lower leads without affecting the signal quality.

C. Setting the Edi "neural" trigger and neural cycling-off
   1. The Edi "neural" trigger is the minimum increase in Edi that triggers the ventilator to recognize an inspiratory effort and not just baseline noise.
   2. The concept is comparable to the sensitivity settings when using flow- or pressure-triggered ventilation; it is the amount of Edi increase needed to initiate the NAVA-supported spontaneous breath from the ventilator.
   3. If the Edi trigger is set too low, the ventilator will recognize small insignificant signals and deliver small ineffective breaths which may result in clinical deterioration.
   4. If the Edi trigger is set too high, small neural efforts may go undetected and the infant will not receive support.
   5. In most cases, the factory default of 0.5 μV is satisfactory.
   6. Neural cycling-off is fixed (nonadjustable) at 70% of Edi peak.

D. Setting the NAVA level
   1. The amount of assist during NAVA is controlled both by the patient's Edi and the NAVA level. Since assist is delivered in proportion to Edi, at an unchanged NAVA level, increasing Edi will provide increasing pressure delivery, and less Edi will reduce pressure delivered.
   2. The NAVA level is a proportionality factor that converts the quantitative phasic Edi (calculated as Edi peak – Edi min) in microvolts into a delivered inspiratory pressure. The NAVA level (cm H_2O/μv) used in the neonatal mode can range from 0 to 15 but typically ranges from 0 to 4 cm H_2O/ μv.
   3. The pressure delivered is the inspiratory pressure applied above a fixed, clinician-determined PEEP. Note that delivered pressure (and hence tidal volume) cannot be targeted as in other modes of ventilation. This is because the patient will respond to changes in the assist, and adjust their Edi, which in turn affects the pressure and volume delivered.
   4. An increase in the NAVA level can result in either increased ventilator pressure (if little or no change in Edi) or similar ventilator pressure (as the patient decreases their Edi). Regardless, the NAVA level is what determines the amount of "work" done by the infant vis-à-vis the ventilator.

E. Setting the apnea time
   1. The apnea time is the amount of time the neonate can have a respiratory pause (no Edi signal) before the patient is given backup ventilation.
   2. This provides a minimum respiratory rate and is an important safety feature in the extremely preterm neonate with irregular breathing patterns and frequent desaturations.
   3. Apnea time is unrelated to the backup rate, which is the rate at which the neonate is ventilated during the apneic event and is preset by the bedside clinician. Table 48.2 shows how apnea time relates to minimum rate.

F. Setting the backup ventilation parameters
   1. Backup ventilation is provided when the patient is apneic for the predetermined time set by the clinician.
   2. Backup with NAVA ventilation can only be delivered with pressure control ventilation.
   3. Backup settings should deliver adequate ventilation with sufficient backup support to ventilate the neonate appropriately when apneic without overventilation. If the neonate

is overventilated with these settings, the respiratory drive would decrease and prevent the neonate from resuming spontaneous respiration with NAVA.

G. Setting PEEP
   1. The PEEP during NAVA is fixed and determined clinically.
   2. PEEP should be set as with other modes of mechanical ventilation.
   3. In infants, monitoring the tonic Edi may aid with adjustment of PEEP, as it is known that applying PEEP can reduce tonic Edi.

H. Summary of initial NAVA/NIV NAVA settings

Table 48.3 is a summary of recommended initial NAVA settings. It is important to stand at the bedside and evaluate the response of the patient to the initial settings and fine-tune them based on work of breathing and Edi levels.

Table 48.2 The relationship between apnea time and minimum rate

Apnea time (sec)	Minimum rate (breaths/min)
5	12
4	15
3	20
2	30
1.8	33
1.6	38
1.4	43
1.2	50
1	60

Table 48.3 Recommended initial settings for both NAVA and NIV NAVA in neonates

Parameter	Settings	Management
NAVA level (0–4 cmH2O/μV)	2.0 cmH_2O/μV	Titrate to neonate's comfort and Edi peak 10–15 μV: if there is increased work of breathing and Edi peak >20 μV, increase the NAVA level in 0.5 cmH_2O/μV increments until the patient is comfortable and the Edi peaks are <15 μV If the patient is comfortable and the Edi peaks are <5 μV, decrease the NAVA level in 0.5 cmH_2O/μV increments until the Edi peak values are >5 μV
PEEP	5–8 cmH_2O	Set clinically appropriate for disease process
Edi trigger (0c2 μV)	0.5 μV	Manufacturer default
Pressure alarm	30–40 cmH_2O	Set high enough to allow recruiting breaths Increase if peak pressure limited is consistently reached. Note: PIP is limited 5 cmH_2O below set value
Apnea time (1–20 seconds)	2 seconds	Set short enough so that the patient gets a rescue (backup) breath before any clinical decompensation is noted
Backup settings	PC 15–25 cmH_2O PS = PC PEEP 4–8 cmH_2O Rate 40–60 b/min IT 0.3–0.4 seconds	Adjust to maintain clinical stability when the neonate is apneic

PC pressure control; *PS* pressure support (for invasive NAVA only with Servo-i); *IT* inspiratory time; *PEEP* positive end expiratory pressure

I. Management of neonates on NAVA
   1. Escalating NAVA: Some neonates will continue to have increased work of breathing after NAVA ventilation has been initiated and require escalation in their ventilatory support. Table 48.4 describes how to use the Edi values and blood gases to escalate NAVA in neonates with increased work of breathing.
   2. Weaning with NAVA: Once the neonate has clinically improved, attempt to wean with NAVA. The neonate will demonstrate lower Edi values and improved blood gases as lung compliance improves. They will autowean by decreasing their respiratory drive (Edi), thereby decreasing the delivered PIP and VT. Table 48.5 describes how to accomplish weaning with NAVA using the Edi and blood gases. Neonates with RDS can rapidly wean, and ventilator changes can be made 2–3 times a day as tolerated. Successful extubation from NAVA to NIV NAVA can occur with most neonates within the first 72 hours, including those as premature as 23–24 weeks.

VI. Troubleshooting on NAVA
   A. Adjustment of ventilatory support may be needed for some neonates who experience periods of clinical instability.
   B. Table 48.6 is a troubleshooting guide that will assist the bedside clinician in adjusting the ventilatory support.
   C. The first step is to always start with checking catheter position.

VII. Noninvasive (NIV) NAVA and Central Apnea
   A. Premature infants often experience severe and frequent central apnea.
   B. While some neonates respond to CPAP, many continue to have central apnea severe enough to require noninvasive or even invasive support.
   C. Current CPAP modes do not offer any backup support when the neonate becomes apneic.
   D. A novel approach of this mode is to use NIV NAVA as CPAP: the NAVA level is set at zero, and adequate backup support is provided for those periods of central apnea.

Table 48.4 Escalating NAVA and NIV NAVA in neonates

Presentation	Issue	Solution
Edi peaks consistently >20 μV and/or acidosis or hypercapnia	Mostly in backup ventilation	Increase backup rate Increase backup PIP Optimize caffeine
Edi peaks consistently >20 μV and/or acidosis or hypercapnia	Mostly in NAVA ventilation	Increase NAVA level Decrease apnea time
Edi min >5 μV	FiO_2 high	Increase PEEP by 1cmH_2O

Table 48.5 Weaning NAVA and NIV NAVA in neonates

Presentation	Issue	Solution
Edi peaks <5 μV and/or acceptable pCO2 and pH	Mostly in NAVA	Decrease NAVA level by 0.5cmH_2O/μv until a level of 1 cmH_2O/mcv is reached: If intubated, extubate to NIV NAVA If on NIV NAVA, change to CPAP/HFNC
Edi peaks <5 μV and/or acceptable pCO2 and pH	Mostly in backup ventilation	Decrease NAVA level Decrease backup rate Decrease backup PIP Optimize caffeine
Edi min <2 μV	Low FiO_2	Wean PEEP by 1 cmH_2O
Edi min >5 μV	Clinically stable	No change

E. As long as Edi is present, the neonate will receive CPAP.
F. When the neonate experiences central apnea (no Edi) for a predetermined amount of time (apnea time), backup ventilation is initiated, and the neonate is ventilated with a predetermined PIP and rate until an Edi signal returns.
G. CPAP then resumes if spontaneous breathing is present. This gives the neonate sufficient support during episodes of central apnea to prevent clinical decompensation.

VIII. Clinical Advantages
A. Positioning of Edi catheter
1. The incidence of improper (conventional) feeding tube placement has been reported to be quite high in neonates.
2. Having the center of the array of Edi sensors at the gastroesophageal junction suggests the feeding holes are below the diaphragm, and could offer more certainty about feeding tube placement.
B. Monitoring spontaneous breathing during conventional ventilation
1. In the past, bedside evaluation of respiratory drive was limited to examining waveforms of airway pressure, flow, and volume.
2. Use of these final "pneumatic" waveforms may be misleading during mechanical ventilation, as they are often affected by the disease process in themselves, or because they represent a "mix" of both the patient and the ventilator's activity.

Table 48.6 Troubleshooting NAVA and NIV NAVA in neonates

Presentation	Issue	Solution
Baby retracting and/or Edi peak >20 μV and/or FiO_2 rising	Catheter malpositioned	Reposition catheter position
	Peak pressure limit alarming:	Increase pressure limit
	Needs increased PIP to recruit the lung	Increase NAVA level
	Increased WOB:	
	Insufficient unloading to ventilator	Increase backup pressure
	In backup ventilation often:	
	Insufficient backup support	Intubate and place on invasive NAVA
	Failing noninvasive support at maximum support	
FiO_2 rising and/or desaturations and/or Edi peak <5 μV Undersupported	Catheter malpositioned	Reposition and adjust catheter
	Spontaneous breathing rate is low or periods of apnea	Apnea time set too long
	Trend screen switches to backup often and/or % time in backup high	Increase backup pressure and/or rate
	Failing noninvasive support at maximum support	Needs invasive ventilation
	Low Edi peaks	Decrease NAVA level
Oversupported	Low pCO_2	Decrease backup pressure or rate
	High % of time in backup Edi peak low Spontaneous rate suppressed Edi low or absent excessive chest rise	
Absent Edi signal	Catheter malposition Prolonged apnea Overventilation	Adjust catheter position[a] Treat cause of apnea Decrease backup ventilation
False neural triggering	Non-diaphragm electrical signals trigger the vent	Adjust catheter position[a]

[a]Use the catheter-positioning screen to adjust and confirm catheter placement

3. Use of the Edi allows a more reliable measure of neural respiratory drive, with information about presence (or absence) of diaphragm activity, neural breathing pattern, neural responses to interventions such as changing PEEP, the level of assist, sedation, or other pharmacological treatments.

C. Monitoring patient-ventilator interaction
   1. Another important aspect of Edi monitoring is the ability to detect patient-ventilator asynchrony at the bedside during conventional modes of ventilation.
   2. This is done by comparing the patient waveform (Edi signal) with the ventilator-delivered pressure waveform.
   3. Patient-ventilator interaction is extremely common in infants. Comparing the timings of the two waveforms reveals delayed onset of ventilator breaths, as well as too early or delayed cycling-off of breaths.
   4. "Wasted inspiratory efforts" (most-severe form of asynchrony) occur quite frequently as well, where the patient makes a neural effort to breathe, but the ventilator does not trigger.

D. Insensitivity to leaks
   1. Leaks in the respiratory circuit cause serious problems for controlling the ventilator when pneumatic sensors are used.
   2. Different from the pneumatic sensors, the error measurement induced by a leak cannot influence the Edi. Hence, NAVA can safely deliver synchronized assist regardless of leaks.

E. Improvement of patient-ventilator synchrony
   - NAVA significantly improves patient-ventilator interaction in animals, adults, and children, in terms of the proportionality and timing, and minimizes wasted efforts.

F. Preservation of respiratory drive
   1. One problem with conventional modes of mechanical ventilation is severe suppression of respiratory drive (hyperventilation) due to high levels of assist during mandatory breaths or breaths that are auto-triggered.
   2. Diaphragm inactivity can lead to diaphragm atrophy and/or injury.
   3. During NAVA, such excessive assist delivery cannot totally suppress the Edi.
   4. NAVA has been demonstrated to be diaphragm-protective in animals and adult patients.

G. Prevention of excessive assist delivery
   1. Because of the neural integration of NAVA with the respiratory control system, reflexes (e.g., downregulation of Edi) preventing too large a lung-distending pressure/volume will terminate inspiration, and/or reduce respiratory drive.
   2. In studies where the NAVA level is increased progressively, excessive delivery of ventilator and transpulmonary pressures and tidal volumes are prevented in animals, healthy subjects, and adult and neonatal patients.

H. Response to changes in respiratory demand
   - The Edi responds to changes in respiratory demand induced by load, muscle weakness, and metabolism. Therefore, NAVA instantly adjusts the pressure delivered in response to altered respiratory demand.

IX. Limitations

A. Absence of respiratory drive
   1. NAVA is only applicable in the presence of respiratory drive.
   2. Any disorder and injury that abolishes respiratory drive to the diaphragm would disqualify the use of NAVA.
   3. General anesthesia, sedation, neuromuscular blockers, and other drugs or interventions that inhibit respiratory drive may also interfere with NAVA.

B. Uncontrolled respiratory drive
   1. The neural output to the respiratory muscles may be of extreme magnitude and/or rate as well as erratic and may not respond to the assist delivered by NAVA.
   2. The Edi monitoring will, in combination with tidal volume and respiratory rate, aid to detect such situations.
   3. If combined with high severe airflow limitation, uncontrolled respiratory drive may result in dynamic hyperinflation.
   4. Also, myoclonia (e.g., hiccups), muscle spasticity, and other uncontrolled breathing actions due to neuromuscular disorders may trouble the use of NAVA.
   5. As in all modes of mechanical ventilation, it is important to ensure that upper pressure limits and respiratory rate alarms are set adequately.
   6. Excessive ventilation (e.g., crying).
   7. Very short inspiratory times (e.g., extremely preterm infant) may preclude adequate tidal volume delivery.

C. Too high NAVA level: Too high loop gain results in irregular breathing pattern.

D. Contraindication to naso-/orogastric tube insertion: Although the insertion of nasogastric or orogastric tubes is routine in critically ill patients, in certain patient groups, they may not be recommended, and hence the Edi catheter cannot be used for Edi monitoring or for NAVA.

E. Signal disturbances
   1. The heart and the esophagus also generate electrical signals that can interfere with the diaphragm signal, so-called cross-talk.
   2. Although numerous algorithms are in place to prevent disturbance from adjacent muscles, it is sometimes possible that fractions of an ECG signal leak through into the Edi waveform.
   3. The algorithms used to detect ECG-disturbed signals will intermittently disallow the direct measurement of Edi and output a predicted signal for a brief moment.
   4. Known external sources of electrical noise, e.g., electricity from the mains, cellular phones, etc., do not interfere with the Edi; however, new devices may induce disturbances that need to be identified and managed.

X. Conclusion

A. NAVA is a mode of ventilatory assist for spontaneously breathing patients and uses the electrical activity of the diaphragm (Edi) to trigger, to deliver assist, and to cycle-off the ventilator.

B. Neural triggering and cycling-off improve patient-ventilator synchrony and are unaffected by leaks in the respiratory circuit.

C. Since NAVA is modulated by neural feedback, assist is adjusted instantaneously in response to changes in the patient's respiratory demand. NAVA improves patient-ventilator interaction, and inherently limits peak inspiratory pressures.

D. Even in conventional modes or CPAP, the Edi – which represents the neural output from respiratory centers – can be continuously monitored at the bedside, providing important information about neural breathing pattern, response to therapies, and patient-ventilator interaction.

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.

Dr. Stein and Ms. Firestone are on the speakers' bureau for Getinge and Chiesi.

Suggested Readings

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Servo Ventilator Systems

49

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Servo-u


Servo-n


Servo-i

I. Introduction

A. The Servo-u (universal), Servo-n (neonatal), and Servo-i ventilator systems (Maquet Critical Care AB, Solna, Sweden) have the capability to support ventilation for all patient ranges, age, size, and weight, including very low birth weight infants, while the Servo-n ventilator system covers only neonatal and pediatric patient categories. In addition to multiple conventional

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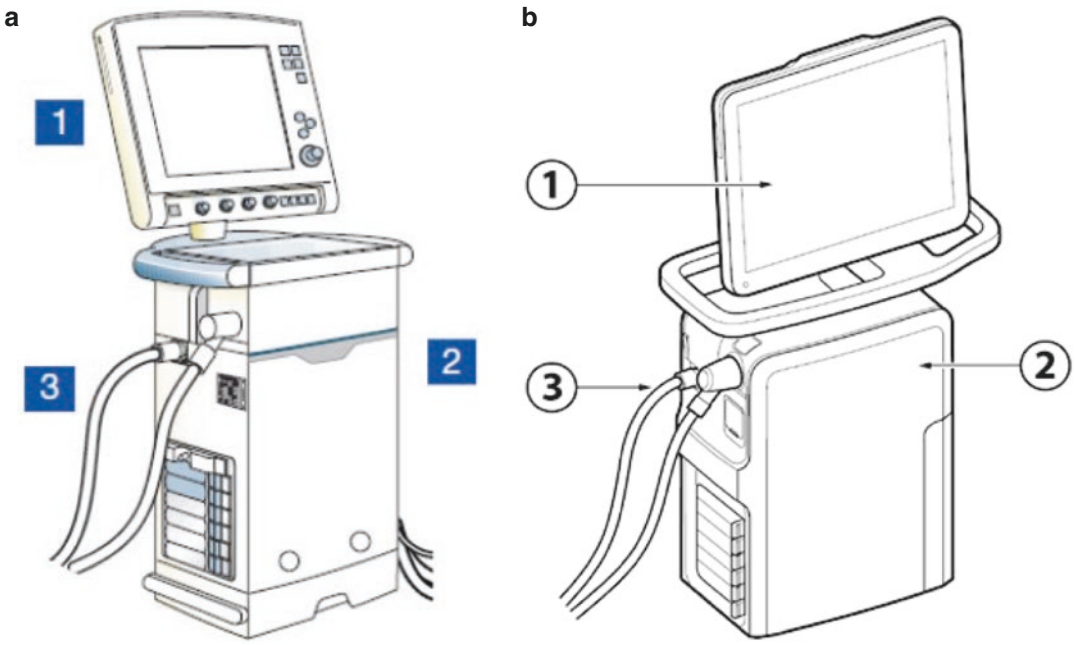


Fig. 49.1 Components of the Servo-i (panel A) and Servo-u/Servo-n (panel B) ventilators. 1, user interface; 2, ventilator unit; 3, patient circuit. (Adapted from Servo-i Ventilator System Service Manual and User's Manual Servo-u Ventilator System v4.1, Getinge)

Table 49.1 Servo-i ventilator systems for patient weight ranges in kilograms

Patient category	Invasive ventilation	NIV (PC)	NIV NAVA	NIV nasal CPAP
Infant	0.5–30 kg	3–30 kg	0.5–30 kg	0.5–10 kg

Adapted from Servo-i Ventilator System Service Manual, Getinge

ventilation modes, Neurally Adjusted Ventilatory Assist (NAVA) is a mode of ventilation available on the Servo-u/Servo-n and Servo-i ventilator systems and will be described in Chap. 48.

B. This chapter will be based primarily on the newer Servo-u/Servo-n ventilator systems and is an update from this publication's previous edition which focused on the Servo-i.

C. The Servo-u/Servo-n and Servo-i ventilator systems consist of the following components (Fig. 49.1):
   1. User interface – for setting ventilation modes and therapies, displaying patient data, and indicating alarms
   2. Patient unit – for mixing gases and controlling gas delivery
   3. Patient circuit – for delivering and exchanging gases

D. The Servo-u/Servo-n and Servo-i ventilator systems can be configured to meet clinician-specific requests on ventilation and monitoring functionality. The available weight ranges based on ventilation modes for specific patient categories are shown in Table 49.1 (Servo-i) and Table 49.2 (Servo-u/Servo-n).

E. Many of the features are specifically designed for neonatal ventilation as shown in Table 49.3.

Table 49.2 Servo-u/Servo-n ventilator systems for patient weight ranges in kilograms

Patient category	Invasive ventilation	NIV	NIV NAVA	NIV nasal CPAP	High-flow therapy
Neonatal	0.3–8 kg	3–8 kg (PC)	0.3–8 kg	0.3–8 kg	0.3–8 kg
Pediatric	3–30 kg	3–15 kg	3–15 kg	3–15 kg	3–15 kg

Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge

Table 49.3 Features specifically designed for neonatal ventilation

Servo-u and Servo-n	Servo-u, Servo-n, and Servo-i
Invasive leakage compensation Automatically adapts to changes in leakage around the endotracheal tube accounting for airway pressures When used in invasive modes, such as PRVC and VS, it ensures volume delivery at the set level Adjustable O_2 boost function Delivers a set oxygen concentration for 1 minute to minimize and optimize oxygen delivery temporarily Inspiratory tidal volume limitation and alarm Optional Y sensor using hot wire technology for proximal flow sensing	Circuit compliance compensation Flow triggering in all modes Apnea alarm delay Apnea support with backup ventilation

PRVC Pressure Regulated Volume Control; *VS* Volume Support
Adapted from Servo-i Ventilator System Service Manual and User's Manual Servo-u Ventilator System v4.1, Getinge

F. The exhalation valve 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.

G. The Servo-u and Servo-n can display the information in several different views, including a family view that can be used during family visits where a comforting image is shown and only the most necessary information and alarms are presented.

H. The Servo-u/Servo-n and Servo-i ventilators have the capability of monitoring the electrical activity of the diaphragm (Edi) in all ventilation modes as well as in standby. The Edi is also used to control the patient's assist during Neurally Adjusted Ventilatory Assist (NAVA) and Noninvasive Neurally Adjusted Ventilatory assist (NIV NAVA). See Chap. 48 for specifics about NAVA.

I. The Servo-u, Servo-n, and Servo-i have the ability for in-hospital transport with minimum 1-hour backup or up to 3 hours with additional batteries. There are MRI conditional versions available for Servo-u and Servo-i which can be used in MR environment:
- With 1.5 T or 3 T MR scanner
- Outside magnetic fields >20 mt (200 Gauss)

II. Modes of Ventilation
- All modes can be patient-triggered.
- The ventilator may be set to flow or pressure trigger in all modes of ventilation. The Edi provides a neural trigger during NAVA and NIV NAVA with flow or pressure triggers providing backup triggers if the Edi catheter is removed or out of position.
- The following ventilation modes and therapies available in the Servo-u, Servo-n, and Servo-i ventilators:

A. *Invasive ventilation* (Fig. 49.2):

1. Controlled modes of ventilation: Patient-triggered breaths have the same characteristics (flow, inspiratory time, volume, or pressure) as the set ventilator breaths.

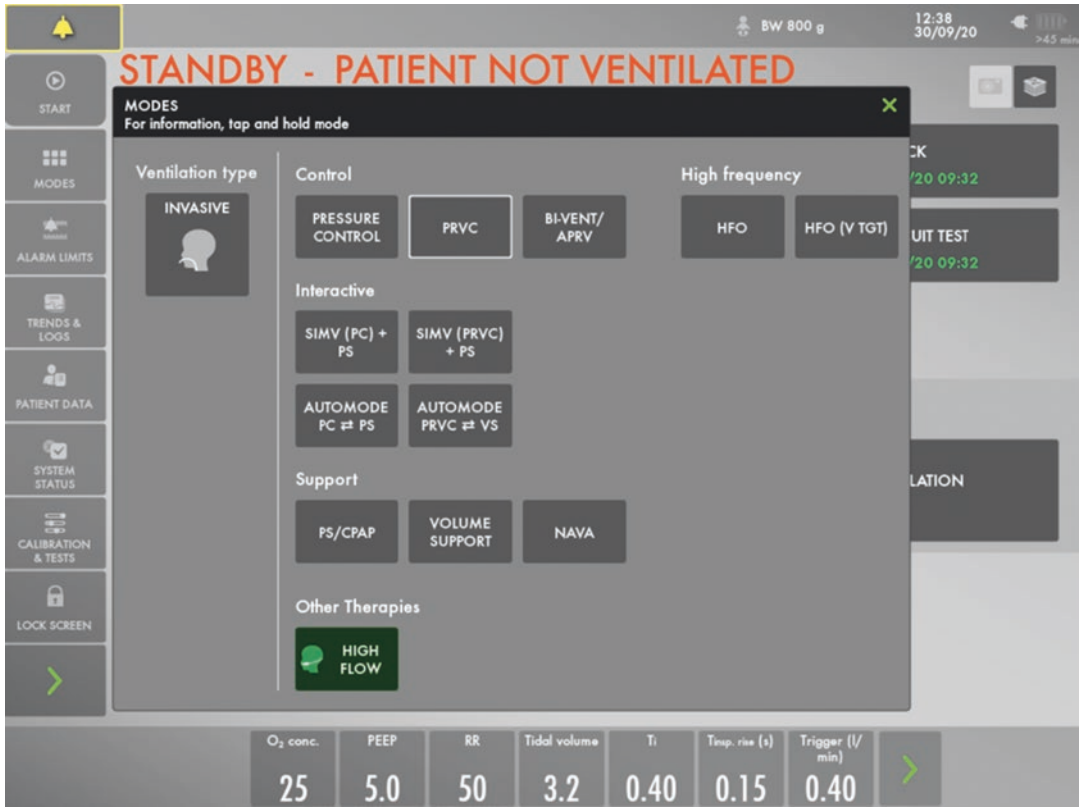


Fig. 49.2 Invasive ventilation modes and therapies available in the Servo-u/Servo-n. High flow is accessible from the invasive ventilation screen to facilitate extubation to high-flow therapy

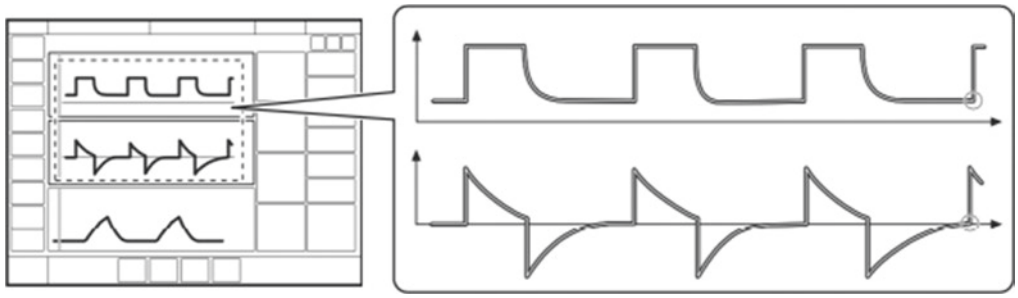
(a) *Pressure Control (PC)*

This mode of ventilation employs a variable flow rate, which is microprocessor-controlled to provide a constant inspiratory pressure:

1. Tidal volume is variable.
2. Peak inspiratory pressure is constant.
3. Square pressure waveform with a decelerating inspiratory flow waveform. The variable flow rate differentiates this from time-cycled, pressure-limited ventilation, which imposes a preset peak inspiratory flow (Fig. 49.3).
4. Clinician set parameters and alarm settings for PC ventilation are shown in Table 49.4.

(b) *Pressure Regulated Volume Control (PRVC)*

1. PRVC combines the advantages of volume control and pressure control by delivering a preset tidal volume with a decelerating inspiratory flow at a preset respiratory rate.
2. PRVC maintains the lowest possible constant pressure throughout inspiration.
3. The patient can trigger additional breaths.
4. The tidal volume can be measured via Y sensor proximal to the patient or via an internal sensor during PRVC and is regulated as described below. For tidal volumes below 10 ml, it is recommended to use a Y sensor to increase the accuracy of gas delivery and monitoring.
5. The first breath is a volume-controlled test breath with the pause time set to 10%. The measured pause pressure of this breath is then used as the pressure level for the following breath (Fig. 49.4).



The circles in the figure indicate patient triggering.

- PC ensures that the preset inspiratory pressure level is constant throughout inspiration. Breaths are delivered in accordance with the preset respiratory rate, inspiration time and inspiratory pressure level, resulting in a decelerating flow.
- The preset pressure level is controlled by the ventilator system. The resulting volume depends on the set pressure level, the inspiration time and the mechanical properties of the patient's lungs during each breath.
- Inspiration starts in accordance with the preset respiratory rate or when the patient triggers.

Expiration starts:

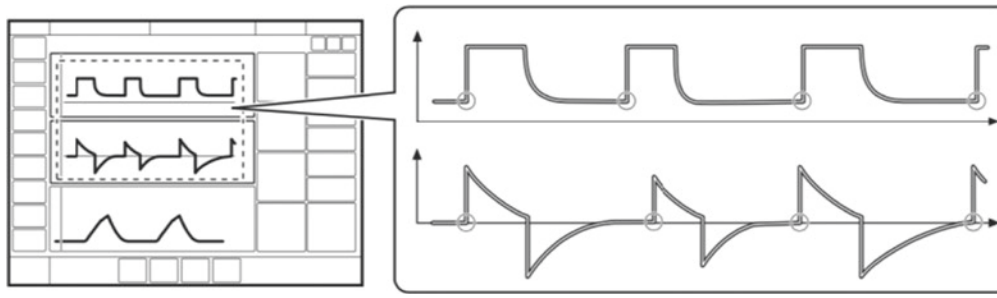
- After the termination of the preset inspiration time.
- If the upper pressure limit is exceeded.

Fig. 49.3 Schematic describing how PC ventilation operates. The top line is inspiratory pressure and second line is flow. (Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge)

Table 49.4 Clinician set parameters and alarm settings for PC ventilation

Clinician set parameters	Clinician set alarm limits
Peak inspiratory pressure level (PC above PEEP)	High and low minute ventilation
I:E ratio or inspiratory time	High pressure
Inspiratory rise time	High and low respiratory rate
Respiratory rate	High and low PEEP
PEEP	
Oxygen concentration	
Trigger level	

6. For the neonatal patient category, when leakage compensation is activated in PRVC, the first breath is a pressure-controlled breath given with 5 cm H_2O above PEEP.
7. Following the initial breath, the ventilator system calculates and continuously regulates the pressure needed to deliver the preset inspiratory tidal volume.
8. The inspiratory pressure level is constant during each breath, but automatically adapts in small increments on a breath-by-breath basis to match the mechanical properties of the patient's lung. The inspiratory tidal volume target is reached while adjusting the inspiratory pressure based on mechanics and efforts of patient.



The circles in the figure indicate patient triggering.

- PRVC ensures a preset tidal volume during a preset inspiratory time at a preset respiratory rate.
- The inspiratory pressure level is constant during each breath, but automatically adapts in small increments on a breath-by-breath basis to match the mechanical properties of the patient's lungs, thus ensuring delivery of the target volume.
- Inspiration starts in accordance with the preset respiratory rate or when the patient triggers.

Expiration starts:

- After the termination of the preset inspiration time.
- If the upper pressure limit is exceeded.

Fig. 49.4 Schematic describing how pressure-regulated volume control ventilation operates. The top line is inspiratory pressure and second line is flow. (Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge)

Table 49.5 Clinician set parameters and alarm settings for PRVC ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%)	High and low minute ventilation
PEEP (cmH_2O)	High pressure
Respiratory rate (b/min)	High and low respiratory rate
Tidal volume (ml) or minute volume (l/min)	High and low PEEP
I:E ratio or inspiratory time (s)	
Inspiratory rise time (% or s)	
Trigger level	

9. Inspiration starts in accordance with the preset respiratory rate or when the patient triggers.
10. Expiration starts after the termination of the preset inspiration time or if the upper pressure limit is exceeded.
11. An alarm is activated if the set target volume cannot be delivered due to the fact that the pressure required to deliver it is higher than 5 cm H_2O below the set upper pressure limit.
12. Clinician set parameters and alarm settings for PRVC ventilation are shown in Table 49.5.

(c) *Volume Control (VC)* (only available in the neonatal patient category for Servo-i):
1. VC delivers a preset inspiratory tidal or minute volume over a preset inspiratory time and at a preset respiratory rate, regardless of changes in lung or thorax resistance or compliance.
2. Maintains a set flow with varying peak pressure.
3. Delivers a square flow waveform.
4. Clinician set parameters and alarm settings for VC ventilation are shown Table 49.6.

(d) *Bi-Vent*
1. Bi-Vent is a time-cycled, pressure-limited mode that allows spontaneous breathing throughout the entire ventilatory cycle.
2. Bi-Vent has two time-cycled pressure levels and switches between these two levels. The patient can breathe spontaneously at both these levels, and it is possible to give pressure support at both levels.

(e) APRV – Airway Pressure Release Ventilation
1. APRV is time-cycled, pressure-limited that allows spontaneous breathing throughout the entire ventilatory cycle.
2. Alternates between two levels of positive airway pressure, with the main time on the high level and a brief expiratory release to facilitate ventilation (Fig. 49.5).

Table 49.6 Clinician set parameters and alarm settings for VC ventilation

Clinician set parameters	Clinician set alarm limits
Tidal volume or minute volume I:E ratio or inspiratory time (controls flow rate) Pause time (optionally added to inspiratory time to help increase mean airway pressure, does not affect flow rate) Inspiratory rise time Respiratory rate PEEP Oxygen concentration Trigger level	High and low minute ventilation High pressure High and low respiratory rate High and low PEEP

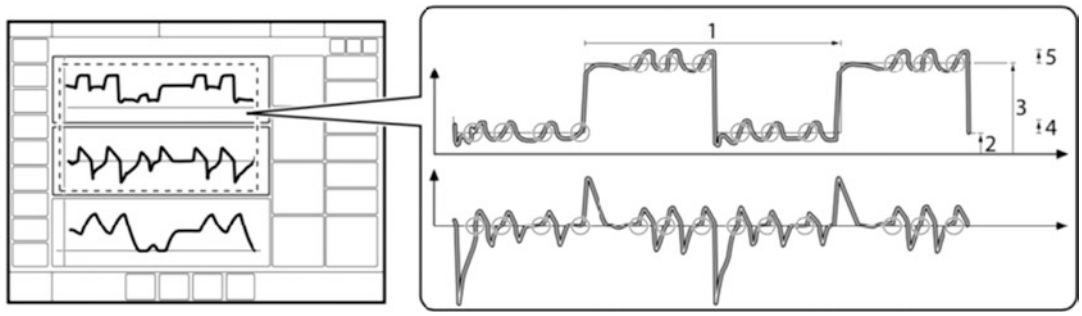


Fig. 49.5 Schematic describing how Bi-Vent/APRV operates. The circles in the figure indicate patient triggering. 1, Bi-Vent/APRV cycle = T_{high} + T_{PEEP}; 2, PEEP; 3, P_{high}; 4, PS above PEEP; 5, PS above P_{high}. The top line is inspiratory pressure and second line is flow. (Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge)

3. APRV differs from Bi-Vent in that it uses an inverse I:E ratio.
4. Clinician set parameters and alarm settings for Bi-Vent/APRV are shown in Table 49.7.

2. *Interactive modes*

For spontaneously breathing patients (where ventilator breaths are patient initiated). All the above modes are also offered in combination with spontaneous-triggered breaths. This provides the clinician the ability to support ventilator-delivered breaths and spontaneously triggered breaths with different parameters:

(a) *SIMV Pressure Control with Pressure Support (PC + PS):*
   1. Delivers mandatory controlled breaths using a preset respiratory rate and a preset pressure.
   2. Delivers PS during spontaneous breaths taken between the mandatory breaths (Fig. 49.6).
   3. Clinician set parameters and alarm settings for SIMV (PC) with PS ventilation are shown in Table 49.8.

(b) *SIMV with PRVC (PRVC + PS):*
   1. Delivers mandatory controlled breaths using a preset respiratory rate and a preset volume.
   2. Delivers PS during spontaneous breaths taken between the mandatory breaths (Fig. 49.7).

Table 49.7 Clinician set parameters and alarm settings for Bi-Vent/APRV

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%)	High and low minute ventilation
Pressure at the lower pressure level (PEEP)	High pressure
Pressure at the higher pressure level (P_{high}) (cmH_2O)	High and low respiratory rate
Time at the higher pressure level (T_{high}) (s)	High and low PEEP
Time at the lower pressure level (T_{PEEP}) (s)	
Inspiratory rise time (s)	
Trigger	
PS above PEEP (cmH_2O)	
PS above P_{high} (cmH_2O)	
End inspiration (%)	

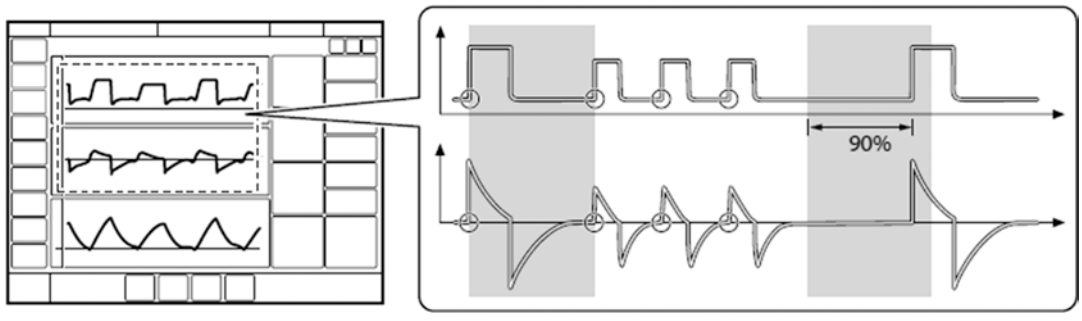


Fig. 49.6 Schematic describing how SIMV (PC) with PS operates. The circles in the figure indicate patient triggering. The top line is inspiratory pressure and second line is flow. (Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge)

Table 49.8 Clinician set parameters and alarm settings for SIMV (PC) with PS ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%)	High and low minute ventilation
PEEP	High pressure
PC above PEEP (cmH_2O)	High and low respiratory rate
PS above PEEP (cmH_2O	High and low PEEP
SIMV rate	
I:E ratio/inspiratory time (s)	
Inspiratory rise time (s)	

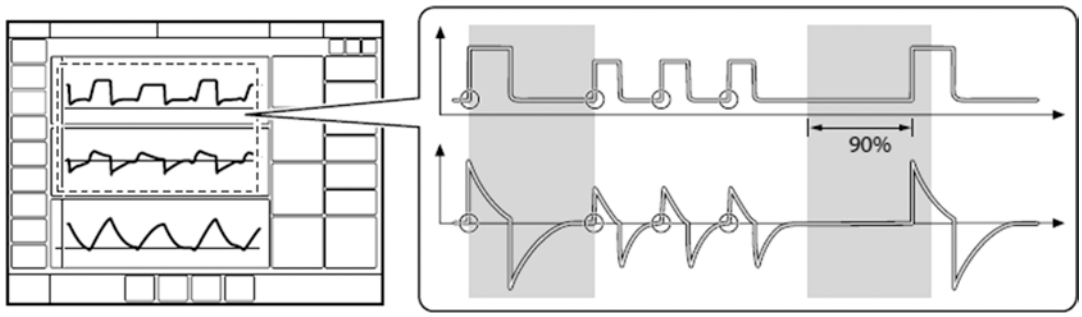


Fig. 49.7 Schematic describing how SIMV (PRVC) with PS operates. The circles in the figure indicate patient triggering. The top line is inspiratory pressure and second line is flow. (Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge)

Table 49.9 Clinician set parameters and alarm settings for SIMV (PRVC) with PS ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%)	High and low minute ventilation
PEEP	High pressure
Tidal volume/minute volume	High and low respiratory rate
PS above PEEP (cmH_2O)	High and low PEEP
SIMV rate	
I:E ratio/inspiratory time (s)	
Inspiratory rise time (s)	

3. Clinician set parameters and alarm settings for SIMV (PRVC) with PS ventilation are shown in Table 49.9.

(c) *Automode Pressure Control changes to Pressure Support (automode PC ⇄ PS):*

1. Automode is an interactive mode automatically switching between PC and PS based on patient triggering.
2. Automode delivers Pressure-Controlled breaths in the absence of patient breathing effort, switching to Pressure-Supported breaths when a breathing effort is detected (Fig. 49.8).
3. Serves as an aid when initiating the weaning period and adapts to the patient's breathing capacity.
4. Clinician set parameters and alarm settings for automode PC ⇄ PS ventilation are shown in Table 49.10.

(d) *Automode PRVC changes to volume support (automode PRVC ⇄ VS):*

1. Automode is an interactive mode automatically switching between PRVC and VS based on patient triggering.

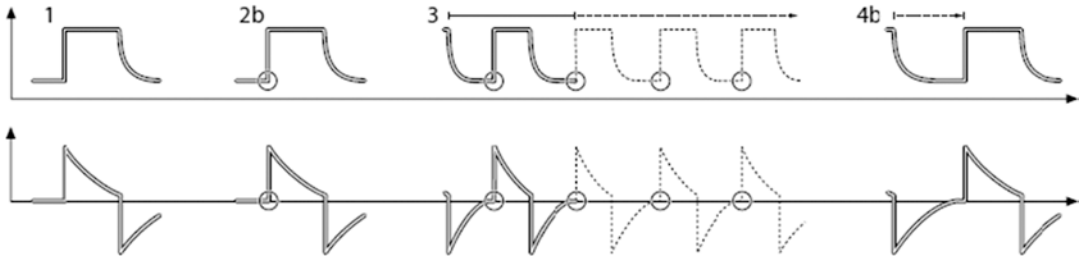


Fig. 49.8 Schematic describing how automode PC ⇄ PS operates. The top line is inspiratory pressure and second line is flow. The circles in the figure indicate patient triggering. 1, system starts in PC; 2b, PS (if breathing spontaneously); 3, for the spontaneously triggering patient, the apnea time increases successively until the level set in the settings window for the maximal apnea time parameter is reached after ten consecutive spontaneously triggered breaths; 4b, if the maximal apnea time is exceeded, a PC breath is delivered. (Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge)

Table 49.10 Clinician set parameters and alarm settings for automode PC ⇄ PS ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%)	High and low minute ventilation
PEEP (cmH_2O)	High pressure
Respiratory rate	High and low respiratory rate
Tidal volume	High and low PEEP
End inspiration (%)	
Inspiratory rise time (s)	
Trigger	
Apnea time (s)	
Inspiratory time (s)	

2. Automode delivers PRVC breaths in the absence of patient breathing effort, switching to VS breaths when a breathing effort is detected (Fig. 49.9).
3. Serves as an aid to starting the weaning period and adapts to the patient's breathing capacity.
4. Clinician set parameters and alarm settings for automode PRVC ⇄ VS ventilation are shown in Table 49.11.

3. *Support modes*
   (a) *PS/CPAP (Pressure Support/CPAP)*
      1. *Pressure support (PS)*
         (a) PS is initiated by the patient, who controls the respiratory rate and tidal volume.
         (b) Provides backup (PC) ventilation in the event of apnea and this apnea time can be set by the clinician. The ventilator will revert to the spontaneous mode once respiratory effort is sensed by the ventilator.
         (c) This mode functions similarly to automode PC ⇄ PS and can be used if automode is not included in the software package.
      2. *Continuous positive airway pressure (CPAP)*
         (a) CPAP when intubated may be seen as a special case of PS in which the inspiratory pressure level is set to zero and is used when the patient is breathing spontaneously.
         (b) CPAP maintains positive pressure in the airways at all times.
         (c) Clinician set parameters and alarm settings for PS/WCPAP invasive ventilation are shown in Table 49.12.

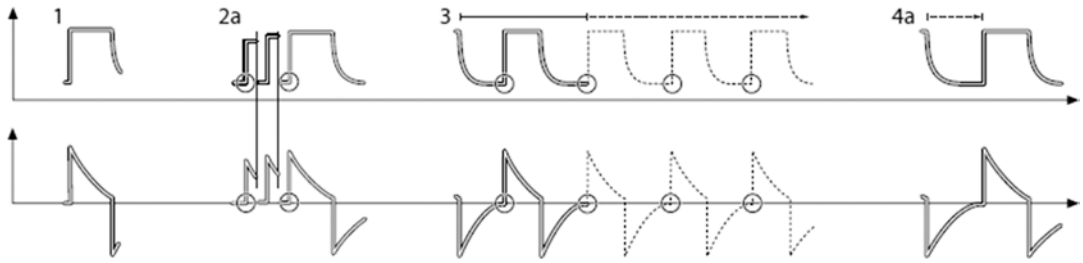


Fig. 49.9 Schematic describing how automode PRVC ⇄ VS operates. The top line is inspiratory pressure and second line is flow. The circles in the figure indicate patient triggering. 1, system starts in PRVC; 2b, VS (if breathing spontaneously); 3, for the spontaneously triggering patient, the apnea time increases successively until the level set in the settings window for the maximal apnea time parameter is reached after ten consecutive spontaneously triggered breaths; 4b, if the maximal apnea time is exceeded, a PRVC breath is delivered. (Adapted from User's Manual Servo-u Ventilator System v4.1, Getinge)

Table 49.11 Clinician set parameters and alarm settings for automode PRVC ⇄ VS ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%)	High and low minute ventilation
PEEP (cmH_2O)	High pressure
Respiratory rate	High and low respiratory rate
Tidal volume	High and low PEEP
End inspiration (%)	
Inspiratory rise time (s)	
Trigger	
Apnea time (s)	
Inspiratory time (s)	

Table 49.12 Clinician set parameters and alarm settings for CPAP invasive ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%)	High and low minute ventilation
PEEP (cmH_2O)	High pressure
PS above PEEP (cmH_2O) (PS level)	High and low respiratory rate
End inspiration (%)	High and low PEEP
Inspiratory rise time (s)	
Trigger	
Apnea time (s)	
Backup respiratory rate (b/min)	
Backup PC above PEEP (cmH_2O)	
Backup I:E or Ti (s)	

(b) *Volume support (*VS*)*

1. VS is initiated by the patient.
2. 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:
   (i) Inspiratory tidal volume is set; inspiratory pressure is automatically adjusted.
3. Backup ventilation (PRVC) is set so that if a patient becomes apneic, based on an apnea time set by the clinician, the ventilator will alarm and changeover to configurable backup ventilation settings that are predetermined by the clinician. The apnea time determines the minimum ventilatory rate and is different from the predetermined

backup rate (see Chap. 48 on NAVA, section on apnea time for further details). The ventilator will revert to the spontaneous mode once respiratory effort is sensed by the ventilator.

4. This mode functions similarly to automode PRVC ⇄ VS and can be used if automode is not included in the software package.

(c) *Neurally Adjusted Ventilatory Assist (NAVA) (see* Chap. 48*)*

1. NAVA is a supported mode of ventilation based on the electrical activity of the diaphragm (Edi).
2. The ventilation is controlled by the patient via the Edi and delivers assist in proportion to and synchronized with patient breathing efforts.
3. This allows the patient to control their own tidal volume, peak inspiratory pressure, inspiratory time, and respiratory rate.
4. Backup ventilation is provided (PC) in case of apnea or dislodgment of the Edi catheter.
5. Edi monitoring is available in all ventilatory modes to evaluate synchrony.

4. *High Frequency Oscillatory Ventilation (HFOV)*

(a) High Frequency Oscillatory Ventilation (HFOV) is available only in Servo-n ventilator systems and solely for neonatal patients. It is not available in the USA as of 2020.

(b) HFOV i*m*plies:

1. Ventilation with frequencies in the range 5–20 Hz.
2. Oscillating volumes (tidal volume) are ideally 1–3 ml/kg.

(c) The oscillation is generated by high flow to a well-synchronized, rapid valve that creates oscillation in a rigid, bigger diameter HFOV circuit.

(d) High frequency can be delivered by either a pressure control strategy (HFO) High Frequency Oscillation or a volume target strategy (HFO (V TGT)) High Frequency Volume Target Ventilation, resulting in two HFOV modes:

1. HFO (Fig. 49.10) delivers:
   (a) Pressure signal with a mean airway pressure of P_{mean} at the Y piece
   (b) Peak-to-peak amplitude of P_{ampl} at the inspiratory outlet
   (c) A ratio between inspiratory and expiratory flow durations of $I{:}E_{HF}$
   (d) Oscillation frequency of f (Hz), i.e., with a cycle duration of 1/f (s)
2. HFO (V TGT) (Fig. 49.11) delivers:
   (a) Adjusts the pressure amplitude to achieve the set tidal volume target (VT_{HF}) at the Y piece.
   (b) The CO_2 diffusion coefficient or DCO_2 is calculated as $f * VT_{HF}^2$, and it is proportional to ventilation or CO_2 washout during HFO ventilation.
   (c) The DCO_2 value requires Y sensor volume measurements at the Y piece.
3. Clinician set parameters and alarm settings for HFO and HFO (V TGT) ventilation are shown in Table 49.13.

B. *Noninvasive ventilation (NIV)* (Fig. 49.12)

1. *NIV Pressure Control (NIV PC)*

NIV PC is a noninvasive ventilator mode that delivers a constant pressure with a preset inspiratory time and respiratory rate. It delivers the inspiration with a decelerating flow. It is leak compensated using an algorithm designed for neonates to compensate for leaks around the noninvasive interface and deliver the set inspiratory pressure. Clinician set parameters and alarm settings for NIV pressure control ventilation are shown in Table 49.14.

Fig. 49.10 HFO mode in the Servo-n

2. *Nasal CPAP*

   Nasal CPAP is a noninvasive, spontaneous breathing mode of ventilation. It maintains a set continuous positive airway pressure via a noninvasive nasal patient interface. It delivers the flow necessary to maintain the set pressure. It is leak compensated. The patient interface must be the appropriate size and correctly applied in order to avoid excessive leakage. Clinician set parameters and alarm settings for nasal CPAP are shown in Table 49.15.
3. *High Flow Therapy*
   (a) High flow therapy delivers a set flow of h*eated and humidified gas with a set* concentration of oxygen to the patient.
   (b) It can be initiated while on invasive and noninvasive ventilation as well as in standby.
   (c) It can be started manually when the noninvasive interface is set and connected to the patient.
   (d) The patient must be breathing spontaneously.
   (e) Edi monitoring is available during high-flow therapy.
   (f) Table 49.16 shows the clinician set parameters and alarm settings for high-flow therapy.
4. *NIV NAVA (see* Chap. 48*)*
   (a) NIV NAVA is a supported mode of ventilation based on the electrical activity of the diaphragm (Edi).
   (b) The ventilation is controlled by the patient via the Edi and delivers assist in proportion to and synchronized with patient breathing efforts.

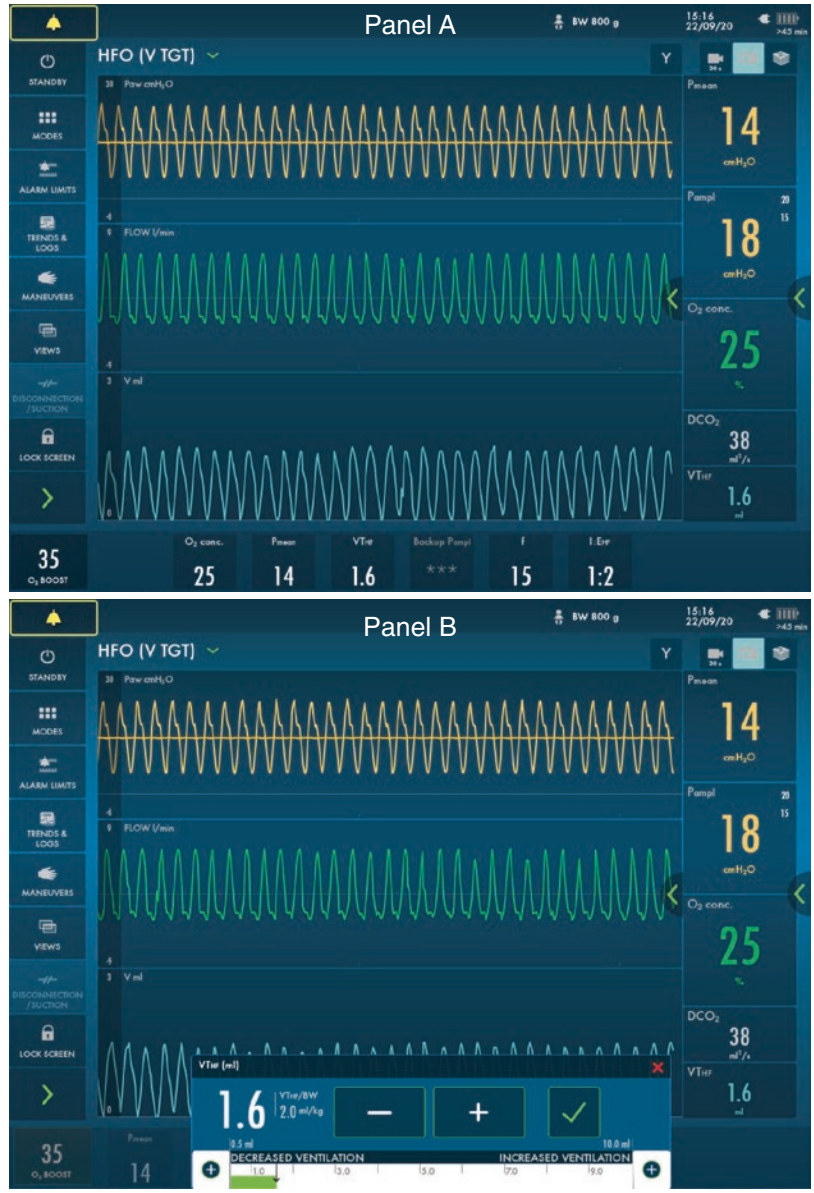


Fig. 49.11 HFO (V TGT) mode in the Servo-n. Panel A shows the waveforms, and panel B shows how the tidal volume can be adjusted and is shown in both ml and ml/kg

Table 49.13 Clinician set parameters and alarm settings for HFO and HFO (V TGT) ventilation (VTHF – high-frequency tidal volume)

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%) Mean airway pressure (cmH_2O) Pressure amplitude (cmH_2O) - (HFO) Frequency, f (Hz) High-frequency tidal volume, VTHF (ml) – only during V TGT High-frequency I:E ratio	Pressure amplitude High-frequency tidal volume

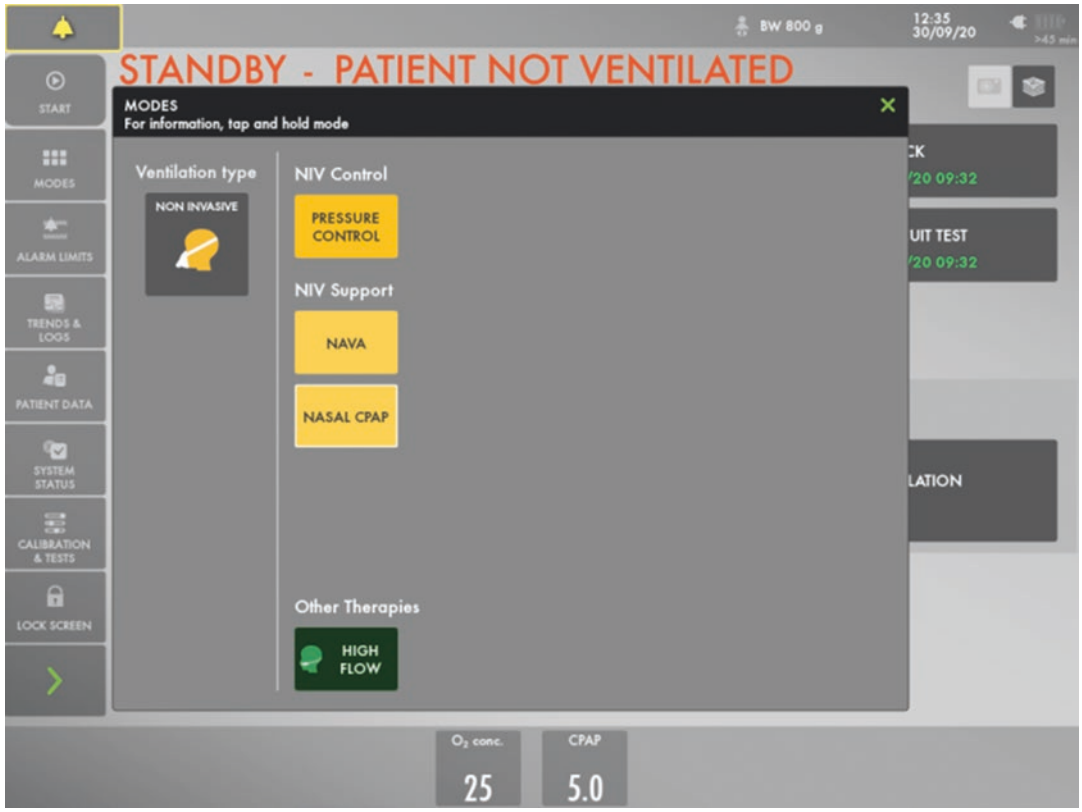


Fig. 49.12 Noninvasive ventilation modes and therapies available in the Servo-u and Servo-n

Table 49.14 Clinician set parameters and alarm settings for NIV pressure control ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%) PEEP (cmH_2O) Respiratory rate (b/min) PC above PEEP (cmH_2O) I:E ratio or inspiratory time (s) Inspiratory rise time (% or s)	High and low minute ventilation High pressure High and low respiratory rate

Table 49.15 Clinician set parameters and alarm settings for NIV CPAP ventilation

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%) CPAP (cmH_2O)	High pressure High and low respiratory rate High and low CPAP

Table 49.16 Clinician set parameters and alarm settings for high-flow therapy

Clinician set parameters	Clinician set alarm limits
Oxygen concentration (%) Flow	None

Table 49.17 General specifications for Servo-u and Servo-n ventilator systems for the neonatal and pediatric patient category, and for Servo-i ventilator systems for the infant patient category

General specifications	Servo-i	Servo-u/Servo-n
Level of continuous flow for flow and/or pressure triggering	0.5 L/min	0.5 L/min
Maximum inspiratory peak flow	33 L/min	33 L/min
Tidal volume range	2–350 mL	2–350 mL
Apnea alarm/backup ventilation ranges	2–45 sec	1–45 sec

Adapted from Maquet Servo-u/n and Servo-i Service Manuals, Getinge

(c) This allows the patient to control their own tidal volume, peak inspiratory pressure, inspiratory time, and respiratory rate.
(d) Backup ventilation is provided (PC) in case of apnea or dislodgment of the Edi catheter.
(e) Edi monitoring is available in all ventilatory modes to evaluate synchrony.

III. Additional Features

Table 49.17 shows the general specifications for Servo ventilator systems for the neonatal patient:

A. CO_2 monitor. The Servo-i and the Servo-u/n are equipped with a port to monitor end-tidal CO_2 ($ETCO_2$), VCO_2, and $VtCO_2$ using the Capnostat $ETCO_2$ sensor.
B. Nebulizer. There are two choices: Aerogen Solo and Aerogon Pro. With either system, the nebulizer software has an automatic shutoff, which may be set to run for a maximum of 30 minutes in 5-minute intervals, but with the Aerogen, there is a continuous nebulization option as well.
C. Trend monitoring. The user interface has a comprehensive trend monitoring with information stored for 24 hours with a time resolution of 1, 3, 6, 12, 24, and 72 (Servo-u/Servo-n only) hours. Data can be downloaded:
   1. Measured parameters (listed above)
   2. Ventilator changes
   3. Event log
D. 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 seconds. If the patient is reconnected to the ventilator prior to 60 seconds, the ventilator resumes ventilation. It will stay at selected FiO_2 until changed or ventilator rebooted.
E. 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 and appropriate software. The Edi catheter serves also as a feeding tube, and is available in sizes 6F and 8F for infant patients. (Note: catheter must be exchanged every 5 days per the FDA.) The Edi catheter is not compatible with MRI.
F. HeO_2 heliox. A heliox-enabled 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:
   1. Helium/oxygen mixture 80:20
   2. Helium/oxygen mixture 79:21
   3. Helium/oxygen mixture 78:21

G. MR conditional option. The MR Servo-i is conditionally approved for use in the MR suite with open scanners up to 10 mt (100 Gauss) and 20 mt (200 Gauss) tunnel scanners. The allowable field strength of the scanner for the MR conditional option is 1.0 T, 1.5 T, and 3.0 T.
H. 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.
I. 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. This is available in the pediatric and adult mode and not available in the neonatal mode. 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)

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COI

Kim Firestone and Howard Stein are on the Speakers Bureau for Getinge
Miray Kärnekull and Edita Almonte are employees of Getinge

Suggested Readings

Beck J, Fuentes L, McDonald H. Servo-i Ventilator and NAVA, Chapter 50. In: Donn SM, Sinah SK, editors. Manual of neonatal respiratory care. 4th ed. Springer, ISBN 978-3-319-39839-6; 2017.

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

User's Manual Servo-i https://www.getinge.com/dam/hospital/documents/user-manuals/english/servoi_operman_6883284_r01_v7dot1_141118-en-non_us.pdf

User's Manual, Servo-u/Servo-n Ventilator System v4.1, Getinge.

SLE6000/5000/4000 Infant Ventilators

50

David G. Tingay, Barbara Pilgrim, and Peter Dargaville

I. Introduction
   A. The SLE6000 is a combined noninvasive (including nasal high-flow cannula), conventional and high-frequency oscillation ventilator with respiratory monitoring capabilities, volume targeting in conventional and high-frequency modes, and closed loop oxygen targeting.
   B. The SLE5000 is a combined conventional and high-frequency oscillatory ventilation (HFOV) with respiratory monitoring capabilities.
   C. The SLE4000 is a dedicated conventional ventilator with respiratory monitoring.
   D. The SLE6000 was released in 2016 to supersede the SLE5000/4000 and varies significantly from previous models with regard to the inclusion of noninvasive ventilation modes, automated oxygen and other feedback systems, and newer HFOV options.

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
   E. Volume-targeted ventilation (VTV) during conventional modes (SLE4000/5000)
   F. Volume-targeted ventilation (VTV) during conventional and HFOV modes (SLE6000)
   G. Closed loop oxygen titration (SLE6000 only)
   H. Dual- and single-limb triggered and untriggered noninvasive ventilation options including high-flow nasal cannulas with automatic flow compensation of leak (SLE6000 only)

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S. M. Donn et al. (eds.), *Manual of Neonatal Respiratory Care*,
https://doi.org/10.1007/978-3-030-93997-7_50

III. Ventilation Modalities
  A. Continuous positive airway pressure (dual and single limb).
  B. High-flow nasal cannulas compatible with all commonly available nasal interfaces (SLE6000 only).
  C. Bilevel noninvasive positive pressure ventilation (triggered and untriggered): dual-limb options NIPPV and NIPPVtr; single-limb option DuoPAP.
  D. Nasal HFOV (SLE6000 only).
  E. Continuous mandatory ventilation (CMV).
  F. Patient-triggered ventilation (PTV).
  G. Pressure support ventilation (PSV).
  H. Synchronized intermittent mandatory ventilation (SIMV) +/− pressure support.
  I. Targeted tidal volume (TTV/VTV) on all conventional modalities (all models) and HFOV (SLE6000).
  J. High-frequency oscillatory ventilation (HFOV).
  K. High-frequency oscillatory ventilation combined with CMV.
  L. The SLE5000 can support high-frequency jet ventilation with the Bunnell Life Pulse jet ventilator.

IV. Design Details and Principles of Operation
  A. The SLE infant ventilators consist 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 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 failure. If the main power fails with the battery fully charged, then operation will continue for approximately 60 minutes depending upon ventilation mode.
  C. Pneumatic system
    1. The pneumatic system is comprised of the tubing and electromechanical valves necessary to provide the gas in conventional and oscillatory ventilation modalities.
    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 second and air at the same flow rate for 2 seconds will result in a mixture of 1 part oxygen to 2 parts of 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 setup, 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).
   3. These three jets are used in various combinations to generate all ventilation modes.

5. Conventional ventilation (all SLE models):
   (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 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 modes.
   (d) The rise time of the inspiratory phase is regulated 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 baseline 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 peak pressure.

6. HFO ventilation. The SLE5000 and SLE6000 ventilators are capable of functioning as dedicated HFOV devices with active exhalation:
   (a) In pure HFOV, the mean jet pressure regulator is used to set the mean pressure (relative to atmospheric pressure).
   (b) The generated HFOV waveform is a square wave with complex harmonics.
   (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 HFOV 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 pres-

sure 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 HFOV 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 HFOV 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 patient-triggered ventilation (PTV) 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 form of triggering.
   (b) Flow triggering. This mechanism requires the use of a flow sensor. The SLE5000/4000/6000 uses the same heated-wire anemometer, which is calibrated at setup. The sensitivity is adjustable between 0.2 and 20.0 LPM (0.2 LPM resolution). 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 waveforms 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 SLE5000/6000 displays pressure in mbar; practically this is the same as cmH_2O (1 cmH_2O = 0.98 mbar). The display format differs between SLE models and is configurable by the user.
10. The SLE5000 and 6000 have the capability to connect with the external monitoring systems via the Philips VueLink and IntelliBridge modules. All SLE ventilators allow minutely data output (HP7 compliant).
11. 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) For the SLE4000/5000 ventilators, 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) For the SLE6000 ventilator, the pressure rise time is set in seconds (range 0.0–3.0 s) and is available through additional settings options in the main LCD display. A shorter rise time creates a more square-like pressure waveform.
(d) Targeted tidal volume (termed TTV on SLE4000/5000 and VTV SLE6000) 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.
(e) Pressure support ventilation with flow cycling has automatic compensation in the presence of a leak, thereby ensuring that all breaths are flow triggered and flow-terminated.
(f) Complete respiratory monitoring with measurements of C20/C and DCO_2 (gas transport coefficient for carbon dioxide) and loops and waveforms.
(g) Ability to trend all measured parameters for 24 h (SLE5000/4000) or 14 days (SLE6000).
(h) Ability to take a snapshot of a loop, save it, and compare future loops with this reference loop to observe changes in compliance.
(i) 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.

12. Advanced modes of ventilation
(a) Patient-triggered ventilation (PTV) 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 20.0 LPM. The user selects PEEP, PIP, T_i, 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 T_i and flow termination sensitivity.
    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 T_i) and 20 spontaneous inflations in PSV mode (flow-cycled with T_i set by infant).
    3. Unlike PSV used in isolation, in SIMV+PSV mode, the pressure support level for spontaneous breaths above the mandatory rate is set independently from the PIP for mandatory breaths. This mode is often used if prolonged weaning is anticipated.
(c) Targeted tidal volume plus (TTV/VTV)
    1. TTV/VTV 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 manner, 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. SLE6000/5000/4000 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%. (4) The TTV/VTV algorithm determines the required PIP from the measured expiratory tidal volume.
4. To avoid excessive volume delivery due to active spontaneous breathing, the TTV/VTV algorithm will terminate PIP if 130% of set tidal volume is measured at any time during a supported inflation.

(d) High-frequency oscillatory ventilation:

1. The delivery of pressures in HFOV in the SLE6000/5000 is different from that of the superseded SLE2000.
2. It is derived from the fast switching of the high-speed solenoid valves.
3. The user manual states the SLE6000/5000 is able to oscillate infants up to 30 kg with a maximum mean airway pressure of 45 mbar.
4. Inspiratory to expiratory ratios of 1:1, 1:2, and 1:3 are available.
5. Frequency is set directly (3–20 Hz).
6. 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 continuous CO_2 monitoring.
7. The use of the flow sensor allows accurate measurements of end tidal volumes and minute volumes.
8. There is also the option of viewing a flow-volume loop.
9. The SLE6000 has the option of expiratory tidal volume VTV. In HFV+ VTV the intended tidal volume is set by the user (range 2–50 mL in 0.2 mL increments to 10 mL and then 1 mL above 10 mL). In addition, a maximum permissible pressure amplitude is also set. The SLE6000 ventilator will then adapt the pressure amplitude to maintain the set VTV volume target using an algorithm of coarse and fine adjustments over 3–4 inflations. Note that HFV+ VTV is not the same as VTV during conventional ventilation due to the dependence of tidal volume on pressure amplitude, I:E ratio, and frequency.
10. The SLE5000/6000 has the option of HFOV combined with CMV. In this mode the user sets CMV parameters (PIP, PEEP, T_i, and rate) and can also superimpose a 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.

13. Closed loop oxygen control (OxyGenie; SLE6000 only)

(a) The SLE6000 ventilator contains the OxyGenie module that allows automated control of inspired oxygen delivery to maintain SpO_2 within a predefined SpO_2 range.

(b) The OxyGenie module controls oxygen delivery using the VDL1.1 proportional-integral-derivative (PID) algorithm, receiving SpO_2 input from a sensor, and computing an updated value for set FiO_2, which is then automatically actuated via the air-oxygen blending system.

(c) SpO_2 is measured directly within the ventilator using a Massimo SET pulse oximeter and compatible SET sensor. A "signal intelligence quotient" (SIQ) is also determined as a measure of the fidelity of the SpO_2 signal.

(d) Beyond the second-by-second calculation of set FiO_2, the OxyGenie module periodically updates an indicator of basal oxygen requirement over the previous hour known as "reference O_2," upon which some of the adaptive function of the control algorithm is based. Set FiO_2 can deviate by no more than ±40% from the reference O_2 value. The algorithm defaults to a "fallback" mode when SpO_2 signal is low or missing, holding FiO_2 steady for up to 60 seconds and then using a slower adjustment algorithm until adequate SpO_2 signal returns. Manual override of closed loop control is possible via simply making manual FiO_2 adjustments in the usual way. Closed loop control will automatically reactivate after 30 seconds unless further manual adjustments are made.

(e) SpO_2 and FiO_2 trends along with plethysmography wave, heart rate, reference O_2, and SIQ are displayed in a dedicated configurable graphic user interface accessed via the main display.

(f) When the OxyGenie module is activated, the user sets the intended SpO_2 target range.

(g) When the OxyGenie is active, the oxygen setting displays "Auto" beneath the delivered oxygen concentration display, as well as an additional status display.

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Suggested Readings

Farrell O, Perkins EJ, Black D, et al. Volume guaranteed? Accuracy of a volume-targeted ventilation mode in infants. Arch Dis Child Fetal Neonatal Ed. 2018;103(2):F120–F25. https://doi.org/10.1136/archdischild-2017-312640. [published Online First: 2017/07/01]

Salverda HH, Cramer SJE, Witlox RSGM, et al. Automated oxygen control in preterm infants, how does it work and what to expect: a narrative review. Arch Dis Child Fetal Neonatal Ed Published Online First: 30 July 2020. https://doi.org/10.1136/archdischild-2020-318918.

SLE6000/5000/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

51

Helmut D. Hummler and Christian F. Poets

Stephanie Ventilator

I. Introduction. The Stephanie ventilator (Fig. 51.1; Fritz Stephan GmbH, Gackenbach, Germany) was designed as a device for newborn and pediatric patients up to 25 kg body weight. This review will focus only on the use in the neonatal population. All specifications given in this chapter are based on the latest edition (manual 11/2018, Version V4.1a).

A new version of the Stephanie ventilator will be released by the manufacturer soon. This device will be designed for the respiratory support of the complete range of newborn, pediatric, and adult patients up to 200 kg body weight. It is designed for invasive and non-invasive ventilation and will provide the full range of ventilator modes (including PAV and HFO), including an integrated humidification system, non-invasive synchronization, several back-up features, various methods of flow measurements, a dead space free flow sensor system, an automated SpO_2 controller, a 15″ color touch screen, and an expiration valve with an integrated HEPA filter.

II. Description. The Stephanie ventilator (Figs. 51.1 and 51.2) can provide non-invasive and invasive volume- and pressure-controlled ventilation, proportional assist ventilation (PAV), and high-frequency oscillatory ventilation (HFOV) as well as some pulmonary function diagnostic techniques.

A. A proximal flow sensor (pneumotachograph) can be used to detect patient efforts 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 pressure-triggered ventilation (drop in airway pressure induced by patient effort) or with an external pressure capsule placed on the abdomen.

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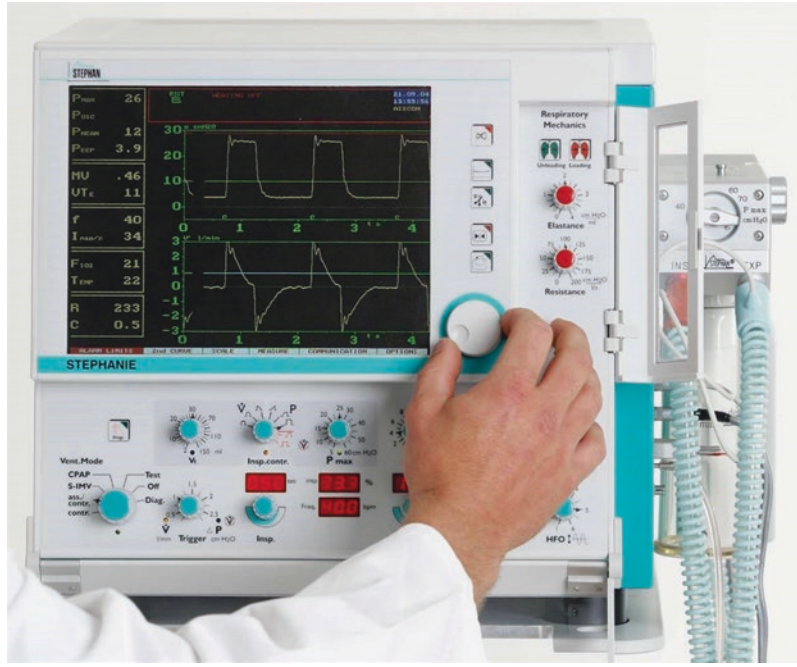

Fig. 51.1 Stephanie ventilator

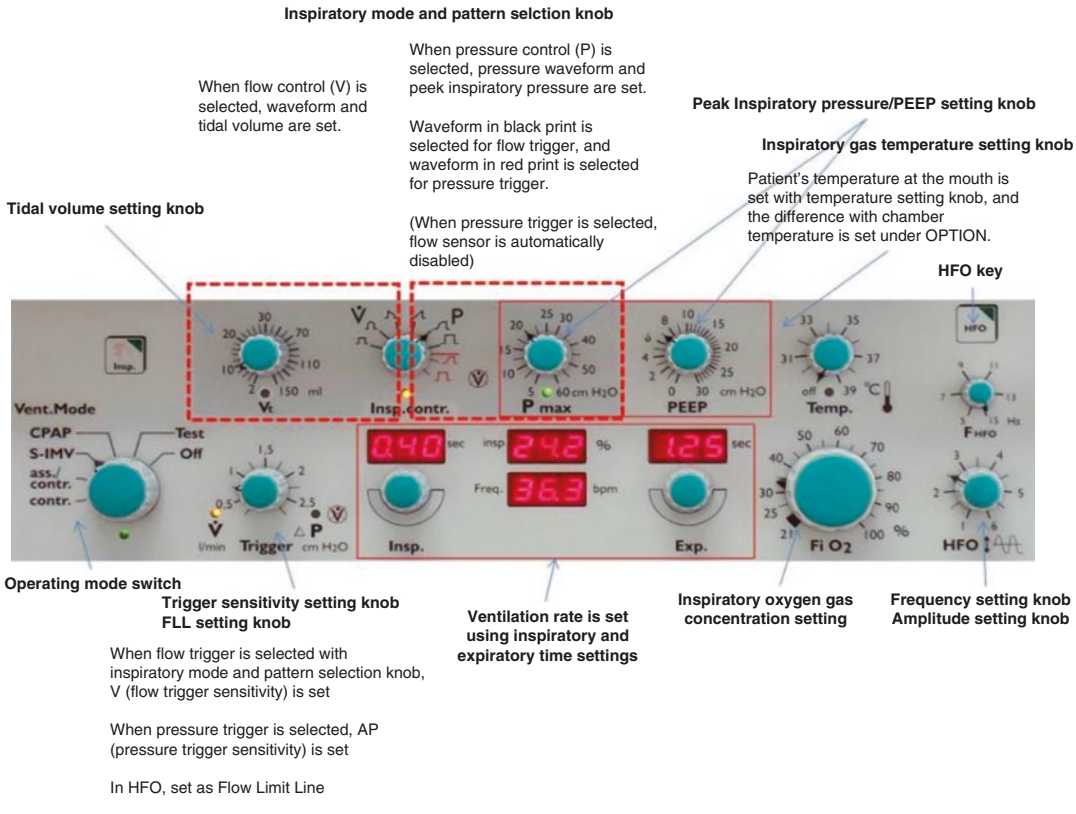

Fig. 51.2 Stephanie ventilator operator menu

D. Several mechanisms to trigger and to cycle off mechanical breaths are available.
E. The Stephanie has an integrated humidification system with heated tubes to prevent water rainout with an automated refill system. The combined in- and expiration valve is located downstream of the humidifier, which decreases compressible volume of the patient circuit. Function and use of this humidification system in different patient settings (incubators vs. overhead warmers) is beyond the scope of this manual and is described in detail in the operating manual (see also Chap. 12). For use in incubators, the manufacturer recommends the use of fully heated in- and expiration tube systems (all the way to the wye-piece) to avoid water condensation if the difference between the incubator and gas temperature is >4 °C.
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.
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 sec ("apnea duration"). Furthermore, the user can choose between instantaneous stopping of 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 measurement 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 patients' 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 controller mechanisms.
2. Combination with back-up features is possible.
D. Pneumotachograph: Several pneumotachographs with different specifications are available: type A (PNT A) is designed to measure airflow up to 10 LPM and has a dead space of only 0.5 mL. PNT B is designed to measure up to 12 LPM and dead space is 0.6 mL. PNT C can measure up to 25 L/min and dead space is 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 mins, 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. Preparations for Operation
A. Power supply: The power supply should be connected for charging the internal battery.
B. Connection of gas supply (oxygen and pressurized air).

C. Filling of the humidifier: Use 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 expiration filter has to be inserted between the ventilator and the expiratory limb if nebulization of drugs is used to protect the valve system of the ventilator (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 of the ventilator and for leaks. This test program is usually used each time before operation, but it can be overridden in emergency cases by turning the "Operating Mode Switch" right to the desired ventilation mode straight away.

V. Settings Available
A. Ti: 0.1–2 s
B. Te: 0.1–60 s
C. V_t: 2–150 mL (enhanced scale for fine-tuning, 0.2–15 mL)
D. $P_{max.}$: 5–60 cm H_2O
E. PEEP: 0–30 cm H_2O
F. Inspiration pattern:
1. Pressure controlled: square wave, half sinus, and ascending ramp (linear acceleration) in pressure
2. Flow controlled: square wave, sinus, and descending ramp (decelerating) flow
G. Trigger sensitivity:
1. Flow: 0.1–2.9 LPM, activated when inspiratory airflow 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% peak flow
2. Pressure during PSV: 0–100% P_{max}
K. High-frequency oscillation
1. Frequency: 5–15 Hz
2. % inspiration time: 33, 40, or 50%
3. Mean airway pressure: up to 30 cm H_2O
4. Amplitude: 1–6 (arbitrary units) max. 24 mL at 10 Hz
L. Inspiration 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 sec.
M. PAV
1. Elastic unloading: 0–4 cm H_2O/mL (enhanced scale for fine-tuning 0–1 cm H_2O/mL)
2. Resistive unloading: 0–200 cm H_2O/L/sec (enhanced scale for fine-tuning 0–50 cm H_2O/L/sec)
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). Displayed 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) 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 airflow
   (b) 0.5-, 1-, 2-, 4-, 12-, and 24-hour 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 operating 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. The Knob "Inspiration Control" (Fig. 51.2) is used for initial decision by the operator to decide for pressure- or flow-controlled ventilation:
   A. Pressure-controlled ventilation:
      1. The pressure is controlled. In this mode 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 toward the end of the inspiratory time to reach the desired PIP), or a "square" profile (immediate steep 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 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 respiratory system 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 airflow, pressure trigger, or the abdominal pressure capsule. The thresholds can be adjusted for flow (0.1–2.9 LPM) and 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, 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 msec.
      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 pre-specified synchronization window. This window opens 2 sec before the end of expiration time, or at the beginning of the second half of the calculated expiration time if it is <4 sec. If no effort is 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 patients' 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 rate 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 the time-cycled A/C, a high spontaneous respiratory rate will reduce inspiratory time automatically. Flow cycling enables complete 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 inhaled before PSV actively terminates inspiration can be set.
      4. Pressure support 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 provide 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 sec, and the duration of back-up is

adjustable (5–60 sec). 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 predefined (5–60 sec) back-up duration (BUD). Any spontaneous breath within this period would reduce the back-up frequency to 1/2, 1/3, and 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 activated 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 operating 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 in the pressure control, but it can be used in the volume control as well.
   (b) In the pressure-controlled mode, V_t depends upon the mechanical 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. Three different pressure profiles can be used.
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 (PSV):
   (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 (VMIN), which has to be inhaled 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 (including synchronized non-invasive pressure-controlled ventilation:
   (a) Non-invasive modes of ventilation are available including non-invasive triggering using the abdominal pressure capsule. The trigger signal can be displayed on the screen. The trigger threshold can be adjusted (arbitrary units). For details on abdominal pressure capsule placement, see Sect. 5.5.6.2 of the manual of operations.
   (b) "Expiratory cycling" of the external trigger can be activated if desired. If the pressure is not rising any more within 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, which are always present during non-invasive ventilation.

B. Volume-controlled modality (volume control). There are several ways volume-targeted ventilation may be achieved using the Stephanie, first by using a true volume-controlled mode, or second by using a pressure-controlled mode with adaptive targeting (called "volume limitation"; see above):
   1. A preset 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. Any leak would result in the desired volume not completely being delivered to the lung.
   2. The scale for the "tidal volume" knob (usually 2–150 mL) can be enhanced for fine-tuning by 1:10 (to 0.2–15 mL).
   3. The volume is measured with the pneumotachograph located between the wye-piece and the endotracheal tube.
   4. The volume delivered by the ventilator is the independent variable, and the pressure as the dependent variable will depend on the mechanical characteristics of the respiratory system (compliance and airway resistance). There will be a loss of volume secondary to compression of the tubing system especially if the lungs are stiff.
   5. With the pneumotachograph in place, the user can choose "V_{Tex} on" in the menu "Options," "Modify." With this setting the inspiratory volume delivered is increased to compensate for leaks, if present. The maximum permitted inspiratory volume for leak compensation corresponds to leaks that are twice the measured expiratory volume.

C. Proportional assist ventilation (PAV):
   1. PAV is a servo-targeting mode, which adjusts the airway pressure during each individual breath in proportion to the patients' inspiratory effort. The pressure delivered during PAV is based on the equation: $p(t) = K_1 V(t) + K_2 \dot{V}(t)$, where inspiratory pressure relative to PEEP is a function of time (t) 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 (*K1*, i.e., Gain B) is used (see Fig. 51.3).

      The second is the "flow assist" as reflected by $K_2 \dot{V}(t)$, 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 (*K2*, i.e., Gain B) is used (see Fig. 51.4).

      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 patients' respiratory disease.
   2. PAV is initiated in a separate control area at the Stephanie front panel with the basic mode being CPAP. There is an option to limit the delivered Vt (for safety reasons) to avoid volutrauma in case *K1* is chosen arbitrarily too high. The user must always adjust the following safety limits: first the pressure knob is acting 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. 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 sec.

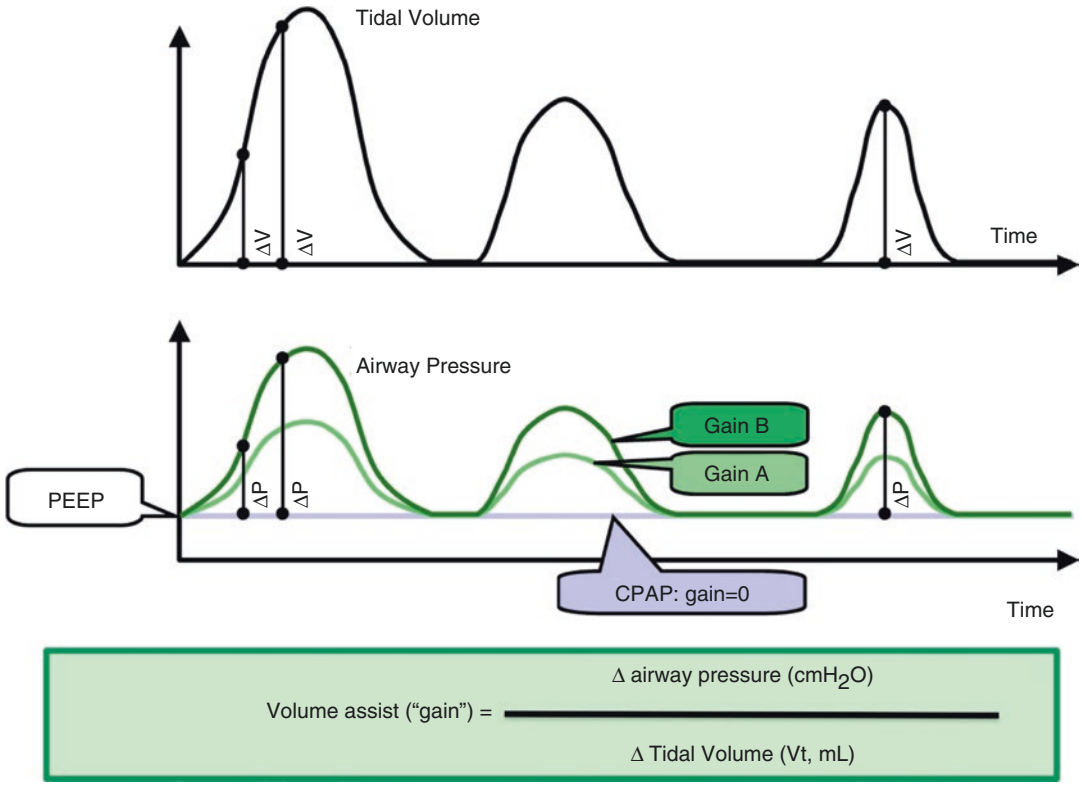

Fig. 51.3 Elastic unloading during proportional assist ventilation (Gain B > Gain A)

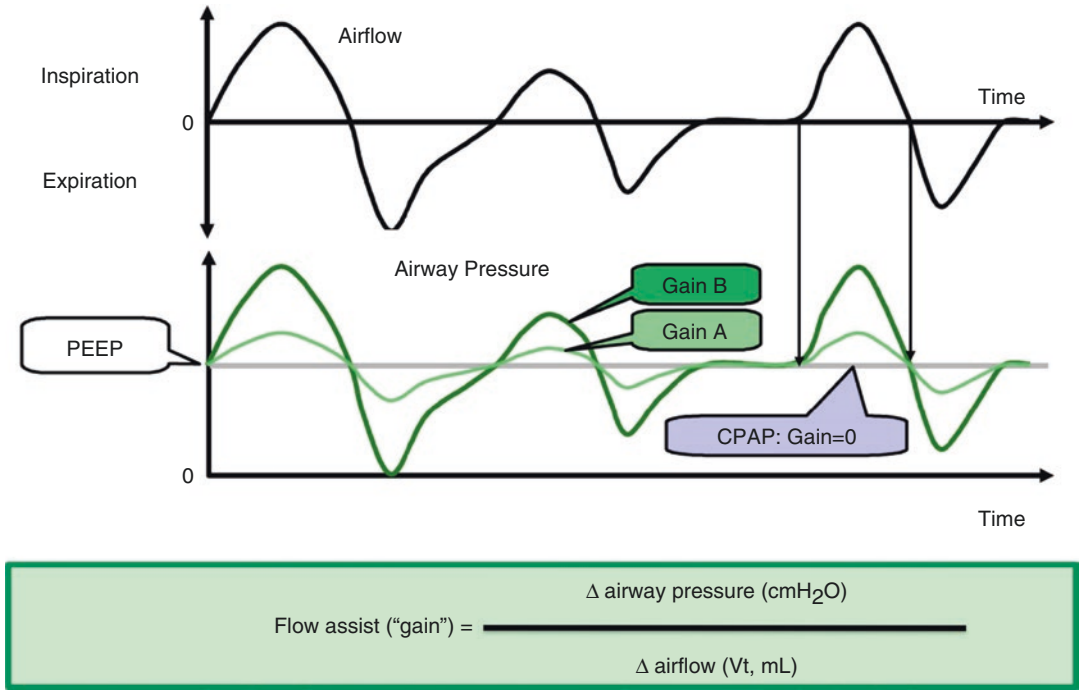

Fig. 51.4 Resistive unloading during proportional assist ventilation (Gain B > Gain A)

3. A detailed description on how to use PAV clinically is beyond the scope of this manual, but is available in the manual of operations (Chap. 8) and in the references listed below. Briefly, the simplest and most practical procedure to initiate PAV is to start with the gain (*K1* and *K2*) = 0 (zero) and gradually increase both gains. The gain for resistive unloading (*K2*) may be adjusted to compensate the expected resistance imposed by the endotracheal tube (i.e., approximately 25 cm H_2O/L/sec with a 2.5 mm ID endotracheal tube). Then, the gain for elastic unloading (*K1*) must be increased keeping in mind that smaller infants have a higher elastance as compared to more mature infants, because compliance and tidal volume are related to body weight. When PAV is well 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 is chosen too high, the pressure "runs" away, and when the tidal volume and/or pressure limits are set properly, PAV converts to assist/control (overcompensation). The scales for both "elastance" and "resistance" can be changed for fine-tuning if only little support is needed.

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: adjustable 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 can be 24 mL at 10 Hz. The full scale of the control knob for amplitude adjustment (usually 1–6 arbitrary units) can be changed by a factor 1:3 to 1–2 units full scale for fine-tuning when a low amplitude is needed.
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				
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
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

Mode name	Mode classification				
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
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 interest 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 button "occlusion." Depending on 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 to result in temporary apnea. During this condition airway reflects intrapulmonary pressure which 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 identify certain points on the graphics display for further calculations of respiratory mechanics. However, it is important to remember that spontaneous efforts adding to the driving pressure to the lungs are not measured during routine mechanical ventilation and will therefore not be considered in calculations of respiratory mechanics during mixed (assisted) breaths.

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 body weight (Fig. 51.5). This review will focus only on the 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:
   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 efforts 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.

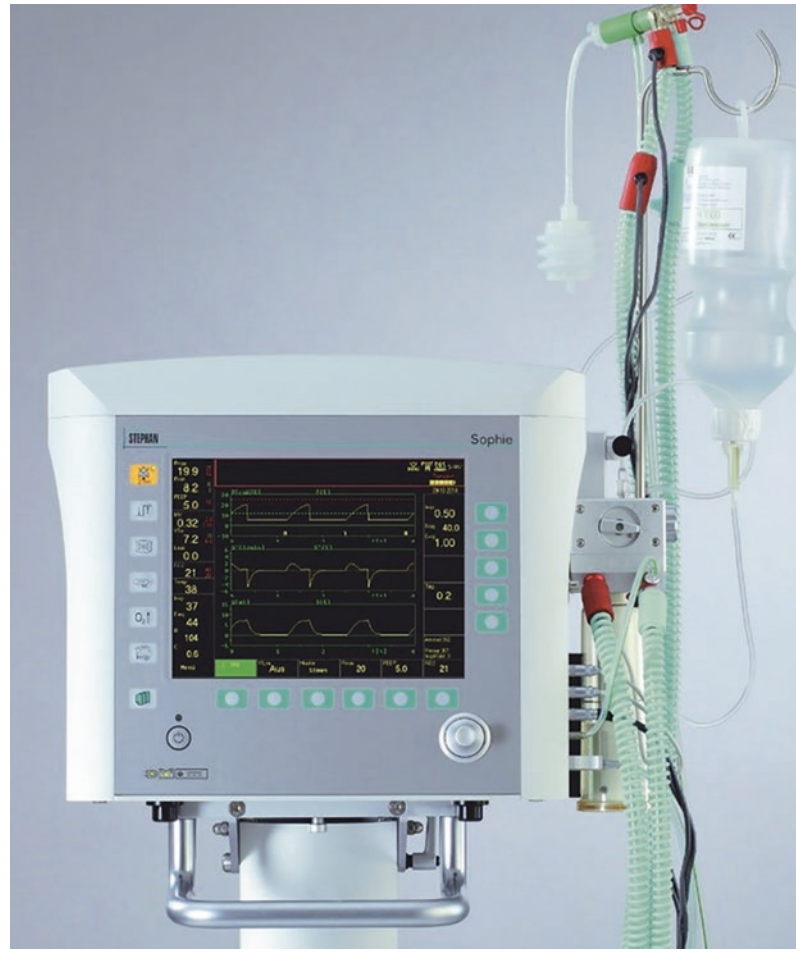

Fig. 51.5 Sophie ventilator

D. The Sophie has an integrated humidification system with heated tubes to prevent water rainout with an automated refill system. The combined in- and expiration valve is located downstream of the humidifier, which decreases compressible volume of the patient circuit. Function and use of this humidification system in different patient settings (incubators vs. overhead warmers) is beyond the scope of this manual and is described in detail in the operating manual (Chaps. 6 and 10). For use in incubators, the manufacturer recommends the use of fully heated in- and expiration tube systems (all the way to the wye-piece) to avoid water condensation if the difference between the incubator and gas temperature is >4 °C.

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 is initiated (called "apnea duration") is adjustable from 0.5 to 15 sec. Furthermore, the clinician can choose between an instantaneous stop of the back-up ventilation once the patient has resumed its own 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 by apnea detection using flow during invasive ventilation, or by using an abdominal pressure capsule during non-invasive ventilation.

C. Preoxygenation: If the "Preoxy" button is pressed, a pre-configurable (increased) FiO_2 will be delivered for a certain preset time interval. This time interval can be set between 30 and 420 sec, or switched off entirely.

D. SpO_2 controller (SPOC): An integrated, automatic SpO_2 controller (SPOC) is available, which adjusts FiO_2 automatically depending on the measured SpO_2, reduces variation of SpO_2 and increases the patients' time with SpO_2 within the target range, and reduces the number of necessary adjustments in FiO_2 by the staff.

E. Pneumotachograph: Several pneumotachographs with different specifications are available: type A (PNT A) is designed to measure airflow 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 and 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: The power supply should be connected for charging the internal battery at all times.

B. Connection of gas supply (oxygen and pressurized air).

C. Filling of the humidifier: Use distillated water. The humidifier may be filled manually, requiring regular refills. Alternatively an automated refill system is available. A humidity level of "0" is the default for invasive conventional ventilation. For HFO or non-invasive ventilation, humidity level is increased to "+2" (preset) to ensure adequate humidification of the higher gas flow.

D. Connect the patient circuit to the ventilator. An expiration filter has to be fitted between the expiratory limb and the ventilator if nebulization of drugs is used to protect the valve system of the ventilator (formation of crystals).

E. The entire "Ventilation menu" can be controlled by one central "push and turn" knob. Pop-up submenus show up 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. V_t: 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 airflow 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 (30°–40 °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. % inspiration time: 33–50%
   3. Mean airway pressure: 0–30 cm H_2O
   4. Oscillatory amplitude: 5–100%
L. Inspiration hold: 1–7 sec. 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 sec).

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 airflow
      (b) 0.5-, 1-, 2-, 4-, 12-, and 24-hour 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 PIP), or a "half-sinus" pressure profile (steep pressure increase from PEEP initially, with a plateau toward 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 operator.
   B. The half-sinus and the square wave pressure profile can be chosen without pneumotachograph in place. However, no flow/tidal volume monitoring or flow-triggered ventilation is possible in this situation.
   C. Volume varies with changes in respiratory system compliance and airway resistance.

IX. Modes for Triggering and Cycling Off Ventilator Breaths
   A. General comment: Synchronized breaths can be triggered using airflow and pressure trigger or using the abdominal pressure capsule. The abdominal capsule can be used during invasive and non-invasive modes. The thresholds can be adjusted for flow (0.2–2.9 LPM) and 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 its effort/spontaneous respiratory rate decreases below the back-up rate (safety cushion).
   C. Synchronized intermittent mandatory ventilation (S-IMV)
      1. A preset number of controlled breaths are delivered (i.e., they are mandatory), whenever the patient effort occurs within a pre-specified trigger window. This trigger window opens 2 sec before the end of expiration time, or at the second half of the calculated expiration time, if it is <4 sec. If no effort is sensed by the time the window period elapses, a time-triggered mandatory breath will be delivered.
      2. If the patients' spontaneous effort triggers the ventilator above the set control rate, the additional breaths will be spontaneous.
   D. Assist/control and S-IMV with inspiratory time termination (ITT (PSV))
      1. During assist/control and during S-IMV, the clinician 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 pressure support ventilation (PSV) and may reduce the risk of gas trapping with 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 (CPAP):
         (a) During CPAP the patient is breathing spontaneously with a set continuous positive airway pressure. The Sophie compensates for pressure level changes due to leaks with 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 sec. With standard back-up (BU), the first spontaneous breath that exceeds the set trigger threshold stops back-up ventilation. 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 predefined (10, 30, or 60 sec) BUD. Any spontaneous breath within this period would reduce the back-up frequency gradually to 1/3 of the set back-up rate. The duration of back-up is at least 5 x the BUD. Back-up breaths can be synchronized.
      2. Intermittent mandatory ventilation (IMV):
         (a) The ventilator provides a preset rate and preset inspiratory time. The patient cannot actively influence the timing of these ventilator breaths.
         (b) In the pressure-controlled mode, the tidal volume 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. 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 breaths). The minimum peak inspiratory pressure will be PEEP + 4 cm H_2O.
         (b) The mode is activated by adjusting "V_t Lim" to the desired value. The "P_{max}" is used to set the maximal pressure allowed. In general a tidal volume 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 in Section IX.
      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 may lead to abdominal distension. The clinician 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 sec (standard back-up). Frequency-controlled back-up (FBU) with reduction of IPPV every 10/30/60 sec (adjustable) is available.

6. Non-invasive positive pressure ventilation (NIPPV):
   (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. For details on abdominal pressure capsule placement, see Sections 6.5.6 and 9.2 of the manual of operations.
   (b) The trigger is suppressed for 150 msec 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 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 due to 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 sec.

C. High-frequency oscillatory ventilation (HFO)
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 submenu (5–15 Hz).
3. HFO amplitude: The HFO amplitude can be adjusted in the submenu. The actual amplitude (measured in airway pressure change) will depend on the respiratory characteristics of the tubing and the respiratory system of the patient.
4. Inspiratory time: The inspiration time as a percentage of the total cycle time can be adjusted in the "Options." "HFO" menu: 33–50%.
5. HFO can be combined with IMV ("HFO-IMV").

XI. Mode Map

Mode name	Mode classification				
	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 to identify certain time points of interest during a single breath and to calculate pulmonary mechanics, such as compliance, resistance, and time constant.
   B. Pulmonary function: Reference cursers can be activated to identify certain points on the graphics display for further calculations of respiratory mechanics. However, it is important to remember that spontaneous efforts adding to the driving pressure to the lungs are not measured during routine mechanical ventilation and will therefore not be considered in calculations of respiratory mechanics during mixed (assisted) breaths.

XIII. SpO_2 Controller (SPOC) for Automated FiO_2-Control (Auto-FiO_2); See Also Chap. 60 and Manual of Operation Version V1.8
   A. General description:
      1. An integrated, automatic SpO_2 controller is available, which adjusts FiO_2 automatically depending on the measured SpO_2. It has been shown to reduce variation of SpO_2, to increase the patients' time with SpO_2 within the target range, and to reduce 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 every 2 sec. In general preductal SpO_2 (sensor placed at the right arm of the patient) is recommended. The SpO_2 target values are defined by the clinician with an upper and lower limit. The SpO_2 target will be the arithmetic mean of the upper and lower limit. It takes into consideration the SpO_2 target range (adjusted by the clinician) and the actual FiO_2 (initially set by the clinician and readjusted automatically thereafter). If the measured SpO_2 is higher than the target, the FiO_2 will be decreased and vice versa. SPOC systematically analyzes trends and fine-tunes FiO_2 even before the upper and lower limits of the SpO_2 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 as 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 for the response of the controller.
      4. In case of malfunction of the pulse oximetry signal, the system will alarm and adjust the FiO_2 to a clinician-selected back-up FiO_2 for safety reasons.
      5. If CPAP is used with back-up ventilation, SPOC can initiate back-up breaths not only with apnea but 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) as shown in Fig. 51.6. 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 set "base FiO_2 (usually the current FiO_2), and the back-up FiO_2 are chosen by the clinician. Then, SPOC is started by activating "auto-FiO_2." The base FiO_2 corresponds to the patients' average FiO_2 and will be adjusted automatically using the previously delivered "historic" 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

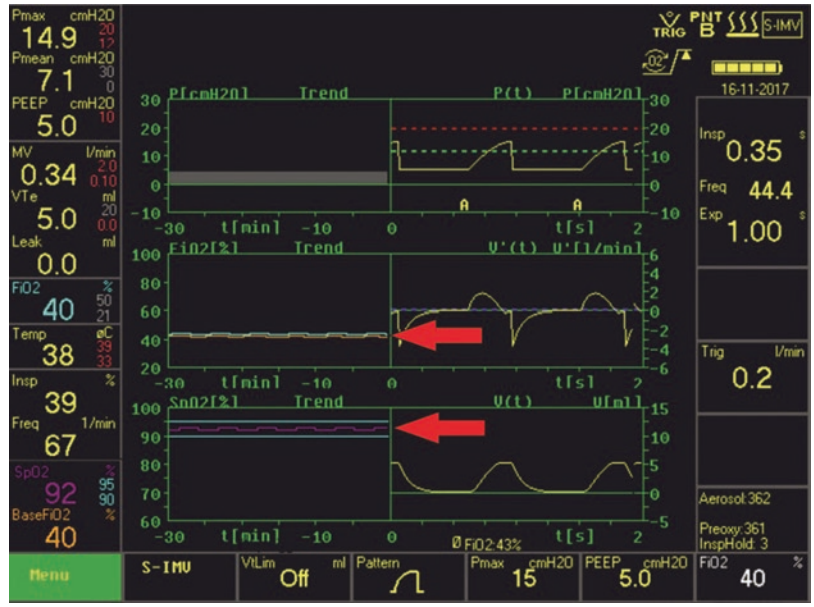

Fig. 51.6 Trend view of FiO_2 and SpO2 (left panel, red arrows). Numeric displays on the left side show the measured FiO_2 (40%, cyan), the base FiO_2 (40%, orange), and the measured SpO_2 (92%, purple) along with the upper and lower SpO_2 target range (90–95%, cyan)

1. If "preoxygenation" is activated during use of SPOC, the increase in FiO_2 secondary to preoxygenation will be terminated early as soon as SpO_2 is >88% for more than 10 sec.
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 non-invasive ventilation modes:
1. If CPAP is used along with auto-FiO_2, desaturations 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 (even without apnea), and switched off once the SpO_2 returns to the target range and 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, back-up with 2/3 of the set ventilator rate is activated. If SpO_2 returns to the 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 Readings

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Leoni Plus Ventilator

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Felix Neunhoeffer and Christian F. Poets

I. Introduction

The Leoni Plus ventilator and the Leoni Plus Transport ventilator (Löwenstein Medical, Bad Ems, Germany) are constant flow pressure control ventilators 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:

1. Peak inspiration pressure is available from 4 to 60 mbar.
2. PEEP is 0–30 mbar.
3. Frequency is adjustable from 2 to 200 inflations/min.
4. Inspiration time and expiration time are available from 0.1 sec and 0.2 to 30 sec, respectively.
5. Inspiration flow can be chosen from 1 to 32 L/min and expiration flow from 2 to 10 L/min.

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 noninvasive respiratory support.

E. An integrated high-frequency module of the diaphragmatic type with integrated membranes can be used with standard ventilator tubes (HFO) and noninvasively (nHFO):

1. The frequency range is between 5 and 20 Hz.
2. Oscillation setting range is 5–100 mbar.
3. Mean pressure setting ranges from 0 to 40 mbar.

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4. I:E (invasive) and I:E (noninvasive) can be chosen from 9:1 to 1:99 and from 30:1 to 1:299, respectively.
5. 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 via a 12″ 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 waveforms and two loops are available.
H. Triggered spontaneous breaths are displayed.
I. An internal battery provides backup for loss of electric power for up to 2 h.
J. A closed-loop automatic oxygen controller is available as an optional feature.

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 of 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 (s)
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. Modes of Ventilation
A. IPPV Intermittent positive pressure ventilation (PC-CMVs): Continuous mandatory ventilation. A preset 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 sec.

B. IMV Intermittent mandatory ventilation (PC-IMVs): Additional spontaneous breaths are possible between mandatory breaths.
C. S-IPPV Synchronized intermittent positive pressure ventilation (PC-IMVs): The respirator's rate depends on the patient's breathing effort. All breaths are supported with the preset parameters by the ventilator. In case of apnea, ventilation is carried out at a preset rate.
D. S-IMV Synchronized intermittent mandatory ventilation (PC-IMVs): A preset number of control breaths are delivered. A patient's inspiratory effort 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 preset respiratory rate.
E. PSV-SIPPV Pressure support ventilation – synchronized intermittent positive pressure ventilation (PC-IMVs): 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 at the set inspiratory time. In case of apnea, ventilation is carried out with a preset respiratory rate.
F. PSV-SIMV Pressure support ventilation – synchronized intermittent mandatory ventilation (PC-IMVs): Breath is patient-triggered like PSV-SIPPV. The ventilator only supports the preset respiratory rate. In case of apnea, ventilation is carried out at a preset respiratory rate.
G. CPAP Continuous positive airway pressure (PC-CSVs): CPAP is achieved by continuous gas flow through the circuit with expiratory resistance to provide the desired pressure in the intubated patient. Backup ventilation can be chosen.
H. nCPAP Nasal continuous positive airway pressure (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. nIPPV Nasal intermittent positive pressure ventilation (PC-CMVs): Continuous mandatory ventilation via patient interface. A preset number of control breaths are delivered without synchronization.
J. HFO High-frequency oscillation (PC-IMVs): Spontaneous breathing is possible.

VI. Mode Map (Table 53.1)

Table 53.1 Mode map for the Leoni Plus Ventilator

Mode name	Mode classification				
	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

(continued)

Table 53.1 (continued)

Mode name	Mode classification				
	Control variable	Breath sequence	Primary targeting scheme	Secondary targeting scheme	TAG
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

VII. Special Features

A. Volume guarantee (V_{TG}): The ventilator automatically adjusts inspiratory pressure to achieve an average preset tidal volume (i.e., adaptive targeting). It may be very useful in attempting to control ventilation when treating patients with variable compliance.

B. Volume limit ($V_{T\ limit}$): If the preset tidal volume is exceeded, the ventilator stops inspiration to avoid volutrauma (i.e., volume cycling of pressure-controlled mandatory breaths).

C. Closed-loop automatic oxygen control (CLAC):

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 predefined 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. The user has the option to set a control period to 30–180 sec during which the controller does not effect further changes.
6. In case of low SpO_2 values and if the "alarm" mode is activated by the user and emergency criteria are detected, CLAC signals this condition, and the algorithm changes the control period to 30 sec, regardless of the period selected by the user, and increases FiO_2 by 10%. This maneuver is repeated every 30 sec until SpO_2 is again within the control range, or the user makes manual adjustments. SpO_2 values below 70% cannot be measured reliably. For this reason, CLAC will sound an alarm and suspend the algorithm.

Fabian HFO Ventilator (Acutronic)

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Hendrik J. Niemarkt and T. Mohns

I. Introduction
   A. The Fabian HFO ventilator (Acutronic, Hirzel, Switzerland) is designed for invasive and noninvasive respiratory support for neonates and infants up to 25 kg. This review will focus on the neonatal applications.
   B. *Description*
      1. For the neonatal population, a wide range of basic modes of respiratory support are available: IPPV, SIPPV, SIMV, PSV, SIMV+PSV, HFO, (n)CPAP, and flow (including HFNC).
      2. A volume-targeted tidal volume guarantee mode is available in the pressure-assisted ventilation and HFO modes.
      3. A volume limit function, limiting the delivered tidal volume, is present in modes that deliver mandatory breaths
      4. Available noninvasive modes are nCPAP, bi-level CPAP (DUOPAP), nIPPV, and HFNC.
      5. HFOV (pressure) module is integrated on the Fabian HFO. Volume guarantee is also available.
      6. A proximal hot-wire flow sensor enables synchronization of ventilator breaths and flow-volume measurements. Both inspiratory and expiratory flows are measured. Trigger sensitivity can be adjusted.
      7. Ventilation modes and setting can be changed by a touch screen display and/or a control knob. All essential settings, measurement, alarm limits, and graphical information (such as pressure, flow, and volume curves) are displayed
      8. Breath triggering is available in synchronized modes using a flow sensor.
      9. An internal battery provides backup power for 2.5-hr conventional mode and 1 hr in HFO mode
      10. End tidal CO_2 can be measured and displayed on the ventilator with the Micropod sensor module.
      11. A Predictive Intelligent Control of Oxygenation (PRICO) module is available as an optional feature:
          (a) Manually, an extra FiO_2 flush can be administered at a preset level.

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(b) Lung mechanics and recruitment can be assessed with a new forced oscillation technique (FOT) module.

II. *Internal Graphic Monitoring*
   A. Waveforms and loops
      1. Pressure
      2. Flow
      3. Volume
   B. Mechanics
      1. Pressure-volume loop
      2. Flow-volume loop
   C. Trends: up to 5-day storage and display of 15 monitored parameters

III. *Alarms*
   A. Low minute volume (LPM)
   B. High minute volume (LPM)
   C. High tidal volume (mL)
   D. Low tidal volume (mL)
   E. High tube leak (%)
   F. High breath rate (bpm)
   G. Apnea alarm (sec)
   H. High Ppeak
   I. Low Ppeak
   J. High Pmean
   K. Low Pmean
   L. Vte not reached
   M. Tidal volume limited
   N. Inspiratory Pressure not Reached
   O. Low PEEP
   P. High DCO_2
   Q. Low DCO_2
   R. High $ETCO_2$
   S. Low $ETCO_2$
   T. High $FiCO_2$
   U. Low $FiCO_2$
   V. FiO_2 at max
   W. Lower minimum FiO_2

IV. *Ventilation Modalities*
   A. IPPV: intermittent positive pressure ventilation. Per minute, a preset number of mandatory mechanical inflations are delivered via a preset pattern (Pinsp, PEEP, Ti, I-flow, E-flow) independent of possible spontaneous breathing efforts of the patient (non-synchronized). IPPV can also be applied as a noninvasive mode: NIPPV.
   B. SIPPV: synchronized intermittent positive pressure ventilation. Each spontaneous inspiratory effort of the patient triggers a mechanical inflation by the ventilator with preset parameters (Pinsp, PEEP, Ti, I-flow, E-flow). The sensitivity of the trigger for detecting a breathing effort of the patient can be adjusted. The ventilator rate is controlled by the patient. Therefore, the patient must be closely monitored to prevent hyperventilation. When patient shows no breath-

ing activity, the backup rate set in on ventilator will be delivered. To prevent auto-triggering, another inflation cannot be triggered for 180 msec following each inflation.

C. SIMV: synchronized intermittent mandatory ventilation. Ventilation with specified parameters and frequency, synchronous to the patient's independent breathing. If the ventilator detects a breathing effort within a certain time window, this will be supported by the ventilator (synchronization window). The number of mechanical inflations is limited by the set ventilatory rate. The patient can spontaneously breathe in between mechanical inflations but will only be supported by the PEEP level.

D. PSV: pressure support ventilation. Respiratory effort of the infant will be "rewarded" with an inflation by the ventilator at preset values. However, the end of inspiration is not time cycled but flow cycled. If inspiratory flow decelerates to a predefined threshold (range 1–85%) of the maximum flow, the inspiration will be terminated.

E. SIMV+PSV: combination of both modes during which spontaneous breaths between the mandatory SIMV inflation will be supported by pressure support. The Pins can be set separately for the SIMV and PSV inflations.

F. CPAP: continuous positive airway pressure. Endotracheal CPAP is achieved by continuous gas flow through the circuit with expiratory resistance to provide the desired pressure. CPAP can also be delivered noninvasively: nCPAP.

G. DUOPAP (bi-level CPAP) can be provided with preset high CPAP and low CPAP at set frequency.

H. High-flow nasal cannula is an option which allows use of a continuous flow of blended gas with a preset FiO_2 level and ranging between 0 and 15 LPM. It can be provided with different cannulas.

I. HFOV: The Fabian delivers HFO oscillations with use of an electronically controlled membrane. Frequency range is 5–20 Hz, Pmean range 5–50 mbar and amplitude range 5–100 mbar. HFO can be combined with volume guarantee. Besides, I:E ratio can be adjusted (1:3–1:1). HFOV can be applied also in noninvasive mode (nasal HFO) with nasal prongs, mask, or cannula.

V. *Additional Features*

A. Volume limit: the volume limit function automatically terminates inspiration when a preset threshold V_t is reached.

B. Volume guarantee is used as an add-on to a pressure-limiting mode. The device automatically adjusts the ventilation pressure (Pinsp) to reach the preset target expiratory tidal volume (Vte). Pinsp can be escalated to the preset maximum inspiratory pressure. Pinsp is gradually increased breath by breath to achieve the preset Vte. The breath-by-breath Pinsp increase is limited to one-third of the pressure delivered in the previous breath.

C. PRICO: the FiO_2 is automatically adjusted by an algorithm which uses both actual SpO_2 and the trend of SpO_2 over time. Once every 30 sec, an FiO_2 adjustment is made, which is based on the actual SpO_2. When the SpO_2 is outside the target range, the FiO_2 adjustment (0.01–0.1) is determined by actual SpO_2, the trend of SpO_2 data, and an extrapolation of SpO_2 data. When the SpO_2 is in the lower half of the target range, no adjustment in FiO_2 takes place. When SpO_2 is in the upper half of the target range, FiO_2 is decreased by 0.01. The FiO_2 adjustments are kept within preset FiO_2 ranges. When SpO_2 monitoring is disconnected, FiO_2 is administered at a preset level (backup FiO_2). Target SpO_2 range and maximum and minimum FiO_2 administered by PRICO can be adjusted.

D. The forced oscillation technique (FOT) is a noninvasive method suitable for monitoring lung mechanics without interfering with the breathing activity of the patient or ongoing ventilatory modes. It is based on the application of high-frequency low-amplitude pressure oscillations at the airway opening while measuring the resulting changes in flow. FOT can be used on the HFO and conventional ventilation modes. The procedure takes less than 18 sec. Lung mechanics are presented on a graph with on the x-axis PEEP or mean airway pressure and on the y-axis respiratory reactance Xrs (mbar/mps).

Suggested Reading

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Hutten MC, et al. Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs. Pediatr Res. 2019;78(6):657–63.

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Bunnell LifePulse High-Frequency Jet Ventilator

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I. The Bunnell LifePulse 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 sparsely in Europe and elsewhere.
II. The LifePulse 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. Two models of the LifePulse are currently in use. The time-tested 203 model has recently been replaced by a smaller and lighter model 204, which can be mounted on a pole. Functionally the two devices are very similar, but there is a built-in battery, updated electronics, enhanced user interface, prioritized alarm hierarchy, and a quieter water pump in the newer model.
IV. 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 patient's airway. This arrangement minimizes dampening of the pulses and allows more effective pulse delivery with unimpeded exhalation.
V. 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.
VI. Intermittent puffs of gas purge any condensation or secretions and maintain patency of the pressure monitoring line.
VII. 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

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VIII. PEEP and superimposed low rate IMV (when desired) are generated by a conventional ventilator used in tandem with the LifePulse through a conventional ventilator circuit attached to the top of the LifePort adapter.

IX. Mean airway pressure, abbreviated as 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.

X. 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.

XI. The FiO_2 of the two ventilators are 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).

XII. Monitored 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 a value determined by the jet valve on time and rate)

XIII. 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 first turned on.

XIV. The ventilator settings start with default values of PIP 20 cm H_2O, rate of 420 (7 Hz), and valve on time (T_i) of 0.02 s when the device is turned on; these, along with the resulting I:E ratio, will be displayed in the "NOW" row in the control panel.

XV. The user selects "NEW" settings in the row below and activates them by pressing the "Enter" button. Please see Chap. 41 for recommended settings under a variety of circumstances.

XVI. In the LifePulse 204, the NOW and NEW rows have been consolidated into one with the current settings displayed, until they are changed by the user.

XVII. Once the PIP comes to within ±1.5 cm H_2O of the set PIP and has stabilized there for at least 20 s, the "Ready" light comes on. At that point 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.

XVIII. A variety of safety features and alarms are built into the device. These include:
- JET VALVE FAULT
- VENTILATOR FAULT
- LOW GAS PRESSURE
- CANNOT MEET PIP
- LOSS OF PIP
- HIGH PIP

XIX. The details of these alarm conditions are explained in the user manual, referenced below, and available on the manufacturer's website.

XX. Changes in servo pressure provide important clues to the patient's condition and ventilator operation.

XXI. When more gas volume is needed to reach set PIP, the 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, 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

XXII. When less gas volume is needed to reach set PIP, servo pressure goes down. Low servo pressure may result from:
   A. Worsening lung compliance (e.g. atelectasis, tension pneumothorax)
   B. Main bronchus intubation
   C. Obstruction of endotracheal tube (e.g., secretions, abutting the carina or wall of the trachea)
   D. Increased airway resistance

XXIV. 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.

XXV. 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.

XXVI. Like any servo-controlled device, the actual PIP will fluctuate around the set value, especially when the patient is breathing actively.

XXVII. 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 sigh settings that activates a MAP or servo alarm.
      2. The rare situation when the ventilator has not been able to reach steady state and activate the "Ready" button because of a leak or partial disconnection.

XXVIII. An efficient low-volume humidifier is built into the device/patient circuit, assuring optimal heating and humidification of inspired gases.

XXIX. The humidifier panel allows the user to independently set the cartridge and circuit temperatures within the range of 32–42 °C.

XXX. A water pump automatically maintains an optimal water level in the humidification cartridge.

XXXI. 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.

XXXII. 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 down 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 sweeping out of secretions or aspirated material. Optimal

effectiveness of HFJV depends on the jet stream penetrating unobstructed down the airway:

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 main bronchi.
B. Position the infant's head in 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.

XXXIII. Inhaled nitric oxide can be safely and effectively delivered via the LifePulse 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.

Suggested Reading

Bunnell LifePulse 204 Ventilator Quick Start Guide. https://www.bunl.com/uploads/4/8/7/9/48792141/204_quick_reference_guide.pdf.

Bunnell LifePulse 204 User's Manual. https://www.bunl.com/uploads/4/8/7/9/48792141/204_user_manual.pdf.

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High-Frequency Oscillatory Ventilators

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David G. Tingay

I. Physiology of High-Frequency Oscillatory Ventilation (HFOV)
   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 (Fig. 55.1). 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 B 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. In addition, the TXP-2D High-Frequency Ventilator (International Biomedical, USA) is a dedicated oscillator for use in transport that the manufacturer reports can deliver a

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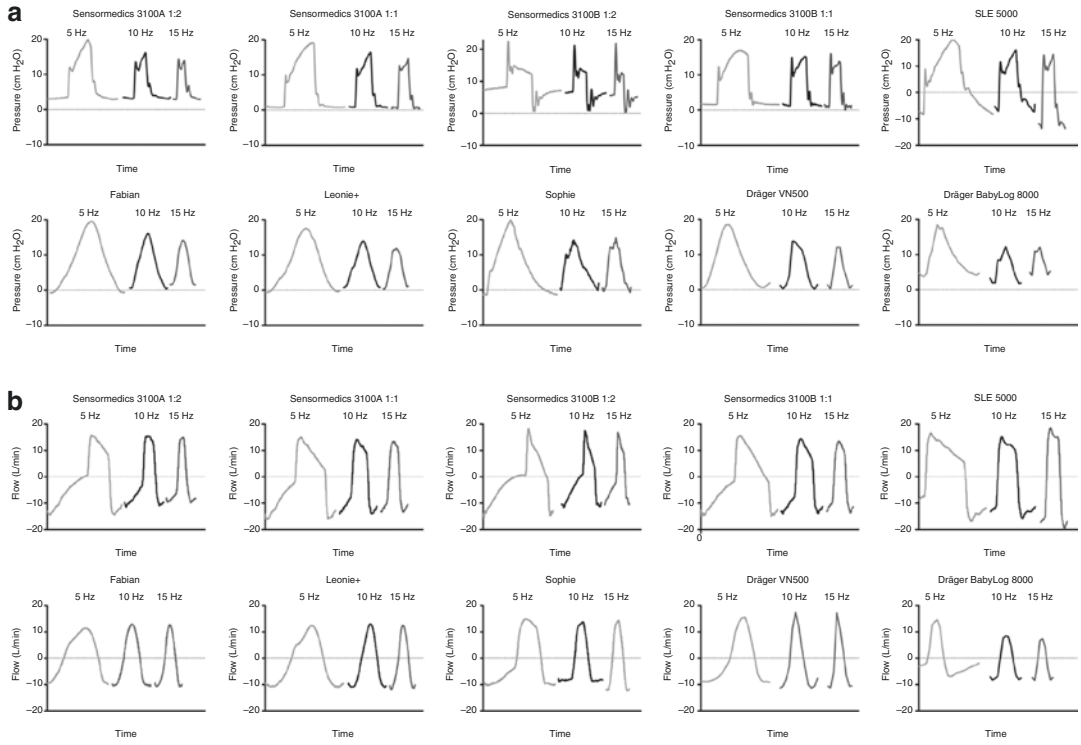

Fig. 55.1 Representative pressure (**a**) and flow (**b**) waveforms measured at the airway opening during a single oscillation at 5 (light gray), 10 (black), and 15 Hz (dark gray) in eight commercially available high-frequency oscillators (see Table 55.1). The top row of each panel demonstrates devices having a square-shaped pressure wave and the second row devices with a sine wave. Note the incisurae peak in the square wave devices. (Reproduced with permission from authors from Harcourt ER et al. *Pediatr Crit Care Med* 2014; 15(5):e234–240)

mean airway pressure up to 30 cm H_2O (note: frequency is set in breaths per minute).

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"), this is the principal determinant of tidal volume.
   (c) Frequency (the number of inflations per minute).
   (d) The Inspiratory to expiratory (I:E) ratio (the proportion of each respiratory cycle in inspiration and expiration). Usually 1:2 or 1:1 for most neonatal patients. Most hybrid devices also offer 1:3, although this very short inspiratory ratio has not been subjected to extensive clinical or trial reporting. Tidal volume is higher with a 1:1 ratio but expiratory time 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.

Table 55.1 Summary of current neonatal high-frequency oscillators

Ventilator	Manufacturer	Principle of operation	HFOV waveform	DCO/V_T monitoring	VTV	Manufacturer's 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	Yes	30 kg	80	5–20	80	1:1–1:3
Sensormedics 3100A	Vyaire (USA)	Electromagnetic flow generator	Square	No	No	35 kg	45	3–15	90	1:1–1:2
Sensormedics 3100B	Vyaire (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)	Bidirectional jets	Square	Yes	No	20 kg	45	3–20	180	1:1–1:3
SLE6000	SLE (UK)	Bidirectional jets	Square	Yes	Yes	20 kg	45	3–20	180	1:1–1:3
Sophie/ Stephanie	Stephan (Germany)	Valve oscillator with active expiration	Sine	Yes	Yes	6 kg	30	5–20	% max[b]	1:1–1:3
Servo-n	Getinge (Sweden)	Inspiratory valve oscillator (utilizes inertia of air in circuit)	Not reported	Yes	Yes	8 kg	40	5–20	100	1:1–1:2
Humming Vue	Metran (Japan)	Linear motor piston pump	Not reported	Yes	Yes[c]	20 kg	40	5–17 Hz	200[c]	1:1–1:2

Abbreviations: *VTV* volume-targeted ventilation mode, *DCO*, diffusion coefficient of CO_2 (frequency × V_T^2), V_T tidal volume, P_{AW} mean airway pressure

Information correct as of 10 December 2020

[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]The Humming Vue only operates in a volume-targeted mode. The user sets a stroke volume (tidal volume) in ml (0–160 ml range), and the amplitude is adjusted to maintain stroke volume

(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, are 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 air 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:
         (a) 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*.
         (b) 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 which can be adjusted:
   A. Mean airway pressure:
      1. Increasing mean airway pressure recruits alveoli, leading to improved ventilation-perfusion matching, improved oxygenation and 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, e.g., RDS), then a *high lung volume strategy* must be used.
      3. For lung diseases without atelectasis (e.g., pulmonary hypoplasia and congenital diaphragmatic hernia), overdistension is common, and a mean airway pressure at or below conventional mean airway pressure maybe 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 B:
      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 space (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. Then, follow $PaCO_2$ closely (it can change dramatically), using transcutaneous CO_2 or tidal volume/minute ventilation (DCO) monitoring to help with initial adjustments in amplitude, and prevent rapid $PaCO_2$ changes.
   C. Frequency:
      1. Measured in Hz (1 Hz = 1 inflation/sec 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 nonuniform disease.
5. In general, use a lower frequency for patients with nonhomogeneous lung disease, airway disease, or air trapping. If a patient has an unacceptable degree of air 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 so should be reserved for preterm infants.
   (f) Due to 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 3100.

D. Inspiratory to 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 delta pressure and frequencies.

E. Flow, measured in liters per minute (LPM), can be set in some HFO ventilators (Sensormedics 3100A and B, 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 (e.g., respiratory distress syndrome):
   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 ventilation to perfusion 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 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 a 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 minutes, increase mean airway pressure by steps of 2 cm H_2O and observe SpO_2. The time between pressure steps depends on the underlying lung condition (time constant). In homogenous lung disease, like RDS, steps can be taken every 2–3 minutes. In more heterogeneous lung disease (bronchopulmonary dysplasia or meconium aspiration syndrome), the effect of an incremental or decremental pressure step on lung volume may take up to 15–20 minutes.
   (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 the "opening pressure" value, mean airway pressure should now be judiciously decreased (2 cm H_2O steps every 2 minutes) 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 minutes), and FiO_2 can again be decreased.
   (h) Mean airway pressure should then be immediately decreased to 2 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, tracheoesophageal fistulas, and congenital cystic lung disease.
3. Pulmonary hypoplasia:
   (a) Reduced functional residual capacity 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 is 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) because of 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:

Identifying the optimal frequency is an imprecise process. In most cases, the frequency ranges listed above are adequate. However, 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. 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 authors' current approach is to extubate from HFOV using the following criteria:
    (a) Preterm infants:
        1. There is good spontaneous respiratory effort.
        2. Mean airway pressure <6–8 cm H_2O, although extubation at higher levels may be necessary when dealing with heterogeneous lung disease.
        3. Maintaining adequate SpO_2 in FiO_2 less than 0.3–0.4.
        4. pH >7.25, and acceptable CO_2 with delta pressure 10–15 cm H_2O.
    (b) Term infants:
        1. There is good spontaneous respiratory effort.
        2. Mean airway pressure is less than 6–10 cm H_2O.
        3. Maintaining adequate SpO_2 in FiO_2 less than 0.3–0.4.
        4. 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 seven oscillators offer volume-targeted ventilation (VTV) modalities in HFOV (termed "volume guarantee" by some manufacturers); see Table 55.1.
2. In principle, VTV in HFOV is similar to conventional ventilation in that the clinician sets a desired tidal volume and the ventilator algorithms adjust 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 (due to 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 by 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. In case VTV is activated during HFOV, the impact of a change in frequency on tidal volume will be automatically corrected by the ventilator via a change in amplitude. This way the delivered tidal volume will remain stable and on target. This means that changes in frequency during VTV will have a similar effect on CO_2 clearance as during CMV: an increase in frequency will lower CO_2 and a decrease will increase CO_2.
8. 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 minutes. 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 (DCO) 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 (DCO) is the true determinant of CO_2 clearance. To maintain the same CO_2, the VTV setting will need to be readjusted to establish the same DCO 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 of 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. Oxygen saturation or transcutaneous O_2 and cardiovascular monitoring must be used during HFOV to guide the level of lung inflation and mean airway pressure. Some hybrid oscillators (Fabian, SLE6000, Sophie, Leonie+) offer in-built oxygen saturation monitoring and automated oxygen control during HFOV.
3. Monitoring of CO_2 clearance can be achieved using:
   (a) Transcutaneous CO_2.
   (b) Tidal volume measured at the airway opening.
   (c) Minute volume (DCO):
      1. DCO is calculated from (frequency) × (tidal volume)^2.
      2. As DCO 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 DCO values are dependent on patient and device characteristics, so it cannot be translated between patients or diseases. Rather the trend in DCO should be used (higher DCO = more CO_2 clearance)
   (d) Tidal volume and DCO monitoring are available in all modern oscillators except the Sensormedics 3100A and B. External devices that reliably monitor these parameters during HFOV, and can be used in conjunction with the Sensormedics 3100A and B, 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 gas analysis.
   (f) Monitoring of spontaneous (tidal) breathing during HFOV can also assist the clinician in assessing CO_2 clearance. Absence of spontaneous breathing may be a sign of hypocapnia and excessive breathing (often with signs of distress) of hypercapnia.
   (g) Chest radiography:
      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 hemidiaphragm, radiolucency of lung fields, heart size, and intercostal shape of lung edges (e.g., bulging) have all been described as methods of assessing 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 hemidiaphragm is between 8 and 10 ribs.
   (d) A higher location of the right hemidiaphragm (e.g., 6–8 ribs) will represent normal lung inflation in conditions of reduced functional residual capacity (e.g., pulmonary hypoplasia).

4. 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.

B. 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:
   1. 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.
   2. 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 diseases.
   3. Multiple animal models have shown advantages of HFOV over conventional ventilation, particularly in models of severe RDS or with severe acute lung injury.
   4. The human data on the advantages of HFOV over conventional ventilation is 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.
   5. 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.
   6. 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.

7. 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.
8. There are several conclusions which can be drawn from the animal and human trials of HFOV:
9. HFOV is as at least as effective as conventional ventilation in supporting oxygenation and ventilation in patients with significant restrictive disease.
10. HFOV is at least as safe as conventional ventilation, when used properly (with a high lung volume strategy).
11. HFOV is superior to conventional ventilation for infants with pulmonary interstitial emphysema or bronchopleural fistula. However, HFOV is probably not as effective as HFJV in treating patients with severe disease.
12. HFOV may be superior to conventional ventilation for patients with severe restrictive lung disease.
13. HFOV probably offers no advantages over conventional ventilation in patients with minimal lung disease.
14. In experienced hands HFOV has an important place in NICU care, but in inexperienced hands, HFOV can be harmful.
15. General indications for HFOV in most centers which are experienced with HFOV include:
16. Treatment of air leak syndromes, including pulmonary interstitial emphysema and bronchopulmonary fistula.
17. Severe restrictive lung disease, including RDS, meconium aspiration syndrome, or pneumonia, especially in centers familiar with the use of the open lung approach.
18. Severe lung hypoplasia, including congenital diaphragmatic hernia.
19. Small preterm infants at high risk of developing BPD. This indication is more controversial than those listed above.

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Part IX

Adjunctive Therapies

Hemodynamic Support of the Newborn

56

Samir Gupta and Sanoj K. M. Ali

I. Introduction
   A. Newborn infants are not small adults and their cardiovascular physiology is different, even from that of older infants.
      1. Cardiac Morphology and Function
         (a) The neonatal cardiac myocyte is different from the mature myocyte and is rounded, relatively short, and intracellularly disorganized. The extracellular matrix, which gives a structural framework, is also not well developed.
         (b) The immature heart is more dependent upon the extracellular concentration of calcium for myocardial contraction.
         (c) The immature myocardium is less compliant, generates less contractile force, and is inefficiently shaped compared to a mature heart. There is a risk that increased afterload and the demand on cardiac function, which may not be met, resulting in impaired perfusion.
         (d) Newborn infants primarily change cardiac output (CO) by changes in heart rate, but they can also alter stroke volume (but to a lesser extent). Mild tachycardia can increase CO; however, excessive tachycardia results in reduced coronary blood flow and preload causing impaired CO.
         (e) Increases in afterload usually observed during transition after birth, post-ductal ligation, and in the setting of cold shock often lead to decreases in ventricular output.
         (f) Drug responses and volume of distribution are often quite different in the newborn; metabolic immaturity of the myocyte may lead to responses which are in a different direction in the newborn than in an older subject.

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2. Vascular Responses

The development of vascular receptors in newborn infants is poorly studied. Alpha-mediated vasoconstriction is seen with the administration of catecholamines, 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) is unknown.

3. Shunts
   (a) Transitional circulation is affected by the presence and direction of fetal shunts, such as the ductus arteriosus, ductus venosus, and foramen ovale (Fig. 56.1).
   (b) Cardiac output is difficult to quantify accurately in newborn infants because of the presence of extracardiac and intracardiac shunts.
   (c) Total perfusion of the body is the sum of SVC flow and IVC flow.
   (d) When the ductus is open, left ventricular output (LVO) is the sum of pulmonary venous return and any net left-to-right shunting across the ductus arteriosus.
   (e) Right ventricular output (RVO) is the sum of systemic venous return and any net left-to-right shunting across the foramen ovale.
4. Cardiopulmonary Interdependence
   (a) Lung hyperinflation can occur with positive pressure ventilation when high mean airway pressure or high PEEP is used. This in turn can lead to decreased pulmonary and systemic venous return and decreased ventricular output, as it is preload dependent.
   (b) The direct compressive effect of the lung on the heart secondary to over-distension of the lungs, diaphragmatic hernia, or mediastinal shift from pneumothorax can impair ventricular function and reduce cardiac output.

B. Normal transition

1. The fetal Circulation

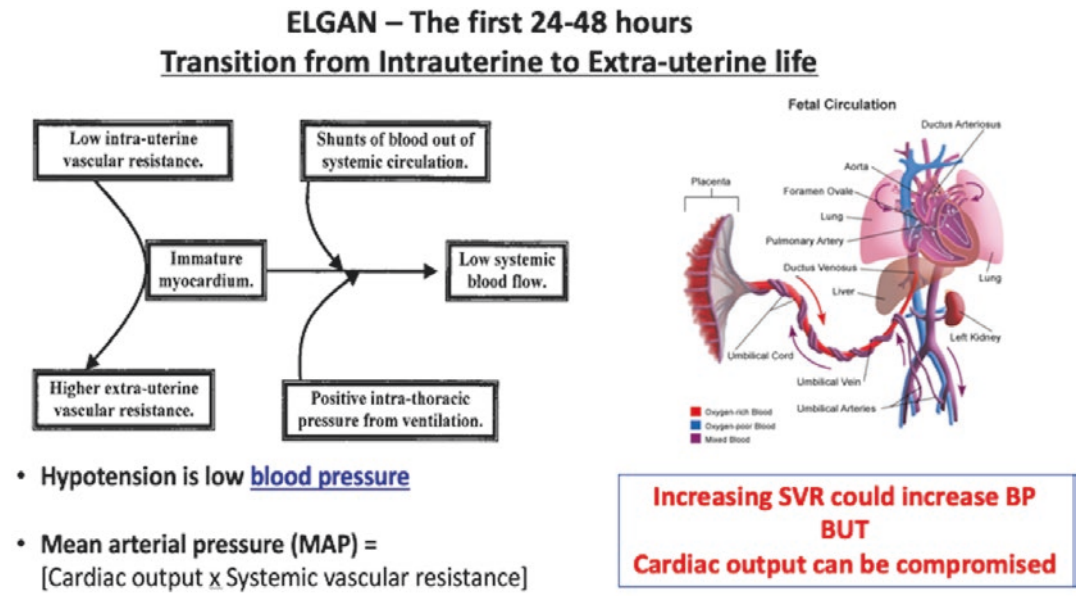

Fig. 56.1 ELGAN: transition from intrauterine to extrauterine life

(a) In utero the pulmonary vascular resistance is very high, which keeps pulmonary blood flow low (<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. Birth Events
(a) 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.
(b) Ventilating the lungs before clamping the umbilical cord markedly improves cardiovascular function by increasing pulmonary blood flow, thus further stabilizing the cerebral hemodynamic transition.

C. Hemodynamic Monitoring
1. Goals
(a) Early recognition of cardiorespiratory compromise before progression to irreversible circulatory failure and end organ damage.
(b) Timely initiation of targeted therapy based on the underlying pathophysiology.
(c) Assess response to treatment and facilitate escalation or weaning of hemodynamic supports based on objective criteria.

2. Monitoring Tools
(a) Clinical signs such as heart rate, blood pressure, capillary refill time, urine output, serum lactate, and central-peripheral temperature difference are commonly used to assess perfusion but are usually deranged only when the infant is already in an uncompensated state.
(b) The use of neonatologist-performed echocardiography (NPE) to monitor hemodynamics in the newborn infant has exponentially increased over the past decade.
(c) Noninvasive continuous monitoring techniques such as near-infrared spectroscopy (NIRS) for end-organ perfusion, perfusion index (PI) from the plethysmographic signal of the pulse oximeter, and thoracic electrical bioimpedance for cardiac output (electric velocimetry®) are useful options already in clinical use for trend monitoring but need further validation.

II. Hemodynamic Problems
A. Pulmonary hypertension (PHT) (see Chap. 71)
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, resulting in hypoxemia.
(b) This may occur as a complication of meconium aspiration, pneumonia, pulmonary hypoplasia, congenital diaphragmatic hernia (Fig. 56.2), other respiratory disorders, such as respiratory distress syndrome and is a known complication of severe bronchopulmonary dysplasia (BPD). Around 10% of infants with PHT have no underlying cause apart from abnormal vascular modeling noted on autopsy.
(c) Right-to-left ductal shunting, although pathognomonic, is seen only in those with severe disease and an open PDA.
(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 high right ventricular after-

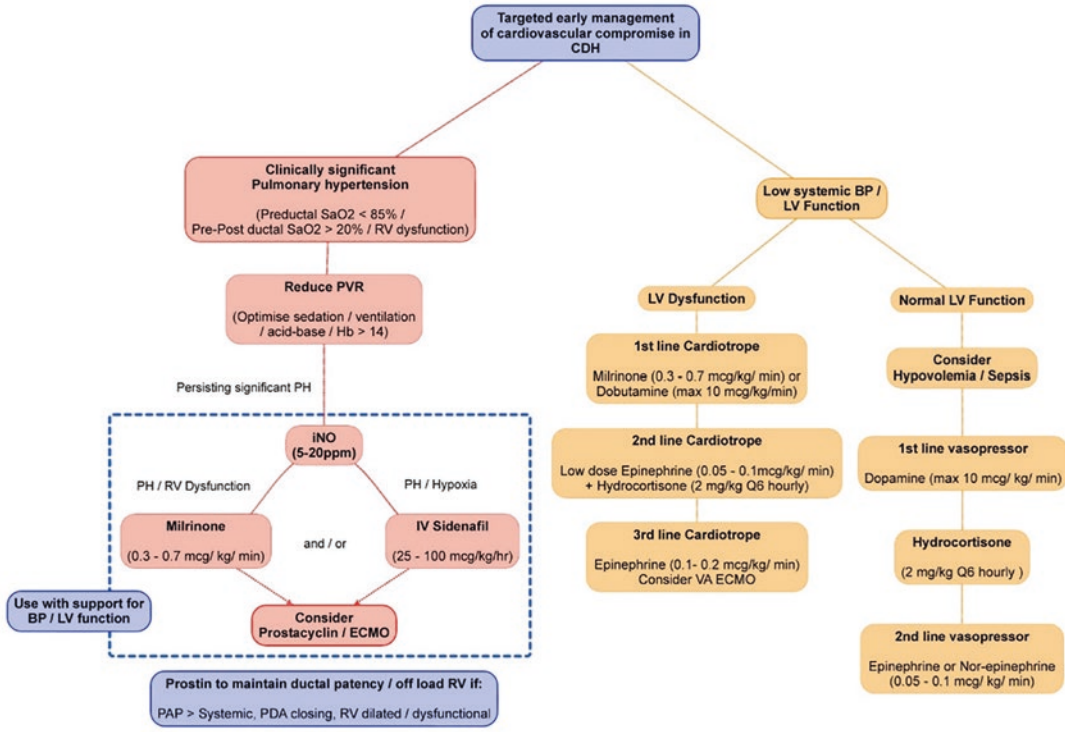

Fig. 56.2 Congenital diaphragmatic hernia: schema for management

load. Thus, right ventricular function is an important determinant of a good outcome in infants with PPHN.

(e) Finally, hypoxemia may result from intrapulmonary shunting (i.e., V/Q mismatch).

2. Clinical Evaluation
   (a) PHT 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 disorder.
   (c) In most infants with severe respiratory failure, there is some elevation of pulmonary vascular resistance, which may contribute to the severity of their illness.
3. Supplementary Testing
   (a) Echocardiography is used to assess cardiac function, pulmonary artery pressure, pulmonary vascular resistance, and the direction of fetal shunts (PDA and ASD/PFO). Tricuspid regurgitation is used to calculate right ventricular pressure in the presence of normal RV function. Abnormal flattening (D-shaped) or bowing to the left (banana-shaped) of the interventricular septum may give an indirect estimate of increased pulmonary arterial pressure.
   (b) Echocardiogram should be performed before or as soon as possible after commencement of inhaled nitric oxide (iNO), as conditions resulting in pulmonary venous hypertension will worsen with initiation of pulmonary vasodilator therapy.

(c) Cranial and abdominal ultrasound may be useful in detecting rare causes of PHT like arteriovenous malformations in the brain and liver.
(d) Calculation of the oxygenation index, ideally from pre-ductal arterial blood, helps to assess severity of illness and to direct therapy.

4. Therapy
(a) Supportive therapy, assisted ventilation, warmth, oxygen, and fluids are used, with extracorporeal membrane oxygenation (ECMO) reserved for the sickest infants who do not respond to the standard therapy.
(b) Sedation and paralysis may help in the acute phase of illness.
(c) The only proven directly acting therapy is iNO (see Chapter XX).
(d) Hyperoxia should be avoided, as it may impair nitric oxide-mediated pulmonary vasodilation and increase pulmonary vascular reactivity.
(e) Inducing alkalosis using bicarbonate and hyperventilation has been associated with increased need for ECMO, hearing deficits, and poor neurologic outcome.
(f) Cardiotropic 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. Inodilators, such as milrinone, reduce pulmonary vascular resistance as well as systemic afterload along with newer drugs like sildenafil. Alprostadil is used to maintain patency of the ductus arteriosus to offload the failing right ventricle in severe PPHN.
(g) Prostacyclin and bosentan have a role in selective cases, but their use should be limited to tertiary/quaternary centers under echocardiographic guidance or after consultation with a pediatric cardiologist.

B. Septic Shock
1. Pathophysiology
(a) The hemodynamic presentation of septic shock in the newborn is highly variable.
(b) Older infants with gram-negative septic shock commonly have excessive vasodilation with a normal or increased cardiac output, 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 different cardiovascular physiology. Neonatal *animals* with group B streptococcus demonstrate vasoconstrictive "cold shock," with reduced cardiac output and hypotension being pre-terminal events.

2. Clinical Evaluation
(a) In cold shock, signs of peripheral vasoconstriction are common: prolonged capillary refill, 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 (IVC characteristics and LV end diastolic volume measurements), contractility, and systemic blood flow to guide therapy.
(b) Objective assessment for response to therapy can utilize trend monitors, such as NIRS® or ICON®.

4. Therapy
(a) There is paucity of high-quality evidence regarding therapeutic options in infants with septic shock.

(b) Infants in shock with evidence of myocardial dysfunction but with adequate blood pressure may benefit from dobutamine.
(c) Infants with shock and hypotension may preferably be treated with epinephrine, which increases both blood pressure and systemic perfusion. Norepinephrine can be used for neonatal "warm" septic shock, and vasopressin is usually reserved for refractory cases.
(d) Fluid boluses are often administered, based on the assumption that sepsis leads to functional hypovolemia.
1. Although this may be true in certain cases, a recent trial in older infants and children reported an increase in mortality in children with early septic shock who received fluid boluses.
2. If fluid boluses are required, it would be reasonable to use normal saline in the newborn.
(e) Hydrocortisone is a useful adjunct for septic shock in very preterm neonates, who tend to have relative adrenal insufficiency that can accentuate hemodynamic instability and hypotension.

C. Hypovolemic Shock
1. Pathophysiology
(a) Hypovolemia can result from blood loss (e.g., ruptured vasa previa, large intracranial or subgaleal hemorrhage) or occasionally in infants following placental abruption (in this situation the blood lost is almost always 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 *acute* feto-maternal hemorrhage will also lead to hypovolemia but is rare before 28 weeks' gestation.
(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, high lactate, and reduced urine output.
3. Supplementary Testing
(a) Echocardiographic assessment of cardiac filling may be helpful, but clear indices of circulating blood volume do not exist. Reduced cardiac output with low end diastolic volume is an indicator of hypovolemic shock.
(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 transfusion should be given as soon as possible, if there is history of blood loss, to restore oxygen-carrying capacity.

D. Cardiogenic Shock
1. Pathophysiology
(a) Cardiomyopathy
(b) Congenital heart disease (e.g., hypoplastic left heart syndrome)
(c) Pericardial effusion

2. Clinical Evaluation
   (a) Poor perfusion and tachycardia are the hallmarks of primary cardiac dysfunction.
   (b) Metabolic acidosis with increasing serum lactate and oliguria or anuria are danger signs.
3. Supplemental Testing
   (a) Echocardiography is essential; identification of the coronary artery origins should be considered unless another diagnosis is likely.
   (b) Structural heart disease and cardiomyopathy should be ruled out.
   (c) Pericardial effusion with diastolic collapse of the right atrium is a sign of cardiac tamponade requiring immediate aspiration under echocardiographic guidance.
4. Therapy
   (a) Excessive fluid therapy and agents that increase afterload should be avoided.
   (b) Dobutamine and low-dose epinephrine are reasonable first choices. Milrinone is commonly used in infants after cardiac surgery.
   (c) Ensuring patency of the ductus arteriosus and an interatrial shunt is critical for certain cyanotic congenital heart diseases.

E. Hypoxia-Ischemia and Therapeutic Hypothermia (TH)
1. Pathophysiology
   (a) Circulatory impairment is common in hypoxic ischemic encephalopathy (HIE) and, if not appropriately managed, will result in worsening of preexisting multi-organ injury.
   (b) Bradycardia resulting in decreased cardiac output, RV dysfunction, and PHT are known associations with HIE and TH.
2. Clinical Evaluation
   (a) Standard assessments (temperature, capillary refill, and pulse volume) have limited usefulness in the setting of TH.
   (b) Seizures and the need for anticonvulsant therapy can result in significant hemodynamic disturbances.
3. Supplemental Testing
   (a) Early echocardiographic assessment may help identify myocardial dysfunction that is not clinically apparent.
   (b) Cardiac troponin I and electrocardiography may help to objectively quantify myocardial injury and ongoing monitoring.
4. Therapy
   (a) Judicious use of fluids taking care to avoid overload.
   (b) RV dysfunction and PHT are best managed by reducing pulmonary vascular resistance. In rare cases of refractory PPHN, therapeutic hypothermia may have to be discontinued or escalated to ECMO support if available (Fig. 56.3).

F. 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 but are supplying adequate oxygen to their vital tissues.
   (c) Hypotensive babies with good clinical perfusion can have good outcomes without intervention.

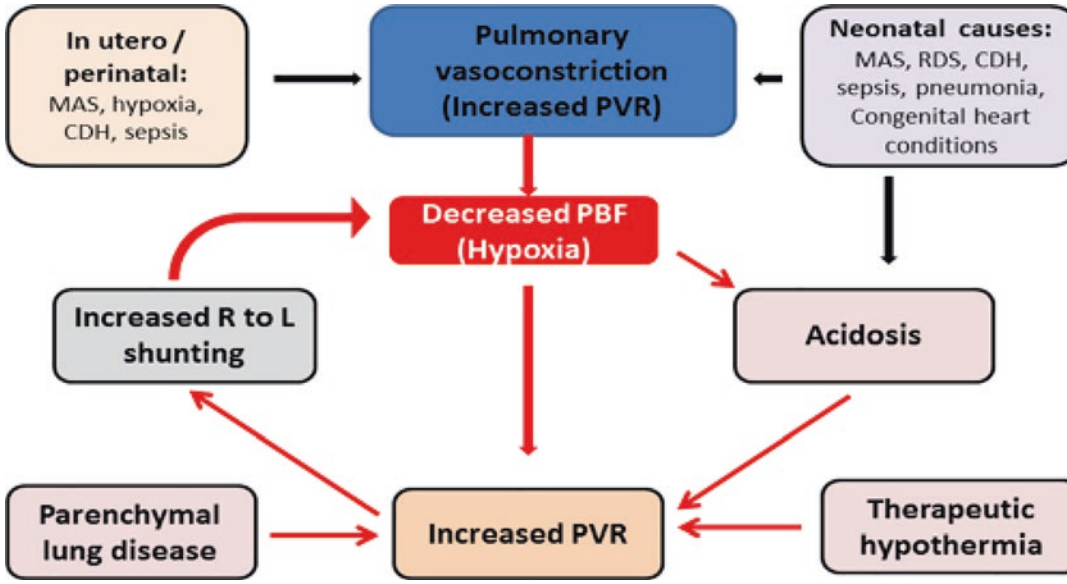

Fig. 56.3 Hypoxic-ischemic encephalopathy and PPHN pathophysiology

(d) Hypotension in association with poor perfusion is a very hazardous situation with poor outcomes; some babies in this situation are septic, and others may have primary cardiac dysfunction.

(e) Hemodynamically significant PDA resulting in a high volume shunt can cause reduced cardiac output, diastolic hypotension, and impaired organ perfusion in the first week of life.

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 and requires treatment.
   (b) The clinical evaluation includes heart rate, capillary refill, warmth of periphery, 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 in the first 24–48 hours is associated with increased risk of intraventricular hemorrhage and poor long-term outcome).
   (b) A structured assessment for the hemodynamic significance of a PDA may be warranted within the first 72 hours of life in extremely preterm neonates to decide on therapy.
   (c) An elevated or rising serum lactate is a sign of inadequate tissue oxygen delivery. A combination of an elevated lactate and prolonged capillary refill is associated with low systemic perfusion.
   (d) Near-infrared spectroscopy (NIRS) to measure cerebral fractional oxygen extraction seems promising, 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, epinephrine (or perhaps a combination of dopamine and dobutamine) is physiologically justified. In babies with reduced cardiac output but normal blood pressure in first 72 hours (in the absence of sepsis), dobutamine is recommended.
(c) Fluid boluses are over-used and infants are rarely hypovolemic. It should only be used in the presence of a history compatible with volume loss; 10 mL/kg of normal saline can be tried empirically.
(d) Corticosteroid administration in preterm infants for hypotension has been associated with increase in BP and reduction in the duration of inotrope use.
(e) Management of PDA in the extremely preterm infant is controversial. Early targeted intervention based on the hemodynamic significance of the shunt and utilizing predictive factors that indicate spontaneous closure appear to be the way forward.

Suggested Reading

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Nutritional Support in Respiratory Failure

57

David H. Adamkin

I. Introduction

Respiratory distress syndrome (RDS) remains a leading cause of neonatal morbidity despite new strategies with surfactant and both invasive and noninvasive mechanical ventilation. Nutrition also plays a key role in the support of these infants and in the prevention and management of bronchopulmonary dysplasia (BPD).

The neonatal period for the very-low-birth-weight (VLBW) infant, i.e., <1500 grams, represents a time in which the brain is highly vulnerable to nutritional deficits; therefore, attention to detail of nutritional management is critical for these infants who have missed the last trimester of pregnancy and are more likely to develop RDS. This study shows how important nutrient intake in the first 2 weeks of life is for brain growth and development.

A. Forty-nine infants with approximate gestational age of 27 weeks had serial MRI scans at 29, 32, and 41 weeks' postmenstrual age (PMA). Results showed that greater enteral nutrient intakes predicted:
   1. Increased total brain and basal nuclei volumes over the course to term equivalent age.
   2. Greater fractional anisotropy values in selected white matter tracts indicative of increased neurodevelopment.
   3. Brain growth predicted psychomotor outcomes at corrected age of 18 months.
   4. Duration of assisted ventilation was associated with smaller brain volumes which was attenuated by higher energy intakes.

   The relationship between early nutrition and its impact on severity of illness in extremely-low-birthweight (ELBW) infants (birthweight <1000 g) also indicates why nutrition is so important in infants with RDS.

B. 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

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(b) An increased risk of BPD
(c) An increase in neurodevelopmental impairment
(d) Decreased growth velocity of 2 g/kg/d 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/d versus the more ill babies at 42.7 cal/kg/d for the week.
   (c) However, fluid intake was greater in the more ill babies versus the less ill (130 mL/kg/d compared to 123 mL/kg/d, 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.
      1. If the more critically ill babies received the same nutrition as the less critically ill, then for each increase of 1 cal/kg/d 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

C. The following lessons are learned from this study:
1. Early nutritional decisions for 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 better 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 in 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.

D. Conclusions that optimize nutritional support for these infants include:
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 supported with higher protein containing human milk fortifiers, preterm formulas, and caloric dense strategies for volume-restricted infants.

   The American Academy of Pediatrics (AAP) handbook on Pediatric Nutrition eighth edition states “Current recommendations for parenteral and enteral nutrition for very preterm infants are designed to provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age, and to maintain normal concentrations of blood and tissue nutrients.”

E. A principal reason that preterm infants do not always grow as the normal fetus does has to do with inadequate nutrition.

1. Inadequate nutrition may be evidenced by cumulative deficits in energy and protein.
2. We are practicing more aggressive and optimal nutrition, but still many ELBW infants still experience inadequate nutrition with postnatal growth failure.
3. Historically, there have been several common causes of inadequate nutrition in these VLBW infants. The next study, while older, before early TPN with higher protein was embraced, and prior to the arrival of higher protein containing formulas and human milk fortifiers, demonstrates what cumulative deficits in energy and protein look like and how they affect meeting nutrient goals for growth.

F. Sixty-nine ELBW infants were divided into those <750 g birthweight and 751–1000 g birthweight and had dietary intakes, weight, and head circumference data collected until discharge.
   1. Figure 57.1 demonstrates cumulative protein deficit over the first 12 weeks of life through discharge.
   2. The graph shows that the largest accumulation of protein deficit is week 1 of life, as protein intake received by the two weight groups is contrasted with the reference requirement of 3.85 g/kg/d. Protein deficit is shown by the open bars. Week 1 was predominantly TPN, and as mentioned above, first week protein intakes are higher now.
   3. In week 2 and weeks 3–12, the deficit lessens but is still present.
   4. Figure 57.2 shows the relationship between enteral protein intake and weight gain. Each additional gram of protein was associated with weight gain of 6.5 g/d. The correlation between protein dose and weight gain was 0.45, meaning over half of growth velocity was related to something other than protein intake, meaning other factors clearly also affect growth. These infants received an average of 3 g protein and 100 cal/kg/d of energy, respectively. They grew identically to a fetus with a growth rate of 15 g/kg/d.

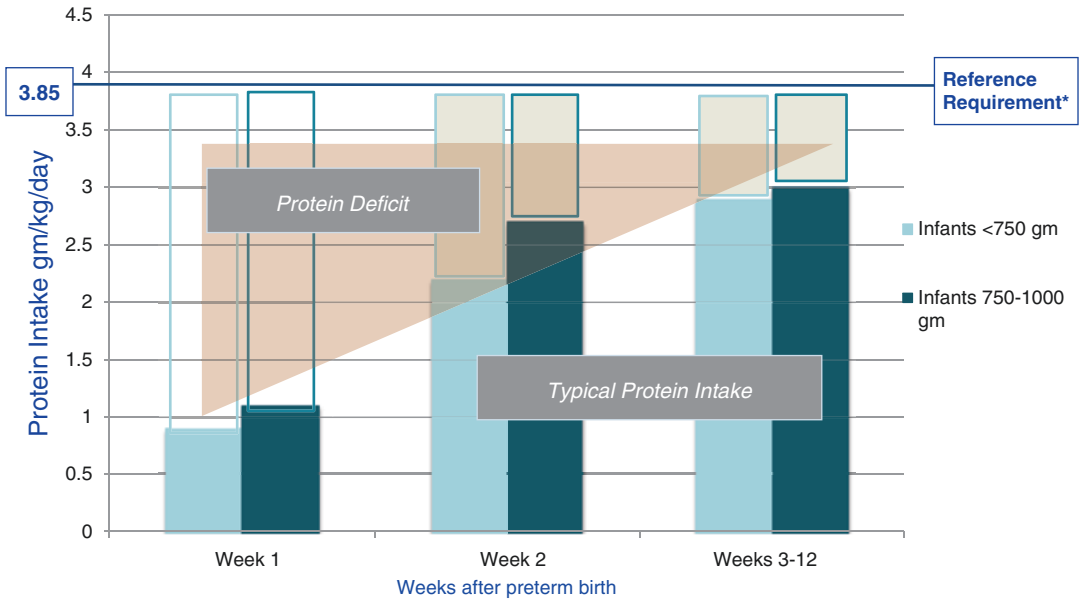
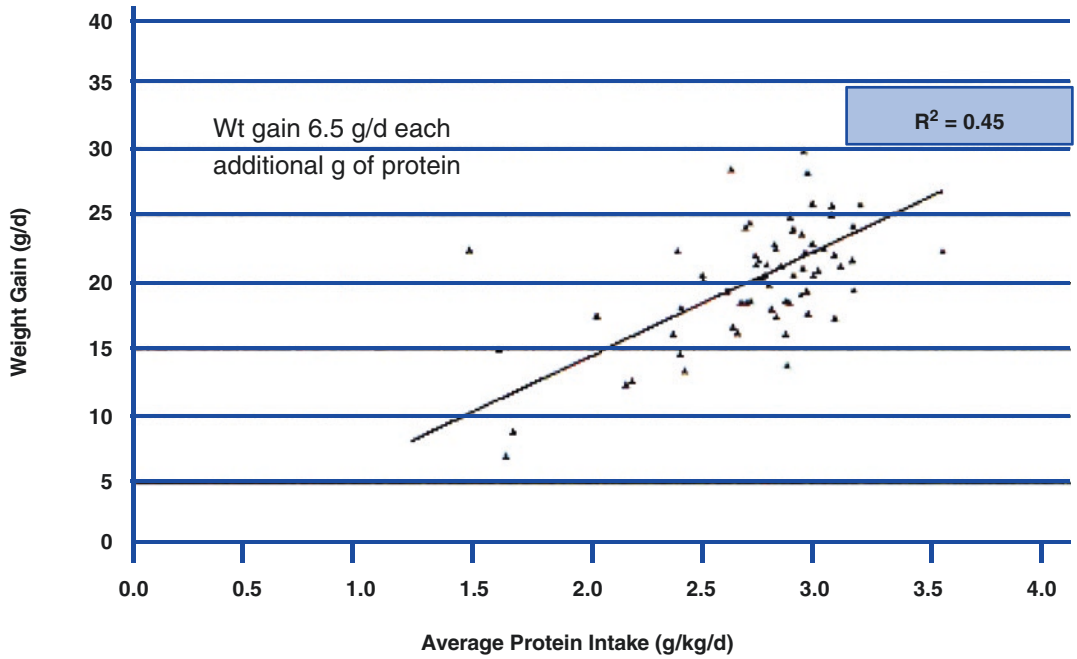


Fig. 57.1 The cumulative protein deficit*. (*Graphic adapted from Ernst et al. Journal of Perinatology 2003 with reference requirement based on intrauterine protein accretion rate from Ziegler EE World Review Nutr Diet 2014)



N = 69 infants <1000 g.

Fig. 57.2 Enteral protein intake associated with (15 g/k/d) improved weight gain (3 g prot and 100 cal/k/d) goal 18 g/k/d. (Ernst KD, et al. J Perinatol 2003;23:477–82. Reproduced with Permission)

5. Figure 57.3 shows enteral protein intake associated with improved head circumference gain. The growth rate was 0.7 cm/week. Forty-seven percent of variation in head circumference growth was not related to protein intake.
6. Goals for weight gain and head circumference adapted from the NICHD dataset from the large observational study are 18 g/kg/d and 0.9 cm/week, respectively, for weight and head circumference, which were associated with improved growth and neurodevelopment on follow-up.

G. Two studies modeled after the ESPGHAN recommendations demonstrate how we have progressed with more aggressive nutrition and the availability of higher protein preterm formulas and the advent of human milk fortifiers.
1. A European study included 102 VLBW with average birthweight of 1 kg.
   (a) The average protein for day 1 is 2.4 g/kg/d, for days 1–7 is 3.2 g/kg/d, and birth through discharge is 3.7 g/kg/d.
   (b) Energy for day 1 was averaged 38 cal/kg/d, days 1–7 was 80 cal/kg/d, and birth through discharge was 122 cal/kg/d.
   (c) Postnatal weight loss and lowest Z score were limited to the first 3 days. Maximal weight loss was 8+ 5%, and return to birthweight was 7 + 3 days.
   (d) This shows the impact of aggressive nutrition strategies.
   (e) Growth was also around fetal growth rate for the entire stay.
2. Finally very recent a cohort of ELBW infants from New Zealand and Australia in ELBW included 434 infants from 8 centers. This was a prospective randomized controlled trial.

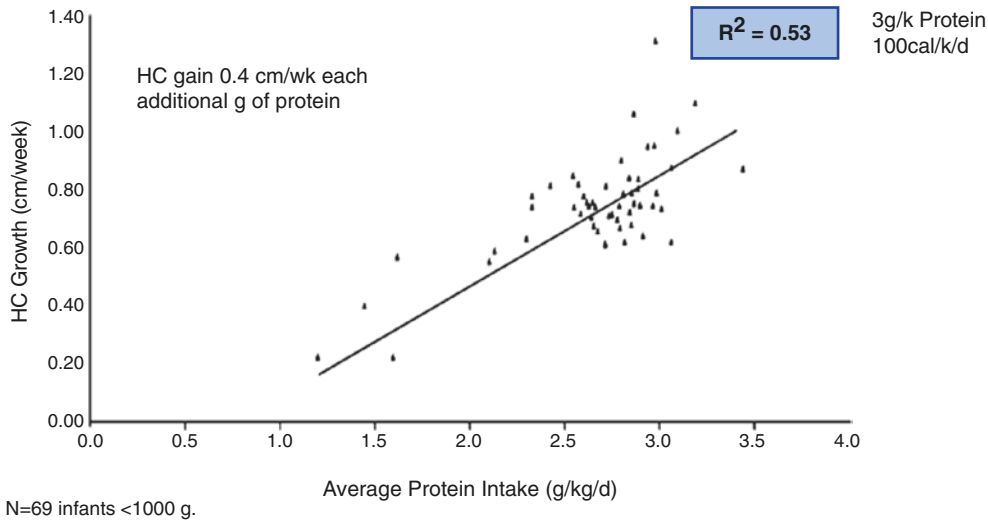


Fig. 57.3 Enteral protein intake associated with improved head circumference gain (0.7 cm/wk) goal 0.9 cm/wk. (Ernst KD, et al. J Perinatol 2003;23:477–82. Reproduced with permission)

(a) Following ESPGHAN recommendations for protein and energy, they found that changes in negativity of z scores were found to be improved and correlated to protein intake.
(b) Head circumference z scores were significantly improved with each 1 g/kg/d of protein.
(c) Correlations between nutrition and growth, and the observed differences in nutrition among sites, indicate there may be potential to improve growth with enhanced nutrition practices with best practices among sites.
(d) First week protein was 3.3 g/kg/d, 14 day was 3.5 g/kg/d, and 1 month was 3.5 g/kg/d. Energy was 76 cal/kg/d at week one, 92 cal/kg/d at 14 days, and 109 cal/kg/d at 1 month.
(e) Growth was greatest for those infants receiving the highest quintile of protein and had fourfold higher odds of achieving target growth compared to babies in middle quintile.

As we look at almost 20 years of typical studies, we see improvement in intakes, but growth differences perhaps are not as dramatic as we might have anticipated. We also see institutional variety in practice. We will review strategies for these VLBW infants with respiratory distress next but must be aware that there is still the perception that when anything goes wrong with the VLBW infant, feeding must be decreased, delayed, interrupted, or withheld. These perceptions cause nutritional delays and under-nutrition and delayed growth. They are not helpful in treating the VLBW infant suffering with RDS.

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 comorbidities of hyperglycemia and non-oliguric hyperkalemia
6. Synergy with early enteral feedings to maintain growth
7. Enhancing neurodevelopmental outcome

H. The guiding principle for all nutritional strategies is that undernutrition is, by definition, non-physiologic and undesirable. Any measure that diminishes under-nutrition 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 with 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 with term formula.
   3. The NICHD growth observation study alluded to earlier 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.

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 are:
      (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. It does not provide requirements for catch-up. This is the so-called Ziegler reference fetus.
      (b) Empirical method looks at actual intakes clinically 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. It also does not include many ELBW neonates.
   2. Table 57.1 shows requirements for protein and energy as best estimates by factorial and empirical methods.

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.

Table 57.1 Requirements for protein and energy: best estimates by factorial (fetal) and empirical methods

Body weight, g	500–1000	1001–1500	1501–2000
Weight gain of fetus g/kg/d	19.0	17.4	16.4
Protein, g/kg/d	4.0	3.9	3.7
Energy, Kcal/kg/d	106.0	115.0	123.0
Protein/energy, g/100 kcal	3.8	3.4	3.0

Adapted from Ziegler EE World Rev. Nutr Diet 2014. (Reproduced with permission Karger)

TPN should be considered as a short-term bridge to provide nutritional support until full enteral nutrition can be provided.

C. Energy expenditure measurements in critically ill VLBW receiving assisted ventilation are extremely difficult to perform using existing measurement techniques. Collectively, studies suggest a mean energy expenditure of approximately 54 kcal/kg in the first week of life.
   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. In general, a total energy intake varying from 90 to 100 kcal/kg/d is sufficient for most neonates receiving mechanical ventilation as long as they are normothermic and receiving parenteral nutrition. Additional intakes from 10 to 20 kcal/kg/day to reach 120 kcal/kg/d are indicated for infants who are premature, physically active, and receiving full enteral feedings.
   4. Intravenous carbohydrates should supply 50% of total calories in TPN. Glucose infusion rate (GIR) will depend on 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 glucose infusion rate. The three different colors indicate the following: first, where energy will be inadequate, insulin should be considered because of glucose intolerance and the infant will be catabolic (<4 mg/kg/min); next color the acceptable GIR 4–13 mg/k/min depending on the phase of TPN; and final color where GIR >13 mg/k/min which is excessive and where lipogenesis occurs as glucose is converted to lipid.
      (a) A steady infusion of 6–8 mg/kg/min of glucose should be provided parenterally.
      (b) GIR (mg/kg/min) = % glucose × total mL × 100 mg ÷ 1440 (minutes/day) ÷ wt (kg) (Table 57.2).
      (c) Glucose intake of >18 g/kg/d or >13 mg/kg/min or >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 and is especially undesirable for a baby on assisted ventilation.
      (d) Glucose intakes at or below energy expenditure have no effect on respiratory gas exchange (CO_2 production).

Table 57.2 Quick calculation rate of glucose infusion rate (GIR)

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

Chowning R and Adamkin DH J of Peri 2015. (Reproduced with permission)

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 stimulated by specific parenteral amino acids explain 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.

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 the first hours of life to prevent excessive catabolism by providing energy and protein and to prevent hypocalcemia, hyperglycemia, and non-oliguric hyperkalemia. This nutritional strategy initiates efforts at preventing growth failure in ventilated ELBW infants and avoids metabolic abnormalities. Lipids may or may not be included in the initial prescription or added on the first or second day of life.
   2. This early TPN may include as little as 40 cal/kg/d. The energy intake should be increased as quickly as possible. Transition from early TPN to full TPN should be accomplished within 3 days of birth. This will be dependent on whether the ELBW infant tolerates glucose and/or lipids to reach the nutrient targets. Although energy intakes of 40 cal/kg/d and protein intakes of 1–1.5 g/kg/d are probably sufficient to limit catabolism on early postnatal days, much higher energy intakes are needed to achieve near-normal rates of growth. Traditionally, protein and lipid intakes were slowly increased over the first days of life, but there is evidence that shows that this slow advancement is not necessary in most VLBW infants.
   3. A moderate increase in blood urea nitrogen (BUN) after the start of TPN amino acids is usually not adverse or a sign of toxicity; rather, it is related to metabolism of the amino acids. Just as in utero the early fetus uses half of the amino acids from the placenta to metabolize for energy, producing carbon dioxide and ammonia, which is converted to urea. The early fetus has a higher BUN than the mother because of this use of amino acids for energy, which we are duplicating in the first hours of life with early amino acids with stock solutions.
   4. Several controlled studies have demonstrated the efficacy and safety of amino acids initiated within the first 24 hours after birth. No recognized metabolic derangements, including hyperammonemia, metabolic acidosis, or abnormal aminograms, have been observed.
   5. A minority of patients, especially those with <25 weeks of gestation, may develop hyperazotemia with BUN values exceeding 50 mg/dL, and occasionally the parenteral amino acid dose 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. Amino acid dose does not directly correlate with BUN. An elevation of BUN is also related to acuity of illness, state of hydration, and renal function.

6. 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 deficiency 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 which is very desirable in babies with RDS.
7. 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.
   A. Early TPN amino acids may be initiated with a stock solution of 4% to easily provide 2.4–3.0 g/kg/d 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%.
   B. Parenteral amino acid intakes of up to 4.0 g/kg/d for ELBW infants may be used when enteral feedings are delayed or withheld for prolonged periods. Otherwise, 3.5 g/k/d has more evidence.
   C. Intake of amino acids should not exceed 12% of total calories.
8. Intravenous lipids serve as a source of linoleic acid to prevent or treat essential fatty acid deficiency (EFAD). Essential fatty acid deficiency can occur within the first week of life or as early as the second day of life in the tiniest babies on assisted ventilation. Larger quantities serve as a partial replacement for glucose as a major source of calories (balanced TPN).
   A. Use 20% lipid emulsion to decrease risk of hypertriglyceridemia, hypercholesterolemia, and hyperphospholipidemia.
   B. Premature infants can clear 0.15–0.2 g/kg/h of lipids. Lipid infusion hourly rate correlates best with plasma lipid concentrations. Therefore, hourly infusion should not exceed 0.15–0.20 g/kg/hr. However, SGA infants and infants with sepsis may not be able to clear standard doses of intravenous lipids and will demonstrate hypertriglyceridemia and should be monitored more frequently. We check triglycerides after initiation and with any dosage advancement. We accept triglycerides between 180 and 200 mg/dL before lowering the dosage.
   C. Lipids are typically initiated at 1–2 g/kg/d and can be safely started with initial TPN or the next day.
   D. Lipids should be infused continuously over 24 hours which is better tolerated than infusions of 15–22 hours daily.
   E. Dose of lipids should be advanced to 2–3 grams as tolerated to ensure adequate caloric intake.
9. Total Parenteral Nutrition (TPN) Issues with RDS
   A. 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. Of course, enteral nutrition with colostrum and human milk should be initiated as early as possible.

B. TPN is usually continued until enteral feedings are providing sufficient volume and protein to replace TPN. The transition from TPN to enteral feeding especially with human milk is critical in preventing postnatal growth failure and will be discussed below.
C. 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.
   1. 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.
   2. There are also significant losses of vitamin A into the delivery system used for parenteral nutrition.
      (a) Over 15 years ago, a large randomized controlled trial was performed in 807 premature infants with a birth weight of <1 kg who received 5000 IU of vitamin A IM three times per week for the first month of life.
      (b) 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 because of that reason as well as the discomfort associated with injections.

10. The "routine" use of intravenous lipid emulsions has not been universally accepted in critically ill ventilated ELBW infants because of potential pulmonary complications.
    A. 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/hr).
    B. In an effort to reduce risk of liver toxicity, alternative forms of intravenous lipid solutions instead of the standard soy solutions have been developed based on fish oil (Omegaven) or a combination of soy, medium-chain triglycerides, and olive oil and fish oils (SMOF lipid). These provide docosahexaenoic acid, an important nutrient for visual and cognitive development. It is found in human milk and may also be associated with lessening the risk of BPD.
    C. A recent systematic review and meta-analysis included 22 studies and almost 4000 infants. Thirteen studies compared the SMOF lipid versus soy lipid solutions, and there was no difference in risk of BPD between the two lipid solutions.
    D. Another recent study compared SMOF lipid with soy-based lipid among over 700 VLBW infants and found no significant difference in death or neurodevelopmental impairment. However, language scores on the Bayley III of <85 and <70 were significantly less with SMOF lipid.
    E. A study from the Netherlands looked at the safety and efficacy of early TPN lipid and higher dose of amino acids to VLBW infants and included 144 with gestational age around 27 weeks.
    F. Controls received 2.4 g/kg of amino acids only, the first intervention was 2.4 g/kg of amino acids with 2–3 g/kg/d of fat, and the second intervention was 3.6 g/kg of amino acids with 2–3 g/kg of fat soon after birth.
    G. Hyperglycemia was 6% in controls vs over 20% in the interventions. Therefore, over 20% in interventions received insulin. It was felt the fatty acids from early TPN lipid competed with glucose for oxidation and inhibited insulin.

H. Also using triglyceride levels >265 as abnormal (higher than our suggested limit), 44% had to have their lipids decreased.
I. There were also no differences in growth and the incidence of BPD.
J. They concluded that early higher dose lipids from birth were tolerated in VLBW infants. However, between hyperglycemia at 24%, lipid adjustments at 44%, and BUN adjustments for >28 mg/dL (lower than a value used in USA) in 80% of the patients. Therefore, the majority of the patients did not reach desired goals of study for protein or lipids.
K. An editorial questioned whether or not their conclusion about tolerance of lipids and protein in the first days of life was correct. The values they used for managing BUN, glucose, or lipids led one to question whether it was safe or worth it.
L. 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.
M. Fig. 57.4 shows that the high polyunsaturated fatty acid content of soybean lipid emulsions as linoleic acid may lead to pathways resulting in elevated vasoactive prostaglandins, leukotrienes, and thromboxanes through their conversion from arachidonic acid. This may exacerbate pulmonary hypertension.
N. 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).
O. Initiate lipids the day following birth after starting the amino acid stock solution at a dose of 1.0 g/kg/day for ELBWs with respiratory disease, although some consider initiating with TPN without using a stock solution.
P. Plasma triglycerides are monitored after each increase in dose, and levels are maintained at 180–200 mg/dL.

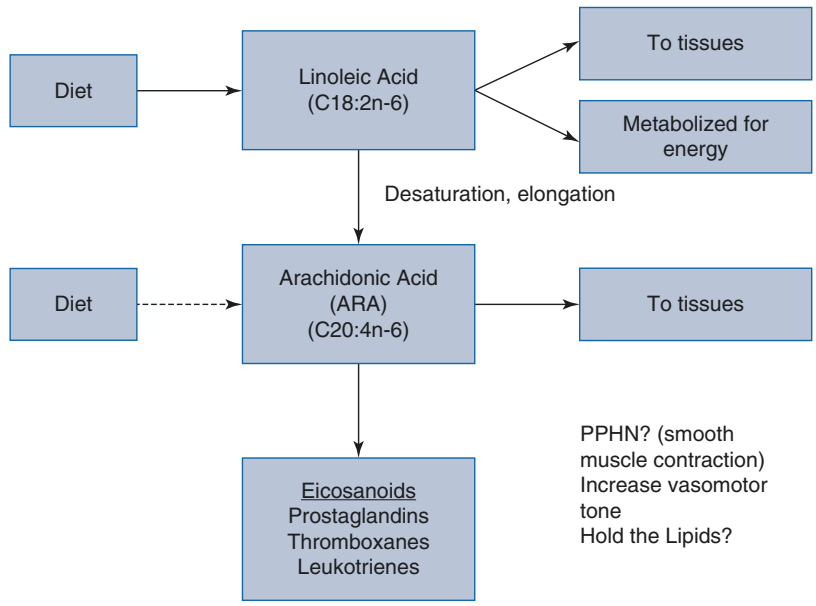


Fig. 57.4 Metabolic derivatives of linoleic acid and ARA. (Adamkin DH Nutritional Strategies VLBW Cambridge Press 2009. Reproduced with Permission)

Q. Maximum lipid administration is usually 3 g/kg/d over 24 hours of infusion to not exceed 0.2 g/kg/h.

11. Transitioning from TPN to Enteral Nutrition and the Prevention of Postnatal Growth Failure
    A. A recent study showed a 50% rate of postnatal growth failure among VLBW infants. The study divided nutritional management into three phases, TPN, transition, and exclusive full enteral nutrition.
    B. The growth failure was linked to inadequate protein during the transition phase from TPN to enteral nutrition particularly associated with the use of human milk that had not been fortified yet.
    C. For example, an infant weaned off TPN when the enteral feeding volume of unfortified human milk reached 100 mL/k/d would provide a protein from its own mother's milk of approximately 1.4 g/kg/d. If that infant was on donor milk, the protein would be even less at 1.0 g/kg. Remember the requirement from the reference fetus is 4.0 g/kg/d.
    D. If the milk had been fortified at 40–60 mL/kg/d, the protein would be around 3.0 g/kg/d in the mother's own milk but lower with the donor milk, still not reaching the desired 3.5–4.0 g/kg/d.
    E. Therefore, an additional 0.5–1.0 g/kg would still be necessary with TPN to prevent this dip in protein during transition associated with postnatal growth failure.
    F. Therefore, continue TPN protein until enteral feeds reach 120 mL/kg/d. Calculate the protein to reach 4 g/kg/d when transitioning to human milk feedings, fortify earlier, and use TPN protein supplement until enteral feeds reach 120 mL/kg/d.
    G. The infants did not receive adequate protein during the transition which correlate with growth failure and can be resolved with earlier fortification of human milk (40–80 mL/kg/d) and continuing supplemental TPN protein at 0.5–1.0 g/kg/d.
12. Enteral Nutrition

    Enteral protein feeding requirements are shown in Table 57.1. It shows that as weight increases, the protein requirement decreases a bit and energy increases. The protein energy (P/E) ratio decreases. Protein (g) in the numerator is decreasing and energy is increasing in the denominator, so P/E ratio of grams of protein per 100 calories decreases. This is very important for all preterm infants and very helpful as we discuss management of fluid-restricted babies with BPD because the ratio affects the proportionality of growth. The relationships between protein and energy to promote lean body mass and limit fat accretion are shown in Fig. 57.5.

    A. 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 important and must be addressed to allow catch-up growth to occur and improve both growth and neurodevelopmental outcome.
    B. An increase in the protein/energy ratio of feeding is mandatory to improve the lean body mass accretion and to limit fat mass deposition (Fig. 57.5).
    C. Human milk plays a significant role in promoting lean body mass and avoidance of maldistribution of adipose tissue.
    D. Table 57.3 shows current enteral nutrition requirements for VLBW infants. These apply to stable growing preterm infants through 1800 g. It shows a range of protein intake and energy ratio for these preterm infants.
    E. Our newer preterm formulas and new human milk fortifiers have increased the protein levels which will impact the proportionality of growth by enhancing the P/E ratio.

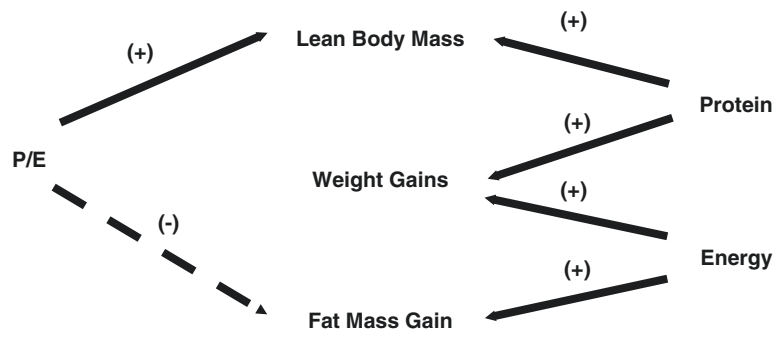


Fig. 57.5 Impact of protein/energy (P/E) ratio on body composition. (Rigo J, Senterre J. J Pediatr. 2006;149:S80-S88. Reproduced with permission)

Table 57.3 Nutrient comparisons of caloric dense preterm infant formulas per 100 kcal

Nutrient	27 kcal/oz (SSC 24 HP + SSC 30)	SSC 30	EPF 30	30 kcal/oz (SSC 24 + Polycose® + MCT oil)
Protein (g)	3.15	3.0	3.3	2.2
Fat (g)	6.09	6.61	5	5.53
CHO (g)	8.9	7.73	10.8	10.73
Ca (mg)	180	180	165	133
P (mg)	100	100	90	74
Vitamin D (IU)	150	150	300	122
mOsm/kg/H20	305	325	320	N/A
Volume (mL)	111	99	100	100

Abbott Nutrition, Columbus, Ohio, Mead Johnson Nutritional, Evansville, Indiana 2020

F. Human milk, beyond the initial trophic feeds, either from mother's own milk or from pasteurized donor human milk, is a priority for all preterm infants. This is supported by the American Academy of Pediatrics (AAP).
G. The AAP recommendations on breastfeeding management or preterm babies in 2012 included the numerous potent benefits with human milk, and since then a German Neonatal Network study showed a reduction in BPD with human milk. Mother's own milk (fresh or frozen) should be the primary diet and requires a multi-nutrient fortifier to meet the nutritional demands.
H. For example, Fig. 57.6 clearly shows that human milk requires fortification to meet the protein nutritional needs of VLBW infants where the protein requirement for such

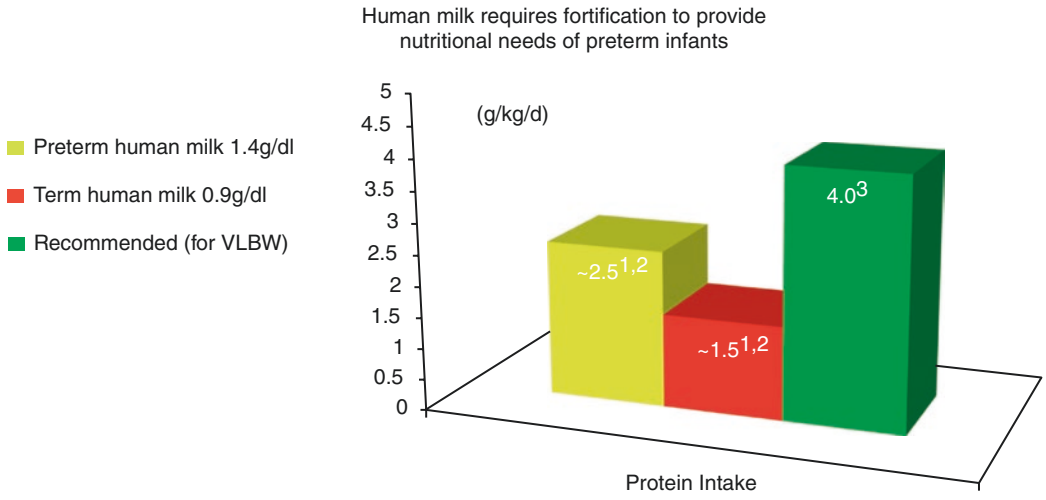


Fig. 57.6 Human milk alone does not meet the nutritional needs of VLBW infants. (Adapted from Adamkin and Radmacher SFNM 2017)

a VLBW infant is 4.0 g/kg/d. For example, such an infant taking its own mother's milk would receive around 2.5 g/kg/d of protein on full feeds, while the same infant on pasteurized donor milk would receive 1.5 g/kg/d. Both are far short of the 4.0 g/kg/d requirement for protein (Fig. 57.7).

I. The need for human milk fortification particularly for protein and minerals calcium and phosphorous came from clinical observations and dietary trials.

J. There are some nutrient differences among the fortifiers available as well as sources of protein. The majority of human milk fortifiers have bovine (cow) milk as their base, with one fortifier with donor human milk as the base.

K. For optimal growth as mentioned above, premature infants need fortification of human milk to meet their increased nutrient needs. Table 57.4 shows the recommendations for macronutrients and important micronutrients used to develop the fortifiers.

L. The ranges of nutrients provided with fortified own mother's milk or fortified donor milk vs the requirements and also unfortified human milk vs the requirements are shown (Table 57.4).

M. Preterm formulas and supplemented human milk provide protein intakes of 3.6–4.8 g/kg/d at an energy intake of 120 kcal/kg/d. The "higher" protein preterm formulas with P/E ratio of 3.3–3.6 instead of 3.0 in standard preterm formula will promote more lean body mass accretion when meeting a protein requirement of 4.0 g/kg/d than will the standard preterm formulas which must be fed at higher volumes (165 mL/kg and 132 cal/kg/d) and excessive energy to achieve 4.0 g/kg/d.

The higher protein levels found in the sterile concentrated liquid bovine fortifiers and preterm formulas allow for catch-up growth and protein sufficiency.

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 devel-

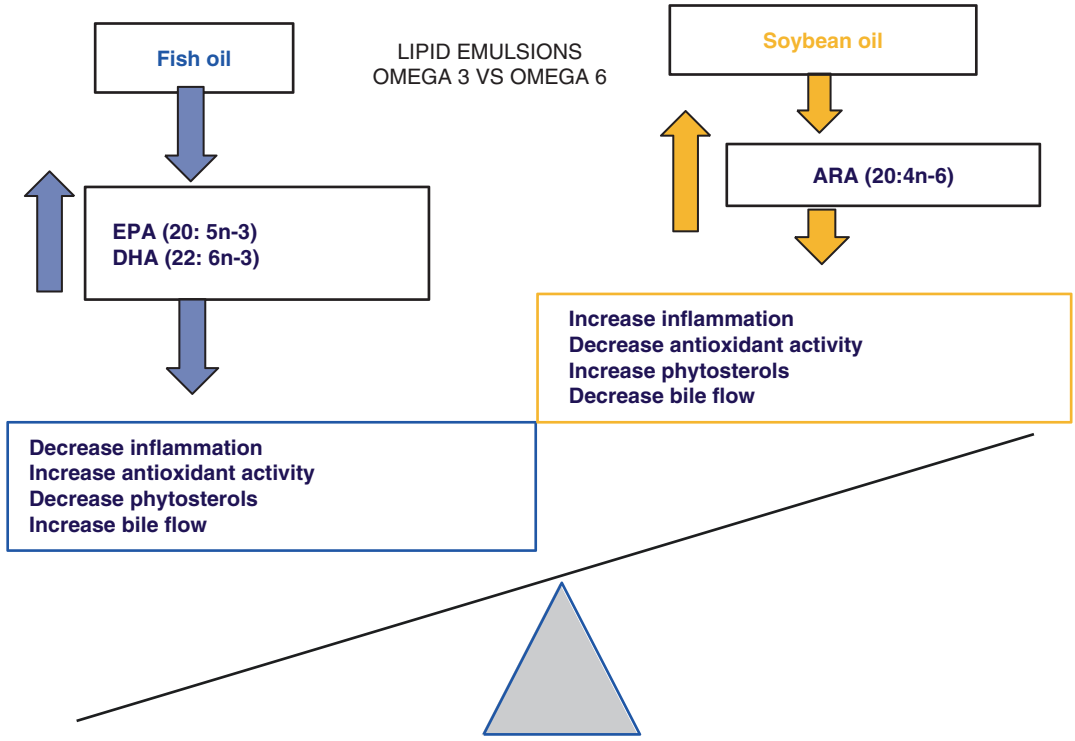


Fig. 57.7 Lipid emulsions omega 3 vs omega 6

oping BPD or those with established BPD. The general measures provided to babies with established BPD include:

A. Adequate nutrition to promote growth and lung healing.
B. Fluid restriction without causing disproportional growth.
C. Understanding the importance of early nutrition on outcomes like BPD.
D. As discussed earlier, early nutrition which can mitigate severity of illness if we do not allow our perceptions of severity of illness to limit nutrition unnecessarily.
E. Caloric dense enteral feedings (>24 kcal/ounce) which 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/d from return to birthweight to discharge and had the worst growth and developmental outcomes at 18–22 months.
    2. Table 57.5 shows the nutrient comparisons among caloric dense preterm formulas that are available today and to a strategy used before these caloric dense formulas became available.
    3. Before the advent of feeding 27 and 30 calorie per ounce formulas, many clinicians would devise their own “recipes” to make a 30 cal/oz. milk by adding glucose polymers and MCT oil to a base of 24 cal/oz. preterm formula. The resultant P/E ratio of this was 2.2 g protein/100 calories of energy. This inadequate protein w ll only promote the

Table 57.4 Enteral nutrient requirements for fully enterally fed preterm VLBW infants (<1500 g)

Nutrient	Koletzko, et al. 2014	ESPGHAN, 2010
Fluid	135–200 mL/kg	135–200 mL/kg
Energy	110–130 kcal/kg	110–135 kcal/kg
Carbohydrate	11.6–13.2 g/kg	11.6–13.2 g/kg
Protein	3.5–4.5 g/kg	4–4.5 (<1 kg) 3.5–4 (1–1.8 kg)
Fat	4.8–6.6 g/kg	4.8–6.6 g/kg
DHA	55–60 mg/kg	12–30 mg/kg
AA	35–45 mg/kg	18–42 mg/kg
Calcium	120–200 mg/kg	120–140 mg/kg
Phosphorus	60–140 mg/kg	60–90 mg/kg
Magnesium	8–15 mg/kg	8–15 mg/kg
Sodium	3–5 mEq/kg (69–115 mg/kg)	3–5 mEq/kg (69–115 mg/kg)
Potassium	2–5 mEq/kg (78–195 mg/kg)	1.7–3.4 mEq/kg (66–132 mg/kg)
Chloride	3–5 mEq/kg (105–177 mg/kg)	3–5 mEq/kg (105–177 mg/kg)
Iron	2–3 mg/kg	2–3 mg/kg

Abbreviations: *DHA* docosahexaenoic acid, *AA* arachidonic acid, *VLBW* very low birth weight

growth of fat and not lean mass but was the only way to make a concentrated milk with caloric density above 24 cal/oz.

4. Using the ready-to-feed 30 cal/oz. milk, a protein of 3.0 g/kg/d can be reached even at 100 mL/kg/d. At 130 mL/kg/d, the protein is 3.9 g/kg/d. Using the 27 cal/oz. formula at 130 mL/kg/d, one can provide 3.5 g/kg/d 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/oz. human donor concentrated product, a volume of 120 mL/kg/d will provide approximately 4.0 g/kg/d.
6. In a study including 200 ELBW infants, we diagnosed BPD in 45% of those with gestational age of 25 weeks and BW 739 grams using the oxygen requirement and X-ray findings at 36 weeks' PMA to make the diagnosis.
7. Their nutritional data showed the receipt of less protein and energy over the first 14 weeks of life and more reliance on TPN than those ELBW infants who did not develop BPD. Therefore, long before the diagnosis of BPD, these babies were on a different course nutritionally than their peers 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 that significant differences in growth and nutritional management had taken place for these infants over the decade.
10. That later cohort showed that two-thirds of ELBW infants with BPD were growing at or above the fetal weight gain rate of 15 g/kg/d. These infants were approximately 800 g BW and have 26 weeks' gestation. In fact, 40% grew at 18 g/kg/d, 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 latter group. The comparison of time to return to birthweight decreased from 20 days to 10 days, respectively, over the decade.

Table 57.5 Comparing fortifiers and fortification of own mothers milk versus donor human milk. Enteral nutrient requirements for fully enterally fed preterm VLBW infants (<1500 g)

Nutrient per 100 cal	2014 Global Expert Recommendation for Preterm Nutrition[a]	PHM	Range of nutrients provided by current US HMF when mixed with PTHM to 24 kcal/oz. at 150 ml/kg	Term/ donor HM	Range of nutrients provided by current US HMFs[b] when mixed with DHM to 24 kcal/oz. at 150 ml/kg
Protein, g	3.2–4.1 (3.5–4.5 g/kg/d)	2.1	3.2– 4.5[a]	1.40	3.06–3.9[a]
Carbohydrate, g	10.5–12	9.8	9.8–11.3	10.8	10.8–13.5
Fat, g DHA, mg ARA, mg	4.4–6.0 55–60 35–45	6 11.2 16.5	6.7–7.2 11.2–30 16.5–47.5	5.85	6.1–8.32
Calcium (mg)	120–200	33	120–180	33	143–209
Phosphorus (mg)	60–140	21	55–105	21	89–120
Vitamin D, IU	100–350	8	12–263	8	12–263
Iron, mg	2–3 mg	0.09	0.15–2.2	0.09	0.15–2.2
Osmolality, mOsm/kg H2O		290–320	330–450		

[a]Assumes 1.4 g/dL protein in preterm human milk and 0.9 g/dL in donor human milk
[b]Abbott Nutrition, Columbus, OH, Mead Johnson Nutrition, Evansville, IN, Prolacta Bioscience, Monrovia, CA
Koletzko et al. 2014 World Review of Nutrition and Dietetics, Karger (Reproduced with permission

12. There was initiation of amino acids at 3 hours 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 that were volume-restricted on diuretics as part of their management for their BPD.
14. Infants who end up with BPD often receive less energy and protein than those who do not go on to develop BPD.
15. They have variable increases of energy demands, oxygen consumption, carbon dioxide production, and resting energy expenditure. Their resting energy expenditure is associated with their respiratory status. Risk of postnatal growth failure correlates with higher rates of resting energy expenditure.
16. We can conclude that growth failure among VLBW is due to insufficient protein and must be prevented with strategies discussed.

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 oropharynx 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 swallowing 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 and sustain neurologic insults resulting in cerebral palsy, and those with tracheomalacia or subglottic stenosis from prolonged endotracheal intubation.
1. The clinical presentation of pathologic GER includes frequent gastric residuals, 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 and other serious complications. They should not be 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

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Surfactant Replacement Therapy

58

Fernando Moya and Manuel Sánchez Luna

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 more than three decades to prevent and treat respiratory distress syndrome (RDS) in preterm neonates. There are other neonatal diseases that feature an altered surfactant homeostasis for which therapy with surfactant has been suggested. 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, like dipalmitoyl phosphatidylcholine (DPPC), less phosphatidylglycerol (PG), 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 muco-ciliary transport, prevents the formation of edema, improves compliance, and contributes to lung defense against pathogens.

   A. Surfactant Phospholipids
      1. Pulmonary surfactant is a macro-aggregate 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

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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 within type II cells. This process needs the presence of the protein ATP-binding cassette transporter A3 (ABCA3; see below).

2. Phosphatidylcholine (PC) is the most abundant lipid (70–80%), whereas DPPC amounts to about 50% of this 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. At physiologic temperature DPPC is 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. Lipid-protein and protein-protein interactions in the pulmonary surfactant system have been recently reviewed in detail.

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 with evolving 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 on chromosome 2. Many such mutations have now been identified, usually inherited as an autosomal recessive condition.
   (c) Mutations in the SP-C gene located on 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 subgroup of the lectin superfamily. SP-A is encoded by two genes located on 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.
   (c) Other Important Surfactant Proteins
      (i) Adenosine-Triphosphate Binding Cassette A3 (ABCA3). It is a transmembrane protein encoded in chromosome 16 that transports DPPC and PG into lamellar bodies. Over 400 mutations of this gene have been reported, and they are the most common cause of hereditary respiratory failure in newborns.

(ii) Thyroid Transcription Factor 1 (TTF-1). The gene that encodes for this member of the homeobox transcription factor family is located on chromosome 14. TTF-1 has a critical role in transcription of surfactant proteins and ABCA3 as well in thyroid gland development. Lung disease resulting from mutations of the gene encoding for TTF-1 can be variable and may present like neonatal RDS, usually associated with hypothyroidism.

III. Exogenous Surfactants

For exogenous surfactants to be effective after administration, they should be able to adsorb into the lung air-fluid interface very rapidly, thereby achieving very low surface tension during expiration, as well as to re-spread efficiently during inspiration. 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.

IV. Types of Exogenous Surfactants

There are several exogenous surfactants currently available. Although all exogenous surfactants are not alike, they are generally grouped into two categories depending upon whether they derive from animal lungs or are of synthetic origin. New-generation synthetic surfactants contain peptides that mimic the action of SP-B and/or SP-C (Table 58.1). Their composition may influence their clinical behavior and efficacy.

A. Animal-derived surfactant preparations are purified and extracted with organic solvents from either lung minces or lung lavage from bovine or porcine sources. Some characteristics are listed below:

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 exert an effect on their short-term clinical performance. For instance, the concentration of SP-B is substantially lower in the lung mince preparation compared to surfactants extracted from lung lavage. The porcine-derived surfactant, poractant alfa, contains the most phospholipids per unit volume of all surfactants.
3. Synthetic surfactant preparations are composed of one or two phospholipids, usually DPPC and PG.
4. 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 and is mentioned only because the trials comparing animal-derived to synthetic surfactants are still quoted widely.
5. 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.
6. Another synthetic surfactant named CHF5633 that is composed of DPPC, POPG, and peptide analogs of SP-B and SP-C has been evaluated in preterm infants. In recent clinical trials, this new synthetic, protein-containing surfactant was shown to have comparable clinical responses to those seen after administration of poractant alfa. Preliminary long-term follow-up of infants treated with this surfactant is reassuring.

Table 58.1 Different surfactants commonly used 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 to 200 (1.25 to 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)
CHF5633[c]	Synthetic	DPPC and POPG	Peptides analogs of SP-B/SP-C	200 mg/kg	Max 2 doses, 100 mg/kg

[a]No longer available
[b]Not in clinical use as liquid instillate, under study in aerosolized form
[c]Manufactured by Chiesi Pharmaceuticals

7. If further studies of these entirely synthetic surfactants confirm their safety and efficacy, we may have an alternative to replace animal-derived surfactants altogether.

V. Surfactant Responses

The clinical response to exogenous surfactant administration can be generally 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 upon 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 (see Table 58.1).

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.

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), active infection, chorioamnionitis, or lung hypoplasia.
4. There is no proven benefit to giving more than two additional doses of surfactant. Also, the benefit of giving surfactant beyond the first 48–72 hours 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 allow the infant with RDS to accumulate a large amount of surfactant over many days.

VI. 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 minutes 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 that 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 2 hours of life) compared to classic rescue treatment.
      1. 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:
      2. 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. 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). 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 occur-

rence of other complications of prematurity has not been significantly reduced by surfactant therapy. 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 postdelivery stabilization as well as widespread use of antenatal steroids (usually over 80–90%).

3. Currently, surfactant is frequently administered using the INSURE (*in*tubate-*sur*factant-*e*xtubate) approach, in which surfactant is given after elective endotracheal intubation, followed by a variable period of mechanical ventilation and extubation. 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 infants at the highest risk for RDS, in which an endotracheal tube has already been placed during delivery room resuscitation, there is probably very little additional morbidity from giving surfactant, and this is recommended. Newer techniques for surfactant administration are discussed in detail later in this chapter.
4. Several recent randomized trials (COIN, SUPPORT, CURPAP, Vermont Oxford Trial of Delivery Room Management) 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 24 to <30 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, was 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 toward 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 were reported.
   (c) On the contrary, delaying surfactant administration may also increase the risks of pneumothorax and overall air leaks. In both the COIN and SUPPORT trials, more than 50% of infants <26 weeks randomized to CPAP were intubated early; thus it seems reasonable to consider giving surfactant to them once the endotracheal tube has been placed and they demonstrate the need for supplemental oxygen.
5. Clinical use of surfactant administration is based on the severity of the respiratory failure secondary to RDS. With widespread use of CPAP and other noninvasive techniques to stabilize preterm infant with respiratory distress, the FiO_2 threshold at which to administer surfactant has been re-evaluated. Recent large observational studies have shown that many preterm infants, especially those at earlier gestational ages, are either intubated in the delivery room or within the first several hours after birth. Additionally,

failure of CPAP and need for intubation frequently occur once the FiO_2 has risen past 30%. Also, other complications such as air leaks and other morbidities are seen more frequently among infants that surpass this threshold and have not received surfactant. Thus, currently the threshold to consider giving surfactant is defined by the need for a high FiO_2 (>30%) while on noninvasive respiratory support using appropriate mean airway pressures (usually 6 cm H_2O or more). Also, it is recommended to give surfactant if a premature infant is intubated and needs invasive mechanical ventilation soon after delivery and he/she is at risk for developing RDS.

The use of lung ultrasound is becoming more popular as it defines well the need of surfactant even earlier than the high FiO2 needs, with the advantage of being a noninvasive procedure that can be done at the bedside without adverse events.

VII. 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. 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. Despite 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 two decades ago and a recent systematic review comparing poractant to beractant, which showed a lower mortality favoring poractant. However, a more recent systematic comparison of beractant and poractant did not show differences in mortality.

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.

VIII. 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 minutes 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 in two aliquots (although some manufacturers recommend four aliquots) and administered via a 5 French catheter passed through 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 in order to ensure provision of continuous positive pressure and avoid alveolar derecruitment. 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 double-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 transient 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. New Techniques or Approaches for Surfactant Administration

1. To prevent or minimize trauma related to endotracheal intubation and mechanical ventilation, new less invasive techniques for surfactant administration have been described. Clinical trials discussed below have shown potential benefits or at least relatively similar results with these newer techniques compared to traditional surfactant administration through an endotracheal tube. As ventilator-induced lung injury is a causative factor of BPD, it is expected that less invasive surfactant administration techniques may lead to a reduction in the incidence of BPD by decreasing the need for invasive ventilation in premature infants with respiratory failure.
2. Most of the evidence supporting these techniques comes from studies of LISA (less invasive surfactant administration) or MIST (minimally invasive surfactant administration). In summary, a thin catheter or plastic tube is inserted past the vocal cords while the patient is breathing spontaneously assisted by noninvasive respiratory support, most of the times with either nasal CPAP or NIPPV, and surfactant is squirted into the airway. The philosophy is to maintain spontaneous breathing as surfactant is administrated. Detractors of these procedures argue that LISA or MIST still require laryngoscopy and tracheal catheterization and that positive pressure ventilation is not possible through a thin catheter. However, both techniques are becoming more popular because of the evidence describing benefits over standard surfactant administration by tracheal intubation and mechanical ventilation or the INSURE method (see below).
3. A recent network meta-analysis of the randomized controlled trials of LISA and MIST versus INSURE and intubation plus surfactant administration demonstrated a significant decrease in the need for invasive mechanical ventilation during the first 72 hours after delivery. Also, the combined endpoint of BPD and death was significantly less with these less invasive techniques.
4. A decreased risk of air leak was reported in a RCT comparing less invasive surfactant administration versus intubation and standard surfactant administration. Most of these benefits, like survival without major complications, are observed in premature infants of more than 26 weeks of gestation, since very immature infants below that gestational age usually end up needing invasive ventilation.
5. LISA and MIST are not exempt from side effects, and several authors have reported relatively similar short-term 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. In addition, in a large observational study, focal intestinal perforation was described in more immature infants (< 26 weeks of gestation) undergoing LISA; however, this complication was not clearly related to the actual less invasive administration technique.

D. Aerosolization of Surfactant

This technique, if proven clinically feasible and effective, has the potential to revolutionize surfactant administration.

1. It has been suggested that for aerosolized surfactant to work, the particles generated must be of a diameter about 2 μm or less and be able to reach the distal airspaces.
2. There are several types of aerosol generators, namely, jet, ultrasonic, vibrating membrane, and the heated capillary system. How these systems operate has been reviewed recently.
3. Many studies in animal models of RDS have demonstrated that aerosolized surfactant results in improvements in gas exchange and pulmonary mechanics.
4. There has been limited clinical experience with aerosolized surfactant in human newborns.
   (a) First studies with poractant 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.
   (b) 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.
   (c) A larger study using a new-generation vibrating membrane nebulizer demonstrated benefits after giving poractant 200 mg/kg to preterm infants with mild RDS.
   (d) More recently, a phase I study demonstrated the feasibility and safety of beractant aerosolization in premature infants using different dilutions and doses.
   (e) A recent relatively large RCT using aerosolized calfactant at a dose of 210 mg/kg in mild to moderate RDS demonstrated a reduction in the need of intubation and surfactant administration by 50%, although many of the infants in the trial were of a more mature gestational age. These investigators used a novel aerosolization system that did not seem to require sophisticated special equipment to administer surfactant.
   (f) 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 aerosolization, potential loss of surfactant to the upper airway and gastrointestinal tract, and best CPAP system to use concomitantly, among others, are also of major importance.
   (g) A recent review of aerosol delivery to ventilated newborns discusses in detail some of these considerations (Mazela).

IX. 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 some of its components. These disorders are 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. Recent observational data show that surfactant is administered to about one third of infants admitted to NICU for MAS.
2. Several randomized trials have shown that administration of surfactant either as a bolus or lavage (see below) to infants with MAS improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO). There are certain caveats, though:
   (a) Most infants entered in many of 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 that 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) A 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. However, a very recent overview of systematic reviews and trials of surfactant given as bolus or lavage was inconclusive regarding the benefits of this intervention.
   (e) Several randomized trials have assessed the efficacy and safety of bronchoalveolar lavage among infants with severe MAS using dilute bovine (beractant) or porcine (poractant) surfactant and also with peptide-containing synthetic surfactant (lucinactant). In addition, recent trials have compared lavage with bolus administration of surfactant. Collectively, these trials have shown variable improvements in respiratory function (shorter duration of oxygen therapy and mechanical ventilation) and either no or small decrease of the composite outcome of death or requirement for ECMO. However, there are not enough infants studied to date to develop firm conclusions.
   (f) Limited information from an abstract of literature published in the Chinese language described a prospective study of using surfactant combined with budesonide among 70 neonates with MAS. The authors described a beneficial effect of this combination in gas exchange, neonatal complications, and length of hospital stay. These findings need to be validated in larger trials that provide more information on this approach.

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 with evolving 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. Using surfactant as a vehicle for other interventions aimed at preventing BPD may become a viable alternative.
   (a) A clinical trial reported in 2016 randomized 265 very low birthweight infants with significant RDS by 4 hours 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.
   (b) A systematic review of only two such clinical trials revealed somewhat similar findings.
   (c) Since then, several other smaller trials or observational studies have examined the same clinical question with mixed results. Much of this evidence has been reviewed recently (Ruegger 2019). However, which infants should receive budesonide plus surfactant and the timing and dosing of this intervention remain in question.
   (d) These are important aspects to be elucidated since budesonide is rapidly absorbed into the systemic circulation. A recent experience in a small number of extremely low gestational age newborns showed that one tenth of the budesonide dose used previously (only 0.025 mg/kg) appeared effective for lung-targeted anti-inflammatory effects while eliciting minimal systemic metabolic effects.

D. Congenital Diaphragmatic Hernia
   1. Determinations of surfactant phospholipids or surfactant proteins in animal models of CDH, in amniotic fluid from pregnant women with a fetus with CDH, and in some infants with this condition have demonstrated abnormalities in the synthesis of some surfactant components like DPPC and SP-B. Thus, these abnormalities may be involved in the pathogenesis of the respiratory failure seen in infants with CDH.
   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.
   3. A relatively recent survey of pediatric surgeons caring for infants with CDH in Europe reported that 45% of them still use surfactant in their management.

Suggested Reading

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Pharmacologic Agents

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Abbreviations

ET Endotracheal
IC Intracardiac
IM Intramuscular
IN Inhalation
INS Intranasal
IO Intraosseous
IV Intravenous
PO Oral
PR Rectal
SC Subcutaneous

Pharmacologic agents (other than antimicrobials and surfactant) 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 differ according to various sources. Individual and institutional practices, therefore, may also be different.

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I. Analgesics

A. *Acetaminophen*

1. Indication: treatment of mild to moderate pain, postoperative pain, and fever. It is an analgesic and antipyretic with no anti-inflammatory properties; well absorbed orally and, less predictably, rectally; and is conjugated in the liver and excreted in urine. Half-life is about 4 hours.
2. Dose: IV, PR, PO.

   IV: Loading dose is 20 mg/kg followed by 7.5–10 mg/kg/dose every 12 hours (maximum daily dose: 30 mg/kg/day)

   PO: 10–15 mg/kg/dose every 6–8 hours (maximum daily dose: 60 mg/kg/day)

   PR: Loading dose is 30 mg/kg and then 20 mg/kg/dose every 6–8 hours (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.

B. *Fentanyl*

1. Indication: short-acting opioid analgesic used for perioperative 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 hours in the adult and probably twice as long in the newborn. Morphine may be a better alternative for sustained pain relief.
2. Dose: IV, IM, and INS. Fentanyl at anesthetic doses will provide good pain relief for about 1 hour in the newborn.

   Anesthetic doses:

   IV: 5–15 mcg/kg

   Analgesic doses:

   IV/IM: 1–5 mcg/kg/dose repeated 30–60 minutes later as needed. Continuous intravenous infusions of 1–3 mcg/kg/ hour 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.

   INS: For children ≥10 kg, 1.5 mcg/kg once (maximum: 100 mcg/dose); reported range is 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 minutes, 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. Indication: best studied opiate analgesic for use in the newborn period and for relief of severe pain, such as necrotizing enterocolitis or following surgery.
2. Dose: IM/IV/PO. 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

   IV: 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 hours may be sufficient depending upon postnatal age.

   Procedures

   IV: For elective intubation IV morphine at 50–100 mcg/kg at least 2 and preferably 5 minutes 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 with overdose.

II. Bronchodilators and Respiratory Stimulants

A. *Aminophylline/Theophylline*

1. Indication: 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.
3. *IV*: A loading dose of 5–8 mg/kg followed by 2–6 mg/kg IV every 8–12 hours based on postnatal age will generally abolish AOP in most babies. *PO*: Oral treatment may be continued with theophylline.
4. 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.

   Plasma concentrations must be measured to ensure therapeutic range and to avoid toxicity since the therapeutic index is narrow.

   Therapeutic Monitoring of Theophylline
   Plasma concentrations measured as trough concentration
   Apnea of prematurity (AOP): 6–12 mcg/mL
   Toxicity: > 20 mcg/mL

B. *Caffeine*

1. Indications: 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 one 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.

   IV/PO: Administer a loading dose of 20 mg/kg of caffeine citrate PO 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.

   Relevant side effects: common side effects include tachycardia, hyperactivity, and gastrointestinal disturbances. Toxicity is manifested by tachycardia, nausea and vomiting, and convulsions.

   Therapeutic Monitoring of Caffeine
   Plasma concentrations measured as trough concentration
   Apnea of prematurity (AOP): 10–20 mcg/mL
   Toxicity: > 50 mcg/mL
3. 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.

C. *Albuterol (USA)/Salbutamol (UK)*

1. Indications: Selective β_2 adrenergic agonist, bronchodilator. Its adult half-life is 6 hours and is 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 IN or PO.

   Inhaled drug may be delivered by nebulization or metered dose inhaler.

   IN: For nebulization, 1.25 mg/dose, 3–4 times daily, is a commonly used regimen.

   IN: Metered dose inhalers deliver 90–100mcg/actuation. Formulations may vary according to country. One to two actuations administered into the ventilator circuit are 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. Levalbuterol
1. Indications: selective β_2 adrenergic agonist, bronchodilator. Levo isomer of albuterol and slightly longer acting than albuterol.
2. Dose: levalbuterol may be used IN.

   IN: Nebulization solution – initial is 0.31–1.25 mg three times daily at intervals of 6–8 hours.

   IN: Metered dose inhaler: 1–2 inhalations (45–90 mcg) every 4–6 hours as needed.

E. *Ipratropium*
1. Indication: anticholinergic bronchodilator, synergistic with β-agonists. Ipratropium is a synthetic derivative of atropine.
2. Dose: ipratropium is used by IN only. Inhaled drug may be delivered by nebulization or metered dose inhaler.

   IN: Nebulization dose is 25 mcg/kg, three times a day.

   IN: Metered dose inhaler provides 21mcg/actuation. Common dose is 1–2 actuations (puffs) every 8 hours.
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.

F. *Epinephrine*
1. Indications: 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 IN route. 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.

III. Diuretics

A. *Bumetanide*
1. Indications: loop diuretic more potent than furosemide and with similar mechanism of action. Half-life in newborns is 2–6 hrs.
2. Dose: IV, IM, or PO routes of administration can be used. The dose is the same for any route. 0.01–0.1 mg/kg/dose q6h–q24h.
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. Indications: 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: IV and PO routes of administration may be used.

   IV: For acutely ill infants who are *nil per oral*, 10–20 mg/kg/day in two divided doses is used by intravenous injection.

   PO: 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. Indications: 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 nebulized furosemide is given.
2. Dose: IV, PO, and IN are acceptable routes of administration.

   IV: 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.

   PO: 2–4 mg/kg orally two or more times a day for symptomatic control of fluid overload is commonly used.

   IN: 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 hours 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. This may lead to nephrolithiasis, nephrocalcinosis, and osteopenia with chronic use. Evidence to support its routine use in BPD is lacking.

D. *Spironolactone*

1. Indication: competitive inhibitor of aldosterone resulting in potassium sparing diuresis and usually used in combination with a thiazide diuretic such as chlorothiazide, since spironolactone itself is a weak diuretic.
2. Dose

PO: 1 mg/kg orally twice daily. Up to 4 mg/kg/24 hrs 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.

IV. Inotropes (see also hydrocortisone) (Chap. 49)

A. *Dobutamine*

1. Indications: 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: IV only.

   IV: 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. Indication: a naturally occurring catecholamine precursor of noradrenaline.
2. Dose: IV only.

   IV: 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 heartbeat are most common.

C. *Milrinone*

1. Indications: 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 and is 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: IV only.

   IV: Loading dose of 50–75 mcg/kg administered over 15–30 minutes followed by a continuous infusion of 0.5 mcg/kg/min; titrate to effect; range of 0.25–0.75 mcg/kg/minute has been used.
3. Relevant side effects: ventricular arrhythmias including ventricular ectopic activity, ventricular tachycardia, ventricular fibrillation, supraventricular arrhythmias, hypotension, angina/chest pain (rare), and torsade de pointes (rare). Hypokalemia, thrombocytopenia, and abnormal liver function tests have also been reported with prolonged use of milrinone.

D. *Noradrenaline (Norepinephrine)*

1. Indications: sympathomimetic vasoconstrictor. It 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: IV only.

   IV: 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, and pallor. Local side effects: organ ischemia (from vasoconstriction of renal and mesenteric arteries), ischemic necrosis, and sloughing of superficial tissue after extravasation.

E. *Adrenaline (Epinephrine)*

1. Indications: direct-acting sympathomimetic agent with a more marked effect on β-adrenoceptors than on α-adrenoceptors and 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: IV, ET, IO, IC.

   Dosing: neonatal

   Cardiopulmonary resuscitation (NRP, 2010)

   IV: 0.01–0.03 mg/kg every 3–5 minutes as needed

   ET: (note that *IV route is preferred*) ET dose of 0.05–0.1 mg/kg every 3–5 minutes until IV access established or return of spontaneous circulation

   Post-resuscitation infusion to maintain cardiac output or stabilize: continuous IV/IO infusion rate of 0.1–1 mcg/kg/minute; doses <0.3 mcg/kg/minute generally produce β-adrenergic effects and higher doses (>0.3 mcg/kg/minute) generally produce alpha-adrenergic vasoconstriction; titrate dosage to desired effect

   Inotropic support: continuous IV infusion rate of 0.1–1 mcg/kg/minute; titrate dosage to desired effect

   Hypotension/shock, fluid-resistant: continuous IV infusion of 0.1–1 mcg/kg/minute; doses up to 2 mcg/kg/minute may rarely be necessary and may be combined with inotropic support.
3. Relevant side effects: cardiac arrhythmias, palpitations, bradycardia, tachycardia, and hypertension.

V. Mucolytics

A. Dornase alfa

1. Indication: enzyme inhalant to thin secretions following respiratory infections.
2. Dose: 2.5 mg/day through selected nebulizers in conjunction with a Pulmo-Aide®, Pari-Proneb®, Mobilaire™, Porta-Neb®, or PARI Baby™ compressor system. It should not be diluted or mixed with any other drugs in the nebulizer as this may inactivate the drug.
3. Relevant side effects: fever, rash, dyspnea, and infection.

B. Sodium Chloride 3% Solution for Inhalation (Hypertonic Saline)

1. Indication: inhalant to thin lung secretions and relieve mucus plugging.
2. Dose: 4 mL nebulized every 2–4 hours for 3–5 doses and continued every 6 hours until secretions are cleared.
3. Relevant side effects: systemic absorption is possible with increased plasma sodium concentrations.

VI. Skeletal Muscle Relaxants

A. *Atracurium*

1. Indication: 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 minutes. 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/hr. 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. Indications: 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 dose of 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/minute (0.06–0.24 mg/kg/hour)
3. Relevant side effects: cardiovascular effects are minimal and transient. Occasionally, wheezing or increased bronchial secretions may be seen.

C. *Pancuronium*

1. Indications: 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 hours. 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 adjusted 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/hour 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, and skeletal muscle atrophy with prolonged use

D. *Rocuronium*

1. Indications: rocuronium 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.
2. Dose: IV only.

   IV: Tracheal intubation of 0.45 to 1.2 mg/kg

   Intermittent IV dosing: 0.075 to 0.15 mg/kg; dosing interval as determined by monitoring

   Continuous IV infusion: 7 to 10 *mcg*/kg/*minute* (0.42 to 0.6 *mg*/kg/*hour)*

3. Relevant side effects: transient increased peripheral vascular resistance, tachycardia, hypertension, or hypotension.

E. *Vecuronium*

1. Indication: a non-depolarizing competitive antagonist of acetylcholine similar to pancuronium metabolized by the liver and excreted in urine. Vecuronium, unlike pancuronium, is cardiostable and lacks 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 hours. Maintenance doses of 0.03–0.15 mg/kg/dose every 1–2 hours may be used as needed. It may be administered as a continuous infusion at 1–1.5 mcg/kg/minute (0.06-0.09 mg/kg/*hour*).
3. Relevant side effects: arrhythmias, tachycardia, hypotension, hypertension, respiratory insufficiency, bronchospasm, and apnea.

VII. Steroids

A. *Budesonide*

1. Indications: potent corticosteroid most often used by inhalation to prevent or treat advanced chronic lung disease.
2. Dose: IN route preferred in neonates and infants.

   Limited neonatal and infant data.

   IN 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 a 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. Indications: 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 early 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: IV 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) 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 9–10.
   (c) Post-intubation airway edema: IV dose of 0.25 mg/kg given 2–4 hours prior to scheduled extubation and then every 8 hours for a total of three doses; others have used 0.5 mg/kg/dose every 8 hours for three doses with the last dose administered 1 hour prior to scheduled extubation; range is 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, 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. Glucocorticoid with minimal mineralocorticoid effect primarily used for physiologic replacement but can also be useful in the treatment of acute hypotension.
2. Dose: IV/PO administration possible. Dosing is same for IV/PO.

   IV/PO: BPD prevention (preterm neonates with prenatal inflammatory exposure): PNA $\leq$ 48 hours – IV dose of 1 mg/kg/day divided every 12 hours for 9 or 12 days, followed by 0.5 mg/kg/day divided every 12 hours for 3 days; dose may be needed during acute illness. Doses of 2 mg/kg IV followed by 1 mg/kg 8–12 hourly 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.
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.

D. *Fluticasone*

1. Indications: potent corticosteroid most often used by oral inhalation to treat advanced chronic lung disease.
2. Dose: IN limited neonatal and infant data.

   IN: 2–4 actuations (44mcg/actuation (puff) every 12 hours via face mask and spacer.
3. Relevant side effects: respiratory tract infection generally related to local administration. Systemic absorption of locally administered inhaled fluticasone has the potential to cause hypertension, hyperglycemia, and adrenocortical insufficiency in premature and term neonates and very young children. Growth suppression and osteopenia are common with chronic use if significant systemic absorption is present in the very young.

VIII. Sedatives (Chap. 54)

A. *Chloral Hydrate*

1. Indications: sedative, well absorbed orally, metabolized in the liver and excreted in urine. It acts within 30 minutes; half-life of active metabolite is 36 hours.
2. Dose: oral or rectal route of administration. 45 mg/kg is used as a single dose. Higher doses (75 mg/kg) have been used for sedation for imaging but can produce hypoxemia. 30 mg/kg orally every 6 hours can be helpful in babies with cerebral irritability. Drug accumulation may occur if used for more than 48 hours.
3. Relevant side effects: respiratory depression, apnea, and gastric irritation.

B. *Lorazepam*

1. Indication: benzodiazepine anxiolytic and sedative metabolized in the liver and excreted in urine. It does not have any active metabolites and is longer acting than midazolam.
2. Dose: IV or PO dosing.

   IV/PO: Usual dose of 0.05 mg/kg (maximum dose: 2 mg/dose) every 4–8 hours; range is 0.02–0.1 mg/kg.
3. Relevant side effects: risk of propylene glycol toxicity. Monitor closely if used for prolonged periods of time or at high doses. Bradycardia, circulatory collapse, hypertension or hypotension, respiratory depression, apnea are also common side effects.

C. *Midazolam*

1. Indication: 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: IV/IM/IN/PO dosing. 0.15 mg/kg IV, IM, or IN 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 minutes is followed by 10–60 mcg/kg/hr. IV infusion can be used for sedation of ventilated babies for 3–4 days.
3. Relevant side effects: cardiac arrest, hypotension, and bradycardia.

IX. Pulmonary Vasodilators: Systemic and Inhaled

A. *Bosentan*

1. Indications: 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.

   Term neonate: Oral dose of 1 mg/kg 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. Indications: 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

   IV: infusion doses are expressed in units of *nanograms* (ng)/kg/minute.

   Low-dose regimen: initial dose of 2 ng/kg/minute slowly titrated by 1–2 ng/kg/min every 15–30 minutes as tolerated to 20 ng/kg/minute over ~3 hours

   High-dose regimen: initial dose of 20 ng/kg/minute, slowly titrated (according to oxygenation) at 30-minute intervals over 4 to 12 hours to a mean dose of 60 ng/kg/minute (range: 30 to 120 ng/kg/minute)

   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. *Iloprost*

1. Indications: PPHN refractory to inhaled nitric oxide. Iloprost causes direct vasodilation of pulmonary and systemic arterial vascular beds.
2. Dose: IV or IN.

   IV: continuous IV infusion at a dose of 0.2–10 ng/kg/min

   IN: For oral inhalation *only, not for oral ingestion. No current dosing information is available for pediatric patients.*
3. Relevant side effects: flushing, hypotension, tachycardia, agitation, infection, pain, pulmonary edema, and thrombocytopenia.

D. Nitric Oxide (Chap. 55)

1. Indications: acts on receptors within the muscle of blood vessel walls to produce vasodilation. It is rapidly inactivated by hemoglobin producing methemoglobin. Half-life is less than 5 seconds. Vasodilator effect is therefore limited to the pulmonary circulation. Methemoglobin levels need to be monitored and kept below 2.5%.
2. Dose: administered as a gas by IN.

   IN: In babies and those ≥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 dosing.
3. Relevant side effects: methemoglobinemia, pulmonary edema, pulmonary hemorrhage, and toxicity from nitrogen dioxide formation.

E. *Sildenafil*

1. Indications: treatment of pulmonary hypertension by promoting pulmonary vasodilation
2. Dose: PO administration only

   Pulmonary hypertension: initial dose of 0.5 mg/kg every 8 hours; doses are increased by 0.25 mg/kg every 24 hours if needed and if tolerated to a maximum of 2 mg/kg every 6–8 hours.
3. Relevant side effects: cerebrovascular hemorrhage, edema, flushing, hypotension, pulmonary hemorrhage, tachycardia, ventricular arrhythmia, dyspnea, epistaxis, nasal congestion, rhinitis, rhinorrhea, and sinusitis

F. *Treprostinil*

1. Indication: treatment of pulmonary hypertension by promoting pulmonary vasodilation
2. Dose: IV, SC, IN (dosing is based on adult data and should be scaled to pediatric patients using body weight)

   SC/IV: Initial dose of 1.25 ng/kg/min via slow titration

   IN: No pediatric data available
3. Relevant side effects: infusion site reactions or pain, headache, nausea, vomiting, restlessness, and anxiety

Suggested Reading

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Automatic Control of Inspired Oxygen Concentration

60

Nelson Claure and Eduardo Bancalari

I. Introduction and Rationale
   A. Supplemental oxygen is commonly required to maintain adequate oxygenation in preterm infants with hypoxic respiratory failure and chronic lung disease. The need for supplemental oxygen in this population can be prolonged.
   B. Arterial oxygen saturation is monitored continuously by pulse oximetry (SpO_2), and the fraction of inspired oxygen (FiO_2) is titrated by caregivers to maintain a clinically prescribed target range of SpO_2. Because of their respiratory instability, this is not achieved consistently, and preterm infants spend considerable time outside the target range. Episodes of intermittent hypoxemia are for the most part spontaneous. In contrast, hyperoxemia results from an excessive FiO_2 (Fig. 60.1).
   C. Maintenance of SpO_2 within the target range is more difficult with higher infant-to-nurse ratio and increased workload.
   D. Systems of automatic FiO_2 control have been developed to improve maintenance of SpO_2 within a target range. In clinical studies, these systems have been shown effective in reducing the exposure to hyperoxemia, reducing the frequency of the most severe and prolonged episodes of hypoxemia, as well as reducing staff workload.

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 automated 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 SpO_2. The timing, magnitude, and frequency of adjustment determine the automatic response to gradual or rapid changes in SpO_2.

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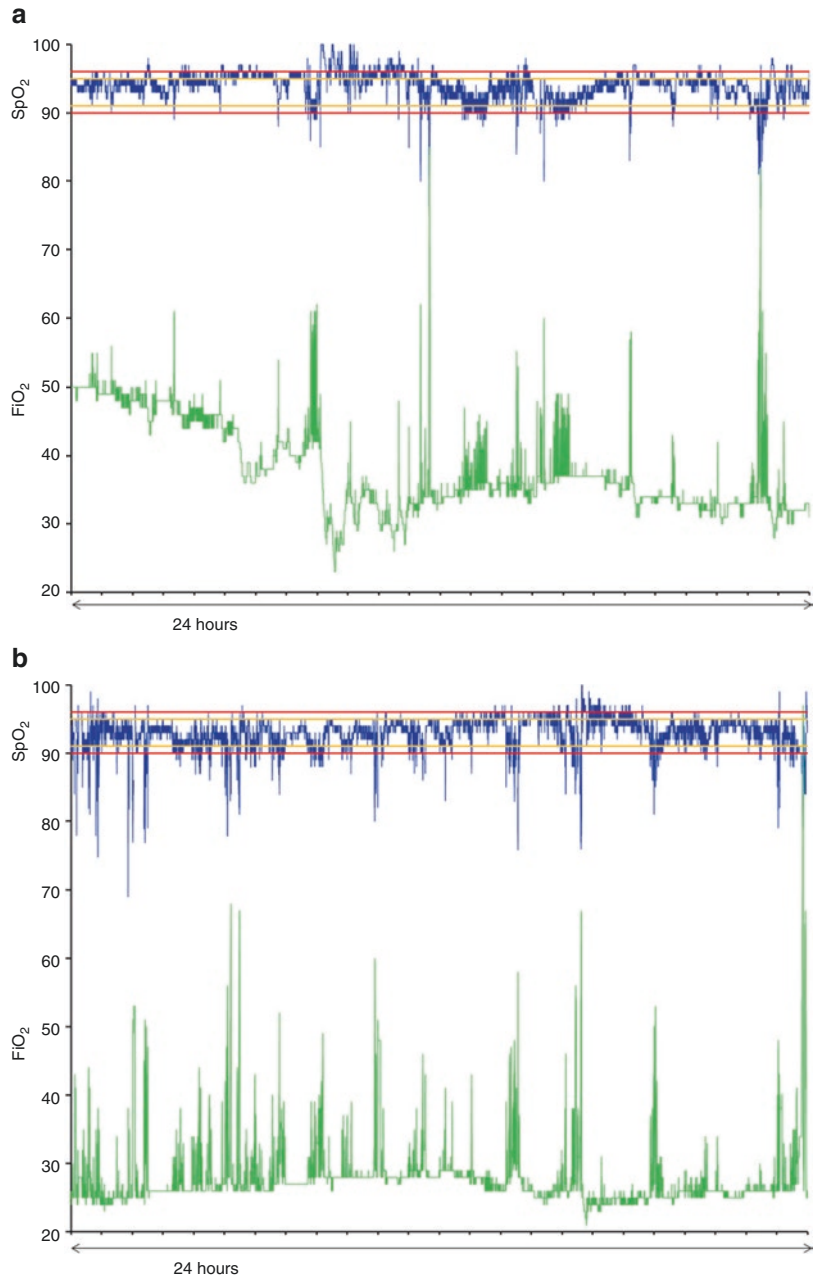

Fig. 60.1 Recordings illustrate automatic adjustments of FiO_2 to maintain SpO_2 within the relatively narrow target range of 91–95% (orange lines) in infants with different degrees of oxygenation instability over 24 hours. Alarm limits are marked by red lines. Panel **A** shows consistent weaning of FiO_2 with relatively few increases during episodes of hypoxemia followed by rapid return to baseline. Panel **B** shows gradual upward and downward changes in the baseline FiO_2 and more frequent increases in FiO_2 in response to hypoxemia episodes. Panel **C** shows more frequent automatic increases in FiO_2 in response to the increased frequency of hypoxemia episodes. Despite the high episode frequency, in a relatively few episodes SpO_2 declines below 80%

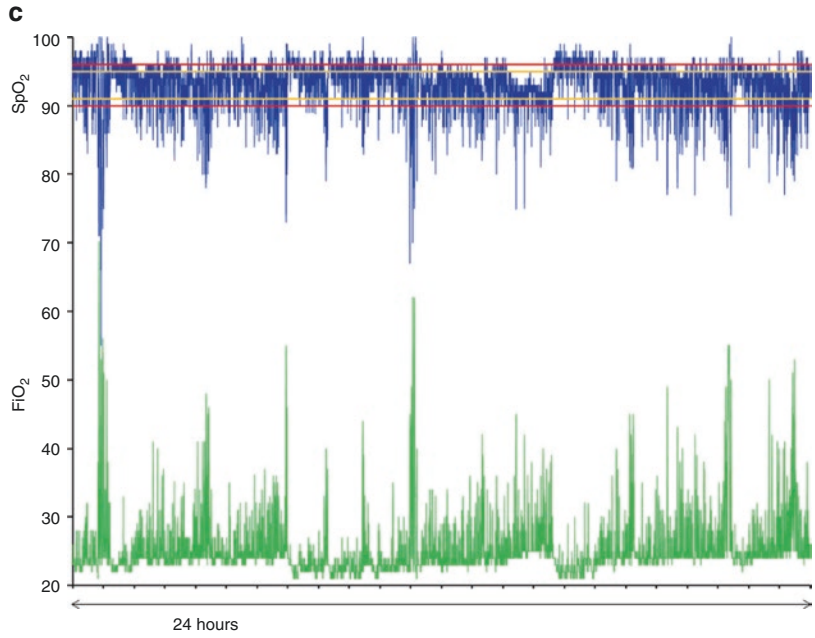

Fig. 60.1 (continued)

III. Effects on Oxygenation, Oxygen Exposure, and Workload
   A. 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.
   B. These studies showed automatic FiO_2 control can achieve substantial reductions in time at hyperoxemia and wean FiO_2 more consistently than manual control.
   C. Hypoxemia episodes are a significant challenge to the staff. Automatic FiO_2 control does not prevent these episodes, but it has been shown to attenuate the more severe and prolonged episodes.
   D. During routine clinical 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 confirms a reduction in workload and the possibility of redirecting staff effort to other patient care tasks.

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, automatic FiO_2 may be more beneficial under conditions when staff limitations exist, during large staff workloads, as well as among infants with greater oxygenation instability.

B. In addition to SpO_2 monitoring, systems of automatic FiO_2 control offer the ability to monitor FiO_2 and provide warnings when the administered FiO_2 to maintain SpO_2 within the targeted range has exceeded or fallen below specific high or low thresholds, as this may indicate a deterioration or improvement in respiratory status.
C. Automatic FiO_2 control can potentially lead to reduced attentiveness and mask conditions that can otherwise result in severe hypoxemia. Because increasing FiO_2 may not always 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. 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 well 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.
E. Comprehensive staff training and understanding of the advantages and limitations of automatic FiO_2 systems are essential prior to the adoption of these systems for routine use.

V. Summary
A. Important detrimental effects can be associated with hyperoxemia and excessive inspired O_2 exposure as well as with inadequate oxygenation in preterm infants. At present, these conditions are frequently observed because manual FiO_2 control does not adapt to the continuous changing needs of preterm infants. Achieving this requires increased workload and constant staff presence at the bedside.
B. Automatic FiO_2 control is an alternative to improve the maintenance of oxygenation and minimize exposure to oxygen and dangerous SpO_2 values. Clinical studies have shown its feasibility and efficacy in achieving these goals.
C. Maintaining a balance between avoidance of hypoxemia without inducing hyperoxemia and increased oxygen exposure may improve respiratory, ophthalmologic, and neurodevelopmental outcomes in preterm infants. The extent to which automatic FiO_2 control can improve these outcomes needs to be confirmed by large clinical trials.

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Aerosolization and Nebulization

61

Steven M. Donn, Mark C. Mammel,
and 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 are a limited number of clinical deposition studies in the neonatal population because of the inability to use radiolabeled aerosols, which makes assessment of effectiveness of inhalational therapies 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 the use of nebulizers and delivery systems in the neonatal intensive care unit (NICU) have been based on adult studies or in vitro simulations.

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 on the air, i.e., into an aerosol.
      2. Nominal dose (total dose of drug prescribed): the amount of drug loaded into the drug reservoir. This dose is device-specific.

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3. Emitted dose: the total amount of drug emitted from the inhaler device and available to the user.
4. Inhaled dose: the amount of the drug available to the patient under breathing conditions (measured in in vitro settings including lung or upper airway models)
5. Lung dose: the mass of drug delivered to the lung. The effect of a lung dose depends on several factors:
   (a) Site of deposition
   (b) Rate of clearance of the drug from the 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): the diameter at which 50% of the particles by mass are larger and 50% are smaller
7. Geometric standard deviation (GSD): a measure of the spread of an aerodynamic particle size distribution, typically calculated as follows:

$$GSD = \left(d_{84} / d_{16}\right)^{1/2}$$

   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.
8. Respirable fraction (RF) or fine particle fraction (FPF): the mass fraction of inhaled particles penetrating to 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 particle size distribution (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
1. Inhalers – devices which require active inhalation by a patient to entrain the aerosolized drugs:
2. Metered dose inhalers (MDIs) – handheld aerosol devices that utilize a propellant to deliver the therapeutic agent and consist of the 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) – 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.
4. Holding chamber – an extension add-on device that permits the aerosol plume from the MDI to expand and slow, 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 – 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 – standalone nebulizer and does not require additional gas flow. Aerosol is generated by mesh vibrations, which push the solution through small pores and generates mist. It produces small particles.
(d) Capillary aerosol generator (CAG) – 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 and 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
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- connector is recommended for metered dose inhalers (MDIs), 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 suggest the utility of placement of vibrating mesh nebulizers in this location whenever a nebulizer with a low residual volume is used.
3. Fok et al. compared different aerosol generators in delivering salbutamol labeled with technetium 99m (^{99m}Tc) to infants with bronchopulmonary dysplasia (BPD). The aerosols delivered 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., $p = 0.009$). 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 (Misty-Neb; Airlife Inc., Montclair, CA), when both nebulizers were placed in the same location (inspiratory limb of the ventilator circuit) with a MMAD of 1.4 μm measured at the tip of the ETT.
(a) Data from Fok et al.'s study 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) Findings from Dubus et al.'s study indicate that device characteristics, such as residual volume and output rate, may drive clinical outcomes.
4. 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) 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, reducing lung deposition.

5. 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 the 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 buildup of a conducting layer on the chamber surface and improved aerosol delivery from plastic HCs.
6. 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.
7. 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, only 0.89% of the nominal dose was deposited.
3. Other studies on infants show 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 of mechanically ventilated macaque monkeys with the use of the Aeroneb Pro and ^{99m}Tc diethylenetriamine pentaacetate. Dubus et al. reported aerosol with MMAD of 1.4 μm at the tip of the ET tube for both tested devices but a 25-fold greater lung deposition of radiolabeled aerosol generated by the Aeroneb Pro when synchronized with inspiration vs. Misty-Neb in a continuous flow mode (14% vs. 0.5% of the nominal dose, respectively).

5. These observations 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 a percent of the nominal dose.
6. Small particles in combination with short inspiratory times and low inspiratory flow rates increase the risk for exhalational drug losses.
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.
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 to avoid significant exhalation losses.
   (b) 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 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.
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 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, compared with that observed with 100% oxygen.
5. Humidity is another variable which can potentially influence the effectiveness of inhalational therapies.
   (a) Standard ventilator support requires delivery of humidified and heated air to patients to avoid drying the airway mucosa.
   (b) Several in vitro studies have investigated the relationship between humidification and aerosol lung deposition.

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.

   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). The study also showed that test lung deposition significantly improved when submicronic aerosol (MMAD = 0.54 μm) was delivered.
3. Crogan et al. showed that the percentage of aerosolized metaproterenol exiting the ETT almost doubled for a 9.0 mm vs. 6.0 mm ET tube.

4. Everard et al. showed a drop in drug delivery when using a smaller ETT (2.5 vs. 3.0 mm) during in vitro testing of a Babylog Dräger neonatal ventilator circuit, and Dubus et al. reported that regardless of different aerosol particles at the nebulizer outlet, the particle size distribution at the end of the 3.0 mm ETT 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, Windtree Therapeutics, Inc. Warrington, PA) used for albuterol delivery under breathing support increased the delivered dose by 5–9-fold. Such significant improvement in aerosol delivery was achieved by 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. These findings show that the patient interface can be a critical variable determining the particle size delivered to a mechanically ventilated patient.

E. Mode of Breathing Support
1. Ventilator settings may play a role in aerosol lung deposition.
2. Fink et al. studied the effect of different modes on aerosol delivery from an MDI in vitro. They 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.
4. High flow nasal cannula (HFNC) is a recent breathing support utilized in the NICU.
   (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 airway 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).
   (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 upon 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) and potential losses at the upper airways. 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 lower respiratory tract (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 dilution 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:

$$\text{Inhaled dose} = C \times \left(V_m \middle/ \text{kg} \right) \times T$$

C = concentration of aerosol (in mg/L)
V_m/kg = minute ventilation normalized to bodyweight (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, to properly assess the amount of inhaled drug, one should measure E_d at the ETT or 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]:

$$C = \frac{E_d \left[\text{mg} / \text{min}\right]}{V\left[\text{L} / \text{min}\right]} = \text{mg} / \text{L}$$

6. The above calculations should be accurate if one eliminates aerosol upper respiratory tract deposition and obtains an appropriate particle size. Upper airway 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 trials.
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 with off-label drugs.

H. Recommendations
1. SIMV, AC, VG, VC, CPAP:
   (a) Clean the artificial airways before nebulization.
   (b) Remove the ventilator flow sensor from the wye connector.
   (c) Nebulizer: vibrating mesh (Aeroneb, Pari e-flow); MDI with HC
   (d) Placement: inspiratory limb of the circuit 20 cm from the wye
   (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 prong design
   (c) Nebulizer type: vibrating mesh; MDI with HC
   (d) Placement: just prior to humidifier
   (e) Breathing support variables: no need to switch off humidifier

IV. Neonatal Clinical Studies of Aerosolized Agents

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 et al., 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 noninvasive 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, 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.
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' postconceptional age and 1015–2370 g) with RDS using nCPAP and aerosolized poractant alfa (Curosurf®, Chiesi Farmaceutici SpA, Parma, Italy). They were also unable to demonstrate the superiority of aerosolized surfactant delivery over nCPAP alone.

8. Finer et al. studied aerosolized lucinactant (Aerosurf®, Discovery Laboratories Inc., Warrington, PA), delivering a peptide-containing synthetic surfactant to newborns with early signs of RDS, within 1 hour 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 wye connector.
   (b) The procedure was shown to be safe with a low occurrence of "peri-dosing events" and some efficacy.
9. A recent study by Minocchieri et al. administered aerosolized poractant alfa nebulized by a vibrating membrane generator (Pari e-flow) to preterm infants (29–34 weeks' gestation) with mild RDS and reported a reduced need for invasive mechanical ventilation in the first 72 hours of life.
10. Additional clinical trials are underway.

B. Corticosteroids
1. There have been multiple 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 (Townsend et al. and Kovacs et al.) used a jet nebulizer, whereas other studies utilized metered dose inhalers (MDIs). Most of the studies placed a holding chamber (HC) between the ETT 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 the 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/d.
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 presence of the HC between the wye and ETT. 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 ETT. There was a significant difference in MMAD of the aerosol emitted directly from the MDI compared to aerosol emitted from the tip of the ETT. This study, as well as others, 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 treatment within the first 24 hours of life with inhaled budesonide to infants 23–27 weeks' GA. The incidence of BPD was 27.8% in the budesonide group vs. 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 a HC between the wye connector and ETT.
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.

C. Bronchodilators
1. Aerosolized bronchodilators comprise another group of pulmonary drugs used to treat infants with BPD and to improve the effectiveness of inhaled corticosteroids.
2. The largest of seven clinical studies enrolled 169 infants, and 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 endpoint 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 a HC placed between the ETT 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 particle size distribution 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 studies evaluated a total of 78 premature infants treated with inhaled furosemide for treatment or prevention of BPD. 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/d 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 endpoint, five of eight 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 researchers 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. Vasoactive Agents

1. Treatment of PPHN aims to reduce 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. To achieve pulmonary selectivity, drugs must be delivered by inhalation or nebulization.
2. Aerosolized therapeutic agents studied among infants with PPHN include prostaglandin (PGE_1), prostacyclin (PGI_2), and sodium nitroprusside.
   (a) Three small clinical trials 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 to iNO. Of these three studies, only the delivery system used by Kelly et al. was optimized for the ventilated infant. This study utilized the 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 circuity, and two of the studies included information on particle size distribution.
   (d) These compounds, however, are not within normal physiologic pH ranges. Their safety has yet to be established.
3. In summary, in 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.

Suggested Reading

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Sedation and Analgesia

62

Gokul Ramanathan and Elaine 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 noninvasive interventions
   C. Pathological 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, nasolabial furrowing, mouth or lip purse, tongue tautness, 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)

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Table 62.1 Causes of possible distress or pain in the newborn infant

1. *Airway manipulation and ventilation*
Laryngoscopy
Endotracheal intubation
Less invasive surfactant administration
Presence of endotracheal tube and fixation devices
Distress of mandatory ventilator breaths
Restriction of movement and posture required for ventilation
Endotracheal suctioning
2. *Repeated acute invasive procedures*
Arterial/venous/capillary blood sampling
Venipuncture and venous cannulation
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. *Postoperative 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 radiological imaging
Ultrasound scans
General caregiving 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 noninvasive procedures*
Transcutaneous gas monitoring probe changes
Bolus feeds
Drug administration
Blood pressure measurement using inflatable cuffs

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"

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 of 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 for Acute Pain
      (a) More than 40 pain assessment tools available
      (b) Designed for use in clinical practice and research
      (c) Unidimensional or multidimensional
      (d) Examples (Table 62.2)
        1. Neonatal facial coding system
        2. Premature Infant Pain Profile
        3. Neonatal Pain, Agitation and Sedation Score
    2. Clinical tools for persistent/prolonged pain:
      (a) Assessment tools for persistent pain are fewer and less well validated.
      (b) During episodes of persistent pain, neonates exhibit a passive state, with limited or no body movements, expressionless facies, reduced physiological variability, and decreased oxygen consumption.
    3. Research Tools
      (a) Neuro-endocrine markers (e.g., cortisol, adrenaline, endorphins)
      (b) Metabolic-biochemical markers of catabolism (e.g., 3-methylhistidine)
      (c) Neurophysiological monitoring (near-infrared spectroscopy (NIRS), aEEG, somatosensory evoked potential (SSEP), fMRI, etc.)
      (d) Computerized analysis of physiologic data (e.g., changes in vagal tone, heart rate variability, pupillary reflex dilatation)
      (e) Multichannel deep learning approach using videos for facial expression, body movements, and/or crying sound
  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 noninvasive 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.

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. Nasolabial 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 sec. Observe baseline; Hheart 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 sec	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	
	Nasolabial 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)

Table 62.2 (continued)

Extremities Ttone	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 apnea	<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

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, or massage, especially from parents
      4. Music as a therapeutic intervention
   B. Behavioral: non-nutritive sucking, breastfeeding, positioning, swaddling
   C. Other strategies: use of central venous catheters instead of multiple skin punctures, individualized monitoring techniques (blood pressure measurement interval, vital signs registration), adapted nursing techniques (e.g., frequency of endotracheal suctioning, skin and wound care, tape, and wound dressing).

VI. Indications for Pharmacologic Management (Table 62.3)
   A. Observed behavioral and physiologic indicators of pain
   B. Anticipated procedural pain
   C. Premedication for intubation – sedative with muscle relaxant is standard practice
   D. Less invasive surfactant administration (LISA) – optimal strategy yet to be determined
   E. Asynchronous respiration interfering with ventilation; routine sedation for ventilated babies should be discouraged.
   F. Physiologic instability
   G. Failure of non-pharmacologic interventions
   H. Distress associated with therapeutic hypothermia
   I. Palliative care

VII. Pharmacologic Interventions (Chap. 59)
   A. Sucrose/Glucose
      1. Reduces behavioral, but not neurophysiological, 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

Table 62.3 Use of analgesics and sedatives

Relatively minor procedures		
Procedure	Comment	Suggested approach
Heel lance	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 nasogastric 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
Elective intubation	Discomfort Gag/cough Vagal reflex	Opiate slow bolus with muscle relaxant
Laser therapy and intravitreal injection of anti-VEGF medication 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 or late preterm infants May be distress associated with cooling and shivering	Opiate infusion if distressed Avoid benzodiazepines

(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. 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 with higher potency than morphine
      2. High lipid solubility (released from fat stores causing physiologic effects even after infusion is stopped following prolonged use)
      3. Less histaminic effect than morphine
      4. Tends to reduce pulmonary vascular resistance; may be preferable in PPHN, CDH, and CLD, during ECMO
      5. Large doses tolerated without adverse hemodynamic effects
      6. Chest wall rigidity if given quickly
      7. Loading dose: 5–15 mcg/kg over 30 min
      8. 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, 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
   (b) Intravenous use has opioid-sparing effect
   (c) Neonates relatively resistant to liver toxicity with no respiratory or cardiovascular depression, G-I irritation, or platelet dysfunction
   (d) Useful in inflammatory and postoperative pain
   (e) Dose
      1. Oral: 10–15 mg/kg q4–6h (may load with 20 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
   (c) Side effects: renal dysfunction, platelet dysfunction, and pulmonary hypertension

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 bronchopulmonary dysplasia
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, 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. Useful before procedures without pain, such as imaging where avoidance of motion artifact is important
      5. Onset of action in 30 min.; duration: 2–4 h
      6. Slow development of tolerance
      7. Dose: sedation is 25–50 mg/kg

E. Local Anesthetics
1. Lidocaine
   (a) Infiltrate skin/mucous membranes
   (b) 0.5% solution, maximum dose 1.0 mL/kg
   (c) With over dosage, 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 methemoglobinemia
   (c) Amethocaine (Ametop): less vasoconstriction

VIII. Assessing Adequacy of Analgesia and Sedation
A. Challenging because of lack of self-report
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 the 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 postoperative 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, and altered sleep and feeding patterns lasting up to 7 days.
(d) Babies born at 28 weeks of gestation, compared to those born at 32 weeks of 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 heel-stick 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.
(e) Prolonged use of sedative agents such as opiates or midazolam can negatively affect the developing brain in animals and humans.
(f) Analgesics/sedation should be used to treat neonatal pain/distress adequately but not routinely for non-painful situations.

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 is required to clarify potential benefits of developmental care

XI. Pain and Distress in Neonatal Palliative Care
A. Non-opioid medications are recommended for mild pain, while opioid medications with or without adjuvant therapies are used for moderate to severe pain
B. Agents may need to be combined for optimal comfort
C. Opioids are the first choice for moderate to severe pain, with fentanyl having advantages of faster onset and the option of intranasal administration
D. Benzodiazepines can be added as an adjunct in severe pain
E. Other distressing symptoms should be addressed such as respiratory distress and agitation (sedatives), excessive secretions (glycopyrrolate), constipation (laxatives), emesis (antiemetics), and edema (fluid restriction/diuretics)

XII. Areas of Ongoing Research
A. Pharmacologic interventions
1. Dexmedetomidine
(a) Alpha agonist, opioid sparing
(b) Causes sedation without respiratory depression
(c) Has good analgesic properties
(d) Adverse effects: bradycardia, seizures, hypothermia

2. Remifentanil
   (a) Ultra-short acting synthetic opioid
   (b) Metabolized by esterases in tissue and plasma leading to very short half-life and no accumulation
   (c) Not suitable for long-term use; can be used for brief painful procedures such as central line placement and tracheal intubation
3. Propofol
   (a) Ultra-short acting anesthetic agent
   (b) Not extensively studied in neonates but has been used for intubation in neonates in research studies
   (c) Hypotension is a serious adverse effect
4. Ketamine
   (a) Dissociative anesthetic that provides analgesia, amnesia, and sedation
   (b) Increases blood pressure and heart rate and respiratory drive and leads to bronchodilation
   (c) Suitable for unstable, hypotensive neonates requiring procedures such as intubation or ECMO cannulation.
   (d) Currently used mainly in research settings

B. Assessment of pain or distress: noninvasive technology
   1. Near-infrared spectroscopy
   2. EEG
   3. SSEP (somatosensory evoked potential)
   4. Functional MRI
   5. Multichannel deep learning approach using videos for facial expression, body movements, and/or crying sound

C. Long-term consequences of opioids and other sedative agents (e.g., behavior, neurodevelopment)

D. Ideal premedication agent for LISA

E. Optimum management of distress and shivering in therapeutic hypothermia

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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 inhaled nitric oxide (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.

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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.
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. In this setting, low-dose iNO therapy can improve oxygenation by redirecting 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 defects 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., tracheobronchomalacia) 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 persistent pulmonary hypertension of the newborn.
3. Interpretation of pulse oximetry measurements
   (a) Right-to-left shunting across the ductus arteriosus causes postductal desaturation.
   (b) Interpretation of preductal (right hand) and postductal (lower extremity) saturation by pulse oximetry provides important clues to the etiology of hypoxemia in the newborn.
   (c) If the measurements of preductal and postductal SpO_2 are equivalent, this suggests either that the ductus arteriosus is patent and pulmonary vascular resistance is subsystemic (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 suprasystemic pulmonary artery pressures.
   (e) When the postductal SpO_2 is lower than preductal SpO_2 (>5% gradient), the most common cause is suprasystemic pulmonary vascular resistance 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 postductal desaturation.
   (g) Anatomic pulmonary vascular disease (alveolar-capillary dysplasia, pulmonary venous stenosis, and anomalous venous return with obstruction) can cause suprasystemic pulmonary vascular resistance with right-to-left shunting across the ductus arteriosus and postductal desaturation.
   (h) The unusual occurrence of markedly lower preductal SaO_2 compared to postductal measurements (assuming the pre-ductal measurement is correct) 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 preductal 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.

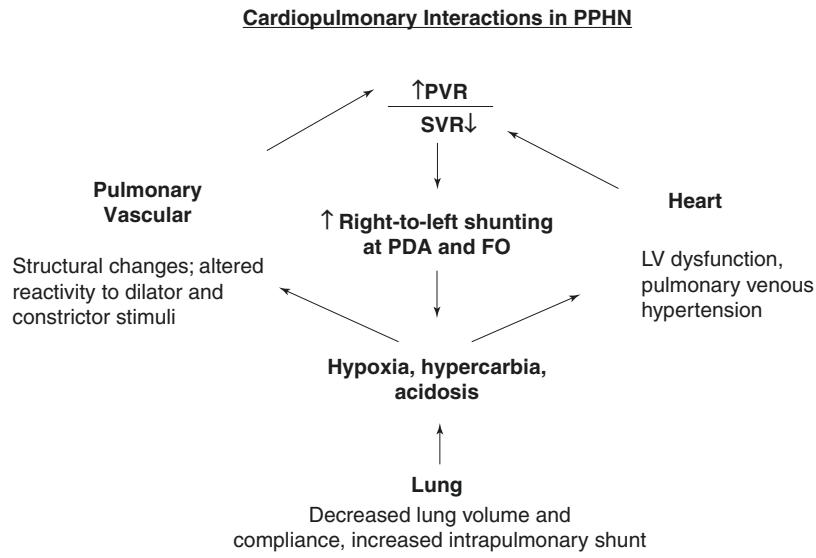

Fig. 63.1 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn

(c) It is critically important to diagnose congenital heart defects 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.
(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 suprasystemic pulmonary vascular resistance), 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 pulmonary vascular resistance. 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. 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 suprasystemic elevations of pulmonary artery pressure by echocardiography.
   4. It is reasonable to discontinue iNO if the F_iO_2 is <0.40 and the PaO_2 is >60 torr (8 kPa) 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 ppm to 6 ppm after 4 hours 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 (≤20 ppm).
4. Because methemoglobin reductase deficiency may occur unpredictably, it is reasonable to measure methemoglobin levels by co-oximetry within 4 hours of starting iNO therapy and subsequently at 24-hour 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. 42).
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 two 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 inhaled nitric oxide 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.
   4. There are insufficient clinical trial results to warrant regulatory approval for iNO use in newborns <34 weeks' gestation with PPHN. The design of a proper RCT in preterm newborns is problematic because, unlike the trials in term newborns, the outcome measure would be mortality since ECMO is not a clinical option for this population.

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Extracorporeal Membrane Oxygenation

64

Robert E. Schumacher and Lindsay A. Ellsworth

Abbreviations

ACT	Activated clotting time
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
SvO_2	Mixed venous oxygen saturation
TBW	Total body water
V-A ECMO	Veno-arterial ECMO
V-V ECMO	Veno-venous ECMO

I. Description
   A. Extracorporeal membrane oxygenation (ECMO) is a treatment for an infant with severe *reversible* respiratory failure, which affords a period of "lung rest" by the use of heart–lung bypass and an artificial lung (membrane oxygenator). Such a period of rest may allow for lung recovery and ultimately survival of the infant.
   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, which is equivalent to respiratory rate × tidal volume (liters per unit of time) through the artificial lung.

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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), a membrane oxygenator, 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.

"Hot water-cold water" analogy: 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. For example, 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.

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 infant is treated with systemic anticoagulation.

Fig. 64.1 Typical ECMO circuit and equipment

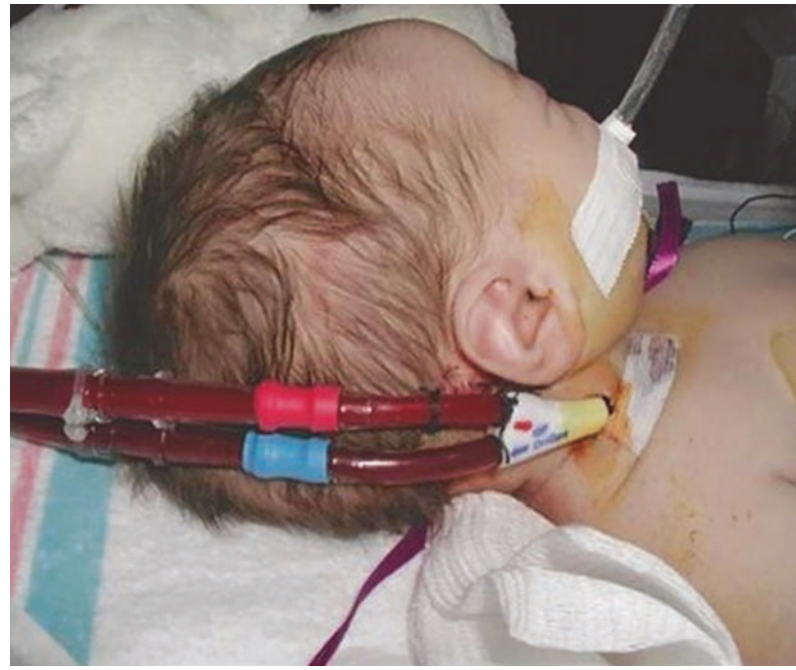

Fig. 64.2 Term infant cannulated for veno-venous ECMO

III. Patient Selection
   A. For neonatal ECMO, the infant 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.
      2. Be >2000 g of current weight. Weight is not an absolute contraindication, discuss based on case and ability to place cannulas.
      3. Have a cranial sonogram with no significant intraventricular hemorrhage. To many, grade I/II is a relative contraindication; determine case by case based on size and stability of the hemorrhage.
      4. Have no major bleeding problem; isolated pulmonary hemorrhage is not a contraindication.
      5. Have *reversible* respiratory failure.
      6. Have no lethal malformation or disorder.
      7. Be "failing" conventional medical management.
   B. Failure of conventional medical management is a definition that should be "individualized" for each ECMO center. Guidelines based on experience with populations are used, but the ultimate decision is up to those caring for the 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.
      1. Oxygenation index (OI):
         (a)

$$\mathrm{OI} = \frac{\text{mean airway pressure} \times \mathrm{FiO_2}}{\mathrm{PaO_2}\left(\text{post ductal}\right)} \times 100$$

(b) *After* stabilization, if the OI is consistently ≥40, ECMO criteria have been met (OI >40 is University of Michigan "absolute" criterion; OI >25 is used as "consider" criterion).
(c) 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."

2. V-V ECMO may not provide the same cardiac support that V-A ECMO does.
(a) 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 (ELSO) registry suggest V-V ECMO is effective even in infants requiring substantial blood pressure support.
(b) Because the risk of carotid artery ligation is not present, consideration for V-V ECMO is sometimes made at a lower entry threshold.

IV. Management
A. Preparation for cannulation
1. Confirm infant meets qualifying criteria without contraindications.
2. Obtain consent for ECMO.
3. Confirm type and screen and request for blood bank to prepare blood products.
4. Consider baseline lab work including CBC, electrolytes, and coagulation studies.
5. Consider genetic testing, if warranted.
6. Obtain newborn screen if not yet obtained.
7. Cranial ultrasound, time permitting.
8. Echocardiogram, if needed.
9. Place central and arterial catheters.
10. Place Foley catheter and a nasogastric tube.
11. Order medications for anticoagulation (typically heparin bolus then infusion).
12. Confirm plan for operative sedation.
13. Consider use of clear drapes to maintain view of the airway during cannulation.
14. Complete a multidisciplinary team time out prior to cannulation.

B. Initiation of bypass potential complications
1. Hypotension
(a) Hypovolemia: The ECMO circuit has high blood capacitance, which can result in "functional" hypovolemia. Treat this with volume resuscitation. The technician/specialist should have blood or colloid available from circuit priming procedure.
(b) Sudden dilution of vasopressors, especially with V-V ECMO. Treat by having a second set of vasoactive infusion pumps to infuse circuit.
(c) Hypocalcemia from stored blood (local blood bank dependent). The ECMO circuit can be primed with calcium to prevent this.
2. Bradycardia may occur from vagal stimulation by catheter(s), which is responsive to atropine.
3. Catheter malpositioning can complicate cannulation, resulting in tachyarrhythmia and impaired venous return with V-V ECMO. Correct catheter placement must be documented radiographically and may use sonography to assist with placement.

C. Initial management on ECMO
1. V-A: Wean ventilator rapidly over 10–15 min to "rest" settings. Rest settings: peak inspiratory pressure 20–25 cm H_2O, PEEP 10–12 cm H_2O, rate 10–20 bpm, T_I 0.5–1.0 s. Utilizing a high PEEP to maintain functional residual capacity can often shorten bypass time. Inotropes can usually be quickly discontinued. The use of an oximeter saturation to mea-

sure 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, as reflected by the difference in mixed venous O_2 and arterial O_2, equals O_2 delivery. Since this can be measured in ECMO patients, the caregiver has a measure of "pump" oxygen delivery/cardiac output.

2. V-V: Wean ventilator support to rest settings as with V-A; however, high PEEP may impair venous return. Wean inotropic support with caution as the infant is still dependent on innate myocardial function for oxygen delivery. With V-V, 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. The innate lung still provides gas exchange.
3. Avoid large swings in pCO_2 and blood pressure, as this can be associated with unwanted rapid changes in cerebral blood flow.
4. Infants have "self-decannulated"; *restraints are strongly recommended*.
5. Head position is critical; head turned too far left will functionally occlude the left jugular vein. Remember, the right jugular vein is already ligated. Such a scenario may lead to central nervous system venous hypertension.
6. Analgesia and sedation are usually required. Narcotics are used for analgesia; if additional sedation is needed, benzodiazepines are reasonable choices.
7. Anticoagulation is typically systemic heparin.
   (a) Prior to cannulation, bolus with 100 U/kg.
   (b) Typical starting drip concentration is 50 U/mL [5 mL heparin (1000 U/mL) in 95 mL D_5W].
   (c) Usual consumption is 20–50 U/kg/h. 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 renal elimination.
   (d) Titrate heparin to keep activated clotting time (ACT) in desired range. Anti-Xa concentration may be useful where immediate results are not needed and discrepancies are occurring.

D. Daily management on ECMO:
1. Chest radiograph: Recommend daily.
2. Cranial sonography: 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 the infant is able to come off ECMO, it is recommended to 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 higher platelet counts (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:
   (a) Total body water (TBW) is high secondary to multiple etiologies. A problem arises when TBW is high but intravascular volume is low, as early vigorous attempts at diuresis in this instance can be harmful. Some argue that this can hasten lung recovery; others state that spontaneous diuresis is a marker for improvement, and attempts to hasten it are fruitless. If diuresis is deemed advisable, use diuretics first and mechani-

cal support (e.g., hemofiltration) last. Furosemide in combination with theophylline may be helpful.

(b) Potassium: Serum potassium values are often low and require replacement. This may be further complicated by alkalosis.

(c) Calcium: The ECMO pump is primed with banked blood and depending upon the preservative, ionized calcium can be low. Checking and correcting the circuit can prevent this complication.

4. Coagulation status (Hemostasis/hemolysis)
   (a) Trend ACT at bedside and titrate heparin to goal parameters.
   (b) Trend daily fibrinogen and serum hemoglobin to follow trends. Some use serum hemoglobin >50 mg/dL as action thresholds (suggest creating local values/plans) with values >100 posing risks for hemoglobinuria and acute tubular necrosis.
   (c) Platelet counts q8 hours and continue to trend for 48 h following decannulation because of risk of ongoing thrombocytopenia.
   (d) Clots are common, especially if using a venous capacitance reservoir (bladder). Prelung clots are usually left alone. Postlung clots are handled by ECMO specialist/technician. When clots appear, review platelet/heparin consumption, consider thromboxane.
   (e) 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. Treat by drainage first. This is more commonly seen if previous surgery has been done (e.g., congenital diaphragmatic hernia, thoracostomy tube placement)
      (3) Treat with blood replacement, higher platelet counts (>150,000/mm^3), lower target ACT or Anti-Xa level.
5. Blood products:
   (a) Minimize donor exposures, give only when indicated.
   (b) Excessive pRBC administration without increasing pump flow on V-A ECMO leads to lower PaO_2 but greater oxygen delivery. In ECMO circles, when one responds to this by transfusing again, one is "chasing his/her tail."
6. Nutrition: A major benefit of ECMO is the immediate provision of total parenteral nutrition and adequate caloric/low volume intake through the use of high dextrose concentrations.
7. Hypertension is a known complication. The mechanism is usually high total body water. It is almost always transient and resolves near the end of a run. Initial treatment is with diuretics.
8. White blood cell count is often low, probably from peripheral migration of white blood cells.
9. Infections are not a common problem on ECMO; however, suspect infection if unanticipated increasing ECMO support is required.
10. Bilirubin can be elevated especially with sepsis or prolonged 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. This is seen more in V-A ECMO patients and may be ECMO induced from increased afterload and decreased coronary artery oxygen content. The stun phenomenon

usually resolves. Treatment is supportive and includes evaluation of cannula position, correction of electrolyte derangements, and flow adjustments.

E. Common circuit complications
   1. Air in circuit: Treatment depends upon location, can often be aspirated.
   2. Pump "slowdowns or cutouts." Consider kinked tube, malposition, low volume, low filling pressure (e.g., pneumothorax, hemopericardium), and agitated infant, which may impact preload and/or afterload.
   3. Pump
      (a) Electric failure: The pump can be cranked by hand.
      (b) With roller pumps: If the occlusion set too loosely, false high flow readings may occur. If the occlusion is set too tightly, hemolysis may occur.
   4. Lung pathophysiology: The membrane lung can get "sick" with resultant pulmonary embolus, edema, etc. Treatment depends upon specific problem.

F. Weaning ECMO support
   1. Use serial measures of oxygen content (on V-A ECMO easiest to follow S_VO_2) and wean by algorithm.
   2. Chest radiography is very helpful to trend throughout an ECMO course. There is typically initial complete opacification that starts to clear prior to "re-ventilating" the lungs as a marker of lung recovery which heralds the ability to trial off.
   3. Evaluation of lung compliance and tidal volume improvement is an early marker of lung recovery.
   4. End tidal CO_2: Increasing exhaled CO_2 is indicative of return of lung function.

G. Trialing off ECMO
   1. Valuable information can be obtained from "trialing off," even if unsuccessful.
   2. Prior to a trial off consider:
      (a) Increasing the ventilator FiO_2 and following S_VO_2 will give a feel for whether or not there is effective pulmonary gas exchange.
      (b) Increasing ventilator settings to achieve adequate tidal volumes 30–60 min before trialing off to allow for lung recruitment.
   3. V-A trial off: There is no circuit flow during trial off, as the cannulas are clamped, and a bridge is used between arterial and venous catheters to keep flow and avoid thrombus; thus, this requires the circuit to be "flashed" every 15 min. Obtain blood gas analyses frequently to assess ventilation. Wean FiO_2 aggressively per oximetry.
   4. V-V trial off: Halt gas flow to membrane lung, but keep the pump flowing. Since infant is still on bypass, but with no effective gas exchange through the membrane lung, use venous 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.
   5. A successful trial off depends upon the individual patient. In general, the infant should be stable on $FiO_2 \leq 0.4$, and reasonable ventilator settings.

H. Inability to wean from ECMO
   1. With prolonged need for bypass (e.g., 7 days) and little to no improvement, consider an underlying "rare" lung disease (i.e., alveolar-capillary dysplasia, surfactant protein B deficiency, etc.).
   2. Bronchoscopy and lavage and/or biopsy may allow for the diagnosis of rare lung diseases.

I. Decannulation
   1. Notify surgeon as soon as possible.
   2. Prepare for operative anesthesia including a skeletal muscle relaxant.
   3. Repair of carotid artery or jugular vein remains controversial.

V. Post-ECMO Follow-Up
   A. Incision site: Sutures removed in 7 days.
   B. Hematology: Platelets will continue to fall post-ECMO. Serial counts are necessary until stable for 48 h.
   C. Brain imaging: MRI is obtained because of relative insensitivity of sonography for posterior fossa and near field parenchymal lesions.
   D. Hearing: Audiology evaluation with brainstem auditory evoke response testing is needed because of the high incidence (20%) of sensorineural hearing loss with persistent pulmonary hypertension. Delayed onset hearing loss has been described, and repeated screening is advised.
   E. Airway: Vocal cord paresis is seen in approximately 5% of infants post-ECMO. If persistent stridor is noted, flexible bronchoscopy is recommended.
   F. Long-term follow-up
      1. Neurodevelopmental follow-up should be provided given the risk of long-term neurodevelopmental impairments.
      2. Medical problems include lower respiratory tract infections.

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Part X

Management of Common Neonatal Respiratory Diseases

Mechanisms of Respiratory Failure

65

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 mm Hg (8 kPa).
   B. In the newborn, the oxygen tension needed to maintain the arterial saturation above 90% varies between 40 and 60 mm Hg (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 mm Hg).

$$PaCO_2 \oplus \frac{CO_2 \text{ production}}{\text{Alveolar ventilation}}$$

   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 mm Hg (6.7 kPa) in an inspired oxygen of at least 50% with/without $PaCO_2$ >55 mm Hg (6.7 kPa)

II. Hypoxemia and hypercapnia 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. Can be assessed using volumetric capnography
      3. Increased physiologic dead space, which can be assessed by capnography
      4. Found in the following conditions:
         (a) Respiratory distress syndrome
         (b) Pneumonia
         (c) Meconium aspiration syndrome

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(d) Bronchopulmonary dysplasia

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 (Cystic adenomatoid malformation)
      6. Asphyxiating thoracic dystrophy

IV. Ventilatory pump failure
   A. Reduced central drive found in
      1. Maternal opiate treatment (high levels of sedation)
      2. Cerebral ischemia
      3. Intracerebral hemorrhage
      4. Apnea of prematurity
      5. Systemic disease such as sepsis
      6. Congenital central alveolar hypoventilation syndrome
   B. Impaired ventilatory muscle function found in
      1. Drugs (corticosteroids, neuromuscular blocking agents—synergism with aminoglycosides)
      2. Disuse atrophy (first signs occur after 1–2 days of 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, anterior abdominal wall defects, diaphragmatic dysfunction)
      7. Phrenic nerve palsy (traumatic birth, Erb's palsy)
   C. Increased respiratory muscle workload, found in

1. Chest wall edema (hydrops)
2. Upper airway obstruction
3. Intubated infants with insufficient compensatory ventilatory support
4. Pulmonary edema, pneumonia
5. 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

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Tissue Hypoxia

66

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 on 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 concentrations; elevation can be present in the absence of tissue hypoxia, particularly in patients with sepsis.
   C. Fractional oxygen extraction increases as oxygen transport is progressively compromised. Fractional oxygen extraction (FOE) can be measured by near-infrared spectroscopy (NIRS). Using spatially resolved spectroscopy, an NIRS method, it is possible to measure regional tissue oxygen saturation in different organs (e.g., brain, kidney, liver, muscle or body regions, preductal, postductal peripheral tissue).

III. Oxygen Transport
   A. Determinants
      1. Cardiac output
      2. Hemoglobin concentration
      3. Hemoglobin saturation (to a lesser extent)

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B. Oxygen–hemoglobin dissociation curve
   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 and hypoxanthine 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

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Indications for Mechanical Ventilation

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I. Absolute Indications
   A. In the delivery room
      1. Failure to establish adequate spontaneous breathing 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 (NICU)
      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 and ventilated with high positive end expiratory pressure (PEEP). Consider skeletal muscle relaxants.

II. Relative Indications
   A. In the delivery room
      1. Infants of extremely low gestational age may be electively intubated to receive prophylactic surfactant therapy, and 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. Increasingly, less invasive surfactant administration is now given in the delivery suite.
      2. Infants <24 weeks of gestational age should be electively intubated, given surfactant, 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 and the specific policies of the individual NICU. In our facility, we utilize the following guidelines:

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(a) <28 weeks' gestation: arterial carbon dioxide tension ($PaCO_2$) >45–55 mmHg (6.0–7.3 kPa), the lower limit if associated with a pH < 7.25 and/or arterial oxygen tension (PaO_2) <50–60 mmHg (6.7–8 kPa) in a fractional inspired oxygen (F_iO_2) of greater than 0.50, although if the infant only has poor oxygenation, nasal CPAP may be tried first.

(b) 28–32 weeks' gestation: $PaCO_2$ >45–55 mmHg (6.0–7.0 kPa), the lower limit being used if the pH is <7.25 and/or PaO_2 <50–60 mmHg (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 mmHg (8 kPa) with a pH below 7.25 and/or PaO_2 <45 mmHg (6 kPa) in an F_iO_2 of >0.80. Consider intubation at a lower threshold if clinical respiratory distress is evident. 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 (>1–2 per hour requiring stimulation) unresponsive to nasal CPAP/NIPPV and administration of methylxanthines
   (b) Severe sepsis
   (c) Need to maintain airway patency
3. To maintain control of carbon dioxide tension (e.g., infants with pulmonary hypertension)

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Respiratory Distress Syndrome

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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.
      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.

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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 nonsurvivors.
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 and maintain dynamic elevation of end-expiratory lung volume.

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. It also improves alveolar patency and gas exchange.

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 in room air. 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 sacculi 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 or even low 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, diaphragmatic hernia)
D. Extrapulmonary abnormalities (e.g., vascular ring, ascites, 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 a nasal cannula or an oxygen hood.
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 $FiO_2 \geq 0.5$), some form of positive pressure ventilation is usually 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. 67) 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) Invasive surfactant administration is planned.
(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 both an appropriate tidal volume and maintains adequate end-expiratory lung volume, while minimizing the risks of complications (see below).

B. Surfactant replacement therapy (Chap. 58)
   1. The development and use of surfactant replacement therapy have revolutionized the treatment of RDS.
   2. Numerous preparations (natural, synthetic, and semisynthetic) 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 INSURE, it is gaining popularity as an alternative to continued mechanical ventilation.
         (3) Still another option is less invasive surfactant administration (LISA) or minimally invasive surfactant treatment (MIST). Under direct laryngoscopy, surfactant is instilled directly into the trachea through a vascular catheter or narrow feeding tube, which is then withdrawn. NCPAP is continued during this procedure.
      (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)
   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. If indicated, maintain adequate sedation/analgesia (Chap. 62) but avoid respiratory depression, which will delay weaning.
   5. Provide adequate nutrition (Chap. 57), but avoid excessive nonnitrogen 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 (Chap. 81)
      (a) Pneumomediastinum
      (b) Pulmonary interstitial emphysema
      (c) Pneumothorax
      (d) Pneumopericardium
      (e) Pneumoperitoneum (transdiaphragmatic)
      (f) Subcutaneous emphysema
   2. Airway injury from the endotracheal tube
   3. Pulmonary hemorrhage (Chap. 83)
   4. Bronchopulmonary dysplasia (Chaps. 78, 79, and 80).

B. Cardiac associations
   1. Patent ductus arteriosus (Chap. 82)
   2. Congestive heart failure
   3. Pulmonary hypertension (Chap. 71)
   4. Cor pulmonale

C. Neurologic associations (Chap. 85)
   1. Relationship to intraventricular hemorrhage
   2. Relationship to periventricular leukomalacia
   3. Neurodevelopmental impact

D. Infectious associations
   1. Nosocomial and acquired pneumonia (Chap. 69)
   2. Sepsis

X. Prenatal Treatments and Conditions That 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/chorioamnionitis

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

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Pneumonia in the Newborn Infant

69

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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 noninfectious 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.

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(d) Immature natural killer (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)).
(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, occasional plasma cells, and rare eosinophils.
   (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) Most women who acquire toxoplasmosis during pregnancy have no manifestations.
   (b) 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.
   (c) Overall risk of transmission to the fetus after primary maternal infection is 30%; the risk increases with advancing gestation.
   (d) 1.4% of maternal infections result in miscarriage, and 2.5% cause fetal death.
   (e) Infected infants may be (1) asymptomatic (>80%), (2) exhibit neurologic findings (chorioretinitis (3–5% at birth), hydrocephalus, seizures, and calcification), or (3) demonstrate a generalized systemic illness (hepatosplenomegaly, pneumonia, etc.).
   (f) Fetal infection has not been associated with growth restriction.
   (g) Neurologic findings and chorioretinitis may have a delayed presentation.

(h) 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 *T. 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) Cord blood may be contaminated with maternal blood and specimens from the umbilical cord may result in false positive tests.
   (i) 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.
   (j) Persistence of IgG titers to *T. gondii* beyond 12 months is diagnostic.
   (k) The absence of IgG antibodies against *T. gondii* (capable of producing IgG antibodies) at any age rules out congenital toxoplasmosis.
   (l) There is a high incidence of false negative results with the IgM indirect immunofluorescent antibody (IFA) test.
   (m) The double-sandwich IgM capture ELISA, and the IgM immunosorbent agglutination assay (ISAGA) has 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 sulfadiazine (plus folinic acid) should be used during pregnancy. *Pyrimethamine should be avoided in the first trimester because of teratogenic effects.*
   (c) Because of concerns about pyrimethamine and sulfonamides, some experts recommend only treating mothers with a positive PCR from amniotic fluid.
   (d) When maternal infections occur in the last 2 months of pregnancy, most experts recommend beginning pyrimethamine and sulfonamides presumptively because of the high risk of fetal infection.
   (e) All infected newborns should receive pyrimethamine and sulfadiazine (plus folinic acid) up to 1 year.
   (f) Prednisone (0.5 mg BID) is added for infants with very high CSF proteins (>1 g/dL) or active chorioretinitis.

(g) When the diagnosis is uncertain, drug treatment can be postponed until a definitive diagnosis is made.
(h) Prevention strategies should be used for pregnant women (cook meat to well done, avoid handling or eating raw meat, avoid contact with material potentially contaminated with cat feces).
(i) Untreated infants with congenital toxoplasmosis have a poor outcome. Infants with CNS manifestations at birth have worse cognitive and motor outcomes.
(j) Children with normal brain imaging or slightly abnormal brain imaging can develop normally. However, infants with subclinical congenital infections can also develop sequelae.
(k) 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.

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 or through blood products. 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) A minimal inflammatory reaction is likely, but in severe cases, there may be focal interstitial infiltration.
3. Manifestations
(a) Most common congenital infection (0.2–2.2% of all newborns).
(b) Seropositivity rates in the United States range from 50% to 85%.
(c) Seroprevalence is higher in African-American and Hispanic populations.
(d) Congenital infection can occur secondary to a primary infection (30% transmission) or reactivation/reinfection during pregnancy (0.2–2.0% transmission).
(e) Women who are seropositive can become reinfected with a different strain of CMV leading to congenital infection.
(f) The majority of congenital infections with CMV result from nonprimary infections and not primary infections.
(g) Exposure to CMV in the genital tract in late gestation is associated with natal transmission in 26–50% of cases.
(h) Ninety percent of infants with congenital CMV are asymptomatic at birth, but may subsequently develop pneumonia or hearing loss.
(i) Primary infections are more likely to be associated with fetal damage than recurrent infection.
(j) 70–90% of seropositive women excrete virus in their breast milk. Peak excretion occurs between 2 weeks and 2 months.

(k) Transmission from breast milk occurs in 39–59% of breastfed infants, if nursing lasts more than 1 month.
(l) A diffuse interstitial pneumonitis occurs in <1% of congenitally infected, symptomatic infants.
(m) Common signs of congenital infection at birth include intrauterine growth restriction, microcephaly, intracerebral calcifications, retinitis, hepatosplenomegaly, jaundice, and purpura.
(n) 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) Virus can be detected in respiratory secretions in infants with pneumonia using PCR.
   (d) CMV-sIgM serology has not been shown to have adequate sensitivity or specificity for the diagnosis of congenital CMV.
   (e) CMV-DNA PCR on blood specimens (including blood stored on filter paper) may be useful in infants with viral sepsis.
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) The incidence of newborn infection is 1/3200 deliveries.
   (c) Perinatal infections account for 85% of neonatal infections, and postnatal infections represent 10% of infections.
   (d) There are two main serotypes of HSV (HSV-1 and HSV-2).
   (e) While HSV-2 historically has been the predominant serotype causing genital and neonatal herpes infections in the United States, HSV-1 now causes the majority of genital infections and probably neonatal infections.
   (f) Most women with serologic evidence of HSV-2 infection have no history of symptomatic primary or recurrent disease.
   (g) Among women with a prior history of genital herpes, 75% will have at least one recurrence during the pregnancy.
2. Transmission
   (a) Estimated incidence of 5–33 infants/100,000 live births in the United States.
   (b) Infection in the mother can be classified as recurrent, primary, or first episode nonprimary infections. In primary infections, the mother experiences an infection with HSV and has never been exposed to HSV 1 or 2. In nonprimary, 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 ruptured membranes.
(d) The risk of transmission is ~50% for infants born to mothers with primary infection, 25% for infants with nonprimary 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 weeks 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 second or third week of life, but occasionally up to 6 weeks. Sixty percent of infants with CNS disease have skin lesions at some point.
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 indicative of infection.
   (b) A positive PCR assay on cerebrospinal fluid is diagnostic (sensitivity of 75–100% and specificity of 71–100%).
   (c) A positive blood PCR for HSV DNA confirms infection, but does not define disease classification.
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. However, that may not prevent neonatal disease.
   (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. If the viral cultures or PCR is positive, a full evaluation is required.

(f) Disseminated disease is treated for 21 days.
(g) Skin, eye, and mouth (SEM) disease should be treated for 14 days.
(h) All infants 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 (83% normal) but not CNS disease (31% 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 or secondary syphilis (60–100%) and lower for early latent infections (40%) or late, latent infections (8%).
(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 nontreponemal antibody tests (RPR/VDRL) in the first trimester. Treponemal tests are only used for confirmation.
(1) Both nontreponemal and treponemal tests can have false positive and false negative results.

(b) In the pregnant woman (and in rare circumstances in the infant), syphilis is *confirmed* by:
  (1) demonstration of *T. pallidum* using dark-filed microscopy, or
  (2) using direct or indirect immunofluorescent from a tissue specimen.

(c) Congenital syphilis is categorized as highly probable, probable, possible or unlikely according to the following criteria.
  (1) Congenital syphilis is considered *highly probable* if the infant has signs of congenital syphilis and a titer > fourfold the maternal titer or a positive CSF VDRL result.
  (2) Congenital syphilis is considered *probable* when the infant is asymptomatic, the nontreponemal titers are < fourfold the maternal titers, but maternal treatment did not occur or was inadequate (dose of penicillin is unknown, inadequate or not documented, a nonpenicillin regimen was used, treatment was given <30 days of the infant's birth and if the mother has early syphilis and had a nontreponemal titer that had increased fourfold).
  (3) Congenital syphilis is considered *possible* when the infant is asymptomatic, the titers are < fourfold the maternal titer, adequate treatment occurred during the pregnancy, and titers remained low or stable.
  (4) Congenital syphilis is considered *unlikely* if the infant's physical examination is normal, RPR/VDRL titers are < fourfold the maternal titer, and the mother was adequately treated before pregnancy and her titers remained low or stable.

(d) Infants who have normal physical findings and a quantitative nontreponemal antibody titer < fourfold the maternal titer do not require any further testing if the mother received adequate treatment for the stage of syphilis 4 or more weeks prior to delivery and either:
  (1) The mother had early syphilis at the time of treatment, her nontreponemal antibody titers have decreased fourfold and have remained stable or low through delivery.
  (2) The mother had late syphilis at the time of treatment, her nontreponemal antibody titers have remained low and stable and there was no evidence for relapse or risk of reinfection.

(e) If those criteria are not met (or there is doubt) evaluation for syphilis is mandatory and should include: a quantitative nontreponemal serologic test (not cord blood), long bone radiographs (unless the diagnosis has been established using other tests), a complete blood count and direct Coombs test, pathologic examination of the placenta including fluorescent antitreponemal staining and a VDRL test on CSF and analysis for cells and protein.

5. Treatment and prognosis

(a) Infants with *proven or highly probable* congenital syphilis should receive 10 days of parenteral penicillin (aqueous penicillin G for 10–14 days).

(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 procaine 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 nontreponemal testing becomes negative. In these infants, evaluation of the CSF is mandatory. If

any part of the evaluation is unavailable, abnormal, or uninterpretable a full 10-day regimen is recommended.

(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 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 bloodstream.

B. Pathology

1. Dense cellular exudate, congestion, hemorrhage, and necrosis
2. *Staphylococcus aureus* and *Klebsiella* may cause micro-abscesses and pneumatoceles.
3. Hyaline membranes are common (especially in preterm infants), and bacteria may be seen within the membranes.
4. Developmental immaturity of macrophages in the neonatal lung predisposes to bacterial infection.

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, 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* (group B *Streptococcus*; GBS)
(a) Most common bacterial pathogen in term infants.
(b) Approximately 18% (mean with a confidence interval of 16.2–19.7) of women are colonized with GBS.
(c) Intrapartum antibiotics have reduced the incidence of early-onset GBS sepsis by 80%, but have not substantially changed incidence of late-onset GBS sepsis.
(d) In the setting of vaginal colonization without intrapartum antibiotic prophylaxis, the vertical transmission rate is ~50% and the risk of infection (sepsis and pneumonia) in colonized infants is 1–2%.
(e) In the United States, the majority of early-onset GBS sepsis now occurs in babies born to mothers who screened negative for colonization (either false negative or colonization was established in the interval between screening and birth).
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 to a woman with Listeriosis will develop neonatal infection.
4. Other pathogens: *Staphylococcus 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 tachy-

Table 69.1 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 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

cardia >160 bpm, maternal WBC > 15,000/mm^3 (without steroid treatment), purulent vaginal discharge, and laboratory evidence of amniotic fluid infection/inflammation (Table 69.1). Isolated maternal fever is not a significant risk factor for sepsis/pneumonia.

2. Colonization with GBS (adequate intrapartum therapy lowers the risk of infection by 85–90%)
3. Maternal urinary tract infection
4. Prolonged and/or 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 (nonpulmonary)
   (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 *not likely* 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, or 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 suspected early-onset sepsis have undergone several recent revisions. The American Academy of Pediatrics Committee on the Fetus and Newborn revised its published guidance in 2018, recommending that providers use either a categorical risk assessment, a multivariate risk assessment (e.g., the online sepsis calculator), or serial physical examinations to decide whether to initiate empiric antibiotic therapy.

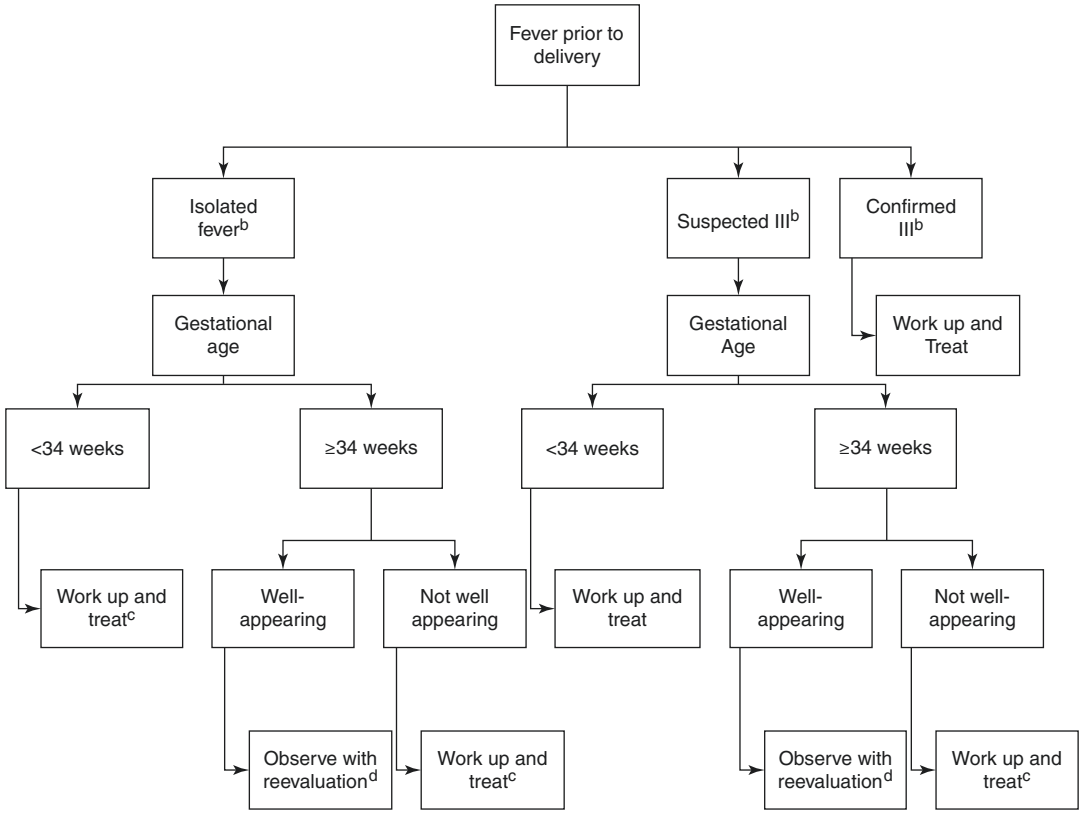
2. Cultures
   (a) A positive blood culture is the "gold standard" for detection of bacteremia in the newborn.
   (b) Urine cultures are rarely positive in infants with early-onset bacterial sepsis and should not be routinely obtained.
   (c) A lumbar puncture should be performed in all infants with a positive blood culture *or* in symptomatic infants with a high probability of infection based on adjunct laboratory 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. CRP concentrations peak 48–72 h after an inflammatory insult.
(1) Maternal CRP does not cross the placenta, so any neonatal elevation is from endogenous production.
(2) A CRP value of ≥1 mg/dL is considered positive.
(e) Procalcitonin is another nonspecific acute phase reactant. It peaks earlier than CRP, generally 24–36 h after inflammation develops.
(1) For both procalcitonin and CRP, serial normal values have a high negative predictive value and are useful for excluding the diagnosis of early-onset sepsis. Neither measure has a high positive predictive value.

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 pneumatoceles (suggestive of *S. aureus*).

5. Chest ultrasound is increasingly studied as an alternative to X-rays for diagnosis of neonatal pneumonia, but is not yet widely used. Chest ultrasound sensitivity and specificity remain highly operator- and technology-dependent.

K. Management (Fig. 69.1)
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 are effective alternatives, 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) *Listeria 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*).



[a] Guidelines should be considered a starting point. Additional factors may warrant alternative management.
[b] III = intrauterine infection/inflammation. See text and Table 69.1 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 reecaluation by members of the medical team may take place on an appropriately staffed postpartum unit.

Fig. 69.1 Suggested algorithm for management of neonates with maternal history of fever[a]

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 from 91% to 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. 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 species* (*U. urealyticum, U. parvum*)
1. Transmission
   (a) *Ureaplasma* spp. are frequent inhabitants of the lower genital tract of asymptomatic women, and isolation of *Ureaplasma* spp. 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 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) *Ureaplasma* spp. infection of the newborn is associated with pneumonia, meningitis, intraventricular hemorrhage, 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, 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 an increased risk of 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/II NICUs.
3. Risk factors include:
   (a) Length of NICU stay
   (b) Prematurity
   (c) Low birth weight

(d) Enteral Feeding
(e) Mechanical ventilation
(f) Frequent endotracheal tube suctioning
(g) Reintubation
(h) Transfusion
(i) Bronchopulmonary dysplasia
(j) Treatment with opiates
(k) 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 three 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 often not helpful, because they merely identify microorganisms colonizing the airway (not necessarily those causing disease).
   (a) The presence of an abundance of polymorphonuclear leukocytes or a significant increase from a prior gram stain is supportive evidence.
   (b) The value of quantitative cultures or the presence of intracellular bacteria has not been adequately studied in neonates.
5. Chest radiographs may indicate new or focal infiltrates, but in infants with chronic lung changes, the distinction from atelectasis is difficult. Point-of-care ultrasound may be helpful.
6. 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.
7. Bronchoscopy is not recommended for neonates with suspected VAP.

D. Bacterial and fungal pathogens
1. VAP is frequently polymicrobial.
2. *Staphylococcus aureus* and enteric organisms (*Pseudomonas aeruginosa, Klebsiella,* spp., *Escherichia 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.
   (a) Vancomycin and gentamicin are an adequate first choice for most neonates. However, if there is a significant risk of VAP with one or more resistant organisms, consider an anti-Pseudomonal cephalosporin (cefepime or ceftazidime) or anti-Pseudomonal carbapenem (meropenem or Imipenem) or a β lactam/β lacta-

mase inhibitor (piperacillin-tazobactam) plus linezolid or vancomycin (for MRSA).

2. 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.
3. Amphotericin or fluconazole is used for fungal infections.
4. 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.
5. Prevention bundles, incorporating multiple practices noted above, may be most effective in the prevention of VAP.

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 United States, 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 United States).
4. RSV is spread by direct or close contact with infected secretions. The virus can live up to 7 h on countertop, 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.

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, or 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 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 congenital heart disease (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, 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. It 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 coinfect 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.

VII. SARS-CoV-2
A. Background
   1. Virus responsible for the coronavirus disease 2019 (COVID-19) pandemic
   2. Affects all age groups, but children appear to be affected less commonly and less severely than adults.
   3. Transmission occurs primarily through respiratory droplets during the postnatal period when neonates are exposed to mothers or other caregivers with SARS-CoV-2 infection. Aerosol transmission may also occur.
   4. The extent of vertical transmission in unclear and perinatal (intrapartum) infection is infrequent.
   5. Incubation period is generally within 14 days of exposure (median 4 days).
B. Pathology
   1. SARS-CoV-2 infects epithelium of the upper and lower airways with diffuse alveolar damage as the predominant pulmonary pathology.
C. Manifestations:
   1. Pneumonia/acute respiratory failure
   2. Other reported manifestations: fever, lethargy, rhinorrhea, cough, tachypnea, vomiting, diarrhea, and poor feeding
   3. Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare complication.
      (a) Signs and symptoms include persistent fever, inflammation (based on laboratory test results), and evidence of organ dysfunction or shock.
D. Diagnosis
   1. RT-PCR is the method of choice.
   2. Serologic tests permit only a retrospective diagnosis.
E. Treatment:
   1. Supportive care (hydration, use of supplemental oxygen, and mechanical ventilation as needed).
   2. Dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who require mechanical ventilation.

(a) Use of dexamethasone in patients with milder disease may be considered on a case-by-case basis.

3. The safety and effectiveness of remdesivir for the treatment of COVID-19 have not been fully evaluated in pediatric patients.
   (a) Remdesivir is currently available through an FDA emergency use authorization for the treatment of COVID-19 in hospitalized pediatric patients <12 years and weighing ≥3.5 kg.

F. Prevention

1. Rates of SARS-CoV-2 infection in neonates do not appear to be affected by mode of delivery or method of infant feeding.

   Infected mothers/caregivers should wear a mask and practice hand hygiene during all contact with their neonates.

Suggested Reading

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Meconium Aspiration Syndrome

70

Thomas E. Wiswell

I. Overview
   A. Meconium-stained amniotic fluid (MSAF).
      1. Frequency is 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 (physiologic) 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 is 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 resuscitation 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 coexisting MAS.

II. Pathophysiology
   A. Complex mechanisms involved (Fig. 70.1)
   B. At any given moment, these mechanisms either individually or in combination will 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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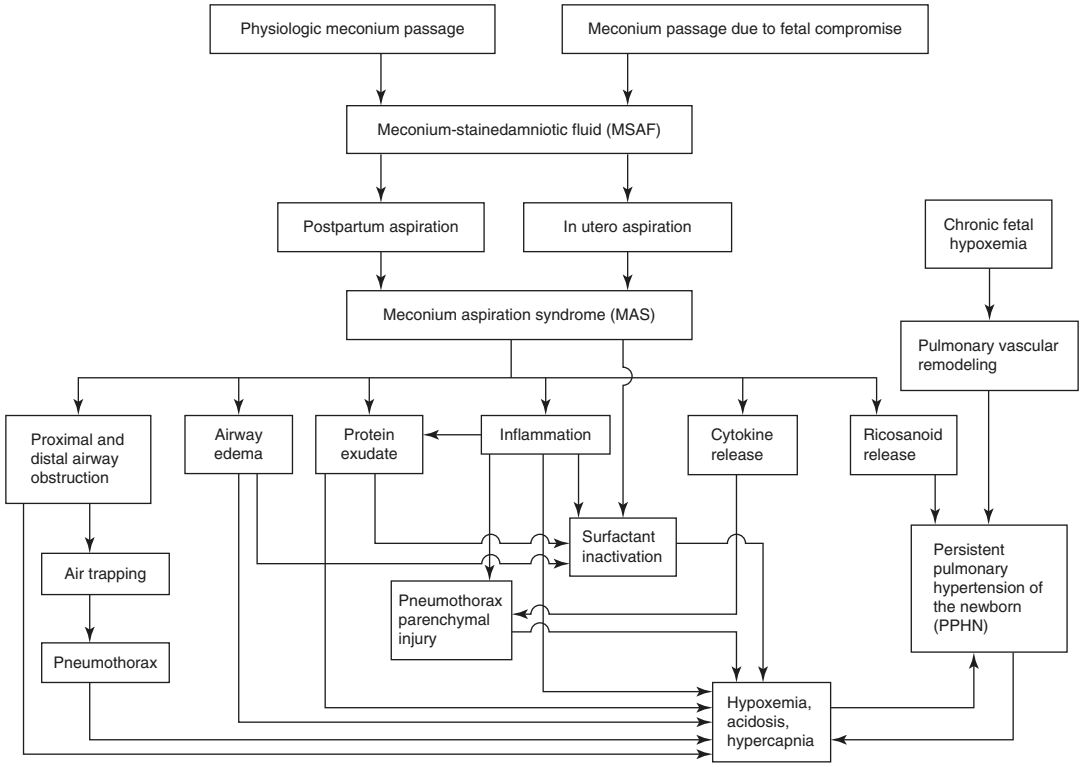

Fig. 70.1 Pathophysiology of the meconium aspiration syndrome (MAS)

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 cricoid area of the infant's airway to prevent intratracheal meconium from descending into the lungs
   2. Epiglottal blockage: insertion of one to three 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 and aspiration of MSAF 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 2016 *Neonatal Resuscitation Program (7th edition)* (NRP) guidelines no longer endorsed routine intubation and intratracheal suctioning of depressed or nonvigorous infants. Although this intervention had been recommended for more than 40 years, the NRP Steering Committee changed its position and stated that evidence present before and during

those four decades was insufficient to support the practice. This committee acknowledged that a definitive randomized, controlled trial (RCT) has not yet been performed to assess the practice in the nonvigorous population. Since 2015 four small RCTs performed in a developing country have assessed the practice and have had mixed results. In these four studies, trainees were the individuals performing the intubation/suction procedure. Unfortunately, residents in training have an exceptionally low success rate (6–20%) in intubating and suctioning. It is no surprise that the results of the aforementioned small RCTs were inconclusive. By contrast, the Chiruvolu et al.'s observational trial, in which experienced intubators performed the procedure, indicated that intubation/suctioning significantly decreases the frequency of respiratory distress, as well as the need for oxygen therapy and mechanical ventilation. The 2016 NRP guidelines do state that intubation and intratracheal suctioning may be performed if clinically indicated for individual 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 postnatal reflux or emesis and frank aspiration of meconium-stained amniotic fluid.
   2. No studies to date have assessed this approach.

IV. Radiographic Findings
   A. Radiographic findings among infants with MAS are diverse and include the following:
      1. Diffuse, patchy infiltrates
      2. Consolidation
      3. Atelectasis
      4. Pleural effusions
      5. Air leaks (pneumothorax, 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 despite respiratory distress (likely reflects the presence of PPHN)
   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 oxygen saturation 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 (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 (saturation 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 noninvasive method of administering oxygen also provides a degree of positive pressure.
   2. Both low (≤1 LPM) and high (2–7 LPM) flow rates have been used therapeutically.
   3. No clinical trials have been performed to assess the use of nasal cannula flow for MAS.

D. Continuous positive airway pressure (CPAP)
   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 increased functional residual capacity. These factors could contribute to gas trapping and 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
   1. Typically provided with time-cycled, pressure-targeted 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 (potentially dangerous).
      (c) "Gentle" ventilation allows accepting higher $PaCO_2$, lower pH, and lower PaO_2 levels in an attempt to prevent lung injury (from barotrauma or volutrauma) and potential side effects from hypocapnia and alkalosis.
   3. To date, there have been no prospective, randomized trials comparing any of the various mechanical ventilation 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, dobutamine) or fluid boluses to maintain high systemic blood pressure to overcome high pulmonary pressures
5. None of these therapies have been rigorously investigated in infants with MAS; some are potentially harmful.

VI. Nonconventional 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 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, 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) A few 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.
5. Further trials are necessary to assess this therapy.

C. Inhaled nitric oxide (iNO)
1. Results of multiple 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 PPHN 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 can be administered either systemically or via the inhalation route.
3. Animal data are intriguing; limited human data indicate some benefit.
4. Additional clinical trials are warranted involving infants with substantial MAS who require mechanical ventilation.

E. Extracorporeal membrane oxygenation (ECMO)
   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 24,000 newborns treated with ECMO since the mid-1980s, 25–30% have had MAS as their underlying pulmonary 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 for the prevention and management of MAS, a few have been adequately investigated.
   C. Further work is needed to elucidate optimal management of MAS.

Suggested Reading

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Persistent Pulmonary Hypertension of the Newborn

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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 postbirth decline. This leads to a variable degree of right-to-left shunting through persistent fetal channels, the foramen ovale and ductus arteriosus, and resultant 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 seen in 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 postbirth event. Intra-acinar vascular development is thus also a postbirth phenomenon. As a consequence, at birth, at the acinar level, there is decreased cross-sectional area available for pulmonary blood flow and obligate high vascular resistance.

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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.
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 nonstructural (and hence more reversible) factors may significantly impact pulmonary vascular reactivity and pressure, including arterial oxygen and carbon dioxide tensions, and pH. Hypoxemia, 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 hypoxemia, 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 overdistention contribute to increased pulmonary vascular resistance at the acinar level.
(c) Concomitant effects of severe parenchymal lung disease
(d) Some infants will also have morphological changes in pulmonary vasculature (see below).
3. Sepsis/pneumonia
(a) Infection initiates an inflammatory response.
(b) Release of cytokines and other vascular mediators increases pulmonary vascular resistance.
(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 hypoxemia.
(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 airway malformation

3. Hypoxia-induced functional abnormalities of the pulmonary vasculature
   (a) Hypoxia downregulates 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, dysmaturity)
   (d) Maternal aspirin or NSAID use (may cause premature ductal closure)
2. Physical examination (findings are nonspecific, but may help to suggest etiologic considerations)
   (a) Murmur or a loud single second heart sound
   (b) Abnormal breath sounds
   (c) Inequality of pulses
   (d) Scaphoid abdomen
   (e) Potter's facies
3. Chest radiograph (again, nonspecific, 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 postductal oxygenation
1. Obtain simultaneous arterial blood gas samples from pre- (right radial artery) and postductal (umbilical or posterior tibial artery) sites.
2. A gradient (20 torr or 2.7 kPa higher in the preductal PaO_2) suggests a right-to-left ductal shunt. Low values from both sites do not rule-out PPHN; shunting may still be occur-

ring at the level of the foramen ovale. If both values are high and essentially equal, PPHN is unlikely to be present.

3. Similarly, dual-site pulse oximetry can be used. Place one sensor preductally, one postductally. A difference of 15–20% suggests a ductal shunt.

E. The hyperoxia-hyperventilation test
   1. Hypoxemia and acidosis augment pulmonary vasoconstriction.
   2. Alkalosis and hyperoxia decrease pulmonary vascular resistance.
   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 versus 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, 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, postdatism).

B. Neonatal
   1. Adequate resuscitation
   2. Avoidance of acidosis, hypoxemia, 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, air leaks)
   5. Minimize factors that may increase PVR, such as adverse environmental stimuli. Sedative, anxiolytic, and/or paralytic agents may help in this regard.

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 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 pulmonary vascular resistance) 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 as low as 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. 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 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 useful.
   4. No matter which approach is chosen, remember that many 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 62)
   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) Multiple case series, retrospective reviews, and open-label pharmacologic studies 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 (≤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) Inhaled nitric oxide (Chap. 63). Inhaled nitric oxide has successfully treated PPHN in term infants, though up to 40% of infants may have an inadequate response. 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. Most commonly used in an enteral form, though an IV form is now available and may result in systemic hypotension. 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 effects are 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 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.
   (e) All systemically administered drugs also have the potential downside of increasing intrapulmonary right-to-left shunt when PPHN is secondary to (atelectatic) lung disease.

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.

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Congenital Diaphragmatic Hernia

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I. *Embryology and Anatomy of the Normal Diaphragm*
   A. The septum transversum forms the temporary infrastructure of the ventrolateral diaphragm leaving dorsolateral gaps bilaterally called the pleuroperitoneal canals.
   B. Pleuroperitoneal folds arise from the dorsolateral body wall and migrate ventrally to meet the septum transversum and close the pleuroperitoneal canals.
   C. Muscle progenitors migrate from cervical somites through the pleuroperitoneal folds and septum transversum to form the costal muscle, crural muscle, and central tendon of the diaphragm with additional peripheral musculature provided by the body wall.
   D. Crural, dorsocostal, and sternocostal branches of the phrenic nerve innervate the diaphragm.
   E. Inferior phrenic arteries arise from the abdominal aorta to supply the inferior diaphragm.
   F. Branches of the superior phrenic arteries arise from the thoracic aorta, and branches from the internal thoracic arteries supply the superior diaphragm.

II. *Pathophysiology*
   A. In CDH, the diaphragm fails to develop normally during the first trimester, but the pathologic mechanism(s) remain under investigation.
   B. Defects of the pleuroperitoneal folds from decreased migration of muscle progenitors, increased apoptosis, failure of differentiation, or defects of the septum transversum have all been implicated.
   C. A hernia sac (present in 20–25% of cases) may occur when muscle progenitors fail to migrate across a patch of pleuroperitoneal fold, leaving a poorly supported, connective tissue sac.
   D. Abdominal organs herniate through the diaphragmatic defect into the thoracic cavity.
   E. Herniated abdominal viscera impede lung development.

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F. Left-sided defects are more common (~ 85% of cases) which might result from the earlier closure of the right hemidiaphragm.

III. *Etiology*
- A. A combination of genetic and environmental factors has been implicated.
- B. Retinoid signaling is important for lung development; alteration of the retinoic acid signaling pathway may be involved in the pathogenesis.
- C. Genetic
  1. Genetic causes are identified in only 30% of cases.
  2. CDH-associated genes have variable penetrance.
  3. Many CDH-associated genes are associated with other congenital anomalies.
- D. Environmental studies have reported increased risk for:
  1. Maternal exposure to tobacco, alcohol, and vitamin A
  2. Pregestational diabetes
  3. Pregestational hypertension
  4. Low maternal body weight
  5. Increased maternal age
  6. Low socioeconomic status

IV. *Defects of the Diaphragm*
- A. Posterior-lateral defect/Bochdalek hernia
  1. Approximately 80% to 90% of CDH cases
  2. Eighty-five percent occur on the left side; 10% occur on the right side; 5% are bilateral.
  3. Posterior-medial
  4. Posterior-lateral
- B. Anterior-medial defect/Morgagni hernia
  1. Approximately 2% of cases
  2. Small posterior-lateral with intact costal muscle margin
  3. Lateral
  4. Anterior-lateral
  5. Anterior-parasternal
- C. Complete absence of the diaphragm
  1. Very rare
  2. Associated with worst prognosis
  3. Hemi-aplasia with anterior intact parasternal costal muscle margin
  4. Complete hemi-aplasia
- D. Eventration
  1. Not a true hernia
  2. Possibly the result of dysfunctional differentiation or migration of myoblasts from cervical somites resulting in muscle deficiency of the diaphragm
  3. Rare

V. *Epidemiology*
- A. Incidence: 2.3–3.6/10,000 live births.
- B. More common in males.
- C. Of the prenatally diagnosed cases, approximately 25% are terminated, 3% are miscarried, and 3% are stillborn.
- D. Familial cases are uncommon.

E. Can occur as an isolated or complex anomaly.
   1. Isolated
      (a) Not associated with other major congenital anomalies
      (b) Fifty percent to 60% of cases
      (c) Survival rate of 70% to 80% for isolated cases
   2. Complex
      (a) Associated with other major congenital anomalies or syndromes
      (b) Forty percent to 50% of cases
      (c) Associated with a worse prognosis

F. Associated anomalies (most common).
   1. Cardiac
      (a) Hypoplasia
      (b) Atrial septal defect
      (c) Ventricular septal defect
      (d) Aortic coarctation
   2. Gastrointestinal
      (a) Malrotation
      (b) Meckel's diverticulum
      (c) Omphalocele
      (d) Anorectal malformation
   3. Genitourinary
      (a) Undescended testes
      (b) Inguinal hernia
      (c) Renal dysplasia
   4. Neurologic- Hydrocephalus
   5. Skeletal
      (a) Limb anomaly
      (b) Hemivertebrae
   6. Craniofacial—Cleft lip and/or palate
   7. Pulmonary sequestration

VI. *Prenatal Presentation*

A. Antenatal ultrasound
   1. Approximately 70% cases are detected on sonographic scan during the 2nd or 3rd trimester.
   2. Herniated abdominal viscera, mediastinal shift, and a small abdominal circumference are characteristic for CDH.
   3. Right-sided lesions are more difficult to detect because of similar echogenicity of the lung and liver.
   4. Polyhydramnios is common. Herniation of the stomach kinks the distal esophagus obstructing fetal swallowing.
   5. Evaluate for associated congenital anomalies.

B. Antenatal MRI
   1. Has prognostic value but is generally performed after a CDH diagnosis is confirmed.
   2. Enables assessment of liver herniation, stomach position, and total fetal lung volume.
   3. In contrast to ultrasound, it is independent of maternal body habitus, amniotic fluid volume, and fetal position.

C. Amniocentesis and chorionic villus sampling for karyotype and/or chromosomal microarray
   1. No specific cytogenetic anomaly is associated with CDH.
   2. Chromosomal anomalies occur in 10% to 35%.
   3. Most frequent aneuploidies: trisomy 18, trisomy 13, and trisomy 21.

VII. *Early Postnatal Presentation*
   A. Cases not detected on prenatal ultrasound may have a smaller defect and possibly a better prognosis.
   B. Signs at delivery
      1. Failure to respond to normal resuscitative measures and progressive respiratory distress
      2. Swallowed air causes intestinal distention, worsening lung compression, and a mediastinal shift.
      3. Barrel chest and scaphoid abdomen may be noted
   C. Most infants develop symptoms within 24 hours of birth.

VIII. *Late Postnatal Presentation*
   A. Approximately 10% of cases
   B. Signs can be variable; acute or chronic
   C. Respiratory
      1. Cough
      2. Tachypnea
      3. Respiratory distress and cyanosis
   D. Gastrointestinal
      1. Pain
      2. Nausea and/or vomiting
      3. Failure-to-thrive

IX. *Diagnosis*
   A. Diagnosis is confirmed by chest radiography
      1. Bowel loops in the thoracic space
      2. Nasogastric tube curling into the thoracic space
   B. Additional investigations
      1. Contrast studies—to confirm stomach/intestine in the chest if radiograph equivocal
      2. Ultrasound—to document position of the liver and assess kidneys
      3. Echocardiography—to assess degree of pulmonary hypertension
      4. CT or MRI scan—to confirm diagnosis if other investigations are equivocal

X. *Differential Diagnosis*
   A. Bronchopulmonary sequestration
      1. May be mistaken for CDH on imaging.
      2. May occur concurrently with CDH.
      3. CDH-associated extralobar sequestrations can be found in the thorax, abdomen, or trapped within the abnormal diaphragm.
   B. Congenital pulmonary airway malformation (CPAM)
   C. Bronchogenic cysts
   D. Enteric cysts
   E. Teratoma
   F. Serpentine-like syndrome—Short esophagus and stomach in the thoracic cavity
   G. Most common misdiagnoses on chest radiograph: pneumothorax, pneumonia, and pleural effusion

XI. *Postnatal Pathophysiology*
  A. Pulmonary hypoplasia
    1. Abnormal cell signaling decreases distal airway branching and alveolar formation.
    2. Studies have suggested that lung hypoplasia precedes herniation of abdominal viscera.
    3. Lack of space within the thoracic cavity may contribute.
    4. Reduced surface area for gas exchange.
    5. Primarily affects the ipsilateral lung but the contralateral lung also affected**.**
  B. Pulmonary hypertension
    1. Results from vascular remodeling in utero.
    2. Theoretically, may result from epithelial dysfunction in hypoplastic lungs causing endothelial dysfunction and subsequently pulmonary artery smooth muscle proliferation.
    3. Pulmonary arterial smooth muscle proliferation results in decreased arterial caliber.
    4. There is also decreased pulmonary arterial branching.
    5. Increased resistance in pulmonary vascular bed causes right heart strain and persistent pulmonary hypertension (PPHN).
    6. Poor oxygenation results from PPHN.
    7. PPHN severity is assessed by echocardiography.
    8. CDH mortality is directly related to the severity of PPHN.
  C. Compromised cardiac function
    1. Left-sided heart hypoplasia can be observed in CDH in utero, but the cause is unknown.
    2. Normal transition from fetal to neonatal cardiorespiratory circulation does not occur because of persistently elevated pulmonary vascular resistance.
    3. Persistent fetal right-to-left shunting at atria and ductus arteriosus can lead to right heart strain or failure.
    4. Overworked right heart dilates and hypertrophies with septal deviation to the left.
    5. Deviated septum impairs the left ventricle preload and output.
    6. Prenatal left-heart hypoplasia and postnatal left ventricular dysfunction result in peripheral hypotension, hypoxemia, and acidosis.
    7. Systemic acidosis exacerbates cardiac dysfunction and increases pulmonary vascular resistance and right-to-left shunting.
  D. Surfactant deficiency
    1. Surfactant deficiency and composition alterations have been described in CDH.
    2. There is no evidence that postnatal exogenous surfactant administration is beneficial.
    3. Postnatal exogenous surfactant may worsen outcomes.

XII. *Prenatal Indicators of Outcome*
  A. Lung size
    1. Measure of pulmonary hypoplasia.
    2. The original lung-to-head ratio (LHR) used ultrasound to estimate the size of the lung contralateral to the hernia, standardized for head circumference.
    3. LHR values <1.0 are associated with poor prognosis.
    4. The observed/expected lung-to-head ratio (O/E LHR) determined by ultrasound between 22 and 32 weeks' gestation
      (a) O/E LHR <15% associated with <5% survival.
      (b) O/E LHR 16–25% associated with 20–30% survival.
      (c) O/E LHR 26–45% associated with 40–60% survival.
      (d) O/E LHR >45% associated with 95% survival .

(e) Right-sided CDH has worse survival than left-sided despite similar O/E LHR.
(f) O/E LHR is presently the tool used to counsel parents and consider candidates for fetal intervention.

5. Observed/expected total fetal lung volume (O/E TFLV) determined by MRI can also be used to assess lung volume as a percentage of expected volumes in a normal fetus.

B. Liver position
1. Liver herniation has demonstrated prognostic value.
2. In right-sided CDH, the liver is usually in the thorax and so not predictive.
3. Liver echogenicity is similar to lung making liver position on ultrasound difficult to discern.
4. In left-sided CDH, liver-to-thoracic area ratio (US-LiTR) has prognostic value.

C. Hernia sac
1. Presence of a sac is associated with improved survival.
2. MRI can reliably predict the presence of a sac but ultrasound cannot

D. Stomach position
1. Can be determined and graded with ultrasound.
2. Echogenic stomach is easier to differentiate from lung than liver.
3. Can be used as an indirect indicator of liver position.

E. MRI-determined defect size may predict the need for a patch repair.
F. Generally, a combination of O/E LHR and liver or stomach position is used to predict survival.
G. Early diagnosis (<25 weeks' gestation), polyhydramnios, herniated stomach or liver, and associated anomalies suggest a poor prognosis.

XIII. *Postnatal Indicators of Outcome*
A. Presence of associated anomalies increases morbidity and mortality.
B. Larger defects are associated with diminished survival and increased morbidity.
C. Severity of pulmonary hypoplasia.
D. Means to identify severe pulmonary hypoplasia after delivery and correlate with survival require investigation.
E. Presence of liver herniation increases mortality.
F. Severity of PPHN.
G. The CDH study group predictive survival (CDHG-PS) score uses the 5-minute Apgar score and birth weight to produce a survival probability.
H. Blood gases and pH are used as predictors of survival; the inability to clear CO_2 is a good measure of poor cardiopulmonary function in CDH.
I. The Score for Neonatal Acute Physiology, Version II (SNAP-II) is predictive of survival and other adverse outcomes.

XIV. *Antenatal Management*
A. Families should be counseled by an obstetrician, neonatologist, and pediatric surgeon.
B. Access to a geneticist, psychologist, and spiritual care should be offered.
C. Antenatal options should include:
1. Continuation of pregnancy with intention to perform postnatal repair if/when the infant is stable.
(a) Delivery should be at a center with resources to manage a CDH infant through resuscitation, surgery, and recovery.
(b) Vaginal delivery will not harm the baby if the mother wishes this option.

(c) Pregnancy should continue until at least 39 weeks.
(d) Mothers at risk of delivering before 34 weeks should be given steroids.
(e) Families may be made aware of extracorporeal membrane oxygenation (ECMO), but they should understand that a survival benefit has not been proven.

2. Termination of pregnancy (regulations vary between countries)
3. Continuation of pregnancy with palliative care postnatally. Birth plan and postnatal care must be well documented.
4. Fetal surgery
   (a) Available at specialized centers around the world and individual center inclusion criteria vary.
   (b) Fetoscopic endoluminal tracheal occlusion (FETO) may promote lung growth and development in fetuses with moderate or severe pulmonary hypoplasia.
   (c) Studies to date comparing FETO to standard postnatal management report equivocal effects on survival, but studies have been hampered by poorly defined inclusion criteria, small sample sizes, and use of historical controls.
   (d) The tracheal occlusion to accelerate lung growth (TOTAL) trial is a randomized controlled study that started in 2011 to determine if FETO improves survival for moderate and severe forms of CDH; survival in fetuses with severe pulmonary hypoplasia increased after FETO whereas survival in fetuses with moderate pulmonary hypoplasia did not change.

XV. *Postnatal Management*

A. Monitors and adjuncts
   1. Heart rate monitor
   2. Preductal O_2 saturation
   3. Postductal O_2 saturation
   4. Intra-arterial blood pressure (ideally in the right radial artery; alternately in the umbilical artery)
   5. Oro- or nasogastric tube with continuous or intermittent suction
   6. Peripheral intravenous access
   7. Chest radiograph
   8. Routine blood gases

B. Ventilation
   1. Intubation should be performed immediately if/when the neonate demonstrates respiratory distress.
   2. Some centers endorse routine intubation of all CDH neonates after delivery to prevent gastrointestinal distension.
   3. Premedication should be considered before intubation.
   4. Bag-valve-mask ventilation should be avoided to prevent inflating the stomach and intestines.
   5. Conventional mechanical ventilation (CMV) is generally the initial modality of ventilation.
   6. Spontaneous breathing can be considered if prenatal assessments predicted good lung development (left-sided defect, O/E LHR >50%, and liver down).
   7. High-frequency oscillatory ventilation or high-frequency jet ventilation should be considered when the peak inspiratory pressure required to control hypercapnia using >35 cm H_2O.
   8. Goals of ventilation:
      (a) Arterial pCO_2 45–60 mmHg (6–8 kPa)

(b) pH 7.25–7.40
(c) Preductal saturation >85%
(d) Postductal saturation >70%

C. Sedation, analgesia, and paralysis
1. Sedation should be provided while the newborn is mechanically ventilated.
2. Deep sedation and neuromuscular blockade should be provided selectively to those with greater ventilation or oxygen requirements.
3. Routine neuromuscular blockade is not beneficial.

D. Hemodynamic support
1. Goals of hemodynamic support:
(a) Maintain a normal arterial blood pressure for age
(b) Capillary refill <3 seconds
(c) Lactate <3 mmol/L
2. Treatment of hypotension

E. Echocardiography
1. Assess pulmonary hypertension, left and right ventricular function, and associated cardiac anomalies.
2. Additional studies may be clinically indicated.

F. Management of pulmonary hypertension
1. Inhaled nitric oxide (iNO), an inhaled vasodilator, is the first choice for confirmed suprasystemic pulmonary hypertension without left ventricular dysfunction, provided lung recruitment is adequate.
2. In the absence of clinical (10–20% decrease in pre–postductal saturation difference, increase of 10–20% of PaO_2, 10% increase in mean Paw, or decreased lactate level) or echocardiographic response, iNO should be stopped.
3. Sildenafil, a vasodilator and bronchodilator, could be considered in patients with PPHN unresponsive to iNO or as an adjunct when weaning iNO, but the evidence is extremely limited.
4. Milrinone, a pulmonary vasodilator and cardiac inotrope and lusitrope, may be used to treat cardiac dysfunction, particularly if it is associated with PPHN.
5. Prostaglandin E_1 can be used to open or maintain patency of the ductus arteriosus to reduce right ventricular afterload in patients with PPHN and right ventricular failure

G. ECMO
1. Available in specialized centers
2. Survival benefits unproven
3. Indications (vary by center) and include:
(a) Inability to maintain preductal O_2 saturation >85% or postductal O_2 saturation >70%
(b) Decreased left ventricular systolic function
(c) Increased $PaCO_2$ and respiratory acidosis with pH <7.15 despite optimization of ventilation management
(d) Peak inspiratory pressure >28 cm H_2O or mean Paw >17 cm H_2O required to achieve preductal O_2 saturation >85%
(e) Metabolic acidosis (lactate >= 5 mmol/L and pH <7.15)
(f) Oliguria (urine output <0.5 mL/kg/hour for >12–24 hours)
(g) Oxygenation index ≥40 for >3 hours

H. Timing of surgery
1. Surgical repair is essential but should only occur once the baby is stable.
2. The following physiologic criteria should be met before surgery:
(a) Urine output >1 mL/kg/h
(b) FiO_2 <0.5
(c) Preductal oxygen saturation 85–95%
(d) Normal mean arterial pressure
(e) Lactate <3 mmol/L
(f) Estimated pulmonary artery pressure < systemic pressure
3. Failure to meet these criteria within 2 weeks should prompt consideration of either attempted repair or a palliative approach.
4. For patients on ECMO, timing of surgery on ECMO is controversial.
5. If the patient cannot be weaned off ECMO, consideration should be given for either surgery or palliation.

XVI. *Survival*
A. Most deaths (78%) occur prior to surgical correction of the diaphragmatic defect.
B. Survival to discharge is ~70%.

XVII. *Long-Term Outcomes*
A. Recurrence
1. Incidence 3–50% long term
2. Increased recurrence reportedly associated with:
(a) Large defects
(b) Minimally invasive repair
(c) Nonprimary repair of the diaphragmatic defect
(d) Liver herniation
(e) Presence of comorbidities
(f) Need for an abdominal wall patch
(g) Extended postoperative hospital admission
(h) Use of lyophilized dura as a patch
(i) ECMO
(j) Right-sided diaphragmatic defects
B. Pulmonary morbidities
1. Chronic lung disease
2. Asthma
3. Decreased exercise tolerance
4. Recurrent respiratory tract infections and pneumonia
C. Gastrointestinal morbidities
1. Gastroesophageal reflux
2. Failure to thrive
3. Oral aversion
4. Small bowel obstruction
D. Musculoskeletal morbidities
1. Pectus deformities
2. Scoliosis
E. Neurodevelopmental morbidities
1. Neuromuscular hypotonia
2. Learning difficulties

3. Neurobehavioral issues

F. Neurologic morbidities
   1. Hearing impairment
   2. Visual impairment

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Pulmonary Hypoplasia

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I. Overview of Lung Development
   A. Lungs first develop via epithelial branching and extension into mesenchymal tissue, then by septation and subdivision.
      1. Embryonic phase occurs during 4 to 7 postconceptional weeks.
         (a) Endodermal outpouchings of the foregut form the tissue that will become the trachea, esophagus, visceral, and somatic pleura.
         (b) Surrounding mesenchyme forms plexuses of blood vessels.
      2. Pseudoglandular phase occurs from 6 to 16 weeks' gestation.
         (a) Lung buds branch, grow, and differentiate, forming bronchi, bronchioles, respiratory bronchioles, and alveolar ducts.
         (b) Epithelial and muscle cells differentiate in the airway.
         (c) Vessels divide and branch.
         (d) Fetal breathing movements begin.
      3. Canalicular phase occurs from 16 to 26 weeks.
         (a) Air-conducting and gas-exchange regions of the lung differentiate, the starting point for acini formation. Epithelium differentiates between ciliated cells in the more proximal airway, and type I and type II epithelial cells in more distal parts of the airways.
         (b) At the end of the canalicular phase, ventilator unit and capillary developments are sufficient to allow survival of normally developed infants born prematurely.
      4. Saccular phase occurs between 26 and 38 weeks.
         (a) The saccules widen and branching morphogenesis ends.
         (b) Growth of lung volume and surface area occurs in the acini, with subsequent thinning of mesenchyme.
         (c) Vessels in the mesenchyme are compressed to form a single capillary layer.

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5. Alveolar phase begins at the end of gestation. Alveolar proliferation occurs, and is mostly complete by 3 years of age.

B. Importance of lung fluid and fetal breathing movements
   1. Lung fluid produced by lung epithelial cells maintains prenatal lung expansion.
   2. Fetal breathing moves lung fluid peripherally, leading to extension of distal airways.
   3. Stretch by lung fluid and fetal breathing stimulates release and delivery of growth factors needed for epithelial cell proliferation, differentiation, and surfactant production.

II. Pathophysiology of Lung Hypoplasia
   A. Primary forms of lung hypoplasia are rare, and most occur secondary to other developmental abnormalities.
   B. Underlying abnormalities that may result in pulmonary hypoplasia include the following:
      1. Oligohydramnios causes negative pressure and reduction of fetal lung fluid, leading to lung hypoplasia and structural immaturity. Oligohydramnios can be caused by:
         (a) Renal abnormalities and failure (i.e., Potter's syndrome)
         (b) Urinary outflow tract obstruction
         (c) Prolonged premature rupture of membranes
         (d) Placental insufficiency or intrauterine growth restriction
      2. Space-occupying lesions such as abdominal contents in CDH, CPAM, or pleural effusions in the setting of hydrops
      3. Malformations of the chest wall
      4. Neuromuscular disorders preventing normal fetal breathing, therefore reducing distal alveolar expansion
   C. Functional pulmonary insufficiency in pulmonary hypoplasia occurs through multiple pathways:
      1. Reduced lung size (e.g., secondary to thoracic dystrophy, CDH)
      2. Structural immaturity (e.g., secondary to oligohydramnios)
      3. Diffusion deficits (e.g., secondary to alveolar capillary dysplasia)
   D. Severity of pulmonary hypoplasia is greatly influenced by the timing of disruption: Earlier disruption causes more lung abnormalities and a worse prognosis.

III. Diagnosis
   A. Antenatal: Pulmonary hypoplasia may be anticipated on the basis of maternal antenatal ultrasound scan suggesting compression (e.g., severe oligohydramnios, small fetal chest cavity, severe diaphragmatic hernia). Magnetic resonance imaging may be useful for clarification.
   B. Postnatal: Diagnosis may be apparent immediately after birth if hypoplasia is severe (e.g., cannot be resuscitated, has severe respiratory distress from birth), or is part of a recognizable syndrome (e.g., oligohydramnios sequence). When the infant presents later with isolated mild to moderate respiratory distress, the diagnosis may be delayed.
      1. Chest radiography may show bell-shaped or reduced thoracic cage size, space-occupying lesion, and/or mediastinal shift.
      2. Consider an assessment of pulmonary mechanics, looking at lung volumes and compliance.
      3. Consider lung biopsy to assess for immature lung structure with reduced lung cells, fewer branching bronchi, immature epithelial cells, fewer and thickened pulmonary vessels, and lower lung DNA content.
      4. Syndromes either primarily or secondarily associated with pulmonary hypoplasia should be considered.
         (a) Consider Genetics consultation if other anomalies are present
         (b) Examination of surfactant deficiency-related genotypes

5. Conditions that can mimic these signs (e.g., infection) should be excluded. These include the rarely reported "Dry Lung Syndrome" which is postulated to mimic pulmonary hypoplasia. It is likely caused by leak or loss of fluid and apparent lung volume loss, with need for significant respiratory support immediately postnatally, but which normalizes soon after birth with dramatic improvement in ventilatory requirements during the first 24 to 36 postnatal hours.

IV. Management
   A. Antenatal: If a diagnosis of pulmonary hypoplasia is made in utero, families should be counseled 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.
      3. Parents may decide between
         (a) Termination of pregnancy (however criteria and regulations vary markedly among, and within, countries).
         (b) Continuing the pregnancy with postnatal interventions.
         (c) Antenatal interventions are practiced only in relation to certain conditions (e.g., bilateral pleural effusions).
            1. Amnioinfusion has not been found to benefit perinatal mortality in the setting of rupture of membranes early in the canalicular period.
            2. Results of other antenatal interventions vary with both the nature and severity of underlying problem. Evidence of benefit for such interventions (e.g., tracheal occlusion for CDH) is not well established, but available research protocols should be discussed with families.
   B. Standard resuscitation should take place at delivery with some special considerations:
      1. Where antenatal scans indicate, special measures (e.g., draining pleural effusions) should be performed.
      2. Vigorous resuscitation of infants with small lung volume often results in air leak. Caution should be taken to minimize lung overdistension while ensuring adequate lung inflation is achieved and maintained to allow for gas exchange and prevent both overdistension and atelectotrauma.
   C. Treatment approaches for hypoplastic lungs in the NICU:
      1. Ensure adequate systemic blood pressure to maintain tissue perfusion and minimize right-to-left shunting. This may require infusion of fluids and inotropes. Take care not to induce fluid overload.
      2. Provide adequate respiratory support. Infants with mild hypoplasia may not require mechanical ventilation. For those requiring invasive support, high-frequency and low-tidal volume ventilation may reduce barotrauma. Aggressive ventilation may damage lungs and further impair lung function.
      3. Introduce pulmonary vasodilators as indicated; pulmonary hypertension is often a complication of pulmonary hypoplasia. Echocardiography may help confirm the diagnosis. There have not been consistent improvements in mortality in the literature with iNO use in the setting of pulmonary hypoplasia, but this is an area warranting ongoing research.
      4. A small retrospective cohort study showed improvement in gas exchange with heliox treatment in infants with CDH.
      5. There is no clear role for surfactant in pulmonary hypoplasia alone; however, it is recommended for the treatment of concurrent RDS, if applicable.

6. Extracorporeal Membrane Oxygenation (ECMO) is able to provide stability, but there is no evidence of long-term benefit over other forms of care in pulmonary hypoplasia.
7. A role for partial liquid ventilation is not established.
8. Investigate to establish an underlying diagnosis, see the above section on 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 etiology and any associated anomalies influence prognosis.
   B. Mild cases often become asymptomatic with further growth. Abnormalities in 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 lung growth relative to somatic growth is uncertain, and death in later childhood can occur.
   D. Severely affected babies have high mortality in the NICU despite full support.
   E. Overall perinatal mortality is between 55% and 100%. Mortality is higher in cases with severe pulmonary hypertension, and other associated neurologic, musculoskeletal, and gastrointestinal comorbidities.
   F. In infants who survive, complications include altered growth, chronic lung disease, low exercise capacity, and recurrent respiratory infections.

VI. Counseling 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. Postmortem histologies can examine radial alveolar count (RAC) for diagnosis, as well as lung volume and lung weight to body weight ratios which have historically been used for the diagnosis of pulmonary hypoplasia.

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Chylothorax

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I. Anatomy and Function of the Lymphatic System
   A. Lymph is generated in the interstitium and carried in lymph vessels with a unidirectional flow to the venous system near the junction of the left internal jugular and the left subclavian veins with estimated two-thirds of the fluid generated by the liver and intestine.
   B. There is variation in the thoracic lymphatic duct anatomy, and 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 left to the esophagus and behind the aortic arch at the 4th to 6th 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 leak to spaces along the rout 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, premature birth, and on the degree of chylothorax interference with lung development (degree of pulmonary hypoplasia) with overall survival of 30% to 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.
      2. Chylothorax is reported in association with other surgical procedures involving the thoracic cavity and the diaphragm.

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3. Patients who develop chylothorax had a higher mortality and a longer hospital course.

III. Lymphatic developmental anomalies associated with chylothorax can be limited to the lungs or involving other organ systems. Chylothorax is usually caused by sluggish lymph drainage and/or by mass formation that impedes lymph 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 lymphatics flow).
   B. Congenital lymphatic dysplasia syndrome is an inherited form of lymph vessel anomaly associated with congenital chylothorax attributed to valvular incompetence causing chyle reflux from 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 patient is not fed and appears creamy if patient is fed.
      2. Contains more than 1000 white blood cell per microliter with more than 70% to 80% of them lymphocytes.
      3. Has similar protein content to plasma, and triglyceride concentration more than 1000 mg/dL (in feeding patients)
   B. Identifying etiology for chylothorax
      1. Prenatal evaluation to determine etiology and inform the plan and the predicted outcome.
         (a) Fetal evaluation for chromosomal, cardiac, and thoracic structural anomalies.
         (b) Maternal evaluations for immunologic and infectious etiologies of hydrothorax.
      2. Postnatal studies to identify anatomy of lymphatic vessels and source of lymph leakage include the following:
         (a) Lymphangiography (requires cannulation of lymphatic vessels and can identify leaks from thoracic duct). Lymphangiography may contribute to further damage lymphatic vessels in lymphatic dysplasia because of the high viscosity of the oil-based contrast agent used.
         (b) MRI lymphangiography (may enable visualization of central lymphatic anatomy)
         (c) Lymphoscintigraphy (a radioisotope injected between digits can identify thoracic duct injury and aplasia and hypoplasia of lymphatic vessels and may be useful in evaluating lymphatic dysplasia.)

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 fluids with venous return and cardiac function.
      2. Prenatal treatments mainly include thoracentesis, pleuroperitoneal shunting, and pleurodesis (creation of adhesions).
      3. Prenatal interventions are considered with 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 informed by response to the treatment that is 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
4. Drained lymphatic fluid is associated with losses in cells (especially lymph cells), proteins (including nutritious elements), electrolytes, and immune and coagulation factors.
   (a) Drained fluids are partially replaced (usually with 5% albumin).
   (b) Both pro- and anticoagulation factors are lost in the drained lymphatic fluid, and a trend toward increased risk for thrombosis may occur.
   (c) Some centers use periodic treatment with intravenous immunoglobulin (IVIG).
5. Other treatment options to decrease lymphatic flow include:
   (a) Using defatted breast milk or a formula high in medium chain triglycerides (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, Novis 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, biliary sludge, hypothyroidism, and pulmonary hypertension.
6. Surgical interventions
   (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.

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Apnea, Bradycardia, and Desaturation

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I. Introduction
   A. Neonatal apnea is widely accepted as the cessation of breathing or absence of air flow for >15 to 20 seconds. 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 air flow), or mixed (central and obstructive). Mixed apnea is the most common type of apnea in premature infants.
   D. Periodic breathing defined as recurring 10- to 15-second cycles of breathing alternating with pauses of 5 to 10 seconds 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, pulse oximetry 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.

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H. Apnea of prematurity typically resolves by term gestation; however, it may take longer (44 weeks' postmenstrual age) in the most premature infants.
I. Central and obstructive apnea may occur in term infants, especially in the first 6 months of life because of relative immaturity of the central nervous system. In all documented cases of true apnea in the term infant, a detailed evaluation must be performed to determine an underlying cause.

II. Pathophysiologic 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.
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 neuroregulation 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 (0.2 kPa) 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, and 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 air flow.
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 may result from malposition of the head and neck.
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.
F. There is insufficient evidence to determine the effects of body positioning on apnea, bradycardia, and oxygen saturation in preterm infants.

III. Hypoxemia
A. Hypoxemia in neonates is typically defined by oxygen saturation (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 is yet to be determined but is dependent upon several variables including postnatal age, gestational age, maturity of the retinal vasculature, presence or absence of structural heart disease, 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% to 90%, from three large randomized controlled trials, it is suggested that functional SpO_2 should be targeted at 90% to 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 the following:
        (a) Central or obstructive apnea
        (b) Periodic breathing
        (c) Respiratory pauses
        (d) Hypoventilation
        (e) Low lung volumes (FRC) with diminished oxygen reserves
        (f) A reactive or poorly developed pulmonary vascular bed
        (g) Anemia
    3. Allowing lower baseline oxygen saturation levels predisposes to more frequent or profound intermittent hypoxemia.
    4. Intermittent hypoxemia has been associated with adverse cognitive outcomes in extremely preterm infants.
F. Inflammation and intermittent hypoxemia (Fig. 75.1)
    1. Exposure to higher oxygen tensions after birth increases the production of oxygen-free radicals that can initiate an inflammatory cascade leading to lung injury and disruption of normal lung and pulmonary vascular maturation.

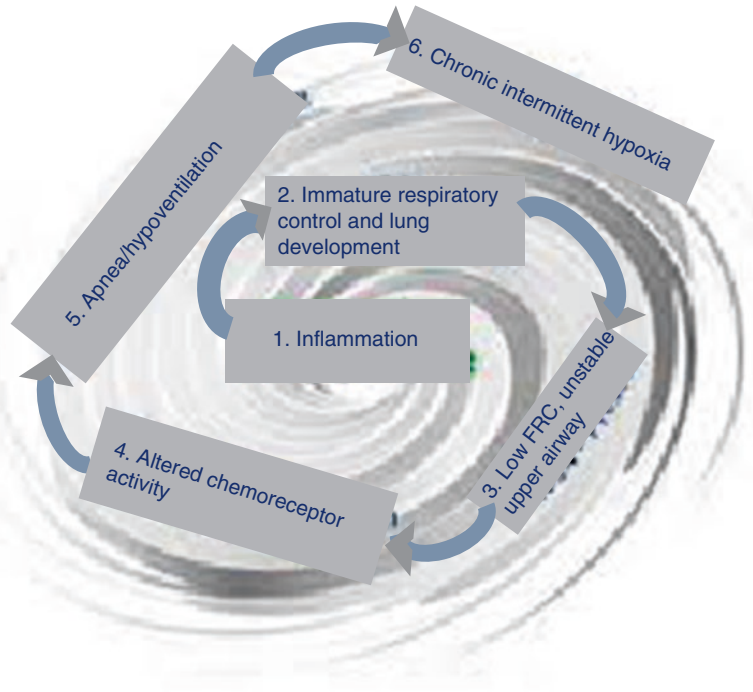

Fig. 75.1 Schematic depicting the perfect strom: the consequences of the adverse effects of perinatal inflammation on the developing lung and respiratory network leading to chronic intermittent hypoxia. (Adapted from Di Fiore JM: Respir Physiol Neurobiol 2013)

2. Intrauterine and/or postnatal infections also lead to inflammation.
3. Inflammation is temporally related to chronic intermittent hypoxemia in animal models.
4. Systemic infection has been shown to upregulate 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. Defined as a drop-in heart rate to <70 to 100 bpm 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 air flow 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 air flow.
      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 semiquantitative volume. RIP is currently limited to the sleep lab setting.
      5. Transcutaneous electromyography of the diaphragm (dEMG) has been shown to be feasible in preterm infants and may improve the classification of central vs. obstructive apnea compared to impedance monitoring.
   B. Oxygen (Chaps. 6, 7, 18, and 19)
      1. Pulse oximetry is the most widely used method for continuous noninvasive 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. Alterations in the signal averaging time will affect the way in which desaturation episodes are detected. For example, a short averaging time of two seconds will increase the

number of short episodes identified, while a longer averaging time of 16 seconds 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 United States) 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 brainstem. Caffeine also enhances diaphragmatic function, increases central nervous system chemoreceptor sensitivity to CO_2, and may have innate anti-inflammatory effects. 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. Eleven-year follow-up studies from the Caffeine for Apnea (CAP) Trial continue to demonstrate the safety and motor benefits of caffeine. The standard loading dose of caffeine citrate is 20 to 25 mg/kg, and the maintenance dose is 5 to 10 mg/kg per dose given every 24 hours IV or orally. Titration of this dose every 1 to 2 weeks may help maintain the therapeutic effect. Although caffeine doses higher than 10 mg/kg appear to demonstrate greater efficacy, they should be used with caution, and close attention should be paid 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. Doxapram, a central respiratory stimulant that acts directly on the carotid bodies, is used worldwide as an adjunctive therapy to caffeine in the treatment of apnea of prematurity. A 2017 meta-analysis evaluated doxapram for the treatment of apnea of prematurity in neonates and determined that no firm conclusion could be drawn about its safety or efficacy based on the available level of evidence. As a result, routine use of doxapram has not been recommended.

C. Noninvasive 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 to 8 cm H_2O; heated, humidified, high flow nasal cannula (HHHFNC) at 3 to 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 the 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.

D. Red blood cell transfusion is often used as an 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 in extremely and very low birthweight infants.

VII. Gastroesophageal Reflux and Apnea of Prematurity

A. Acid suppression therapy is among the most frequently prescribed medications in the NICU. The reason for the prevalence of these drugs appears to be the assumption that gastroesophageal reflux (GER) is responsible for apnea in preterm infants.

B. While apnea and reflux are common in preterm infants, 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 with acid suppression therapy has been associated with significant morbidity secondary to NEC and late onset sepsis, with 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 therapy and appears to be a precursor of bronchopulmonary dysplasia.

C. In a post hoc analysis of data from the Canadian oxygen trial (COT), prolonged hypoxemic events <80% and lasting at least one minute during the first 2 to 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.

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Optimizing Lung Volume

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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 breaths in the delivery room (DR) 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 DR, facilitating fetal-to-neonatal transition.
   B. In spontaneously breathing babies, stabilize with CPAP of at least 6 cm H2O via mask or nasal prongs; early caffeine should be considered for babies at high risk of needing mechanical ventilation (MV) such as those on noninvasive respiratory support; intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs. Babies who require intubation for stabilization should be given surfactant.
   C. The primary choice of ventilation mode and modality is at the discretion of the clinical team; however, if conventional MV is used, targeted tidal volume ventilation should be employed as this modality results in less time on the ventilator, fewer air leaks, and less BPD. High-frequency oscillatory ventilation (HFOV) is an alternative strategy to conventional MV.
   D. A policy of early rescue surfactant should be standard; surfactant should be given in the delivery suite when intubation is needed for stabilization; a suggested protocol would be to treat babies who are worsening when $FiO_2 > 0.30$ on CPAP pressure of at least 6 cm H_2O.

IV. During DR stabilization, different strategies for lung recruitment are suggested: e.g., sustained inflation (SI) (Chap. 30); optimization of CPAP level (using a "static" CPAP or a "dynamic" CPAP strategy).

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A. SI is a peak pressure applied by tracheal tube, face mask or nasopharyngeal tube, maintained for a prolonged time (> 1 sec; ILCOR recommends >5 sec) and usually followed by CPAP.
B. In an experimental lung model of respiratory failure, a recruitment maneuver by SI allowed ventilation with an increased end-expiratory lung volume at moderate PEEP levels.
C. In animal studies, SI delivered by tracheal tube allows early establishment or FRC and uniformity of lung aeration, with facilitation of respiratory and cardiovascular transition (preterm lambs and late preterm asphyxiated lambs).
D. In neonatal settings, SI (peak pressure of 20–25 cm H_2O maintained for 10–15 seconds followed by a CPAP of 5 cm H_2O) seems to reduce only the need for MV within the first 72 hours of life with no beneficial effects versus intermittent ventilation for reducing mortality in the delivery room and during hospitalization.
E. When considering secondary outcomes, such as need for intubation, need for or duration of respiratory support, or BPD, there was no evidence of relevant benefit for SI over intermittent ventilation. Therefore, there is no evidence to support routine use of SI in the DR.
F. In order to enhance neonatal transition in the DR with noninvasive respiratory support, different CPAP strategies are under investigation: increasing (dynamic CPAP) and/or initiating with higher CPAP (static CPAP) levels seem to improve oxygenation and lung aeration.

V. Surfactant Therapy and Lung Recruitment.
A. Tracheal instillation of surfactant (especially when used early in the first 3 hours of life) is a useful treatment for severe RDS, allowing the creation of FRC and improving lung compliance. In the course of noninvasive respiratory support, surfactant is administered by INSURE (IN-tubation, SUR-factant, E-xtubation) or LISA (Less Invasive Surfactant Administration) techniques.
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 in the DR or at NICU entry may allow a better distribution of administrated 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. A 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 is recommended).
2. A single sustained dynamic inflation.
3. Repeated dynamic inflation.
4. Standard set Pāw.

(b) In clinical settings, a similar lung recruitment strategy (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, Fabian HFO Acutronic, or Dräger VN 500) is set at 6 to 8 cm H_2O and the FiO_2 resulting in a targeted SpO_2 (current European RDS guidelines suggest a SpO_2 target of 90% to 94% for preterm babies).
2. Increase the Pāw (CDP) 1 to 2 cm H_2O every 2 to 3 minutes 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 or the FiO_2 is $\leq$0.25. This point is called "pre-surfactant opening pressure" (CDPo).
4. Decrease the CDP 1 to 2 cm H_2O every 2 to 3 minutes until SpO_2 declines ("pre-surfactant closing pressure," CDPc).
5. Recruit the lung once more with the known CDPo for 2 to 3 minutes 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. Five to 10 minutes after surfactant administration, decrease the Pāw of 1 to 2 cm H_2O every 5 minutes until SpO_2 declines ("post-surfactant closing pressure," CDPc).
2. Increase the Pāw with steps of 1 to 2 cm H_2O every 2 to 3 minutes 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 show that during pressure-targeted ventilation, a decrease in lung compliance results in a loss of lung volume (in some cases real "atelectotrauma"), 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 (V_t). 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 V_t close to the set V_t. Volume-targeted ventilation reduces the risk of hypoventilation and hyperinflation. A recent Cochrane 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 lung recruitment strategy (LRS) in spontaneously breathing animals, volume targeting produced equivalent pathophysiologic outcomes without an increase of proinflammatory cytokines (in bronchoalveolar lavage) compared to HFOV.

2. In a lung protective strategy, the "optimal 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 (PIP of 25 cm H_2O delivered by a T-piece, maintained for 15 seconds, followed by an initial PEEP of 5 cm H_2O) or with optimization of the CPAP level, 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 minutes) 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 minutes) 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 minutes) until stable oxygenation at the lowest FiO_2 was reached (optimal PEEP).
   (d) Preterm infants so managed showed a significantly reduced oxygen dependency compared to a control group not treated with the LRM.

(c) During an 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 commons 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 monitoring (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 both on HFOV and CMV 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; regional lung monitoring is possible in critically ill neonates and infants. A standalone EIT monitor has recently been released for neonatal use.
3. 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 thoracoabdominal 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. OEP could be very useful to validate an LRM (e.g., optimal CDP during HFOV or best PEEP during CMV).

VII. 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 reduce length of MV, and to improve both respiratory (lung injury and the occurrence of BPD) and neurological outcomes (PVL and severe IVH).

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Weaning and Extubation

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Steven M. Donn

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 of 240 to 360 mL/kg/min
(c) Inadequate alveolar ventilation can result from inadequate V_T or rate.

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
(e) Spontaneous breathing effort
(f) Adequate end-expiratory lung volume
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 nonnitrogen 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 overventilation.
   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 (of V_T) and PEEP, or T_I
      (c) If PaO_2 is high, $PaCO_2$ low, decrease PIP (of V_T), rate (if SIMV)
      (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 and end-expiratory lung volume.

D. Ventilation
   1. Primary determinants
      (a) Amplitude (ΔP) = PIP – PEEP
      (b) Rate (frequency, f)
      (c) Minute ventilation = V_T x 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 SIMV)
      (b) If $PaCO_2$ is low, PaO_2 normal, decrease rate (if SIMV), 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 SIMV)
   3. Practical Hints
      (a) Try to maintain normal minute ventilation.
      (b) Keep V_T in 4 to 8 mL/kg range.
      (c) Avoid overdistension 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). Note: if ventilator-directed volume targeting is used, PIP will autowean.
      (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 (unless ventilator-directed volume targeting is in use).
   (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. 40, 41. and 42)

III. Adjunctive Treatments for Weaning
A. Methylxanthines (Theophylline, Aminophylline, 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) Periextubation support.
   (c) Apnea or periodic breathing.
3. Complications
   (a) Gastric irritation, vomiting
   (b) Tachycardia
   (c) CNS irritation, seizures
4. Comments
   (a) Follow serum concentrations (aminophylline, theophylline).
   (b) Periextubation support usually discontinued 48 to 72 hours 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 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.

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 nonnitrogen calories, resulting in excess carbon dioxide production

V. Extubation and Postextubation 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. Postextubation Care
   1. Some form of continuous distending pressure (Chap. 29)
      (a) Clinical trials show mixed results. Some clinicians prefer to extubate directly to NCAP, HFNC, or NIPPV to maintain continuous distending pressure and decrease work of breathing.
      (b) Use 4 to 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) Consider removing umbilical catheters.
5. Stridor
   (a) May result from subglottic edema or laryngotracheomalacia
   (b) Treatment options
      1. FiO_2/humidity
      2. CPAP
      3. Inhalational sympathomimetics (e.g., racemic epinephrine)
      4. Corticosteroids, both systemic and inhaled
   (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 periextubation setting.
   (b) Duration of treatment is 24 to 96 hours (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.

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Part XI

Bronchopulmonary Dysplasia

Etiology and Pathogenesis

78

Alexandra M. Smith and Jonathan M. Davis

I. Introduction
   A. Bronchopulmonary dysplasia (BPD) is a chronic lung disease that develops in neonates 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 United States each year. It is the only complication of neonatal intensive care that continues to increase in frequency.
   B. There are many health consequences of BPD including the development of asthma, pulmonary hypertension, repeated pulmonary infections, failure to thrive, and neurodevelopmental delays. There is a higher incidence of postnatal mortality and frequent rehospitalizations in those infants diagnosed 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 are also changing. 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 78.1). This severity-based definition as well as other definitions of BPD correlates weakly with adverse long-term pulmonary and neurodevelopmental outcomes.
   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 oxygen challenge testing. BPD

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Table 78.1 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% O2 to 56 days postnatal or discharge, whichever comes first
Severe BPD	Need for >30% O2 +/− PPV or NCPAP at 36 weeks' PMA or discharge, whichever comes first	Need for >30% O2 +/− PPV or CPAP at 56-days postnatal age or discharge, whichever comes first

Abbreviations: *PMA* postmenstrual age; *PPV* positive pressure ventilation; *NCPAP* nasal continuous positive airway pressure

Table 78.2 2016 NICHD BPD Workshop suggested definition of BPD

Grades	Invasive IPPV[a]	N-CPAP, NIPPV, or nasal cannula ≥3 L/min	Nasal cannula flow of 1–<3 L/min	Hood oxygen	Nasal cannula flow of <1 L/min
I	–	21	22–29	22–29	22–70
II	21	22–29	≥30	≥30	>70
III	>21	≥30			

A neonate born at <32 weeks' gestation with BPD has persistent parenchymal lung disease (with confirmation on radiographic studies), and at 36 weeks' PMA requires 1 of the following FIO_2/oxygen levels/O_2 concentration ranges for ≥3 consecutive days to maintain arterial oxygen saturations in the 90% to 95% range

IIIa = Early death (14 days–36 weeks' PMA) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities

Values are %

IPPV intermittent positive pressure ventilation; *N-CPAP* nasal continuous positive airway pressure; *NIPPV* noninvasive-positive pressure ventilation

[a]Excluding infants ventilated for primary airway disease or central respiratory control conditions

is then defined as the inability to maintain oxygen saturation >90% when the amount of inspired oxygen is slowly reduced toward room air. Despite these approaches, there is increasing evidence that a diagnosis of BPD may not accurately predict which infants will develop subsequent chronic respiratory morbidity now called chronic pulmonary insufficiency of the premature (CPIP), asthma, repeated respiratory infections, need for respiratory medications, and hospital readmissions later in life.

D. In October 2016, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) held a workshop on BPD and developed a proposal for an updated definition of BPD (Table 78.2). This classification scheme, which is proposed to evaluate infants at 36 weeks' PMA, includes various modes of invasive and noninvasive ventilation as well as other forms of oxygen administration and grades the severity of BPD from I to IIIa. It also includes a requirement of radiographic evidence of parenchymal lung disease. The goal is to more closely capture the true epidemiology of BPD, providing a better benchmark to evaluate outcomes of clinical trials and better predict long-term outcomes.

E. A 2019 study recommended using a bedside test to classify BPD severity. Shift, ventilation/perfusion mismatch, and right-to-left shunt were calculated based on the partial pressure of inspired oxygen at which the oxygen saturation decreased from 95% to 86%; this appeared to correlate more closely with BPD severity. Another 2019 study found that the level of respiratory support required at 36 weeks' PMA (none, NC ≤ 2 L/min, NC > 2 L/min, continuous

positive airway pressure, or invasive mechanical ventilation) best predicted early childhood morbidity, independent of the need for supplemental oxygen.

F. A 2015 study developed a clinical severity score for chronic lung disease of infancy based on use of supplemental oxygen, hospitalizations, diuretic use, bronchodilator use, corticosteroid use, and the need for chest physiotherapy.

G. It is clear that a more uniform definition of BPD and associated CPIP is needed to better predict respiratory outcomes later in childhood.

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 preterm neonates, the incidence of BPD remains approximately 30% (ranging from ~10% to ~60%, inversely proportional to gestational age and weight at birth). The incidence might be further decreased by about 10% using the physiologic definition.

B. Using the NICHD severity-based definition of BPD, the incidence of severe BPD is 39% for neonates 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 birthweight, male sex, white race, a family history of asthma, cigarette smoke exposure, and impaired growth for gestational age.

IV. Pathogenesis (Fig. 78.1)

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.

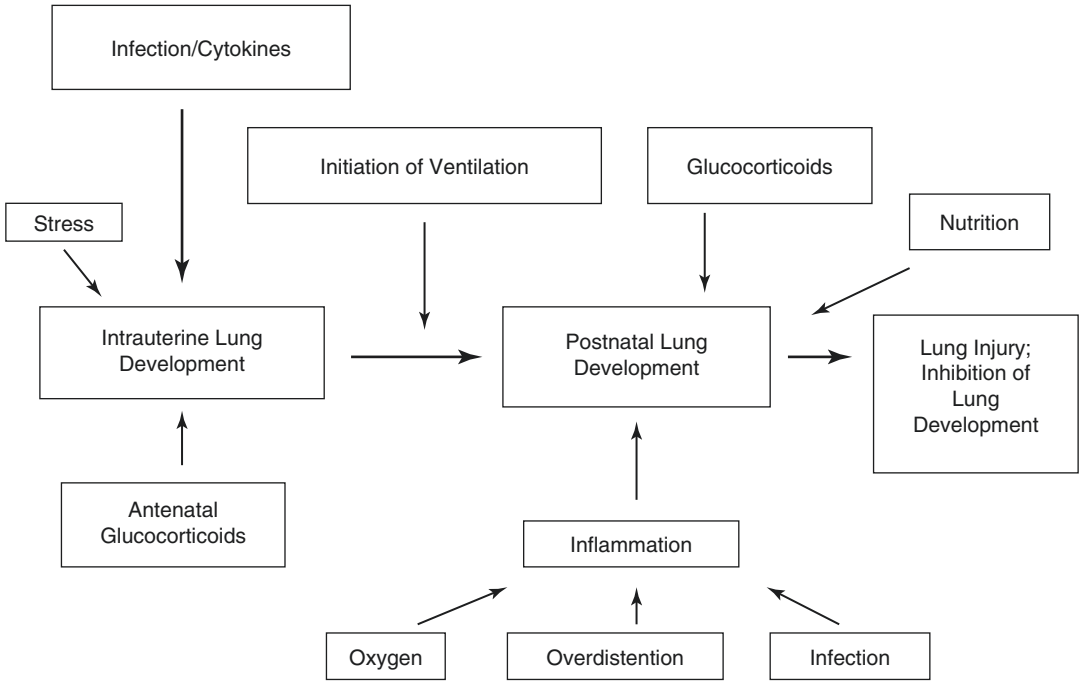

Fig. 78.1 Pathogenesis of BPD

2. "Low-volume injury zone" predisposes an atelectatic lung to shear stress, while the use of high-tidal volumes may cause volutrauma in the "high-volume injury zone." Preterm neonates are more prone to volutrauma because their compliant chest wall allows uncontrolled expansion. Shear stress, in combination with other proinflammatory 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, 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 activation 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.
4. Noninvasive 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. Neonates in the SUPPORT study (Surfactant Positive Pressure and Oximetry Randomized Trial) who were randomized to early CPAP had reductions in serious respiratory morbidity at 18- to 22-month corrected gestational age (CGA) compared to neonates who received early intubation and surfactant. In contrast, Doyle and colleagues conducted a longitudinal follow-up study of premature infants in Australia from 1991 to 2005. Despite significant increases in the use of CPAP and corresponding decreases in intubation and surfactant administration, there was no significant decrease in oxygen dependence at 36 weeks' PMA and no significant improvement in lung function during childhood over time. This suggests that increased use of "gentler" ventilation strategies may not result in significant improvement in longer-term respiratory function.
5. A 2017 Cochrane Review evaluating the risk of BPD in neonates treated with volume-targeted versus pressure-limited ventilation strategies found that volume-targeted ventilation was associated with reductions in death or BPD, further supporting the role of volutrauma in the development of BPD.

B. Oxygen/Antioxidants
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. There is a delicate balance between the production of ROS and the antioxidant defenses that protect cells. Increased generation of ROS can occur secondary to exposure to hyperoxia, reperfusion, or inflammation. In addition, ROS can increase because of inadequate antioxidant defenses.
3. The preterm neonate 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. Macrophages exposed to hyperoxia had an increase in bacterial adherence and a reduction in phagocytosis possibly predisposing neonates to infection, an effect that may ameliorated by supplementation by antioxidant enzymes.
5. A 2018 meta-analysis evaluating outcomes in lower oxygen saturation target ranges (85%–89%) compared to higher target ranges (91%–95%) did not demonstrate a significant difference in the composite primary outcome of death or major disability at 18 to 24 months' CGA. However, the lower target ranges were associated with a higher risk of death but a lower risk of BPD (oxygen use at 36 weeks' PMA). This supports the idea that hyperoxia (even room air is supraphysiologic relative to a corresponding fetus) plays a critical role in the development of BPD.
6. Exaggerated mitochondrial oxidative stress is seen in animal models of BPD. Mitochondrial dysfunction has also been implicated in the development of BPD. Murine models have shown that exposure to hyperoxia during critical developmental windows can lead to alveolar simplification. In these murine models of BPD, over 100 genes related to pulmonary vascular disease were found to be differentially regulated; genes related to the angiogenesis pathways and immune system were also found to be affected. Epigenetic changes have also been seen and thought to be secondary to oxygen exposure.
7. Studies of genetic polymorphisms in superoxide dismutase enzymes have been linked to an increased risk of BPD.

C. Inflammation

1. There is controversy whether antenatal infection and resulting inflammation (chorioamnionitis/funisitis) are risk factors for BPD. Some studies suggest that the presence of inflammation in the chorionic plate or the umbilical cord is not associated with the development of BPD, while others indicate it increases the risk of BPD, and still others show that it may prevent BPD. This may be related to the range of organisms associated with chorioamnionitis and the difficulty in making the clinical diagnosis. A 2019 meta-analysis showed a higher risk for BPD among those preterm infants exposed to chorioamnionitis. Animal models are inconclusive, with variable effects on lung function seen among different animal models of induced chorioamnionitis. This suggests that pulmonary inflammation secondary to chorioamnionitis may lead to alveolar simplification and disrupted lung development, with variable effects based on the types of organisms and degree of exposure. There is also some evidence that levels of IL-6, IL-1β, and IL-8 in amniotic fluid are higher in preterm neonates who ultimately develop BPD compared to those who do not. When cord blood is analyzed in neonates exposed to chorioamnionitis, there are increased circulating pro-inflammatory CD4+ T-cell populations seen in those exposed to chorioamnionitis, while those who go on to develop BPD have decreased CD4+ cells and a trend toward a decrease in the number of regulatory T cells. Although this provides evidence that there may be distinct differences in immune profiles between the two groups, it does not support a direct causal relationship.
2. I-CAM promotes adhesion of inflammatory cells to the endothelium and is critically important in vascular development and lung maturation. I-CAM has been found to correlate with disease severity in infants with BPD. It has potential for use as a predictive biomarker.
3. Mechanism: Early elevations of ROS and cytokines (IL-6 or IL-8), followed by neutrophil/mononuclear cell influx and increased protease/antiprotease imbalance, lead to decreased endothelial cell integrity, pulmonary edema, and exudate. The consequence of exaggerated neutrophil recruitment/activation to the neonatal lung can be severe. Proteases and ROS

generated by these cells can damage lung 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 impaired vascular development.

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, and abnormal blood flow through a patent ductus arteriosus (PDA).
   2. *Ureaplasma* species have been implicated in the pathogenesis of preterm birth and are associated with higher pulmonary neutrophils, alveolar macrophages, soluble intercellular adhesion molecule-1, IL-1ß, IL-6, and IL-8. These pro-inflammatory mediators can cause lung injury, predisposing to the development of BPD.
   3. Recent studies show that although treatment with azithromycin may affect the rates of colonization with *Ureaplasma* species, the rates of BPD are not substantially affected.
   4. Studies in the area of metagenomics and metabolomics have found differences in the microbiome and functional metagenome of neonates who develop BPD compared to those who do not. Pathways involving fatty acid activation and androgen and estrogen biosynthesis are more active in neonates developing BPD, suggesting a cause and effect relationship.
   5. Late-onset sepsis from a variety of bacterial and fungal infections is associated with the development of BPD.

E. Nutrition
   1. Poor caloric intake may result in respiratory muscle fatigue and a longer duration of mechanical ventilation. In one 2006 study, neonates who developed BPD had a lower total caloric intake compared to those who did not.
   2. Two 2019 studies demonstrated that use of breast milk was associated with a lower risk of BPD. While it is clear that the use of breast milk is beneficial for many reasons in preterm neonates, more studies are needed to elucidate the relationship with BPD.
   3. Vitamin A derivatives are critical in regulation of growth and differentiation of lung epithelial cells. Deficiency of vitamin A results in abnormal pulmonary epithelial lining, which leads to increased airway resistance and may predispose to infection. Preterm neonates have lower levels of vitamin A, which has been associated with the development of BPD. Although trials of vitamin A supplementation appear to slightly reduce BPD, it is unclear if any beneficial effects persists into childhood. It is also important to note that rates of BPD remained relatively stable during vitamin A shortages.
   4. 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 oxidative injury. Neonates deficient in these trace elements may be at a higher risk for developing BPD.

F. Fluids/Patent Ductus Arteriosus (PDA)
   1. Pulmonary edema (alveolar, interstitial) has been associated with the development of BPD. A large retrospective study showed that higher fluid intake and lack of weight loss predisposed infants to BPD. In contrast, the longer a hemodynamically significant PDA remains, the higher the incidence of BPD.
   2. While meta-analyses of trials using diuretics have demonstrated improvements in short-term pulmonary mechanics, there was no 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 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. Despite the PDA appearing to be important in the development of BPD, studies on PDA treatment/closure have shown variable responses in the effect on BPD and associated longer term respiratory outcomes. Further studies are needed before any definitive recommendations regarding PDA closure to prevent BPD can be made.

G. Genetics
1. Given the broad phenotypic range of BPD within the population of preterm neonates, it is likely that a genetic component is associated with increased susceptibility. While a twin study published in 2008 suggested a genetic contribution, a 2018 twin study found that heritability did not appear to play a major role in its development.
2. A study from 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. Another study suggests that variants of nuclear factor erythryoid-2 related factor-2–dependent antioxidant response elements, which regulate the protective response to oxidative stress, may contribute to the development of BPD in high risk preterm neonates.
4. Whole-exome sequencing of 146 PROP (Prematurity and Respiratory Outcomes Program) participants found 345 genes with variants unique to BPD-affected infants and 292 variants unique to preterm neonates not affected by BPD. Pathways implicated include protein kinase A, MAPK, and Neuregulin/epidermal growth factor receptor signaling. As these techniques become more widely available and less expensive, further analyses may provide important new information on the role of genetic susceptibility in BPD.

V. Pathophysiologic Changes

A. Radiographic aspects: the radiographic appearance of BPD has changed with time with cystic changes in particular 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). However, there is concern about excessive ionizing radiation with CT. MRI can help define disease severity and predict short term clinical outcomes, perhaps better than BPD severity grading (NICHD definition). Cardiac MRI, specifically the measurement of the pulmonary artery to aorta diameter ratio, also correlates with BPD severity. It may also be useful in evaluating those infants with BPD who develop pulmonary hypertension.

B. Pulmonary mechanics
1. Tachypnea and shallow breathing increase dead space ventilation. Nonuniform damage to the lung results in worsening ventilation/perfusion (V/Q) mismatch.
2. Lung compliance is markedly decreased, even in those infants who no longer require 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. Changes in the pulmonary circulation 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.

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Bronchopulmonary Dysplasia: Clinical Management

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I. The management of the infant with bronchopulmonary dysplasia (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 respiratory support needed to maintain gas exchange are some of the key factors implicated in the progression of the lung damage (Chap. 78).

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 in infants with BPD, but there is some evidence that SpO_2 values above 95% and PaO_2 above 70 torr (9.3 kPa) are associated with a higher incidence of retinopathy of prematurity (ROP) and worse respiratory outcome, while $SpO_2 < 89\%$ may be associated with increased NEC and mortality. Because of this, it is recommended to maintain oxygen saturation levels between 90% and 95% or the PaO_2 between 50 and 70 torr (6.7 and 9.3 kPa) to minimize the detrimental effects of hypo- and hyperoxemia. After extubation, oxygen can be administered through nasal CPAP, a nasal cannula, or a hood. Patients with severe BPD are sometimes discharged home receiving supplemental oxygen and occasionally mechanical ventilation (Chap. 90).
   C. Adequacy of gas exchange is monitored by blood gas levels.
      1. Blood gas determinations done on blood obtained by arterial puncture or capillary sampling may not be reliable because the infant frequently 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.

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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 probably the most effective and safest measure to prevent anemia.

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. Because of increased alveolar dead space, infants with BPD usually require higher tidal volumes (6 mL–10 mL/kg) to achieve adequate alveolar ventilation and maintain $PaCO_2$ within acceptable limits.

C. Use longer inspiratory times between 0.4 and 0.6 s to improve distribution of inspired gas.
   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. Avoid short expiratory times and pay attention to the time constant (Chap. 9) watching closely for evidence of gas trapping (Chap. 22).

D. Adjust end-expiratory pressure between 4 and 10 cm H_2O so that the lowest oxygen concentration necessary to keep SpO_2 above 90% (PaO_2 above 50 torr or 6.7 kPa) is used. Higher PEEP levels can reduce expiratory airway resistance and gas trapping and improve alveolar ventilation in infants with unstable airways and severe obstruction.

E. Wean ventilator settings to 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 MV, it may be necessary to increase the FiO_2 to maintain adequate oxygen saturation.

J. Concurrently, the $PaCO_2$ may rise above baseline values during weaning. As long as the pH is within acceptable range, some hypercapnia should be tolerated to wean these patients from the ventilator.

K. Caffeine can be used as respiratory stimulant during the weaning phase. Caffeine administration prior to extubation increases the rate of successful extubation and reduces the duration of MV and possibly the incidence of BPD.

L. When the infant is able to maintain acceptable blood gases for several hours on low ventilator settings (RR 10–15 breaths/min, PIP 10–15 cm H_2O, and $FiO_2 < 0.3–0.4$), 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 these infants, nasal CPAP 6–10 cm H_2O or nasal IPPV after extubation (Chap. 32) can stabilize respiratory function and reduce the need for reintubation and mechanical ventilation.

IV. Fluid Management
   A. Infants with severe BPD tolerate excessive fluid intake poorly and tend to accumulate water in their lungs, contributing to their poor lung function.
   B. Water and salt intake must be limited to the amount 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 an improvement in lung compliance and decrease in resistance. There is, however, no clear 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 solid evidence that prolonged use of diuretics changes the incidence or severity of BPD, this therapy is not recommended for routine use and is mostly indicated for acute episodes of deterioration associated with pulmonary edema.
   F. Distal tubule 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 safety and long-term efficacy is lacking.

V. Bronchodilators
   A. Infants with severe BPD frequently have airway obstruction secondary to smooth muscle hypertrophy and airway hyperreactivity.
   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. Bronchodilators can be effective in infants with a predominantly obstructive phenotype, but their effect is short lived, and they can produce 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 a 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 into 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 most likely 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 high dose 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 week 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 have also been administered by nebulization or instillation 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 and safety 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 long-term 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

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80 Long-Term Outcomes of Newborns with Bronchopulmonary Dysplasia

Sumesh Thomas and Prashanth Murthy

I. Introduction
   A. Bronchopulmonary dysplasia (BPD) remains the commonest complication of prematurity, and its incidence is rising most likely from improved survival of extremely low birthweight newborns. BPD is a complex disorder of the respiratory system affecting mostly preterm babies exposed to invasive mechanical ventilation and inspired oxygen. This complex disorder represents histologic distortion of normal lung architecture by factors that cause lung injury and disruption of lung development. Gestational age at birth and low birthweight are the strongest risk factors for BPD. Ninety-five percent of all infants with BPD are very low birthweight (VLBW). The reported incidence of BPD is around 80% at gestations of 22–24 weeks and around 20% at 28 weeks. Despite significant improvements in clinical practice, there has been no improvement in the prevalence of BPD.
   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 disrupting alveolarization and microvascular development in the immature lungs. These anatomical changes lead to abnormal gas exchange and abnormal lung mechanics. BPD infants

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require lengthy hospital stays and have delayed discharges, often requiring supplementary home oxygen for several months.

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

(a) Neonates and children with BPD have increased nutritional requirements compared to infants without BPD. Infants with BPD have increased needs from increased work of breathing secondary to poor lung compliance, chronic stress from hypoxic episodes and inflammation, along with growth suppression from the use of chronic steroid or diuretic therapy. Optimal nutritional support should meet expenditure as well as substrate for growth and repair of injured organ systems. Sicker neonates are less likely to be fed, and feeding difficulties associated with aversion, intolerance, and gastroesophageal reflux are well described in infants with BPD. Recent studies suggest that VLBW infants with poor enteral nutrition within the first 2 weeks of life were are more likely to develop BPD. Chronic and episodic hypoxia in infants with BPD during feeding and sleep can contribute to growth failure. VLBW infants with all forms of BPD have been shown to have lower weight, length, and head circumferences 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, increased need for hospitalization in infancy, 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 is intricately linked to issues related to low gestational age and birthweight 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) Infants with BPD have multiple episodes of hypoxia, hypercapnia, and prolonged respiratory acidosis which could predispose their brains to injury. Additionally, a higher proportion of these infants receive postnatal corticosteroids. BPD independently predicts adverse developmental outcome in early infancy, roughly doubling the odds of an adverse neurologic outcome. Furthermore, BPD infants with associated pulmonary hypertension (PH) had significant lower motor, cognitive, and language scores at 18 to 24 months' corrected age. The reason for this is thought to be an increased degree of hypoxemia and hemodynamic instability associated with PH. Volumetric magnetic resonance imaging study of preterm infants with BPD showed uniform reduction in cerebral volumes 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, but may correlate with functional deficits more frequently seen in survivors with BPD. Neuroimaging focusing on the brainstem has documented lower pontine and medullary volumes in BPD infants as a result of abnor-

mal myelination, degeneration of descending white matter tracts, and focal necrotic changes in the brainstem. This is being attributed to an underdeveloped brainstem, which is frequent in babies requiring prolonged ventilation. There is increased awareness of the negative effects of episodic hypoxic episodes frequently seen in infants with BPD and adverse neurodevelopmental outcomes. 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) A recent meta-analysis exploring an association between BPD and cerebral palsy (CP) concluded that BPD was significantly associated with CP with an odds ratio of 2.1 (95% CI, 1.57–2.82). The risk of CP is related to severity of BPD. Infants with severe BPD requiring mechanical ventilation at 36 weeks' postmenstrual age were 6 times more likely to have quadriplegic CP and 4 times more likely to have diplegic CP.
   (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.
   (3) Poorer gross and fine motor skills are noted in BPD infants with scores approximately 1 SD lower in comparison to preterm controls at 10 years of age. Consequently, these infants need greater access to occupational and physiotherapy services.
   (4) 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 to duration of oxygen therapy.

(c) Neurosensory impairments.
   (1) BPD independently predicts neurosensory impairment. PVL, severe ROP, and length of hospital stay are predictive of adverse neurosensory outcome.
   (2) BPD infants perform significantly below controls on Visual-Motor Integration (VMI) testing with roughly a third of BPD infants performing below age expectations. There is an association between difficulties in visual perception and BPD, which in turn is strongly related to the duration of oxygen requirement.

(d) Cognitive and academic consequences.
   (1) Multiple studies have reported a correlation between cognitive deficits and BPD persisting to school age. BPD infants had lower scores when compared to matched VLBW controls without BPD, who in turn had lower scores than term controls. This pattern was seen in general intelligence, reading, mathematics, motor skills, memory, and attention. Severity of BPD correlated with worse scores.
   (2) Infants with BPD have significant language delay with lower scores in receptive language possibly as a consequence of auditory processing difficulties. Presence of a patent ductus arteriosus (PDA) along with BPD was found to predict poorer language development. The precise mechanism for this association is not known, but PDA may simply be a marker of severe BPD.
   (3) 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.
   (4) 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, sug-

gesting important implications for healthcare, social well-being, and cognitive rehabilitation.

B. Other systems
   1. Respiratory system
      (a) In 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. For this reason, monoclonal antibodies for RSV prophylaxis are recommended in the first year for infants with BPD and for a further year while on supplemental oxygen, diuretics, or chronic steroid therapy. A recent meta-analysis concluded that FEV_1 was diminished at the age of 5–23 years in preterm subjects with and without BPD. The nutritional status of children at 2 years of age influences respiratory outcomes in childhood. 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 the use of inhaled bronchodilators are 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 FEV_1; 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 with BPD are at risk of developing COPD later in life. Children with BPD have abnormal lung structure, lower lung function, and declining lung function over time with an increased risk of respiratory symptoms in later life. Healthy lifestyle choices and avoidance of smoking should be advocated.
      (c) Adulthood: Restriction in FEV_1 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 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. Serial assessment of lung function by spirometry may identify patients at risk of COPD and related pulmonary vascular diseases in adulthood.
   2. Cardiovascular system
      (a) Pulmonary hypertension is reported in 6%, 12%, and 39% of infants with mild, moderate, and severe BPD, respectively. Pulmonary hypertension contributes to both increased morbidity, with a mortality rate of 16–40%. Altered lung development and postnatal lung injury can lead to compromised alveolar development and vascular pruning characteristic of BPD. Some infants with BPD develop increased pulmonary vascular resistance as a result of abnormal pulmonary vascularization, vascular remodeling, and increased vascular tone**.** Screening for pulmonary hypertension by echocardiography is recommended in infants with BPD prior to discharge.

(b) BPD is an independent risk factor for systemic hypertension and the most common nonrenal cause of hypertension in preterm infants. Systemic hypertension is reported in about 7–43% in infants with BPD. Fluid retention, increased serum aldosterone levels, arterial wall thickening, and abnormal vasomotor tone have been implicated as mechanisms. Less than 50% of cases will require medical treatment for a short period. A retrospective study reported that most infants did not require treatment beyond 3–6 months of age.

3. Renal
   (a) Nephrocalcinosis is reported in as many as 60% of VLBW infants with BPD. Nephrocalcinosis is more commonly seen in preterm infant who have had severe respiratory disease, acidosis, parenteral nutrition and treatment with diuretics, methylxanthines, 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 should be considered.

IV. Summary
   A. BPD is a multisystem disorder with consequences beyond the neonatal period. A multidisciplinary approach to the management and follow-up of preterm survivors with BPD is advocated.
   B. Further research and long-term follow studies are needed to understand the lifelong implications of this primarily respiratory disorder of the preterm.

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Part XII

Complications Associated With Mechanical Ventilation

Thoracic Air Leaks

81

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 perinatal 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, incidence 8–30%
      4. Transient tachypnea of the newborn, incidence 12–14%
      5. Pulmonary hypoplasia, incidence 35–49%
      6. Congenital diaphragmatic hernia, incidence 10–30%

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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 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 frequently 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) Poor patient-ventilator interaction resulting in dyssynchrony (i.e., infants who actively expire during part or all of the positive pressure plateau).
            (2) Prolonged inspiratory time (I:E ratio greater than or equal to 1.0) with resultant gas trapping and overdistension.
            (3) High mean airway pressure (>12 cm H_2O).
            (4) 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.
      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) Patient-triggered ventilation reduces the incidence of air leak by synchronizing respiration. Using this mode of ventilation, the infant's respiratory efforts trigger the deliv-

ery of the positive pressure inflation. Flow-cycling enables complete synchronization, even in expiration.

(b) Fast 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.

(c) Suppression of respiratory activity by patient sedation and/or neuromuscular blockade may be a "last ditch" means for preventing pneumothoraces in patients who are actively exhaling or "fighting" the ventilator. Almost always this problem can be eliminated by synchronization.

4. Management

(a) 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 until a chest tube can be placed.

(1) Technique

(a) Attach a 23-gauge butterfly needle to a 50 mL sterile syringe by a 3-way stopcock. Consider using either a 10 mL or 20 mL sterile syringe for smaller neonates.

(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 the needle to avoid 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

(b) Chest tube (thoracostomy) drainage is needed for continuous drainage of pneumothoraces. This is often the treatment of choice for infants receiving positive pressure ventilation as the air leak may be persistent under these conditions.

(1) Straight chest tube technique; Fig. 81.1

(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.

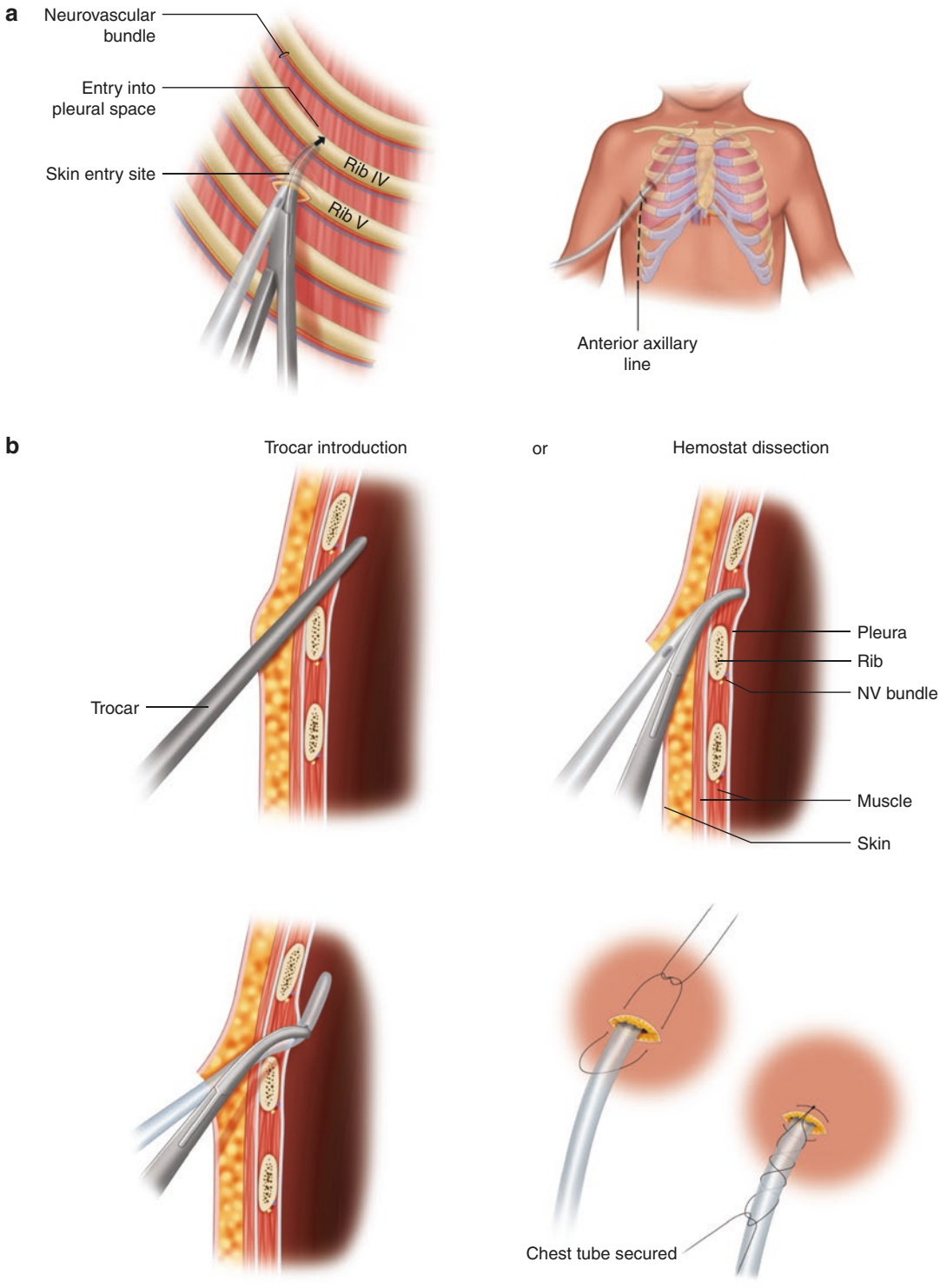

Fig. 81.1 Chest tube insertion in the newborn for pneumothorax. (**a**) Preferably a small hemostat is inserted through a small incision in the anterior or midaxillary line and is tunneled upward, entering the chest above the next rib. The chest tube is inserted and secured with a suture ligature. Several 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. This article was published in Pediatric Surgery, sixth ed., 1, Jay L Grosfeld, 1022, Copyright Elsevier (2006). Used with permission

(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 space.
(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 the 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 preassembled 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 needle 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.

(c) Nitrogen washout is controversial, but it is sometimes used to eliminate small pneumothoraces and alleviate associated 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.
(d) Expectant management is appropriate if infant clinically stable.

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 torr–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. High-frequency oscillation may also be useful; smaller tidal volumes may result in less air leak.

(4) Extubation using all possible treatments to achieve this.

(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 or selective obstruction of the affected lung.

C. Pneumomediastinum is often of little clinical importance and usually does not need to be drained. Cardiovascular compromise is rare, but it 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 for pneumothorax.

(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 most 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. This 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 attached via a stopcock to a syringe.

(3) Locate the subxiphoid space and insert the catheter with the needle at a 30º–45º 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 rarely has 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 can adversely affect the patient's clinical status, and treatment is warranted when the 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 transthoracic 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.

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Patent Ductus Arteriosus

82

Vrinda Nair and Jonathan 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 Arteriosus in Fetal Circulation
   A. Represents a persistence of the terminal portion of the sixth aortic arch.
   B. Communicates between the aorta and the main pulmonary artery close to the left pulmonary artery.
   C. Carries most of RV output (50–60% of total cardiac output) from sixth to seventh week of gestation and beyond; caliber equal to descending aorta.
   D. Patency is maintained both passively from high blood flow and actively from low oxygen tension and prostaglandin production.
   E. May be absent in association with congenital heart disease involving severe right outflow tract obstruction (rare)

III. Postnatal Closure
   A. Closure is facilitated by increase in oxygen tension after birth and increased clearance of prostaglandin by the lungs.
   B. Initiated by spiral medial muscle layer at the pulmonary end
   C. Duct shortens and thickens with functional closure by 12–72 h in most term babies.
   D. Mechanisms mature after 35 weeks' gestation.
   E. Maturation mechanism is poorly developed in preterm infants leading to a higher incidence of PDA in preterm infants.

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.

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B. Preterm PDA is related to:
   1. Immature closure mechanism
   2. Decreased sensitivity to constrictors such as oxygen tension
   3. Increased sensitivity to dilators such as? Prostaglandin
   4. Other associated factors
      (a) Lack of antenatal steroids
      (b) Severe lung disease
      (c) Exogenous surfactant use
      (d) Phototherapy
      (e) Furosemide use in the first few days
      (f) Excessive fluid administration

V. Physiologic Effects of the PDA
   A. Left-to-right shunt
      1. Exacerbation of respiratory disease
      2. Increased pulmonary blood flow worsening pulmonary mechanics
      3. Increased cardiac workload
   B. Diastolic steal: when ductal shunt volume exceeds >50% of systemic blood flow
      1. Impaired perfusion of systemic organs and brain
      2. Risk of necrotizing enterocolitis

VI. Clinical Effects of PDA
   A. Left-to-right shunt
      1. Increased oxygen requirement
      2. Increased ventilatory requirement
      3. Apnea
      4. Impaired non-fluid weight gain
      5. Heart failure

VII. Clinical Features
   A. Usually presents after a fall in pulmonary resistance
   B. Onset related to severity of lung disease and size of baby
   C. Onset may be early in VLBW infants
   D. Signs
      1. Early hypotension and reduced systemic perfusion, which may be non-responsive
      2. Failure of RDS to improve (or deterioration) at 2–7 days
      3. Pulmonary hemorrhage
      4. Acidosis
      5. Apnea
      6. Hyperdynamic precordium (95%)
      7. Bounding pulses (85%)
      8. Murmur (80%)
         (a) Normally silent until day four
         (b) Systolic murmur
         (c) Upper left sternal border
         (d) Variable

VIII. Clinical Outcomes Associated with PDA
   1. Pulmonary hemorrhage
   2. Worsening pulmonary disease
   3. Inotropic resistant hypotension
   4. Impaired renal function

5. Intraventricular hemorrhage and periventricular leukomalacia
6. Necrotizing enterocolitis
7. Bronchopulmonary dysplasia
8. Mortality

IX. Diagnosis
- A. Chest radiograph (poor specificity)
  1. Cardiomegaly
  2. Pulmonary hyperemia
  3. Absence of pulmonary explanation for deterioration
- B. Biomarkers
  1. Brain natriuretic peptide (BNP)
  2. Aminoterminal pro-B-type natriuretic peptide (NT-proBNP)
  3. Urinary NT-proBNP/creatinine ratio
  4. Cardiac troponin
- C. Echocardiogram (Figs. 82.1a and 82.1b)
  1. Ductal patency
  2. Ductal diameter > 1.5 mm
  3. Flow velocity/pattern: pulsatile pattern with pulsatility index ≥2.0
  4. Shunt volume assessment
     (a) Left atrial:aortic ratio (LA:Ao ratio >1.5)
     (b) LVEDD:Aortic ratio >2.0
     (c) Left ventricular cardiac output
  5. Decreased systemic flow: diastolic flow in systemic arteries (descending aorta, superiormesenteric artery) absent or reversed diastolic flow

X. To Treat Or Not to Treat?
- A. Conservative management:
  1. Fluid restriction: Limited evidence, may be justified if causing heart failure
  2. Increase PEEP
  3. Diuretics: Little evidence except in congestive heart failure
- B. Prophylactic treatment: Involves treating within the first few days and usually in the first 24 h

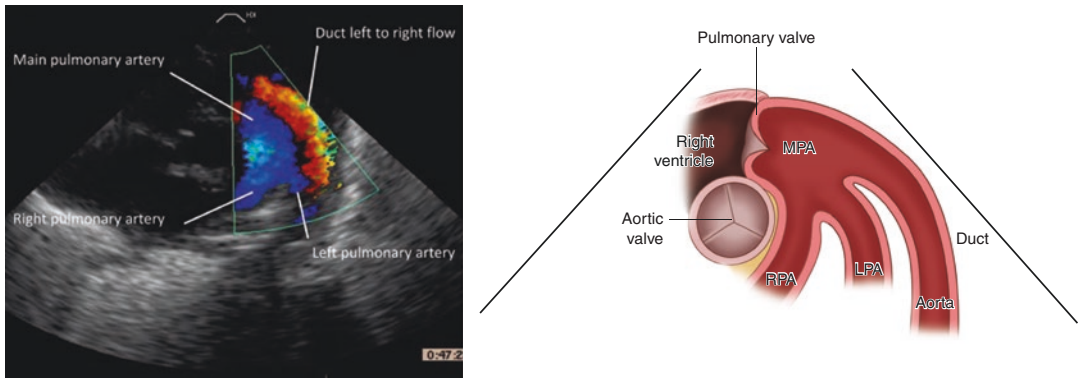

Fig. 82.1 On the left a short axis echocardiographic view of the pulmonary artey with forward (blue) flow and retrograde (red/yellow) ductal flow. On the right a diagramatic representation of the view

1. Indomethacin: Reduction in incidence of symptomatic PDA, PDA requiring ligation, and IVH. No difference in mortality or composite outcome of death/neurodisability.
2. Ibuprofen: Similar to Indomethacin but no effect on IVH.

C. Early symptomatic treatment

D. Indomethacin
1. Now difficult to source in many areas
2. Reasonable renal function
3. No thrombocytopenia (platelets >50,000/mm^3)
4. No significant hyperbilirubinemia
5. Closure in up to 79% but relapse in up to 33%.
6. Early treatment more likely to be effective
7. Dosage regimens:
   (a) 0.2 mg/kg × 2–3 doses
   (b) 0.1 mg/kg/d × 6 doses

E. Ibuprofen
1. Fewer short-term side effects than indomethacin
2. 5% incidence of severe pulmonary hypertension if used prophylactically
3. Dosage: 10 mg/kg loading dose and 5 mg/kg at 24 and 48 h oral or IV

F. Paracetamol (Acetaminophen)
1. Fewer short-term side effects than indomethacin or ibuprofen
2. As yet unproven with no long-term follow-up results available
3. Increasingly used
4. Dosage regimen
   (a) 15 mg/kg per dose. 12 doses every 6 h for 3 days
   (b) Oral or intravenous (limited evidence)

G. Surgical management
1. Ligation
2. Catheter-based percutaneous route: Limited evidence and use limited by the patient size, but promising approach.

XI. When to Treat

A. Prophylaxis:
1. Insufficient evidence to justify as a significant proportion will close spontaneously
2. No long-term advantage demonstrated

B. Early symptomatic: insufficient evidence at present

C. Symptomatic: further studies are needed to evaluate the validity of expectant symptomatic therapy compared to conservative treatment.

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Neonatal Pulmonary Hemorrhage

83

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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.

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 to have pulmonary hemorrhage.

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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 oro-pharyngeal structures, especially from endotracheal intubation.

IV. Pathophysiology: The pulmonary effluent 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 transcapillary 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 6 infants with severe and refractory pulmonary hypertension, Steiner et al. from Austria used sildenafil as a "last resort" 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 6 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. 83.1).
   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 therapy may alter the distribution of bleeding sites rather than causing an increase in the incidence of pulmonary hemorrhage.
   C. Other changes: Reactive leukocytosis, 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.

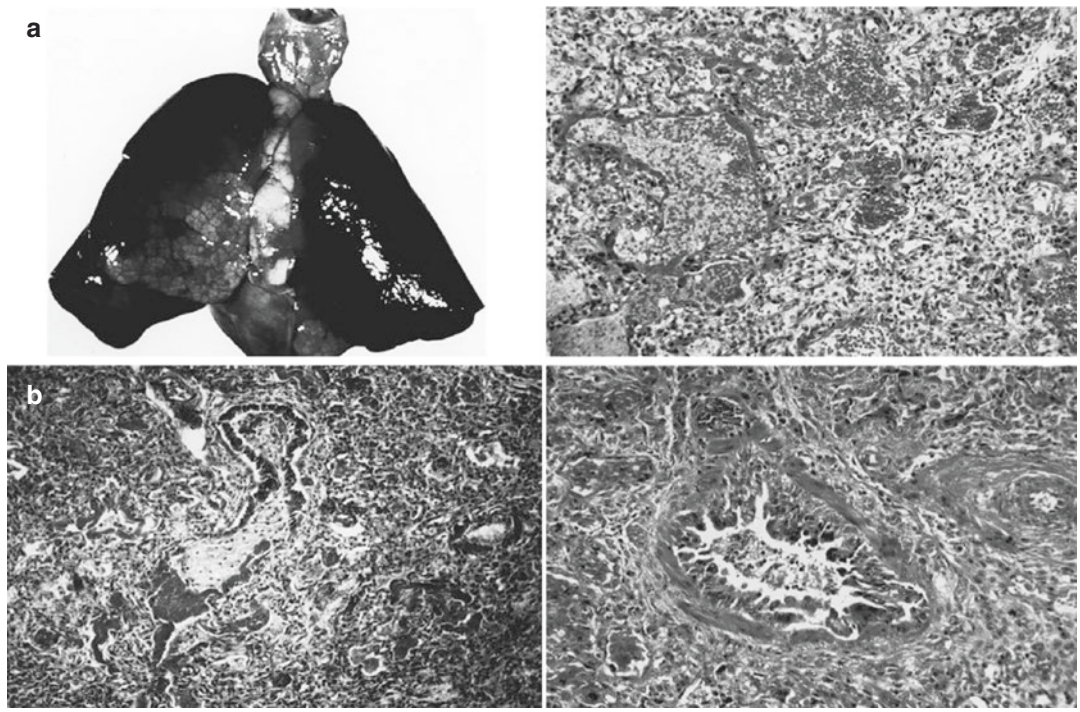

Fig. 83.1 Gross appearance of the lungs in an infant who died of massive pulmonary hemorrhage (top left). Microscopic findings of lung section in the same infant show large quantities of blood in the alveolar spaces and scattered bleeding sites in the interstitial spaces. Generalized features of hyaline 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. **a**) Gross appearance of the lungs in an infant who died of massive pulmonary hemorrhage. **b**) Microscopic appearance of the lung section.

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 oro-pharyngeal 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 is 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 diagnoses.
   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 pulmonary edema must be evaluated, such as congestive cardiac failure (VSD, ASD, or cerebral arterio-venous 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. 83.2 and 83.3).
   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.

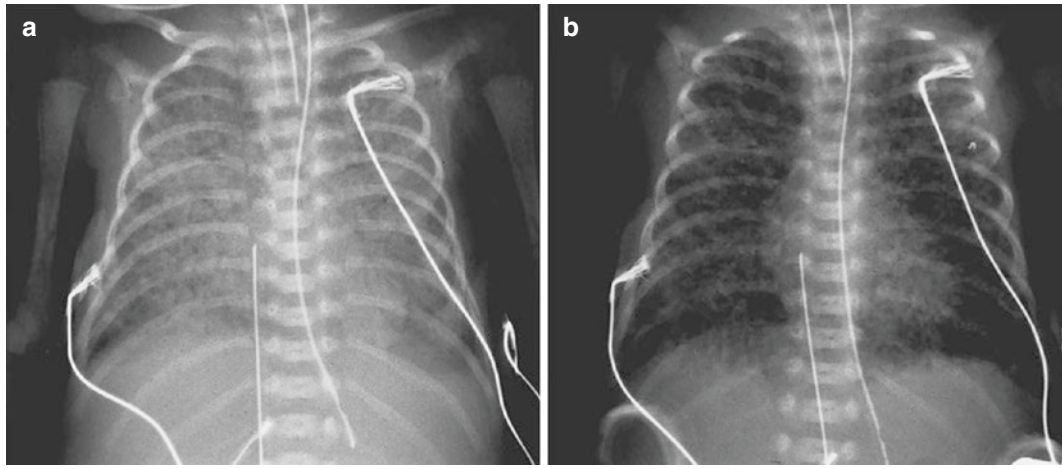

Fig. 83.2 Evolution of pulmonary hemorrhage in an infant with RDS. Chest radiographs show typical features of severe PIE on the fifth day (**a**) and severe pulmonary hemorrhage on the seventh day (**b**). Heart size is normal

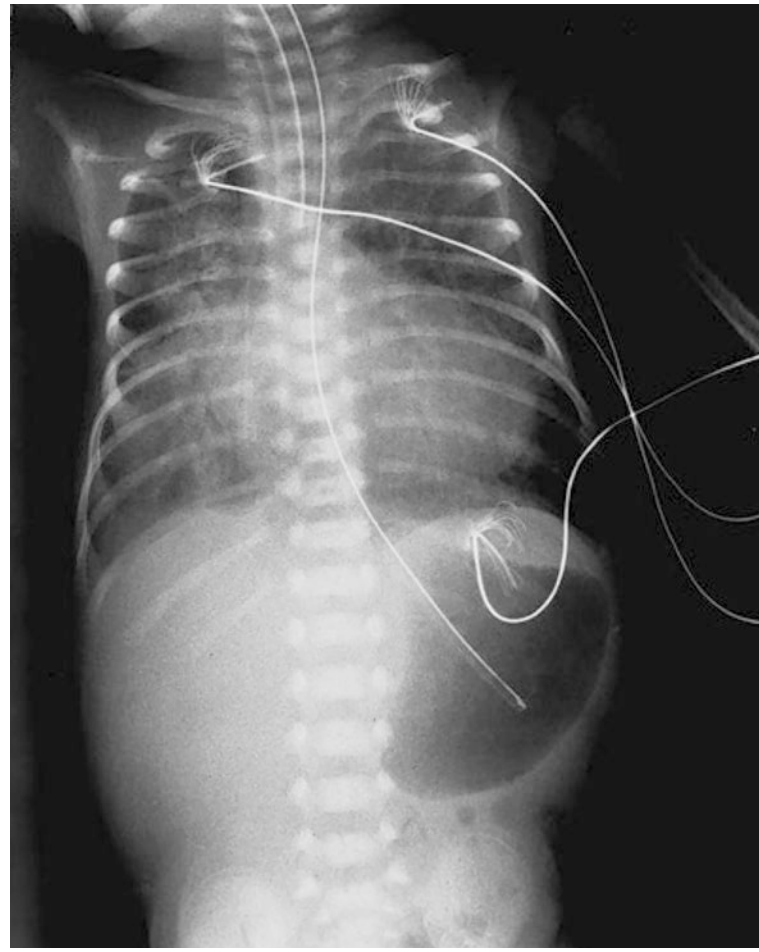

Fig. 83.3 Chest radiograph of a preterm infant developing severe pulmonary hemorrhage on the sixth day secondary to a large, florid patent ductus arteriosus and signs of congestive heart failure. Pulmonary hemorrhage was accompanied by respiratory deterioration. Scattered radio-opaque densities, mostly in both lower lobes can be seen, and there is moderate cardiomegaly

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 antishock 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 mcg/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 mcg/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. Yen 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 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 ($p < 0.02$).

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Retinopathy of Prematurity

84

Alistair Fielder

I. Introduction
   A. Retinopathy of prematurity (ROP) is a major cause of childhood blindness and is particularly important because ROP-induced visual disability can very largely be prevented by timely treatment.
   B. The indication for treatment is Type I ROP and needs to be undertaken within 48–72 h.
   C. Such a short window of opportunity for successful ROP treatment requires precise guidelines for screening and treatment. This 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). These guidelines may not be appropriate for countries with limited resources and where larger babies can be at risk of sight-threatening ROP. Guidelines need to be based on local audit and research.
   D. The international classification of ROP (ICROP) has undergone a third revision to incorporate innovations in imaging and pharmacologic therapies, and also patterns of ROP progression, such as aggressive ROP, seen in some world regions, which did not fit into the previous classification (Table 84.1).

II. Prophylaxis
   A. The standard of neonatal care is critical as to whether a baby develops ROP and its propensity to become sight-threatening.
      1. In countries with high standards of neonatal care, the major risk for sight-threatening ROP is the degree of prematurity and so is largely confined to babies <1000 g birthweight.
      2. Where neonatal care is more variable and resources are limited, severe ROP can develop in larger and more mature babies. In this situation, the overwhelming risk factor is exposure to high levels of oxygen which may be unblended and inadequately monitored. There is a greater risk of aggressive ROP in these circumstances.
      3. Risk factors
         (a) Oxygen
            (1) Hyperoxia, hypoxia, and fluctuations even with the normal range

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Table 84.1 International classification of retinopathy of prematurity, third edition

The third revision (ICROP 3) of the international classification was developed to reduce diagnostic subjectivity, incorporate innovations in imaging and pharmacologic therapies (e.g. anti-vascular endothelial growth factor agents), and to provide detail on the patterns of regression and reactivation following the various treatment modalities. Finally, ICROP 3 incorporates patterns of ROP progression seen in some regions of the world which do not neatly fit into the current classification. Only selected items of ICROP 3 are listed here
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
Aggressive ROP (A-ROP) The term Aggressive Posterior ROP has been altered to Aggressive ROP (A-ROP) in recognition that this subtype is not necessarily posteriorly located and can develop both in the smallest preterm baby and also in the more mature baby in regions of the world with limited resources. A-ROP and stage 3 form the two ends of a spectrum and may co-exist *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
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 more likely to become severe, whereas ROP located in zone III carries a very low risk to become severe. Most severe ROP is seen in zone II and this has been subdivided into posterior and anterior – see figure
C. Extent ROP extent around the retinal circumference is recorded in quadrant sectors
D. *Plus disease* Dilatation and engorgement and the retinal vessels at the posterior pole is referred to as pre-plus or plus disease – now recognised in ICROP 3 to be part of a spectrum of ROP vascular changes. Plus is the indication for treatment but because pre-plus and plus disease are prone to misinterpretation ICROP 3 introduced a traffic light image set to increase diagnostic precision – Fig. 84.5

(2) Based on the 5 trials (SUPPORT, COT, & 3 BOOST trials) comprising the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) collaboration, the consensus recommendation now is that saturation levels are kept between 91% and 94% with the upper alarm set at 95%. Low target saturation levels are associated with increased mortality.

(b) Other risk factors. Numerous associations include vitamin E deficiency, hyperglycemia, transfusions, necrotizing enterocolitis, treatment for patent ductus arteriosus, and other complications of prematurity.

III. Screening

A. Purpose: to identify severe ROP which requires treatment – Type I ROP, which is associated with a high incidence of visually severe sequelae.

B. Which babies should be examined?

1. In countries with a high level of neonatal care, all babies under 1501 g BW should be screened, OR < 30 weeks' GA (USA), <31 weeks' GA (UK). Sweden has a single criterion of <30 weeks' GA. Many countries have an additional sickness criterion for inclu-

sion, but this has not been adopted in the UK on the basis that sickness is difficult to define in relation to ROP risk.

2. Countries with more variable neonatal care. There is a broad range of inclusion criteria ranging from 30 to 37 weeks' GA and BW 1000–2500 g. The differences between countries emphasize the need for locally derived protocols.
3. Note: More mature babies receiving unblended oxygen may rapidly develop aggressive ROP (A-ROP).

IV. Examination Protocol

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) and this stereotypic behaviour is confirmed by studies extending over several decades. Thus, ROP onset is later postnatally in the very immature compared to the more mature baby.
3. Neonatal events influence the risk of developing ROP but not greatly its timing. Sight-threatening ROP is most unlikely to be present before 31 weeks' PMA.
4. The screening program needs to be designed so that Type I ROP requiring treatment is identified timely.
   (a) The mean age for treatment at pre-threshold is around 35 weeks' PMA.
   (b) The time available for treatment is short, but the degree of urgency is not identical for all cases.
      (1) A-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 shown in Table 84.2. In those countries in which babies >32 weeks' GA are at risk, screening will need to commence earlier postnatally compared to more premature babies (Table 84.3).

Table 84.2 Age at first screening examination in weeks

GA	PMA	PNA
22[a]	30–31	8–9
23[a]	30–31	7–8
24	30–31	6–7
25	30–31	5–6
26	30–31	4–5
27	31–32	4–5
28	32–33	4–5
29	33–34	4–5
30	34–35	4–5
31	34–35	4–5
32	36	4
33[a]	36	3
34[a]	36	2

Data for babies 24–32 weeks GA provided by clinical studies (Reynolds et al. 2002)
[a]Estimates based on limited clinical data

Table 84.3 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 A-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 – hence the importance of taking note of the continuum of changes from normal through preplus to plus

6. Subsequent examinations
   (a) Every 2 weeks. Except for eyes with vessels in zone I, with Type 2 pre-threshold ROP which should be examined at least once a week to ensure that treatment, if necessary, is optimally timed.
   (b) 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
   (c) 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. Since assessing the zone of vascularization is open to misinterpretation, it is recommended that screening continues to 37 weeks' PMA.
   (c) For the eye with ROP the need for examinations is dictated by clinical criteria.

B. Screening examination
1. To be done by an experienced ophthalmologist following pupillary dilation.
2. ROP is recorded (Fig. 84.1) according to the following 4 criteria:
   (a) Severity by stage: 1 to 5 and aggressive ROP.
   (b) 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.
   (c) Extent in 30-degree sectors.
   (d) Presence of "*pre-plus*" and "*plus*" disease (Fig. 84.5).
3. It is critical to record each of these criteria on every occasion and record the absence or presence of "plus", even if no ROP is observed (Figs. 84.2, 84.3, and 84.4).
4. Examination by binocular indirect ophthalmoscopy (BIO) or digital imaging. While BIO remains the clinical gold standard, digital imaging (DI) is increasingly used and of proven research value. Digitally obtained mages can be interpreted "directly" in the

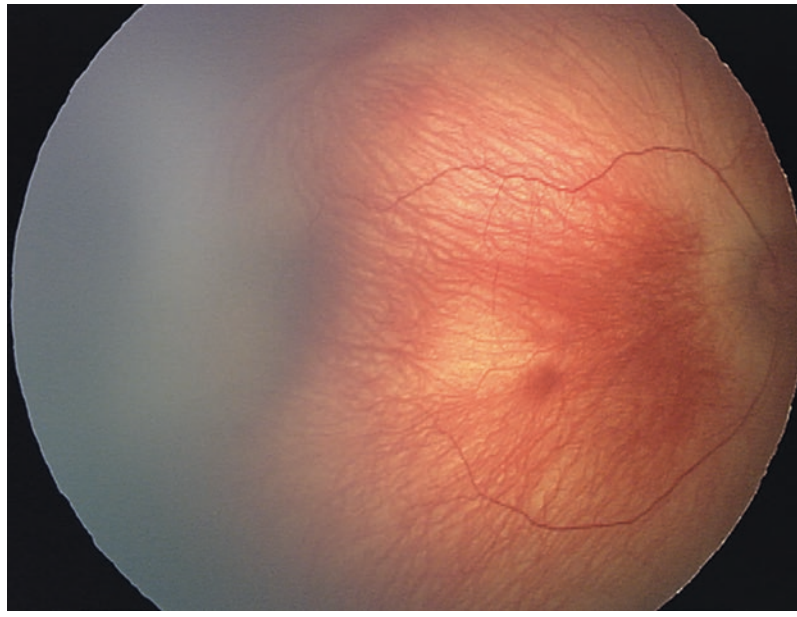

Fig. 84.1 Normal retina of preterm baby. The retinal vessels extend up to the grey area, to the left of the image, but do not reach the retinal periphery. The grey region is the normal, yet to be vascularized, retina. ROP develops at the junction of the vascularized and yet to be vascularized retina. (*No permission needed for this image*)

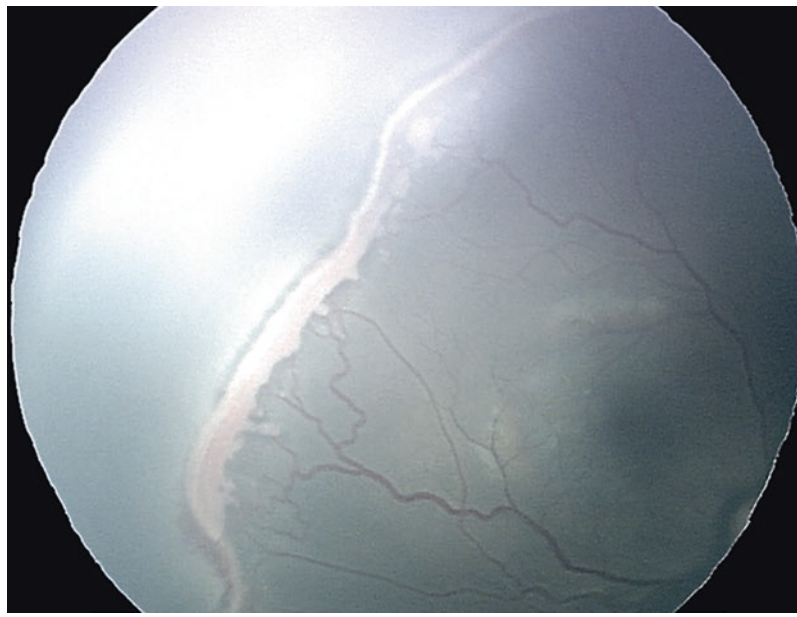

Fig. 84.2 Stage 2 & 3 ROP in the peripheral retina. The grey line towards to top and bottom of the image are stage 2 while in the middle section are fronds of neovascularization, stage 3. The grey appearance is because the image comes from a black baby. (*No permission needed for this image*)

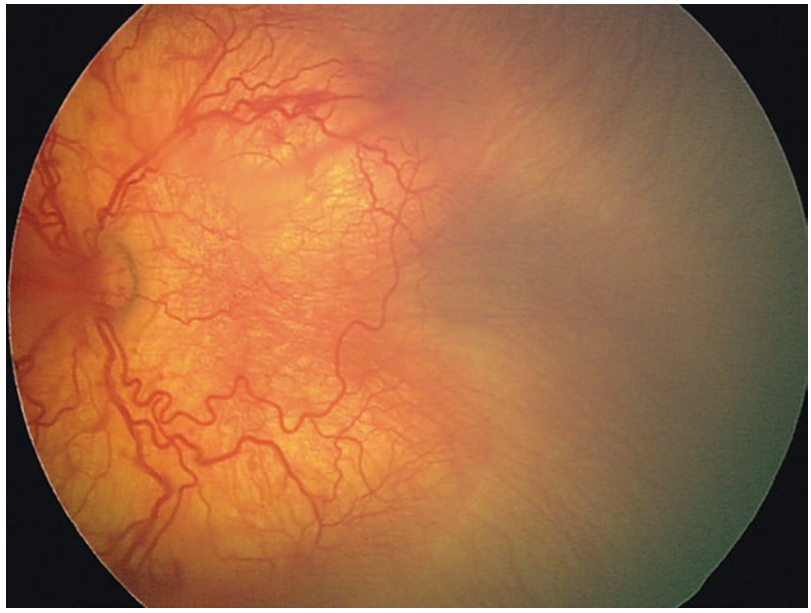

Fig. 84.3 Aggressive ROP (A-ROP). Note extreme vascular congestion and tortuosity but subtle if any peripheral ROP lesion. (*Used with permission in 4th Edition from Archives of Ophthalmology; 2005; 123: 991–999. Figure 12 A page 996*)

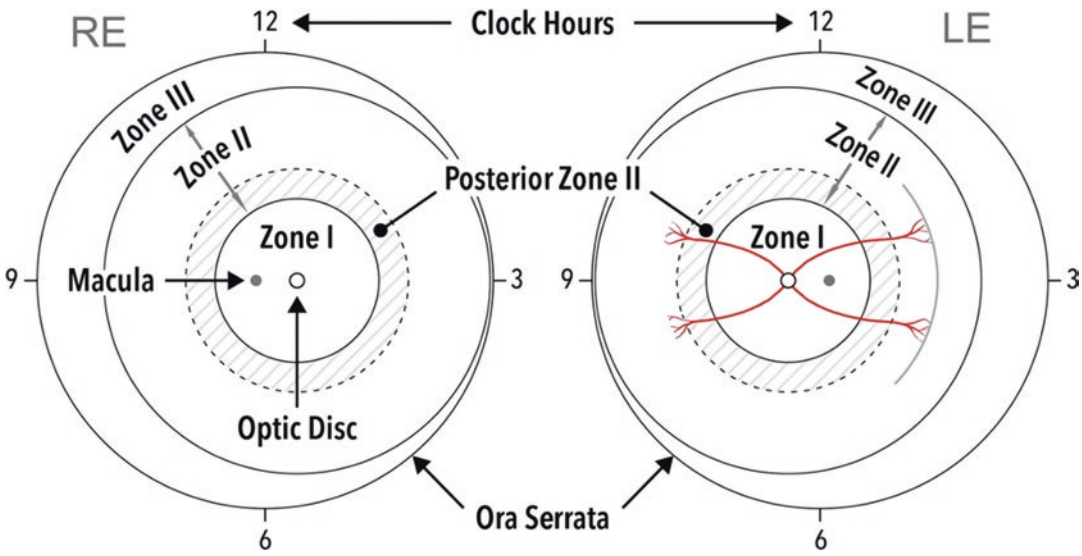

Fig. 84.4 Diagram showing the retinal zones. X marks the macula. (Permission needed from ICROP 3, 2021 – permission to reprint requested)

NICU or transmitted as part of a telemedicine network. Advantages of DI include recording and monitoring progress, displaying the clinical picture to the family and neonatal team, and reducing the need for additional examinations by the ophthalmology trainee. A disadvantage of DI is that it is difficult to visualize the peripheral retina; thus, in the absence of ROP, a final examination by BIO is recommended to ensure safe discharge from the screening program.

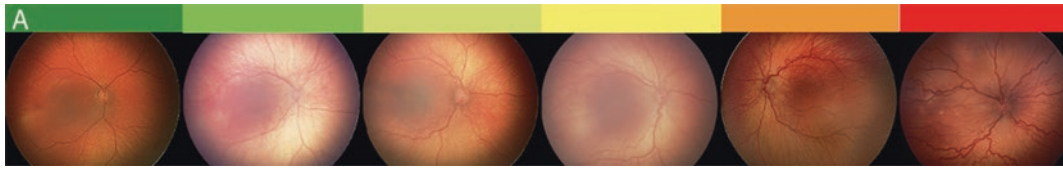

Fig. 84.5 Six representative images demonstrate that the vascular changes associated with ROP are on a continuum so displayed here as a traffic light scheme with green as normal and red as severe plus. (Permission needed from ICROP 32021 – permission to reprint requested)

V Treatment
- 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.
     - (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 closely 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 can become severe and, if it progresses to Type 1 ROP, treatment is required.
  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 (Fig. 84.5).
  4. Unfortunately, as diagnosing plus disease is not robust, it is recommended that the clinical picture is considered in its entirety when treatment is being considered
  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 modality
  1. Laser remains the gold standard, but anti-vascular endothelial growth factor agents (anti-VEGF) are increasingly used.
  2. At the time of writing ROP treatment is in a state of flux
     - (a) Compared to laser, anti-VEGF agents (Bevacizumab and Ranibizumab) are relatively simple to administer, have shorter administration time, require fewer resources and less operator expertise, and hence are widely used in many countries particularly where resources are sparse
     - (b) The response to treatment is faster following anti-VEGF agents (mean 4–5 days) compared to laser (mean 16 days)
     - (c) About 15% of eyes require retreatment secondary to reactivation following anti-VEGF. Retreatment following laser is almost always the result of gaps in its initial application.
     - (d) Both laser and anti-VEGF compounds are effective in the treatment of Type I ROP, but this is a rapidly evolving field. Outcomes are similar, although myopia is less following the latter. To date, studies up to 2 years following anti-VEGF therapy are reassuring as they have not shown an adverse effect on neurodevelopment.

C. Treatment practicalities
   1. Once pre-threshold Type 1 ROP has been diagnosed, treatment should be performed:
      (a) Within 48 for eyes with A-ROP.
      (b) Within 48 and 72 h for eyes with less aggressive ROP but still requiring treatment.

VI Long-Term Follow-Up
   A. All severe ROP requires ophthalmic follow-up, at least till 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. It is important to note that 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 multi-professional teamwork
   B. National guidelines form the basis of protocols which should be developed locally 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 need 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 be made aware of this.
   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 also involve a member of the neonatal team.

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 retinal and retinovascular changes associated with ROP are not well defined. Develop further methods for analysis from digital images of the retina and retinal vessels, including optical coherence tomography, and artificial intelligence.
   C. Postnatal growth-based models (e.g. WINROP and G-ROP) 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 nonphysicians, taking and evaluating the images shows promise for the future in NICUs if there is a dearth of ophthalmic expertise.
   E. Several anti-VEGF agents are being explored for the treatment of ROP at pre-clinical and clinical levels. Ophthalmic efficacy and systemic effects need to be understood before their routine use can be recommended.

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Neurologic Complications of Mechanical Ventilation

85

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 85.1).
   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.
      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 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
      1. Infants breathing out of synchrony with the ventilator

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Table 85.1 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
3. Bronchopulmonary dysplasia
4. Prolonged mechanical ventilation
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
3. Chronic lung disease and systemic inflammation

(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 is often out of synchrony with the ventilator support.

(b) The fluctuations are increased with increasing respiratory effort and are minimized when respiratory effort is absent (Fig. 85.1) Complete synchronization is only assured at times of total ventilator support (e.g., during paralysis).

(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) Minimizing fluctuations
   (1) Optimize patient-ventilator synchrony
   (2) Use of sedatives
   (3) Skeletal muscle paralysis, if needed. Avoid routine use of muscle relaxation.

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
   (b) A combination of an elevated venous pressure and a concomitant decrease in cardiac output (CO) 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 when hypocapnia occurs.

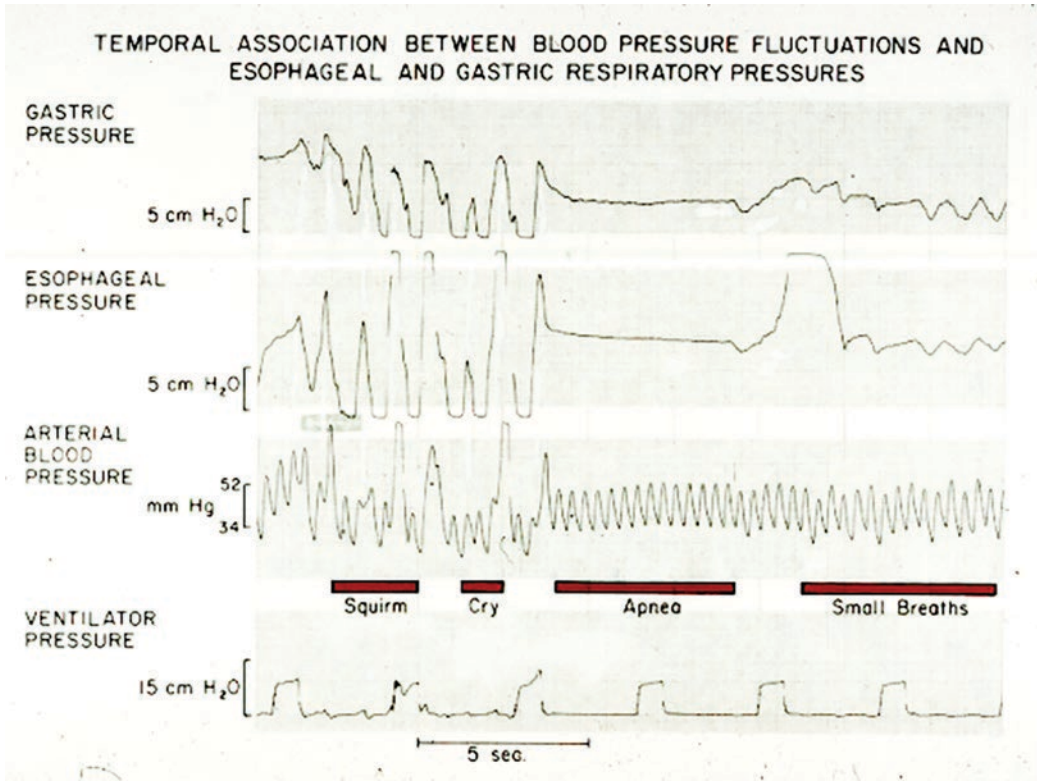

Fig. 85.1 Temporal association between blood pressure fluctuations and esophageal and gastric respiratory pressures

(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 and mortality.

3. Volume-targeted versus pressure-targeted ventilation.

There is evidence that volume-targeted ventilation, 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.

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 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) Provide 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 systemic mean 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
   4. Systemic inflammation from mechanical ventilation
      (a) Mechanical ventilation, especially with large tidal volumes, initiates a cascade of systemic inflammation.
      (b) Systemic inflammation is associated with white matter injury.
   5. Prolonged mechanical ventilation
      (a) Bronchopulmonary dysplasia is associated with impaired neurodevelopmental outcomes (Chap. 80).
      (b) Prolonged mechanical ventilation is associated with impaired abnormal white matter maturation.

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 and as a last resort)
   2. Avoid systemic hypotension and/or hypertension
      (a) Consider inotropic support
      (b) Consider cautious volume expansion
   3. Avoid impedance of venous return by optimizing $P\bar{a}w$
   4. Avoid hypocapnia
   5. Avoid hypercapnia
   6. Avoid pneumothorax
      (a) Surfactant administration for RDS
      (b) Synchronized ventilation
      (c) Wean as rapidly as tolerated

All these risks can be reduced by a complete course of antenatal steroids administered within 48 h of delivery of the premature infant.

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Part XIII

Other Considerations

Respiratory Focused Nursing Care of the Neonate

86

Kim LaMar

As a provider of care for neonates in transport, delivery room, nursery, 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 their 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 the following:
    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 the following:
    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.

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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 premature neonates with very friable skin.

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 the 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, and 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/nutrition

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, intravenously, 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.

D. Consider herbals, maternal medication impact, or breast milk transference of meds

E. 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.

VII. Anticipatory guidance
  A. Should be aware of the 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. Bronchopulmonary dysplasia (Chaps. 78, 79, 80)—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. Nurses must maintain familiarity with institutional policies on documentation and approved abbreviations that align with accreditation or regulatory standards.
  D. 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.
  E. 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.
  F. 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 unrelated to care, such as associated with suctioning, positioning, tube placement
  G. Abbreviations
    1. Use as infrequently as possible
    2. Only use approved abbreviations
    3. Medication documentation with set standards, such as dosage documentation, treatment of trailing or leading zeros, decimal points
    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

IX. Transport of neonates (Chap. 87)
   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
   C. Collaboration with the healthcare team is essential including physicians, respiratory therapists, perfusionists, nutritionists, pharmacists, and ancillary team members.

X. Developmental care
   A. Nurses must collaborate with other healthcare providers in developmental care, speech, physical, music, play, and alternative 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, massage or aromatherapy, may be considered, but in context of other care and needs of neonate and family

XI. 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 parents 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 awareness, patient safety, and ethics as these principles are continuously evident in neonatal nursing.
   G. Neonatal nurses must be educated in the provision of end-of-life care for neonates and their families (Chaps. 92 and 93).

XII. 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 premature neonates.
   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.

XIII. 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, 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.

XIV. 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 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.

XV. Transillumination (Chap. 24)

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 midaxillary line with air leaks in chest
C. Edema, tape, and equipment may decrease its usefulness
D. Assists in locating vessels for cannulation

XVI. Chest drainage devices
A. Should be familiar with the setup 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 every 8 h, 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 setup for emergent need of second setup or replacement of current setup 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.

XVII. 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. Neonates requiring mechanical ventilation require complex monitoring. Nurses should keep themselves familiar with the newer developments and know how to troubleshoot issues that may arise.

XVIII. 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
C. If in-bed scale, usually may leave on the ventilator during weighing process
D. Perform a focused assessment of neonate before and after weighing.

XIX. 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-hour bedside care. Supervised prone playtime should be incorporated for proper cranial development.

D. Massage therapy, touch therapy, stroke therapy has empirical reports of benefits but must be considered in coordination of all care for tolerance by neonate.

E. Kangaroo care is beneficial for many infants 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.

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Transport of Ventilated Babies

87

Steven M. Donn and Carly M. Gisondo

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 may 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 (NICU), 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 the 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)

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(f) Should be adaptable to special needs of neonatal transport

2. Helicopter/rotor wing aircraft
   (a) Provides a more rapid means of transport for longer distances
   (b) Depending on size of helicopter and distance to be covered may require stops for refueling
   (c) Not subject to traffic or road conditions, but weather conditions may preclude use
   (d) Size of vehicle may limit number of team members
   (e) Landing pad may not be adjacent to hospital, requiring extra time and possible ambulance use
   (f) Virtually no access to patient en route
   (g) Must land in event of patient deterioration
   (h) Requires special training of crew
   (i) 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 by ambulance 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 are 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 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
         (3) Thermoregulation bag or plastic wrap
      (b) An electronic cardio-respiratory 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) Ventilation 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 backup 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 non-invasive
(e) Transcutaneous TcPO2/PCO2 device or portable blood gas analyzer for long-distance transport of a critically ill infant

D. Transport Equipment (Tables 87.1 and 87.2)

Equipment should be readily available to treat any emergency that might occur at either the referring hospital or en route. Equipment must be checked regularly for condition and expiration date.

Table 87.1 Typical 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

Table 87.1 (continued)

Forceps, sterile
Gauze squares: see dressings
Gloves, sterile
Glucose screening strips
Heimlich valves
Hemostats, sterile
Labels
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

E. Transport Medications (Table 87.3)

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. 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 or envelope works well.

Table 87.2 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
Laryngeal mask airway
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 87.3 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 mcg/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

2. 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.
3. 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.
4. A digital camera is useful, both to give the parents a picture of the infant and to document any unusual physical findings.

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, work of breathing
        (2) Laboratory assessment
          (a) Blood gas analysis
          (b) Chest radiograph
      (b) Airway management
        (1) If already intubated evaluate tube position by listening for breath sounds, reviewing most recent chest radiograph, and confirming with end-tidal CO_2 monitor, or colorimetric CO_2 detector.
          (a) If the position is satisfactory, adequately secure tube.
          (b) Evaluate patency (suction if necessary).
        (2) 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. 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. Gastrointestinal
      (a) Assess for signs of abdominal distension.
      (b) Palpate softness/firmness of abdomen.
      (c) Assure placement of orogastric tube.
      (d) If abdominal wall defect, evaluate perfusion to intestine, or integrity of sac, and ensure the baby is placed in a thermoregulation bag, or covered in saline-soaked gauze. It is important to keep the tissues moist (consult with neonatologist or pediatric surgeon).
    4. 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.

5. Metabolic
   (a) Perform glucose screen. If low, check serum glucose and treat if indicated.
   (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.
6. 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 obtaining 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.
7. 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 at a minimum.
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. Hand-off should be given to the receiving team including, but not limited to; brief medical history, management provided at the referring hospital, and any changes made prior to and during the transport process.

2. 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.
3. All supplies should be promptly replenished.
4. Any mechanical problems (vehicle, equipment, or other) should be reported and corrected immediately.
5. 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 the following:
         (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.
         (c) Pneumothorax evacuation with chest tube placement, especially prior to air transport, should be considered.
      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 persistent pulmonary hypertension if this is the case.
         (b) The ability to transport a baby on high-frequency ventilation is inconsistently available to transport teams. 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 feet 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 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 therapeutic hypothermia following intrapartum hypoxic-ischemic encephalopathy.
   2. Passive cooling may be initiated at 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 overcooling.
   4. The ability to perform active cooling during the transport process is becoming more widely available.

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
      Normothermia, as previously discussed, unless passive or active cooling is being performed, it is essential to maintain stability during the transport process.
   3. Position the 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. Psychosocial stress

G. Systems Issues
   1. National accrediting bodies exist for transport with recommendations/criteria for organization, education, standards of practice, communication, quality assurance, and quality improvement.
   2. Organized procedures must be in place and communicated to all potential participants for requesting, accepting, dispatching, and conducting neonatal transports.
   3. Periodic review of transports enables identification and correction of system problems.
   4. Contingency planning and prior consideration of unusual circumstances improve response and lessen stress.

Suggested Reading

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Role of the Respiratory Therapist in the NICU

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Timothy Myers and Amber Galer

I. As respiratory therapists spend 24 h per day with critically ill newborns in a neonatal intensive care unit (NICU), respiratory care is essential to the diagnosis, treatment, 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
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

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6. Location and function of baroreceptors and chemoreceptors

C. Pathophysiology
   1. Assessment of fetal status (amniocentesis, echocardiography, fetal heart rate, scalp pH, ultrasonography)
   2. Meconium presence in amniotic fluid
   3. Identify the most common birth presentations
   4. Impact of multifetal gestation.
   5. Physiologic changes during labor, delivery, and post delivery.

D. Cardiac Defects: defects occur in approximately 1 of every 100 deliveries. Depending on defect, a 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 fetal circulation has not converted to normal "adult" circulation necessitates quick interventions for the management and treatment of this condition.
   2. Ductal-dependent lesions
      (a) Patent ductus arteriosus
      (b) Atrial and ventricular septal defects
   3. Mixing lesions
      (a) Tetralogy of Fallot
      (b) Transposition of the great vessels
      (c) Total anomalous pulmonary venous return
      (d) Truncus arteriosus
      (e) Hypoplastic left heart syndrome
   4. Non-mixing lesions
      (a) Subaortic stenosis
      (b) Tricuspid atresia

E. Congenital Defects
   1. Airway
      (a) Upper
      (b) Lower
      (c) Fistulas
   2. Diaphragmatic Hernia (Chap. 72)

F. Pulmonary Conditions
   1. Transient Tachypnea of the Newborn (TTN)—Most commonly found in newborns delivered by Cesarean Section. Inability to properly eliminate fetal fluid leads to interventions based on clinical signs and severity.
   2. Respiratory Distress Syndrome (RDS) (Chap. 68)
      (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 RDS (Chaps. 78, 79, 80)
      (a) Pathophysiology and diagnosis
      (b) Treatment—prevention through optimal clinical management is the primary treatment in 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. 81): 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. 75)
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 defined 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
(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 tracheoesophageal 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 other or routine 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 crackles 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 and/or carbon dioxide tensions through warming of the surface of the 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 typically placed on the abdomen or thigh.
3. Trending—not an absolute reading as there 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 of light 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. These monitors either sample a sizeable portion of the exhaled gas (sidestream) or contribute a significant amount of dead space (mainstream), they are not normally used as part of the management of newborns, especially those that are premature.
   2. One type, a disposable monitor connects to the 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 in a number of ways including orally, intramuscularly, subcutaneously, intravenously, endotracheally, sublingually, or dermally.

IX. Documentation (Chap. 94)
   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. 87)
   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 PIP (Vt) and PEEP on a consistent basis, but can have a highly variable inspiratory time and respiratory rate due to clinician actuation.
4. May see use of these devices in the delivery room as well as the NICU, operating suites, transport, or any areas delivering care to newborns

B. Oxygen therapy. Understanding 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. The least amount of supplemental oxygen to maintain minimal acceptable oxygen saturations is optimal
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 FDO2 (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 FDO2 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 several 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, 28, 29, 30, 31, 32, 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, 35, 36, 37, 38, 39, 40, 41, 42)
1. Design principles and classification of mechanical ventilators (Chap. 43)
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. 40, 41, 42)

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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 backup or mandatory minimum rate.
2. Assuming their lung parenchyma and chest wall mechanics are normal, targeted tidal volume should be adequate to maintain normal EtCO2/pCO2 (typically 6 mL–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 compromise their force-generating capability (muscle fiber length-tension relationship).
2. In order to maintain minute ventilation in the presence of a poorly compliant chest wall, respiratory rates are elevated.
3. In order to minimize energy expenditure and prevent respiratory muscle fatigue, patients often require a high peak inspiratory pressure, sometimes >30 cm H_2O.
4. 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. In a term infant with these disorders, tidal volumes of ~10 ml/kg should be targeted.
2. Mandated or backup rate breaths can be either pressure or volume-targeted and are time-triggered/time-terminated. This is programmed separately from spontaneous pressure-supported breaths that are flow-triggered/flow-terminated.
3. Because of muscle weakness, clinicians must ensure that the trigger is sensitive 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 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

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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 threefold from 1.23 per 100,000 live births in 1984 to 4.77 per 100,000 live births in 2010

II. Indications for long-term home mechanical ventilation
   A. Recognition of chronic respiratory failure
      1. Chronic respiratory failure is a result of an uncorrectable 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 ventilatory support
         (b) Absence of adequate spontaneous respiration
         (c) Failure to extubate after many attempts by a 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, myelomeningocele)
      (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. Alternative means of support have been 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 except for isolated disorders of the respiratory tract (e.g., BPD)
   2. Stable disorders (spinal cord injury, post-polio)
   3. 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 ventilation.

B. Wean as soon as respiratory status stabilizes and can maintain alveolar ventilation without support.
C. SaO_2 normal ± O_2 supplement (<4 LPM for home).
D. End tidal CO_2 ~ normal.

Hypercapnia (capillary blood gas pCO_2 > 55 torr, 7.33 kPa) at the time of NICU discharge was an adverse prognostic risk factor for readmission and pulmonary hypertension.

E. Work of breathing is minimal (if not eliminated).

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 a long-term expectation

VI. Non-medical assessment for initiation of long-term mechanical ventilation
A. Home ventilation care requires invested families, well-trained in-home caregivers, sophisticated technology, financial support, ready access to primary and subspecialty medical care
B. Available resources in the outpatient medical team, home, and community
C. Physical environment
D. Attendant care needs

VII. Modes and types of portable home ventilators
A. Performance of the ventilator and settings are more important than ventilator mode. Home ventilators are less sophisticated than ICU ventilators.
B. Delivery
1. Volume Ventilation
(a) First mode for polio, fixed tidal volume, no leak compensation
(b) Not tolerated in high airway resistance, low compliance, or small children
2. Pressure Ventilation (Negative vs. Positive)
(a) Positive pressure ventilators are the most commonly used for children
(b) Better triggering to overcome low flow or inappropriate spontaneous breath rate
C. Ventilation modes: 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 of respiratory distress or effort
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) Polysomnography—useful for patient-ventilator asynchrony, air leaks
(b) Capillary 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

Extensive standardized training and assessment of readiness of caregivers to manage routine tracheostomy tube and ventilator care and emergency responses to expected complications is critical.

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)

      Consider obtaining tracheostomy aspirate culture at well baseline to inform subsequent antibiotic decisions
   4. Airway injuries
      (a) Tracheal stenosis
      (b) Tracheal dilation
      (c) Tracheomalacia
   5. Stoma injuries
      (a) Tracheo-innominate fistula
      (b) Poor wound healing
   6. Serial endoscopic surveillance by surgical subspecialist with expertise in tracheostomy management is essential

B. Acute respiratory exacerbations
   1. Respiratory exacerbations
      (a) Definition is non-specific
      (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) Antibiotic decision is based on microbial profile from tracheostomy aspirate culture at well baseline.

C. Prolonged mechanical ventilation:

Comprehensive co-management with respiratory subspecialist with expertise in the management of long-term ventilation complications and weaning is essential to avoid complications

D. Pulmonary hypertension, cor pulmonale
   1. May result from primary respiratory disorder or inadequate ventilator support.
   2. Serial echocardiographic surveillance is essential.

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Discharge Planning and Follow-Up of the NICU Graduate

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I. Discharge Planning of the NICU Graduate

A. Introduction

Hospitalization of an ill newborn is not only one of the most costliest 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 readmissions 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 multidisciplinary 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

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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 cardiorespiratory monitoring
      (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 the following:
      (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. Predischarge 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. 84)
         (2) Specific eye examination should be arranged for those with congenital infections, congenital eye abnormalities, chromosomal abnormalities, and an 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, meningococcal, rotavirus and other vaccines need consideration based on local guidelines.
      (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. 69).

2. Predischarge examination is essential to ensure that good general health and growth are maintained in an infant who is ready for discharge. It also flags problems requiring further evaluation (e.g., heart murmur, unstable hip). However, a normal predischarge 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 the following:
   (a) Infant's demographic details (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 (e.g., home oxygen, need for tube feeding or weight monitoring, etc.)
   (f) Medications at discharge
   (g) Type of milk and feeding at discharge
   (h) Instruction on immunizations
   (i) Specific discussion points with family (relevant in babies with high risk of neurodevelopmental problems)
   (j) Plans for follow-up and further assessments
   (k) Copy letter to all healthcare professionals involved

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, 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, 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 involvement of other specialists/therapists.
   (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 care
      (2) To monitor changing patterns of prognosis (mortality and morbidity) over time.
      (3) To evaluate newer treatment and interventions where the long-term neurodevelopmental outcomes are used as primary outcome measures.
      (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 birthweight 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 rates of normal survival can be compared across units. Recent report confirms average follow-up in 70% of eligible children, which is far short of the benchmark of 90%. Hence, it is imperative that arrangements are in place for communicating with families about follow-up at discharge, families who live far from the hospital of care, families who do not attend appointments, families who move to different areas, and for completing and documenting assessments.
      (b) All NICU graduates who required mechanical respiratory support
      (c) Small-for-gestational age babies (birthweight or head circumference >2 standard deviations below the mean for gestational age).
      (d) 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) Intrauterine or severe perinatal infections
      (g) Metabolic derangements like persistent hypoglycemia, hyperbilirubinemia requiring exchange transfusion, etc.
      (h) Significant congenital abnormalities
      (i) Exposure to toxic agents (e.g., drugs) in utero.
      (j) 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 coordinate between the families and other appropriate professionals/agencies.
      (b) Community liaison nurse or nurse practitioner
      (c) Pediatric physiotherapist/occupational therapist/ speech and language therapist
      (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 coordinate 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 is 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 detailed 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. 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 upon gestational age for up to 3 years. This is not necessary once the child is in the educational 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 provide an underestimation of disability. These tools are of little value in very poorly performing children (>3SD below mean). Depending upon the availability of resources, this is done in the form of 2 to 3 assessments within the first 2 years of age. Some units do one formal assessment at 2 years of corrected gestational age.
      (g) Validated parent report questionnaires have 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 and evaluation for toxicity or side effects.
   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 adults.

2. Most do not need follow-up regularly once their growth and development are satisfactorily progressing by about 2 years of age.
3. If the developmental assessment requires for an infant to have long-term follow-up, formal handover and information sharing with the community pediatrician/school is important because of potential social and 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 91.1: 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?
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/choreo-athetoid/unclassifiable

Development – At 24-Month Corrected Age

Is development normal (<3 months delay)?
Is there mild delay (3–6-month delay)?
Is there moderate delay (6–12-month delay)?
Is there severe delay (>12-month 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?

Gastrointestinal 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?

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Part XIV

Ethical and Legal Considerations

Initiation of Life Support at the Border of Viability

92

Janeet Dhauna and Naomi Laventhal

I. Important considerations regarding resuscitation of infants at the borderline of gestational viability
   A. Guidelines for which infants should have resuscitative efforts initiated in the delivery room.
   B. Considerations regarding when discontinuation of resuscitative efforts is ethically permissible.
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, despite acknowledged limitations of gestational age alone as a determinative prognostic factor.
      1. Infants born before 22 and 0/7 weeks are uniformly not resuscitated (physiologic futility, non-maleficence).
      2. Resuscitation is generally recommended for infants born at or after 25 0/7 weeks without complicating comorbidities (best interest standard/beneficence).
      3. Between 22 and 0/7 and 25 and 5/7 weeks, decisions both to initiate and forego initial resuscitative efforts are sometimes contested by clinicians or parents.
         (a) 22 and 0/7 to 25 and 5/7 is the contemporary "gray zone" of gestational viability. Survival of 22-week infants partly depends upon whether they are born in centers offering resuscitation at that gestational age.
         (b) In this gray zone, parental authority and shared decision-making are emphasized (parental authority [in contemporary ethics this term has replaced "autonomy" to describe parents' roles as natural surrogate decision-makers for children]). 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?

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(c) Constraints around parental authority and thresholds for offering or insisting upon resuscitation at birth should be transparent and applied consistently within institutions.
(1) Variation between providers or services is detrimental to the therapeutic alliance
(2) If the parents' desired plan of care is not available at a particular institution, offer of transfer to another hospital for a second opinion should be considered.
(d) Available guidelines within this gray zone may not be specific for gestational age thresholds or definitions of "good" or "bad" outcomes.
(1) Although national and societal guidelines are potentially helpful in developing institutional policies, available guidelines within this gray zone are not always specific in defining gestational age thresholds or definitions of "good" or "bad" outcomes.

B. Besides gestational age, important prognostic factors include estimated fetal weight, fetal sex, administration of antenatal corticosteroids, and single vs. multiple gestation.
C. 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. Clinicians in centers that resuscitate more infants at 22 weeks report more pessimism about outcomes in this group than centers that resuscitate fewer 22-week infants.
D. 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.
(a) Use of local data is not recommended if very few extremely premature infants are born annually.
(b) Parents should be informed whether local data are being used for counseling.
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; decision aids with pictographs for decision making at the margin of viability have been shown to be helpful in some respects.
3. The value of providing numeric estimates of mortality and morbidity remains controversial.
(a) Many neonatologists use population-based outcomes tools for counseling and decision-making about initiation of resuscitative efforts in the delivery room.
(b) Multiple studies suggest that parents rarely rely on specific outcome statistics, and instead rely on spiritual or personal beliefs.
(c) Studies also suggest that parents value counselor empathy and optimism over knowledge of outcome data.

4. Prenatal consultation in the context of anticipated extremely preterm birth is an acquired skill; training programs vary in their approach to teaching prenatal consultation. Research on prenatal consultation emphasizes the importance of active listening, asking open-ended questions, eliciting values, individualized content, and situational awareness.
   (a) Decision aids have been developed to support prenatal counseling.
   (b) A growing collection of counseling tools and trainings are available to support acquisition of prenatal counseling skills.
5. Joint consultation with obstetric providers is advisable, when possible.

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-minute Apgar score of zero despite 10 minutes 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-minute 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.
         (a) Clinicians report using prenatal outcome tools to prognosticate *after* birth, suggesting the need for additional tools for post-natal counseling.
         (b) Focused tools are available for outcomes prediction along specific parameters.
      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 the following:
         (a) Severe physiologic instability
         (b) High likelihood of severe neurologic impairment based upon known congenital defects or acquired brain injury
         (c) Prediction of long-term technology dependence
         (d) Physician prediction of non-survival
         (e) 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 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 (Chap. 93) 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.

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93 Withdrawal of Ventilatory Support: Ethical and Practical Considerations

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I. Introduction
  A. Ventilatory support
    1. Ventilatory support in the setting of the Newborn Intensive Care Unit here refers to oxygen supplementation, nasal cannula, nasal continuous positive airway pressure, nasal intermittent positive pressure ventilation, conventional mechanical ventilation, and high-frequency ventilation.
    2. These modalities may provide effective life-saving support in the setting of respiratory failure, or anticipated respiratory failure, secondary to a variety of causes.
    3. Ventilatory support should generally be initiated when there is a reasonable chance it can be effective, the potential benefits to the patient are believed to outweigh the likelihood and severity of the potential burdens, and the resources are available.
  B. Withdrawal of ventilatory support
    1. There may be times in the treatment of critically ill newborns when previously initiated ventilatory support is no longer seen to meet the criteria in A3.
    2. Just as there are situations wherein it is ethically acceptable to withhold the initiation of ventilatory support, there may also be situations wherein it is acceptable to withdraw such support.
    3. Determination of the best course of action should involve attention to:
      (a) Ethical considerations
      (b) Clinical criteria and timing
      (c) Appropriate roles and responsibilities of parents and clinicians in the decision-making process

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(d) Practical elements
(e) Legal considerations

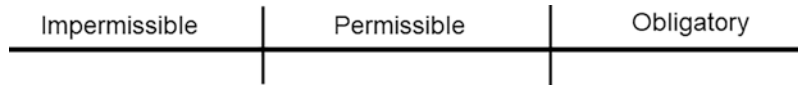
II. Ethical Considerations
A. The Best Interest Principle
1. When patients are unable to decide/speak for themselves, a surrogate decision-maker, commonly a close relative, should speak on their behalf.
(a) In cases of surrogate decision-making for an incapacitated adult, a proxy is asked to make decisions based on substituted judgment, or what the patient would have wanted.
(b) Newborns and infants have never reached the capacity for decision-making and thus substituted judgment is not possible. Surrogate decision-makers (most often one or both parents) must therefore decide based on assessment of what would be in the patient's best interest, by weighing the anticipated short-term and long-term benefits and harms, for any intervention under consideration.
2. The Best Interest Principle guides clinicians to act in a way which promotes the maximum good for the patient, while minimizing the harms. It traditionally weighs benefits and harms of a proposed intervention to the individual patient, though some have argued that the needs and rights of others should also be considered. This is consistent with the widely accepted medical ethical principle of beneficence, which refers to a duty to act for the good of the patient.
3. The clinician's obligation related to beneficence is a prima facie duty. That is, it may in some settings be outweighed by other duties, principles, or considerations, such as the obligation to respect parental authority or to fairly allocate limited resources.
4. In most cases for which ventilatory support has been applied, the benefits of the treatment clearly outweigh the burdens.
(a) Given that mechanical ventilation is generally provided in the setting of apnea or respiratory failure, the potential benefits include survival, both short and long term, as well as improved oxygenation of the brain and other vital organs. Benefits could therefore be seen to include all positive experiences likely to be associated with ongoing life.
(b) Examples of potential burdens include the risks of the therapy itself, such as chronic lung disease, tracheal damage, pneumothorax, infection, and pain/discomfort associated with ventilatory support. The potential burdens could also be seen to include the negative experiences associated with survival that results from this treatment.
5. When the burdens of therapy are great and the prospect of benefit small, it is the duty of the medical team to assess whether previously initiated mechanical ventilation remains in the patient's best interests, and therefore whether it should be continued. That assessment should be made together with informed parent(s), on an ongoing basis over the course of ventilatory support.

B. Parental Rights
1. Parents should be recognized as having a right to *parental authority*, or the right to determine what is done to or for their child.
(a) Parental authority includes the right to refuse or consent to medical interventions on behalf of their child, up to and including potentially life-sustaining medical treatment, such as ventilatory support.
(b) This authority is not unlimited. Clinicians may have an obligation to seek to overrule a parental decision when that decision is clearly opposed to the child's best interest.

2. Parents and medical professionals should work in concert to determine a plan compatible with the best interests of the pediatric patient, consistent with a shared decision-making model. Shared decision-making is a collaborative process that allows patients, their surrogates, and clinicians to make healthcare decisions together, utilizing the best available scientific evidence and respecting the family's values, goals, and preferences.

C. Decision-Making and the Spectrum of Ethical Permissibility:

1. A proposed treatment (including initiation or continuation of ventilatory support) can be considered as being on a spectrum of ethical permissibility, as per the following *Impermissible-Permissible-Obligatory framework*:



   (a) A proposed treatment or action can be viewed as *ethically impermissible* if the gravity and likelihood of anticipated burdens clearly outweigh the hoped-for benefits. Clinicians should generally not offer treatments deemed ethically impermissible, nor provide them if asked.
   (b) A therapeutic intervention can be viewed as *ethically obligatory* when the anticipated benefits to the patient clearly outweigh the burdens, and the consequences of withholding or withdrawing the intervention would be severe. Clinicians should generally provide such treatments, even if parents are opposed.
   (c) The relative importance of the different anticipated benefits and burdens may be a subjective assessment, and significant weight should be accorded to the values of the parents.
   (d) Clinicians should generally not make a decision that is opposed to parental preference in isolation, but rather should consult medical, nursing, and other colleagues, as time and circumstances allow. Consultation with hospital legal counsel and Ethics Committee may also be advisable.
   (e) When the balance of benefits and burdens is relatively close or is unclear, or there is significant prognostic uncertainty, the treatment should generally be considered *ethically permissible.* That is, it would be acceptable either to provide the treatment or not. In such circumstances, clinician preference and recommendations remain important, but deference to the preference of informed parents is generally advisable.
   (f) A treatment could move on the spectrum of permissibility as shown in either direction, as new information about the patient and/or the treatment becomes available.

2. It is the duty of the medical team to determine, and continually reassess, the benefits and burdens of mechanical ventilation in individual cases. With the child's interests at the forefront, and the goal of parental collaboration in mind, clinicians must determine if continued ventilatory support is ethically impermissible, permissible, or obligatory.
   (a) If death is believed to be imminent despite the provision of ventilatory support, it is ethically permissible to withdraw mechanical ventilation. This is often the preference of clinicians and parents, rather than awaiting death on a ventilator, and can offer the parents an opportunity to hold their child, free of tubes and wires, prior to death.
   (b) Similarly, clinicians and parents may reasonably decide together to withdraw ventilatory support when death is not imminent, but survival to hospital discharge is nevertheless believed to be unachievable.

(c) There may be rare circumstances, aside from imminent or unavoidable death, in which the burdens to the child of mechanical ventilation and anticipated long-term suffering are perceived to outweigh the anticipated benefits of ongoing ventilatory support. Here, again, it may be permissible for parents and clinicians to decide together to withdraw ventilatory support, though the threshold for such decisions should be high.

D. The Concept of Medical Futility and Its Limitations

1. Medical futility has been defined in various ways, and thus the use of the term can lead to misunderstanding.
   (a) The term "futile" is generally best understood as a description of an action that cannot bring about the desired goal.
   (b) Thus, any determination of futility should be preceded by discussion and agreement with parents regarding specific goals (e.g., survival vs. survival without profound impairment; survival for one more day vs. long-term survival).
2. Clinicians have sometimes used futility as a justification for refusing to provide a requested treatment, without giving a physiologic rationale or data to support that claim. That is, the term can be used to close off a needed dialogue, rather than encourage one. For this and other reasons, it is suggested that the term be avoided in decision-making or family counseling.
3. Rather than describing a treatment as futile, it may be more helpful to explain why the initiation or continuation of the treatment in question cannot achieve agreed-upon objectives.
   (a) This requires an open discussion of values and goals of treatment.
   (b) Reaching agreement on goals is an essential component of shared decision-making.
4. When the desired goal cannot be achieved, it is ethically permissible to withhold or withdraw life-sustaining therapies and instead focus on minimizing pain and suffering.
5. Every patient has the right to mercy, defined as the right to not endure painful interventions that are unlikely to benefit them.
   (a) This is consistent with the widely accepted principle of non-maleficence, recognizing an obligation not to intentionally harm a patient, unless that harm is unavoidable and outweighed by an anticipated benefit.
   (b) The patient's right to mercy is particularly relevant when clinicians are asked to provide or continue a painful intervention that cannot achieve the desired goals or afford a net benefit to the patient.
6. Clinicians do not have an ethical obligation to provide a requested treatment that offers no benefit to the patient or cannot achieve the desired goal. However, this assessment should not be made lightly or without the validation of colleagues, including appropriate consultants.
7. Determinations of futility, or inappropriateness of a treatment, should be distinguished from rationing.
   (a) Rationing involves acknowledging that a treatment offers a potential benefit to the patient but might nevertheless appropriately be withheld because of inadequate resources for all patients under care, and the need for fair distribution.
   (b) If rationing is necessary, such decisions are ideally made as policy on an institutional, regional, or national level, with appropriate consideration and input from various stakeholders, rather than on an individual patient basis, to ensure fair and just allocation.

E. Quality of Life Considerations
   1. Assessments of anticipated quality of life (QOL) and disability are highly subjective and value-laden, and should be considered in decisions regarding the withdrawal of ventilatory support only with great caution.
   2. It is generally accepted that a decision to withdraw or withhold life-sustaining therapy such as ventilatory support is ethically permissible, if requested by parents, when *profound* long-term impairment is anticipated. That is, parents may be within their rights to decline, on their child's behalf, ongoing ventilatory support in some extreme circumstances. However, the threshold for degree of impairment is subjective and controversial.
   3. Medical assessments of future impairment are often imprecise, and may not reflect the values of the family, or the values eventually held by the patient.
      (a) Commonly used evaluations of neurodevelopmental impairment for former preterm newborns at two years of age have been shown to overestimate the likelihood of moderate or severe disability later in life.
      (b) Assessments of QOL during adolescence for former preterm NICU patients made by parents and pediatricians have been shown to be more pessimistic than assessment by the patients themselves.

F. Withdrawing Versus Withholding Ventilatory Support
   1. Withdrawal of ventilatory support refers to removal of treatment that a patient is receiving, which could include discontinuation of mechanical ventilation and thus also extubation, discontinuation of continuous positive airway pressure, or discontinuation of supplemental oxygen provided via nasal cannula. Withholding ventilatory support refers to a decision not to initiate that support, including the decision not to intubate.
   2. Withdrawing and withholding ventilatory support are generally considered to be ethically similar or equivalent. If, for a given patient, it is considered ethically permissible to withhold intubation and mechanical ventilation, then it should also be permissible to withdraw them from a similar patient with a similar prognosis.
   3. Though withholding and withdrawal of ventilatory support may be ethically similar or equivalent, there are important psychological differences. Parents and/or staff might find it more difficult to forgo mechanical ventilation after it has been provided for a time and they have seen and interacted with the child.
   4. Non-escalation of respiratory support may in some settings be appropriately offered to parents who do not wish to withdraw mechanical ventilation, but also do not want to prolong the dying process.
      (a) If consideration of anticipated benefits and burdens make it permissible to withdraw, it should also then be permissible in that patient to continue but not escalate, if that is what parents prefer, and clinicians are willing. This assumes appropriate pain management with any option selected.
      (b) Non-escalation of treatment could allow avoidance of painful procedures (such as a thoracostomy tube in the setting of pneumothorax), and might also give parents time to accept that their child will not survive to discharge.
   5. Although clinicians might withdraw ventilatory support, they should never "withdraw care." When ventilatory support is withdrawn, physicians should remember, and parents be told, that an emphasis on the patient's comfort becomes paramount. This might better be framed as "comfort care," or "redirection of care" rather than withdrawal of care. In cases of withholding ventilatory support at birth, this can be framed as noninvasive or comfort care, but should not be described as withholding care.

G. The Doctrine of Double Effect
   1. The Doctrine of Double Effect (DDE), which has roots in philosophical, theological, and legal scholarship, states that an act intended to bring about a positive effect may be permissible even if it also brings about a negative secondary effect.
   2. For the act to be permissible, the negative effect may be foreseen, but should not be intended.
   3. A common example of the DDE is the administration of opiates to patients near the end of life. The positive and desired effect is the relief of pain, and the treatment is acceptable even if one anticipates (but does not intend) the possibility that it could result in respiratory depression, and thus hasten death. It is not acceptable, however, if the intention is to precipitate respiratory arrest and death. This distinction may be relevant to the dose selected.

H. Religious and Cultural Considerations
   1. Religious beliefs often influence how parents view withdrawal of respiratory support.
      (a) Clinicians should explore and be attentive to parents' beliefs in end-of-life conversations.
      (b) Knowledge of religious practices might aid clinicians in conducting these conversations with parents and offering ancillary support, such as visits from community religious personnel or hospital chaplains. For example, some Islamic patients might desire to perform Adhan, a short ceremony that includes a declaration of faith, and some Christian parents might desire baptism for their child.
   2. Significant cultural variation exists that may influence how a clinical team approaches care of a dying patient, and clinicians should seek to become familiar with the cultural norms of the patients and families they serve.
   3. Some hospitals, particularly in less wealthy settings, might lack ancillary services such as palliative care consultation, bioethics committees, and chaplain services, placing an added burden on the clinical team.
   4. In more resource-limited settings with few or no ventilators, clinicians may be more accustomed to limiting care, and parents less likely to expect some interventions.
   5. The cultural and legal acceptability of euthanasia varies by location. In most countries, including the United States, active euthanasia of newborns is generally considered ethically and legally impermissible. A small minority of countries have legalized active euthanasia for neonates in extreme circumstances.

I. Moral Distress
   1. Moral distress refers to the anguish felt when one feels compelled to act in a way they perceive as immoral, with a lack of control over the act or situation.
   2. It was first described in the nursing literature and is particularly relevant to those on the clinical team who might be perceived to be lower in the hierarchy and are carrying out instructions from others, such as physicians. However, moral distress may be experienced by any clinician, including physicians, when they perceive that they are doing something immoral at the insistence of another, such as a patient's parent.
   3. All members of the clinical team could experience moral distress as they care for a dying patient, particularly when there is disagreement about the patient's care plan among members of the clinical team and parents. This could occur when ventilatory support is withdrawn, or when it is continued for a child felt to be suffering and very unlikely to survive.
   4. The cumulative impact of moral distress over time can lead to staff burnout. Maladaptive responses to moral distress can include transference of the psychological burden of that distress to other members of the clinical team and/or to parents.

5. Open dialogue should be encouraged to minimize miscommunication, and foster empathy for colleagues, the patient, and the parents.
   (a) It is incumbent on the attending physician to be mindful of this risk to the team in critical settings, and to engage proactively to help all understand the rationale for a difficult and/or controversial treatment plan.
   (b) This may ameliorate moral distress, even it is not eliminated.
   (c) Debriefing members of the care team after a patient has died may aid in the psychological processing of the event, promote resilience, and reduce burnout.

III. Clinical Criteria and Timing: Under What Circumstances Is Withdrawal of Ventilatory Support Permissible?

A. Extremely Poor Prognosis

1. Withdrawal of ventilatory support after it has been initiated may be appropriate when more information about an infant's poor prognosis becomes available, based on clinical course and/or diagnostic studies.
   (a) If treatment is unlikely to prolong life, and only prolongs the dying process, transition from ventilatory support to comfort care is permissible. This applies to situations of imminent death, or inevitable demise before hospital discharge.
   (b) If the treatment would not provide a net benefit for the child, comfort care only may be a permissible choice. This can pertain to treatments or underlying conditions which themselves cause a significant burden. This is best illustrated by the Impermissible-Permissible-Obligatory framework described above in Sect. II C, and an assessment of anticipated benefits and burdens to the child.
2. If a patient is legally dead by cardiac or neurologic criteria, ventilatory support should be withdrawn, though in the setting of death by neurologic criteria it may be appropriate to allow a suitable amount of time for parental visitation and acceptance. This could be on the order of hours but should generally not be on the order of days. If in the setting of death by neurologic criteria parents are resistant to withdrawal, consultation with local expert legal counsel is recommended.
3. Withdrawal of ventilatory support may be appropriate for certain infants who remain severely hypoxemic despite extremely high ventilator settings, and/or remain significantly hypotensive despite maximal medical support including vasopressor infusion. Extracorporeal membrane oxygenation might also be a consideration for some of these patients.
4. It is ethically permissible to withdraw or withhold ventilatory support, upon parental request, from infants prenatally or postnatally diagnosed with congenital anomalies associated with extremely shortened lifespan.
   (a) Examples might include certain metabolic disorders, aneuploidies, and severe congenital anomalies such as bilateral renal agenesis.
   (b) Ongoing ventilatory support is not ethically obligatory for infants anticipated to have an extremely shortened lifespan. Thus, it may be withdrawn upon parental request.

B. Profound Neurologic Injury

1. It may be appropriate to withdraw ventilatory support from an infant who has developed evidence of a devastating neurologic outcome, if so requested by parents.
2. In such a setting, informed parents can be seen to be within their rights to decline ongoing invasive life-sustaining treatment, including mechanical ventilation, on behalf of their child.
3. Examples could include severe bilateral intraventricular hemorrhage, severe periventricular leukomalacia, or profound hypoxic-ischemic encephalopathy.

4. Assessment of prognosis based on the best available information and consultation with relevant subspecialists is essential.
5. The threshold for the level of anticipated disability that would allow for withdrawal should be high. It will inevitably be a subjective judgment that requires careful discussion with parents to elicit their values, and thorough discussion with appropriate members of the care team as well.

IV. Who Should Make the Decision to Withdraw Ventilatory Support?
   A. Role of the Medical Team and Family in Shared Decision-Making
      1. Physicians and parents should work together through the exchange of relevant medical information and an understanding of individual values.
      2. Collaboration with palliative care consultants throughout the clinical course, if available, often proves valuable.
      3. The possibility of withdrawal of ventilatory support should be raised by a physician if it is felt to be an ethically permissible option, even if not raised by parents. Physicians are generally ill-advised to offer any option they deem ethically impermissible.
      4. To assist parents in decision-making, clinicians should share relevant medical facts and prognoses, while also personalizing information to align with parents' concerns and fears.
      5. Physicians should foster an open discussion of the parents' goals of treatment (e.g., survival or minimizing suffering) and the likelihood of achieving those goals based on the best available evidence.
      6. Parents should have the opportunity to include or consult with others, such as family members or clergy, as they wish, and as time and circumstances allow.
      7. Informed parental preference should generally be determinative in such decisions, unless that preference is felt by the physician to be clearly opposed to the child's best interest. In such cases, the rights of the child may outweigh the right of the parents to decide. It is then the role of the physician to advocate on behalf of the child, and, if necessary, to work toward a therapeutic plan more consistent with the child's best interests.
         (a) Within the zone of ethical permissibility (sect. II.C.) as defined above, clinicians should generally defer to the preference of informed parents.
         (b) Physicians should not defer to parents whose preferred plan, by the determination of the physician, is ethically impermissible. In such cases consultation with colleagues, the hospital Ethics Committee, and/or legal counsel may prove beneficial.
      8. All involved members of the clinical team (e.g., nurses, respiratory therapists) should have the opportunity to participate in the decision-making process as time and circumstances allow. A meeting of this larger group to discuss the options is best done prior to a smaller meeting with parents, which should not include a large number of staff.
   B. Navigating Disagreement
      1. Disagreement over treatment course can occur among staff, among family members, and between the family and clinical team.
      2. While disagreements are common, intractable or unresolvable conflicts are relatively rare.
      3. Conflicts between clinical teams and families should be met with an honest discussion of relevant facts and limitations of the data, and an open and nonjudgmental exploration of the family's perspective. In these conversations, it may be helpful to invite other's perspectives, uninterrupted, before offering one's own opinion.

4. An Ethics Committee consultation should be considered, to aid in creating a space for open discussion, to provide careful analysis of the ethical issues at work, and to obtain an opinion from trained and experienced individuals not directly involved in the case.

V. Practical Elements
   A. Conversations with Parents About Withdrawal
      1. The clinical team should meet separately prior to meeting with the family to discuss factors that might affect the family and staff, and how they might influence the conversation. For example, religious and cultural considerations, and prior family interactions with the medical team (positive or negative) may be relevant.
      2. Conversation with parents should, if possible, take place in a calm, quiet setting, preferably away from the NICU, attended by support people (e.g., family) as requested.
         (a) Prepare a dedicated meeting space, with adequate seating for all in attendance. Minimize interruptions.
         (b) At least one physician and one nurse should usually attend, but the number of clinicians present should generally be limited to no more than three to avoid overwhelming the parents.
         (c) If death is imminent the discussion may need to be abbreviated.
      3. The members of the clinical team present should be introduced, and the infant referred to by name if the parents have given one.
      4. Parents should be asked about their understanding of their child's situation, and about their hopes and goals for ongoing treatment.
         (a) Unrealistic goals can be gently redirected. For example, one might say, "Of course you want your child to live a long and healthy life. We wish for that, too. What we know now about your child's condition makes us worry that reaching that goal is not possible."
         (b) It may be helpful for the clinician to ask, "Some parents want to know all the numbers and statistics. Other parents just want the big picture. What do you prefer?"
      5. The medical team should offer information at the level of requested detail and confirm understanding throughout the conversation.
         (a) When giving statistics, double framing can aid in understanding and dispelling biases. For example, "One of 10 children with this condition survive, and 9 of 10 die in the hospital."
         (b) Physicians should avoid too-precise statistics when their use might imply false precision, and/or be a detriment to clarity. Telling parents that, "About one in ten such babies survive," is generally preferable to saying, "Reported survival rates vary from 8.1 to 11.7%."
      6. All feasible and ethically permissible options should be discussed.
      7. Emotions should be recognized and acknowledged, and time allowed for silence as parents consider their response.
      8. Strengths can be acknowledged and praised, such as observing, for example, "It is clear you are both loving and caring parents."
      9. Discussion of and referral for possible organ or tissue donation should ideally occur, if relevant, prior to extubation.
   B. Parental Participation in Care Prior to Withdrawal
      1. Prior to withdrawal of ventilatory support, parents should be encouraged to participate in the care of their infant, such as bathing, taking pictures, making footprints, hand molds, or other mementos.
      2. Parents have reported that being physically present for care was important for anticipatory mourning and fostered a sense of control.

C. Presence at Withdrawal of Ventilatory Support.
   1. Parents should be encouraged, but not required, to be with their child immediately after withdrawal of ventilatory support and hold the baby without electronic monitoring. They may also be given the option to be present during extubation itself.
   2. Parents may be given several options for how they wish to interact with their infant as an endotracheal tube is withdrawn. For example, they may hold the baby while still intubated, lengthening the amount of time they hold before death, and/or hold after extubation.
   3. Parents should be asked privately who among their family and friends they would like present, and every effort then made to accommodate their requests.
   4. The social worker on call should be notified, to provide support during and after the process.
   5. The presence of a hospital chaplain, or their own clergy, should be offered to parents.
   6. The physician and bedside nurse should be present, commonly along with the respiratory therapist, for extubation and removal of the ventilator.
   7. Cardio-respiratory monitoring may be discontinued to make for a more peaceful setting.
   8. After extubation, the family can be offered the choice of privacy with the baby, or the presence of a member of the staff.
   9. If the clinicians leave the room, one should re-enter periodically to check on the parents and child.
   10. Death should be declared and parents informed by the physician after no heartbeat is heard on auscultation.
   11. Some parents may wish to continue holding after the baby is deceased. This should be accommodated for as long as feasible and advisable in the judgment of the clinical team.

D. Medications
   1. Involvement of palliative care or pain management services may aid in appropriate analgesia management.
   2. Anesthetics and/or anxiolytics are commonly given in conventional doses before extubation.
   3. Morphine 0.05–0.2 mg/kg intravenously, intramuscularly, or subcutaneously every 4 hours, or lorazepam 0.05–0.1 mg/kg via slow push intravenously can be given.
   4. For infants previously on a continuous infusion, bolus doses may be appropriate. For highly tolerant infants, higher doses or more potent opiates may be appropriate.
   5. Paralytics such as vecuronium administered at the time of extubation, for example in response to agonal breathing, would inevitably lead to rapid death from respiratory failure, and are generally not provided.
      (a) If the child were in pain, paralytics alone would mask the pain without providing analgesia.
      (b) There are ethical and possibly legal implications associated with administering a medication that provides no analgesic benefit and will hasten death.
      (c) This is somewhat controversial, but at the time of this writing, the ethical and legal prohibitions against the use of paralytics at the time of extubation hold sway in medical settings.

E. A Prolonged Dying Process
   1. For infants clearly dependent on invasive mechanical ventilation, death is likely to occur within minutes to hours after extubation.
      (a) Stopping medically administered nutrition and hydration (MANH) such as intravenous fluids is reasonable to facilitate parents holding their infant.

(b) It may be helpful to leave an intravenous catheter in place should additional analgesic administration be needed.

2. For infants who are intubated but may not be completely dependent on mechanical ventilation, the dying process may last days to weeks after extubation. If the baby survives for several hours after extubation, withholding MANH, such as intravenous fluids and/or tube feeding, may be ethically permissible, and could be offered to parents.
   (a) There is controversy as to whether it is permissible to withhold MANH, though many ethicists and neonatologists (including these authors) feel it is permissible in some settings, by the same reasoning that allows withdrawal of mechanical ventilation, a different form of life-sustaining medical treatment.
   (b) This should be discussed among members of the clinical team before offering the option to parents.
   (c) Discussion with an ethics consultant and/or legal counsel may be advisable.
3. Attempts at breastfeeding or bottle feeding may be reasonable after withdrawal of ventilatory support, for infants for whom it is medically and developmentally appropriate.
   (a) This may provide comfort to the infant and the parents.
   (b) If MANH has been withheld, oral feeding should nevertheless be offered to the baby periodically unless it is certain that she is incapable of taking or tolerating it.
   (c) While it may be ethically acceptable to withhold MANH in some settings, this does not imply that it is ethically acceptable to withhold oral feedings from a baby that appears desirous and capable of taking them.

F. After Death

1. After a patient has been declared dead, the physician should give condolences, offer to answer any questions, and ask the parents if they would like a postmortem examination to be performed.
   (a) Autopsy should be offered for all deceased patients, regardless of whether the cause of death is known, and parental wishes should be documented.
   (b) Autopsy may be helpful in cases for which the cause of death is unknown or might affect future pregnancies.
   (c) A signed consent form may be required.

VI. Legal Considerations

A. Disagreements Between Parents and Physician

1. Parents may desire to continue full intensive care measures when the clinical team believes such treatment to be inappropriate.
   (a) Open and honest communication with the family may help resolve discrepancies in goals of care.
   (b) If requests made by the parents are felt by the clinicians to be ethically permissible and within the scope of neonatal standard of care, the clinical team should usually comply with those requests, even if perceiving them as suboptimal management, or most likely ineffectual.
   (c) In rare circumstances, it might be appropriate to withdraw ventilatory support without parental agreement. This should require, at a minimum, concurrence with a second attending physician, an Ethics Committee consultation, and review with hospital legal counsel.
   (d) Neonatologists should be aware if their hospital has a specific policy that addresses this situation, such as a Futility Policy or a Conscientious Practice Policy, and generally seek to provide care consistent with that policy.

2. The clinical team may wish to continue full intensive measures, while parents want intensive care measures, such as mechanical ventilation, to be withdrawn.
   (a) This is a much less common cause of parent-physician disagreement than VI.A.2 above.
   (b) Open and honest communication with the family may help to resolve discrepancies in goals of care.
   (c) If the clinical team feels a treatment (including ventilatory support) is ethically obligatory based on the anticipated benefits and burdens to the patient and the discussion outlined in sect. II above, that treatment should generally be provided, even over parental objection, at least until a legal authority has rendered judgment otherwise.
   (d) Clinicians should ideally seek legal consultation before the provision of the treatment in question.
   (e) In emergency situations, if the team feels that ventilatory support is ethically obligatory based on the assessment of the benefits and burdens to the child and consideration of ethical issues as outlined in sect. II above, the treatment should be provided, and legal consultation sought as soon as feasible.
   (f) The need for a judicial ruling, which rarely occurs, should be determined in conjunction with hospital legal counsel.

B. Legal Counsel and Ethical Guidance
   1. For significant physician-parent disagreement on critical therapeutic questions, such as withdrawal of ventilatory support, physicians should consult the hospital's Ethics Committee and the hospital's legal service.
   2. Questions of legality and ethical acceptability commonly overlap, but are not the same, and each group provides a distinct service.
   3. Local legal expertise is essential, as relevant laws vary by state and nation.

VII. Conclusion
   A. Withdrawal of ventilatory support is ethically permissible in some clinical situations.
   B. Understanding of the medical status, the prognosis, the parents' goals and values, and the relevant ethical, practical, and legal considerations is essential to determining when and how it might be appropriate to withdraw ventilatory support.

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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)

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D. Medical negligence
   1. Predominant theory of medical negligence
   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.
      (c) Proximate cause (breach directly led to injury)
      (d) Damages
         (1) Economic – medical expenses, 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. Common areas of malpractice risk in neonatology
   1. Delivery room management/resuscitation
   2. Medication errors – wrong medicine, wrong dose, wrong patient
   3. Delay in diagnosis/treatment – acidosis, hypotension, sepsis, congenital heart disease, seizures, hypoglycemia, meningitis, jaundice, others.

II. Documentation

A. Importance of the medical record
   1. Memorialization of the hospital course – "If it wasn't documented, it wasn't done" (lawsuits may be filed years after the events at issue).
   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 (see below).
   6. Fraud and abuse.
   7. Spoliation – altering of records. Remember electronic medical records record not only what was documented, but 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 "cut 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. Electronic Medical Record (EMR)
   1. More healthcare institutions and providers have transitioned to EMR.
   2. While this is still an evolving area of healthcare law, some steps should be taken to minimize liability and practice good risk management.
      (a) Be careful with "copy and paste."
      (b) Express a thought process and reasons for decision making. Do not rely solely on forms or checklists.
      (c) If forms are used, be sure they are completely answered.
   3. Metadata – The EMR tracks not only what was entered, but when it was entered and by whom. Audit trails also track who looked at a patient's medical record and when.

F. 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

G. 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, patient complaints
      (b) Internal (preferred method) – incident reporting, occurrence screening
   2. Calculation of probability of adverse effect from risk
   3. Estimation of impact of adverse effect
   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

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Part XV

Research, Quality, and the Literature

Interpreting Clinical Research

95

C. Omar Kamlin, Brett J. Manley,
and Peter G. Davis

I. Introduction
   A. Clinical research improves 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 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 systemic postnatal corticosteroids cause cerebral palsy?)
      4. Determining the natural history or prognosis of a condition (e.g., what is the respiratory function in adulthood of preterm infants with bronchopulmonary dysplasia?)

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B. Structure of an article and questions you should consider yourself before committing to read the whole article
   1. Title – is this of interest to you?
   2. Authors – what is their track record?
   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 and where flaws in design are likely to be picked up. Is the population representative and recognizable? 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 (a group known to have an outcome and a group known to be free of the same outcome are identified, then the frequency of the exposure(s) of interest are compared)
      (d) Case series
   2. Checklist for evaluation (validity, importance, and applicability) of a study on therapy
      (a) Were treated and untreated infants at equal risk for the outcome before therapy? Best achieved by random allocation of patients.
      (b) Was there a prespecified 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 before the first patient was enrolled?
      (c) Were both groups treated equally apart from the therapy being evaluated? Best achieved by masking (blinding) of caregivers.
      (d) Were important outcomes assessed (e.g., death, neurodevelopment in infancy versus short-term physiological 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 care for?
      (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.e., translatable into practice?)
      (i) Were all the enrolled patients accounted for at the end of the study?

D. Diagnostic Tests
   1. Criteria for evaluation of a study on diagnostic tests
      (a) Was there a blind comparison with a "gold standard"?
      (b) Were the patients similar to those in your practice?
      (c) Was the "normal" range for the test defined?
      (d) Is the diagnostic test precise (reproducible), free of bias, and applicable in your clinical area?
      (e) To determine importance of the results, draw up a 2 × 2 table (Tables 95.1 and 95.2)

E. Causality
   1. Types of study (in decreasing order of validity)*
      (a) RCT
      (b) Cohort
      (c) Case-control

Table 95.1 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 95.2 Using a 2 × 2 table

	Outcome	
	Yes (+)	No (−)
Exposed (+)	a	b
Not exposed (−)	c	d

In a 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

(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. Checklist for evaluation of a study investigating causation
   (a) Was an inception cohort (i.e., a group assembled prior to exposure) formed with exposed and nonexposed 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
   1. Criteria for evaluation of a study investigating prognosis
      (a) Was an inception cohort assembled?
      (b) Was follow-up long enough and complete?
      (c) Were the outcomes assessed by individuals masked to the subject's history/and or interventions?
      (d) Was the assessment objective?
      (e) 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 and increasingly preferred 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.
E. The number needed to treat (NNT) can be used to assess the magnitude/relevance of the treatment effect.

IV. Where to Search for the Evidence
A. Library – physical and online. With ready availability of computers and handheld devices, searching the internet to access primary articles has become much easier using search engines such as Pubmed, Ovid, etc.
B. Social media – "follow" trusted sources (e.g., active researchers in your field and relevant journals) on platforms such as Twitter, Instagram, or Facebook; there are groups dedicated to synthesizing and critically appraising new evidence on social media, such as the Evidence-Based Neonatology (EBNEO) group (www.ebneo.org or @ebneo), blogs from eminent clinician researchers, and means of tracking topics of interest such as "hashtags" on Twitter (e.g., #neoEBM)
C. 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.
D. 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/)
E. Searching for preappraised 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 a published study are applicable to your patients.
C. Studies without a contemporaneous control group are unreliable and potentially misleading.
D. Do not forget to consider the potential harms and economic effects of an intervention.
E. Beware of narrative review articles – these are often biased opinions of the author and may not be a systematic and complete appraisal of the literature.
F. Although systematic reviews with meta-analyses 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.

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Quality Improvement in Neonatal Respiratory Care

96

Helen Healy and Munish Gupta

I. Defining Quality Improvement
   A. Many definitions of Quality Improvement (QI) in health care have been suggested. While there may not be a single best definition, several common themes help provide important context and meaning.
      1. QI seeks to make measurable and sustained improvements in health care services and health outcomes of individuals and populations.
      2. QI focuses on systems and processes of care and works to insure that generalizable scientific knowledge and best practices are optimally implemented to achieve improved patient outcomes.
      3. QI uses structured and systematic approaches to make changes to health care delivery.
      4. QI is driven by data; data are essential to understanding systems, measuring the impact of changes, and assessing patient outcomes.
      5. Changes made through QI are best determined by those working within the system and are specific to that system.
   B. The science of improvement is built on the System of Profound Knowledge, developed by W. Edward Deming, in which there are four critical domains for developing effective change: appreciation of a system; understanding variation; building knowledge; and the human side of change.
   C. QI may occur in a single setting, such as one unit of a hospital or a clinic, throughout a single institution, or collaboratively across multiple institutions.
   D. QI is distinct from research. Whereas the goal of research is to develop generalizable knowledge of mechanism of disease or effectiveness of an intervention, the goal of QI is sustained improvement through the implementation of knowledge. Ideally, QI is integrated into routine care of current patients.

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II. Quality Improvement Frameworks
   A. Many frameworks for QI exist. Three of the more common are the Model for Improvement, Lean, and Six-Sigma. These frameworks have overlapping concepts, and QI efforts may use components of all three.
      1. The Model for Improvement was developed by Associates in Process Improvement based on the System of Profound Knowledge, and has been widely adopted by many health care organizations. The Model poses three questions that guide improvement efforts: (1) what are we trying to accomplish? (2) how will we know that a change is an improvement? and (3) what changes can we make that will result in improvement? Once answered, changes are tested and implemented through *Plan-Do-Study-Act* (PDSA) cycles. The Model for Improvement is likely the most commonly used QI framework in healthcare, and is described in more detail below.
      2. The Lean method, the foundation of the Toyota Production System (TPS), focuses on streamlining processes so as to eliminate waste and provide maximum value. A key element of Lean and the TPS are attention to the Seven Wastes, or opportunities for lost efficiency: Time, Processing, Defects, Motion, Inventory, Overproduction, and Transportation. Lean techniques include Value Stream Mapping (VSM), 5S organization (sort, simplify, standardize, sweep/shine, and initiate self-controls), and the A3 approach, in which a single sheet of paper is used for project organization. Lean also utilizes PDSA cycles to enact change.
      3. The Six-Sigma method focuses on elimination of waste and defects by minimizing variation. Six-sigma refers to performance that is six standard deviations from specification limits, or a process producing results that are 99.99966% defect-free. Six-Sigma utilizes the DMAIC (define, measure, analyze, improve, control) approach for improvement. A well-known feature of Six Sigma is a graduated training and certification process named as colored belts.

III. The Model for Improvement (MFI) in Respiratory Care
   A. Question 1 of the Model for Improvement asks: What are we trying to accomplish? This requires clear identification of the problem to be addressed and the aim of the improvement effort. A useful approach is to develop a general problem statement followed by a specific aim statement. Table 96.1 provides examples of problem statements and specific aim statements for potential respiratory QI efforts.

Table 96.1 Example problem and aim statements for NICU respiratory QI projects[a]

Project goal	Reduce BPD	Reduce pneumothorax	Avoid unplanned extubation
Problem	Our NICU's BPD incidence has been in the top quartile of VON NICUs for the past 3 years	Over the past 3 months, there have been 9 cases of pneumothorax in late preterm infants in our NICU, compared to a previous rate of about 1 per month for the year prior	Staff reported 2 unplanned extubations in past week in the incident reporting system, and informal staff survey suggests these events have increased in frequency
Aim	Reduce the percentage of VLBW infants diagnosed with BPD from 35% to less than 25% by the end of the year	Lower the occurrence of pneumothorax from an average of 3 cases per month to ≤1 case per month over a 9-month project time period	Achieve an average ≥ 50 or more days between unplanned extubations in the next year

Abbreviations: *BPD* bronchopulmonary dysplasia, *NICU* neonatal intensive care unit, *VLBW* very low birth weight, *VON* Vermont Oxford Network

[a]These are selected examples for three potential projects within neonatal respiratory care. Many other problem statements and aim statements could be used for these and other respiratory care projects

1. A problem statement should provide the context for the QI effort by describing the area of need. In respiratory care, problems needing attention may be identified through local patient safety monitoring systems or quality assurance data, such as an increase in unplanned extubations or an increase in the rate of bronchopulmonary dysplasia (BPD). Problems needing attention can also be identified through benchmarking, where an NICU's performance is compared to peer NICUs or larger networks.
2. The aim statement is a one-sentence statement of the goal of the improvement effort. Aim statements ideally meet the "SMART" criteria: specific, measurable, attainable, relevant, and time-bound. The aim statement serves to narrow the focus of the improvement effort from the general need identified in the problem statement to a specific, clearly defined target.

B. Question 2 of the Model for Improvement asks: How will we know that change is an improvement? This requires identification of measures that can be used to understand current systems, evaluate process changes, and assess impact on patient outcomes. Types of measures for QI include outcome measures, process measures, and balancing measures. While a QI initiative may not use all of these types of measures, they should all be considered. An important step in choosing measures for QI is developing operational definitions for each measure selected, meaning clear and specific descriptions of the measure components. Table 96.2 provides examples of outcome, process, and balancing measures for potential QI efforts focused on respiratory care.

Table 96.2 Examples measures for NICU respiratory QI projects[a]

Project goal	Reduce BPD	Reduce pneumothorax	Avoid unplanned extubation
Outcome	Percent of VLBW infants diagnosed with BPD, defined as need for supplemental oxygen or positive pressure support at 36 weeks PMA	Percent of infants with RDS requiring positive pressure support who develop pneumothorax requiring thoracentesis or thoracostomy tube	Rate of unplanned extubations per 100 ventilator days
Process	Percent of VLBW infants to receive any mechanical ventilation Ratio of days on noninvasive ventilation to days on invasive ventilation among VLBW infants Percent of VLBW infants able to wean from noninvasive support directly to room air	Percent of infants with RDS requiring PPV in delivery room that receive PPV with T-piece resuscitator Average time between intubation and surfactant administration for infants with RDS requiring mechanical ventilation Rate of mainstem bronchus intubation on X-ray among infants with RDS requiring mechanical ventilation	Percent of ETT re-taping events done with two staff members Percent of shifts on which ETT position and security is documented appropriately
Balancing	Percent of VLBW infants receiving postnatal steroids for BPD prevention Average PMA at discharge for VLBW infants Rate of nasal septal injury per 100 noninvasive ventilation days	Percent of VLBW infants requiring mechanical ventilation that require reintubation within 72 h of first extubation Average days of ventilation among VLBW infants requiring mechanical ventilation	Staff time spent for ETT taping Rate of X-rays to check tube position per 100 ventilator days Rate of skin injury events related to ETT securement per 100 ventilator days

Abbreviations: *BPD* bronchopulmonary dysplasia, *ETT* endotracheal tube, *PMA* postmenstrual age, *RDS* respiratory distress syndrome, *VLBW* very low birth weight

[a]These are selected examples for three potential projects within neonatal respiratory care. Many other measures could be used for these and other respiratory care projects

1. Outcome measures assess the impact of the improvement effort on the patient or family. Outcome measures reflect what the patient experiences; they typically represent the end results of QI efforts, and as such, are often the most important and meaningful measures used. Common outcome measures in neonatal respiratory care include BPD, discharge home on oxygen, postnatal steroids for BPD, pneumothorax, and unplanned extubation.
2. Process measures assess parts or steps in the system that are thought to influence the end results and outcomes of interest. As changes are tested and implemented, process measures can evaluate whether interventions are occurring as intended. Process measures reflect what we do as a health care system. While outcome measures tend to be the primary measures of interest for QI, they may be slow to change; process measures can be timelier and more sensitive indicators of whether changes are having beneficial effects. Process measures should have strong linkage to outcomes, and in some cases, particularly when outcomes of interest are rare or far downstream from practice changes, process measures rather than outcome measures may be the primary targets of QI efforts. For example, for QI efforts targeting BPD reduction, process measures around the duration of ventilation or need for intubation may be better able to guide improvement efforts. Many possible process measures could be used for respiratory QI; process measures for a particular project should be selected based upon the specific goals and interventions of that project.
3. Balancing measures look at systems from different directions, and seek to detect if changes in one part of the system may cause unintended consequences in other areas. They help ensure that one problem is not traded for another. Like process measures, many possible balancing measures can be used, and specific balancing measures should be chosen based on the goals and interventions of a particular QI effort.

C. Question 3 of the Model for Improvement asks: What changes can we make that will result in improvement? Potential change ideas can come from numerous sources, and changes should be evidence-based. Current best practices are often summarized in consensus statements, practice guidelines, or systematic reviews and meta-analyses. Other QI efforts can also be valuable sources of change ideas. In all cases, potential changes need to be considered within and adapted to local context. Typically, the best change ideas come from examining and understanding local processes of care that impact the aim of the QI effort. Several tools can help guide examination of local practices.
   1. Pareto charts portray the Pareto principal or "80/20 rule," which suggests that a minority (20%) of the aspects of care result in the majority (80%) of the effect. A Pareto chart can help identify the most impactful target areas for intervention.
   2. A Cause and Effect Diagram, also known as an Ishikawa Diagram or Fishbone Diagram, serves to organize elements that contribute to a particular outcome so as to identify opportunities for tests of change. Standard categories of potential contributing factors are used to help teams brainstorm; commonly used categories include people, processes, materials, and environment.
   3. A Process Map, or Flowchart, outlines step-by-step how care is currently delivered. The process map should be developed in a group setting, with input from all members of the multidisciplinary team. Observing the actual clinical process can be an important component of map development.

D. The final step in the Model for Improvement is testing and implementation of changes through Plan-Do-Study-Act (PDSA) cycles. The Model asks teams to test a change in real clinical settings by planning it, trying it, and then learning from it. After a change is tested, a team may decide to adopt it, adapt it, or abandon it. Importantly, this is the stage of the model at which changes to practice are first introduced; a common error in QI is to introduce changes without first answering the three questions above.

1. Initial PDSA cycles are ideally done on the smallest scale possible. A PDSA cycle with one patient or one provider can be very useful. For example, if a team is testing a new approach to initiating CPAP in the delivery room, this can be tested with one patient and one team, and learning from that one test can inform the next steps.
2. PDSA cycles can be used to test the change in different settings. For example, if the new approach to delivery room CPAP was successful with a team on the day shift, it can then be tested on the night shift.
3. After small-scale tests, teams can expand their tests more broadly. If the initial tests of the new delivery room CPAP method were successful, it could then be tested for 1 week or 1 month, and then reassessed. After a team is comfortable that testing has shown that a change is an improvement, then the change can be implemented as a new practice.

E. Key Driver Diagrams

1. A Key Driver Diagram (KDD) can be a powerful tool to outline and guide a QI effort and can help communicate the project effectively to team members and other stakeholders.
2. The KDD visually displays all of the theoretical contributors to the outcome of interest. It can represent a clear overview of a team's theory of change.
3. The diagram begins with the aim of a QI effort, and then describes drivers and change ideas that impact the aim. Drivers are often categorized as primary or secondary drivers. Outcome measures are typically associated with the aim statement; process measures can often be associated with the primary and secondary drivers.
4. The completed KDD is an overall summary of the QI effort, and should be updated regularly as the project progresses. An example KDD for a QI project seeking to reduce the incidence of BPD is shown in Fig. 96.1.

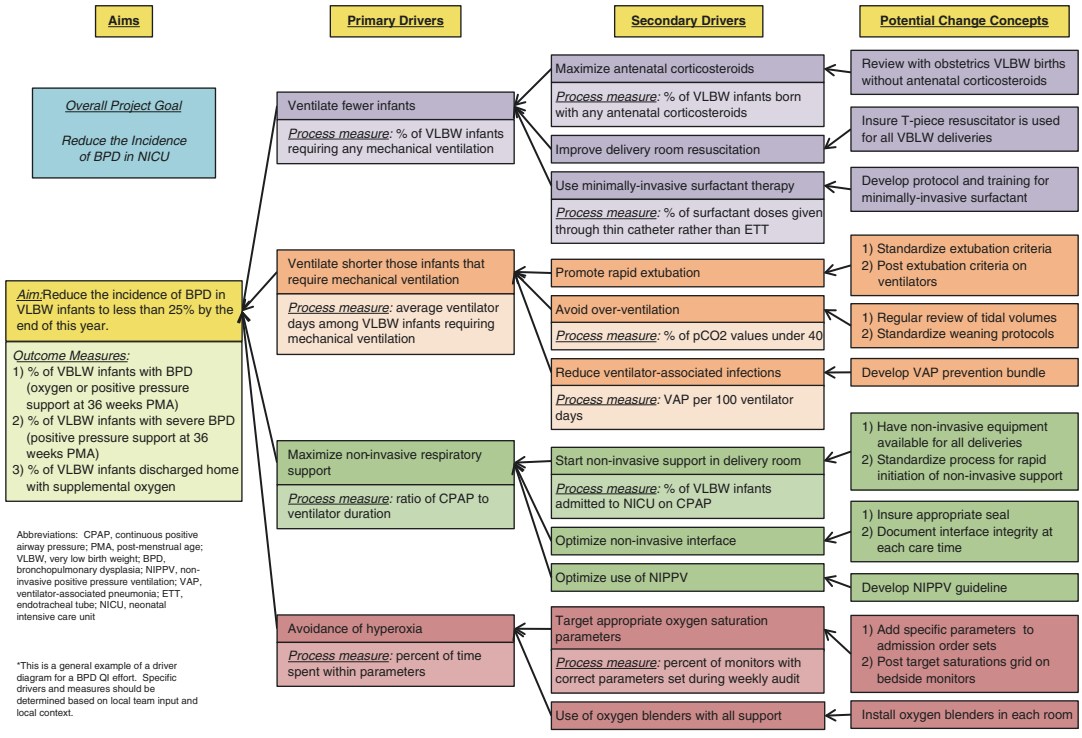

Fig. 96.1 Example key driver diagram for BPD QI project*

F. Data for Quality Improvement
   1. Benchmarking data that compare an NICU's practices or performance to other NICUs can be a valuable tool for identifying areas for improvement and can often provide important baseline data for QI efforts. In neonatology, the Vermont Oxford Network (VON; https://public.vtoxford.org/) and the Children's Hospitals Neonatal Consortium (CHNC; https://thechnc.org/) provide detailed benchmarking data for many aspects of neonatal care. VON includes NICUs of all different levels from around the world, while CHNC is focused on level IV NICUs in the US.
   2. While databases such as VON or CHNC can be used for benchmarking or baseline data, most rapid-cycle QI will require real-time data collection, typically from electronic medical records or from patient medical record review. New data collection tools may be needed in some cases. Efforts should be made to keep the workload of data collection minimal and therefore sustainable and frequent over time.
   3. Data for QI should be analyzed over time. Simple before-and-after data analysis will typically not provide adequate understanding of the impact of interventions on measures of interest. Time-series data analyses using statistical process control methods with run charts or control charts are ideally suited for QI.

G. Multidisciplinary Teams
   1. QI, in general, benefits from multidisciplinary collaboration, and this is particularly true for QI addressing neonatal respiratory care.
   2. Teams should include respiratory therapists, nurses, neonatologists, and advanced practice providers. Including team members that are at the bedside is critical.
   3. Depending upon the focus of the project, involvement of additional disciplines such as nutritionists, pharmacists, therapists, social workers, or consulting teams may also be helpful. Consider involving trainees as QI team members in clinical settings where they have a large clinical role.
   4. Family engagement should be standard. All neonatal respiratory QI efforts should include family members as team members.

Please refer to Chap. 97, for additional information, comments, and examples.

Suggested Reading

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Data Collection and Assessment of Respiratory Outcomes

97

John A. F. Zupancic

I. The Case for Data
   A. The collection of accurate, validated outcome data is the most important tool the clinician has for improving care in the neonatal intensive care unit (NICU). Nothing is more valuable in improving future outcomes for a patient population than knowing the outcomes of previously treated patients.
   B. 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.
   C. An expansive view of the use of data is valuable. The application of previously established principles of care, based upon accurate outcome data, may 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 1980–81. Widespread use of surfactant did not occur in the United States 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.

II. General Principles of Data Collection
   A. The characteristics and type of the data to be collected should reflect its intended use.
      1. External organizations such as departments of health may require reporting of data for purposes of *public accountability*. The selection of metrics and approach to collection are typically specifically defined in order to allow accurate comparisons between institutions.
      2. Comparisons to other institutions, or *benchmarking*, might also be helpful for internal purposes, in order to determine appropriate targets for improvement. Such benchmarking also requires data to be recorded consistently across sites to ensure that comparisons are valid.

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3. Similarly, *research studies* involving prospectively collected data strictly detail the methods for data recording in their protocols.
4. In contrast, data intended for *internal quality improvement* projects may be collected in a less formal manner and customized according to the needs of the front-line improvement team.

B. The choice of data to be collected for any purpose reflects different aspects of the care provided.
1. *Outcome measures* reflect the specific impact of a system on the health and wellbeing of patients (e.g., mortality rates, rate of bronchopulmonary dysplasia, incidence of apnea and bradycardia).
2. *Process measures* refer to the approaches used by the clinicians to treat the patient and thus achieve desirable outcomes (e.g., frequency of ventilator use in a premature infant population, use of high flow nasal cannula or CPAP over time).
3. *Structural measures* describe the framework within which care is provided (e.g., availability of point of care blood gas testing, presence of neonatology-specific respiratory therapists).
4. Because they directly measure something of immediate and tangible value to patients, outcome measures are often considered the most important type of data to examine. However, process and structural measures, as the means to achieving outcomes, provide important information on the mechanisms by which care can be improved.
5. Any intervention, whether examined in the context of research or improvement, may have unintended consequences. *Balancing measures* track such negative effects (e.g., cerebral palsy in a study of dexamethasone, skin excoriation with a new device for endotracheal tube stabilization).

C. Regardless of the anticipated purpose of a data set, it is essential that data accurately reflect what they are purported to measure. Certain dimensions of the quality of a given data element can be considered.
1. *Reliability* refers to the degree to which a measure produces the same results when assessed in the same population in the same time period. Measures that vary over time without a change in care delivery or population case-mix are not reliable.
2. *Validity* refers to the degree to which a variable reflects what it purports to measure. Several types of validity can be defined. *Face validity* simply asks whether a measure appears to clinicians to have a strong subjective connection to its stated target. *Criterion validity* determines whether a variable corresponds to another measure of the same thing. *Content validity* ensures that all aspects of an underlying concept are reflected in a variable. Finally, measures with *construct validity* predict what a theory says they will predict.

D. A number of best practices can optimize the quality of data available for analysis.
1. 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. Partial, incomplete data collections in which some patients are excluded (e.g., late transfers, early mortality) are highly likely to lead to erroneous conclusions about outcomes.
2. There may be a temptation to collect data that is too detailed and excessive for a particular task. It is more valuable to collect limited, accurate information that targets specific questions to be addressed than extensive volumes of incomplete data that cannot be easily compiled or accurately interpreted.
3. With each transcription of a data point, the probability of inaccuracies being transcribed increases. The more that data is copied and moved from one storage resource to another –

such as from a medical record to a manually-entered database – the more likely inaccuracies and outliers (unexpected outcomes that lie significantly beyond anticipated results) will appear within a dataset. It is therefore desirable to minimize such transcription by employing digital methods of transfer whenever possible.

4. In general, the use of electronic health records (EHR) that allow automatically extracted, validated, dataset collections are 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. Electronic systems must be audited on an ongoing basis to be certain that all data entry flows accurately through each step of the data system into the data repository. Clinicians and others entering data into systems should be aware that the data may be important for uses other than those immediately apparent at the front line.

E. Most uses of data in medicine involve comparisons – between interventions, between populations, or between epochs. Prior to making such comparisons, it is important to be sure that one is comparing similar groups of patients.
   1. Failure to consider the underlying differences in groups may lead analysts to conclude that differences in measured outcomes resulted from an intervention or clinical factor, rather than the differences in the risk profiles of the patients themselves.
   2. Multiple means of assuring comparability are available. In the research domain, the use of randomization or deliberate matching of patients by characteristics such as gestational age is employed. Similarly, outcomes may be compared after stratifying data by those characteristics.
   3. Risk (or "case-mix") adjustment refers to the statistical process of stratifying by important prognostic outcomes. It seeks to establish how the performance of two groups would compare if they had exactly the same mix of patients.
   4. The specific characteristics targeted by risk adjustment are known as confounders. These characteristics may be clinical (e.g., severity of BPD), physiological (e.g., blood pressure, blood gases), demographic (e.g., gestational age, birth weight), or socioeconomic (e.g., race, ethnicity, access to care).
   5. Off-the-shelf tools for risk adjustment are available in neonatology. These include the Score for Neonatal Acute Physiology (SNAP-2) and the Clinical Risk Index for Babies (CRIB).

F. Maintaining privacy of data is desirable or required in most settings, especially if consideration is given to possible publication of findings in the future.
   1. De-identification means the effective removal or coding of all information that could be used to potentially identify an individual patient, including birth date, day of birth, medical record number, etc. Researchers and quality practitioners may maintain a secure and confidential key that links the de-identified data to some element of patient identity.
   2. In contrast, anonymization of data indicates that no identifying data are retained even indirectly, and that it is therefore impossible to establish the identity of a patient who has contributed information.
   3. In datasets involving small numbers of patients with rare conditions, it may be possible for an analyst to establish a particular individual's identity through statistical means. For example, a 23-week gestation infant born on a specific date may be easily identified. Methods to avoid this might include randomly shifting birth dates or recording certain data with only the level of granularity that is required to answer a particular question.

4. Submission of the de-identification protocol to a local or national institutional review board (IRB) or ethics committee may be necessary to ensure compliance with regulatory policies, which are typically established at a national level.

III. Application to the Evaluation of 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 syndrome, bronchopulmonary dysplasia), rather than the rare diseases (e.g., congenital diaphragmatic hernia, 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 implies that 20% of problems typically will be responsible for 80% of important outcomes in any patient population.
   C. 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 on duration of ventilation, specific datasets could be created to answer this question. It should be noted, however, that a targeted dataset 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.
   D. The devices employed for cardiorespiratory monitoring and ventilatory support in intensive care units accumulate an enormous amount of physiologic data in real time. Recently, attention has focused on analyzing these data. Partnering with biomedical engineers and data scientists is essential when abstracting and exploring such information.
   E. Data collection over periods of time can be especially helpful in tracking the effects of changes in management upon outcomes and is essential in assessing whether improvements in outcomes have been effected successfully or whether an alternate process strategy is necessary (Fig. 97.1). Further details on the analytic approach to such longitudinal tracking of data are provided in the chapter on Quality Improvement.

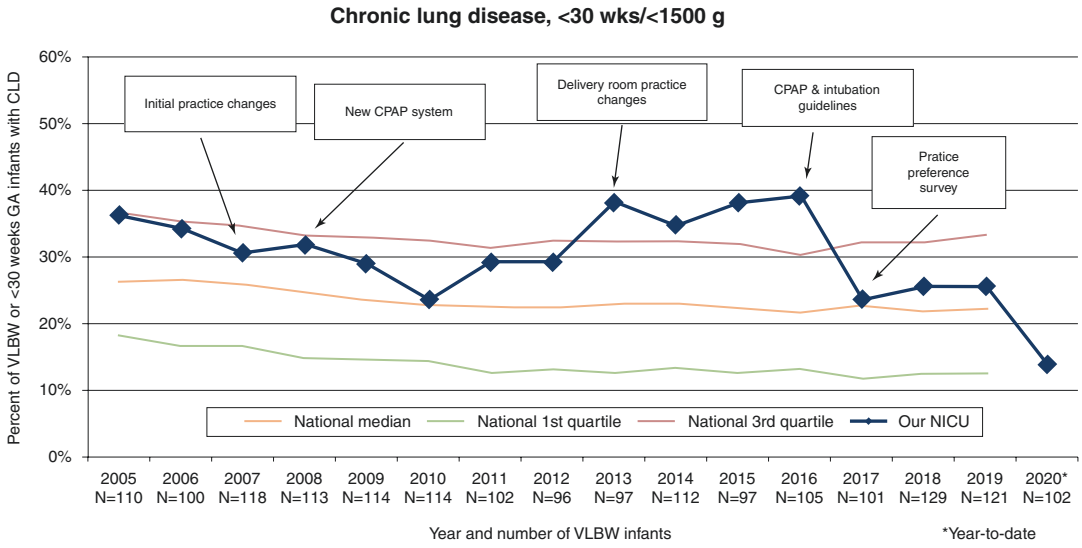

Fig. 97.1 Chronic lung disease incidence in one neonatal intensive care unit over a 16-year period
In this graphical, longitudinal presentation of data, the overall trend in the incidence of chronic lung disease, relative to national rates, is immediately evident. The chart is annotated with the timing of interventions that were instituted with the intention of reducing the incidence of the condition. Longitudinal charts such as these are commonly used to monitor performance and to assess the impact of quality improvement projects. (Modified with permission from Dr. Munish Gupta)

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Contemporary Classics in Neonatal Respiratory Care

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I. Introduction
   A. In this chapter, *the authors* list their selections of the 100 most influential papers published in the past 10 years.
   B. Methods
      1. Medline search using PubMed
      2. Search terms using Yale Mesh Analyzer, selected by authors
      3. Search terms categorized by populations, conditions, and Interventions
      4. Filters: human, 10 years, English
      5. Search limited to high-impact journals
      6. Selections prioritized by:
         (a) Guidelines or statements of academic organizations
         (b) Systematic reviews and randomized controlled trials
         (c) Observational studies
         (d) Physiologic studies
         (e) Basic research

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Part XVI

Ventilatory Case Studies

Ventilatory Cases

99

Brooke D. Vergales and Jay P. Goldsmith

Case 1: Baby A

A. Prenatal data
   1. Mother: 30-year-old G6 P0232 → 3 who presented with Braxton Hicks type contractions and found to have advanced dilation of the cervix at 23 weeks' gestation.
   2. Magnesium initiated for neuroprotection.
   3. First dose of corticosteroids was given about 30 min prior to delivery.
   4. No clinical evidence of infection.

B. Patient data
   1. 700 g male born by emergent cesarean section secondary to transverse lie.
   2. Received 60 s of delayed cord clamping.
   3. Apgar scores of 7 (1 min) and 7 (5 min).
   4. Intubated at 4 min of life, and noted to have stiff lungs requiring high ventilatory pressures.
   5. Surfactant given at 14 min of age in delivery room.

C. Physical findings
   1. Spontaneous respiratory effort with severe respiratory distress: retractions, poor air exchange, and wet rales bilaterally.
   2. Hypotonic, appropriate for gestational age.
   3. Fused eyelids, poor skin integrity, and visible veins.

The recommendations in this chapter do not indicate an exclusive approach to ventilatory management of newborns with respiratory failure. Variable approaches taking into account the resources of the facility, individual circumstances, and local protocols may be appropriate.

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D. Clinical management
   1. Initial ventilatory management:
      (a) 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 cm H_2O, rate 30 breaths per minute (bpm), FiO_2 0.6–1.0 to maintain acceptable blood gases.
      (b) Chronic lung disease. Consider different ventilatory approach or other modes of ventilation.
      (c) Tried volume recruitment with increase in PEEP to 7 cm H_2O and slightly longer inspiratory time but mean airway pressure remained high and FiO_2 could not be lowered.
      (d) Switched to high-frequency oscillatory ventilation (HFOV) at a rate of 15 Hz and Delta Pressure of 22; initial blood gases revealed CO_2 retention; ventilator settings were adjusted by decreasing to 14 Hz and increasing Delta P to 24 to increase V_t and improve CO_2 removal.
   2. Decreasing blood pressure. Dopamine initiated.
   3. Repeat surfactant given via endotracheal tube at 12 h of age.

E. Chest radiographs
   1. Figure 99.1 Chest radiograph (CXR) 3 h after birth showing severe respiratory distress syndrome (RDS) with ground-glass appearance, air bronchograms, and decreased lung volume

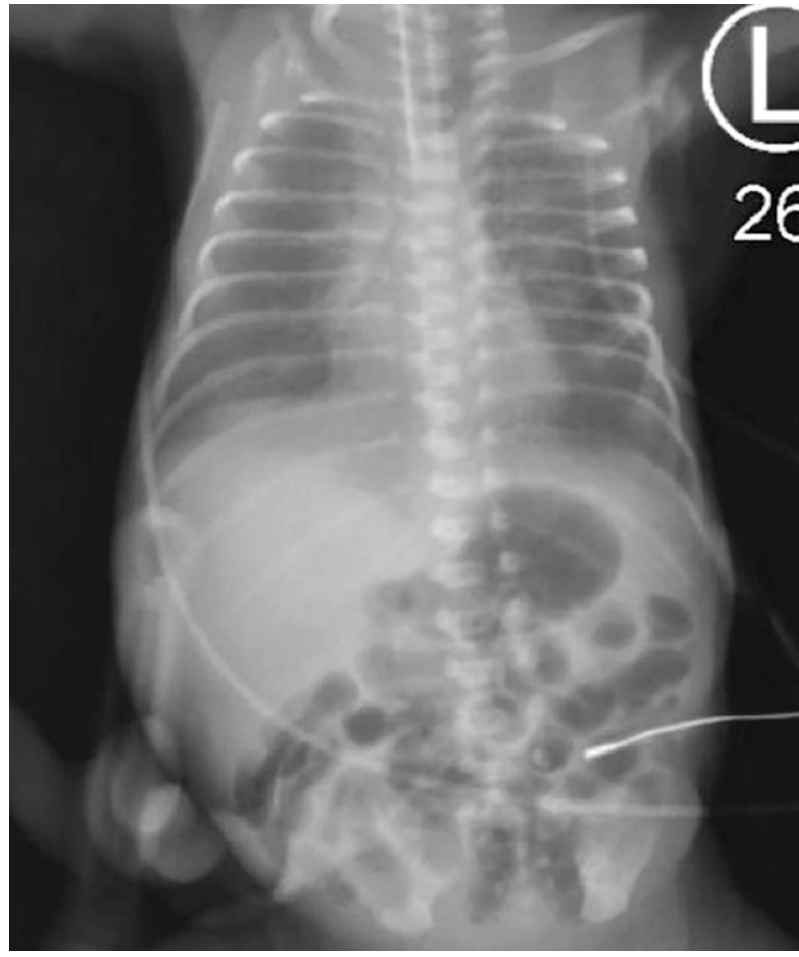

Fig. 99.1 Chest radiograph showing ground-glass appearance, air bronchograms, and decreased lung volumes consistent with RDS

2. Figure 99.2 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. CBC normal except mild thrombocytopenia with platelets of 120 K
   2. Increasing hypercapnia and acidosis with increased base deficit over first 15 h of life

G. Differential diagnosis of chest radiographs
   1. Severe RDS complicated by pulmonary interstitial emphysema (PIE)
   2. Concern for necrotizing pneumonitis (doubt, too early)
   3. Possible lobar emphysema or congenital pulmonary malformation of the lung (doubt, disease process too generalized)

H. Diagnosis: PIE—Potential therapies
   1. Change to a low-volume, high-frequency strategy.
      (a) Reset the HFOV using a lower mean airway pressure and lower amplitudes.
      (b) Switch to high-frequency jet ventilation (HFJV) using low-volume strategy and no sigh breaths if patient is able to maintain oxygenation.

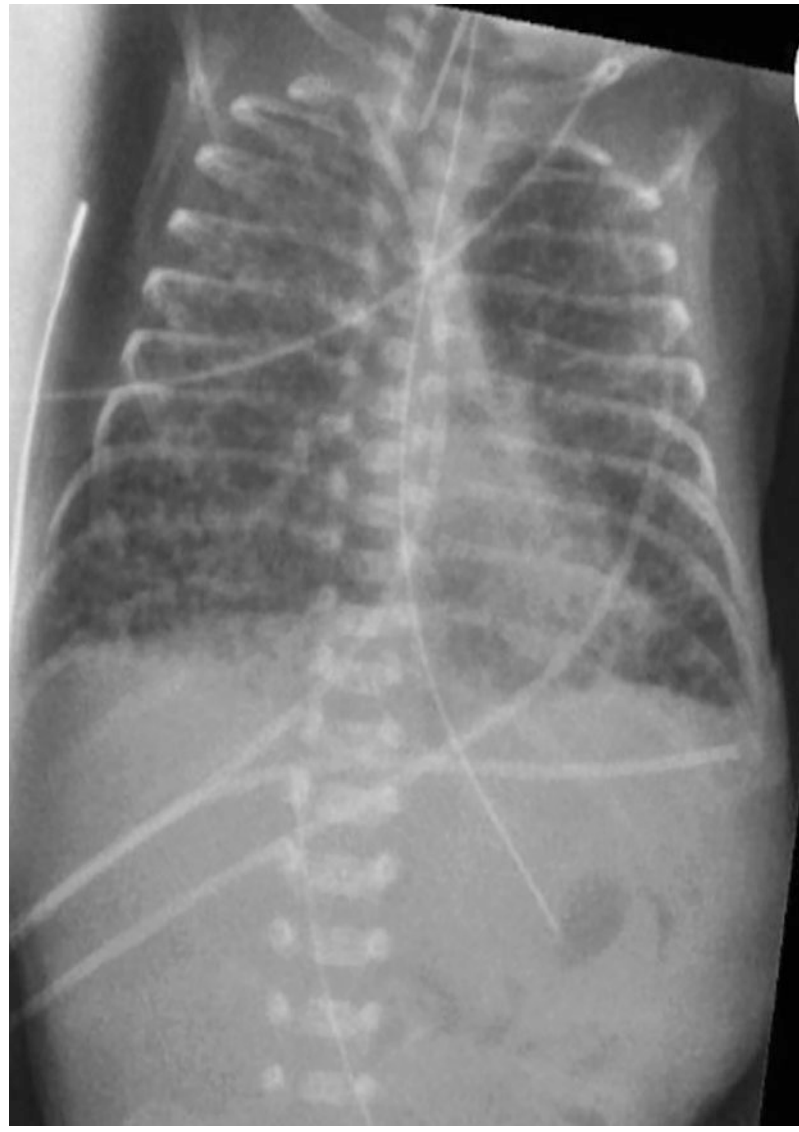

Fig. 99.2 Chest radiograph showing microradiolucencies throughout all lung fields with areas of bullae and hyperinflation

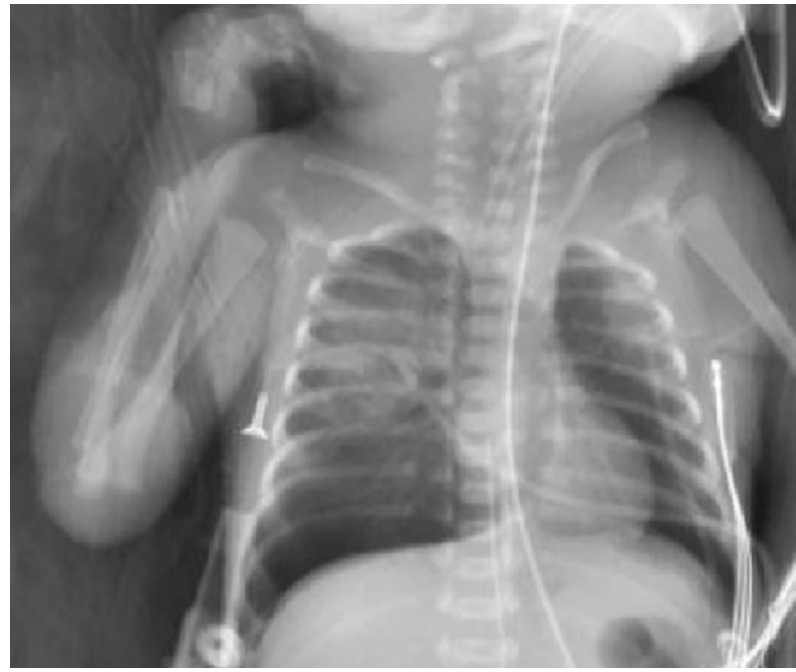

Fig. 99.3 Chest radiograph showing a spontaneous right-sided tension pneumothorax

2. Positional therapy and/or single-lung inflation with selective intubation (older therapy which works best with unilateral PIE and has mostly been replaced with better ventilator techniques using low-volume strategy on a high-frequency ventilator)
3. Echocardiogram to assess for pulmonary hypertension and potential use of iNO (although this would be off-label use)

I. Denouement

1. Conservative therapy and high-frequency oscillation not successful; changed to HFJV using low-volume strategy.
2. Patient developed a spontaneous leftsided pneumothorax at 28 h (Fig. 99.3) which was relieved with pigtail chest tube insertion. (Fig. 99.4)
3. Prolonged ventilatory support with the development of bronchopulmonary dysplasia (BPD) and grade 2 intraventricular hemorrhage (IVH).
4. Discharged on home oxygen of 250 mL/min of 100% oxygen at 5 months of age.

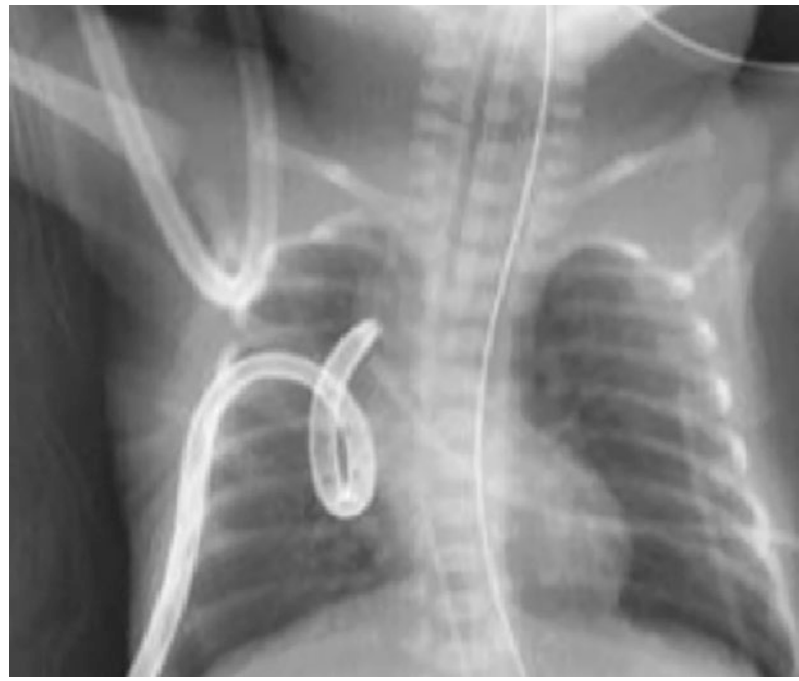

Fig. 99.4 Resolution of right-sided pneumothorax after pig-tail catheter placement

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Case 2: Baby B

A. Prenatal data
   1. Mother: 21-year-old G2P1001 → 2 at term
   2. Pregnancy uncomplicated

B. Patient data
   1. 3510 g female born by precipitous vaginal delivery; vertex presentation.
   2. Thick meconium-stained amniotic fluid.
   3. Infant was limp and not breathing at delivery.
   4. Stimulated and dried with warm towels after oropharyngeal suctioning.
   5. Apgar scores 4 (1 min) and 9 (5 min).

C. Physical findings
   1. Spontaneous respiratory effort with retractions, audible grunting, and nasal flaring
   2. Rales heard over lungs bilaterally
   3. No murmur noted, heart rate 160/min
   4. Skin consistent with term infant

D. Initial respiratory management
   1. Placed on CPAP +5 requiring FiO_2 40%
   2. First arterial blood gas at 30 min:
      pH 7.12; $PaCO_2$ = 59 torr; and PaO_2 = 29 torr
   3. Intubated at 1 h of age and placed on CMV with pressure support, volume guarantee settings: 5 mL/kg, rate 30 bpm, and PEEP 5 cm H_2O; pressure support 15 cm H_2O, inspiratory time 0.35 s
   4. Sepsis workup → antibiotics started

E. Initial CXR, before intubation (Fig. 23.9)
   1. Bilateral alveolar filling
   2. Mild cardiomegaly
   3. Hyperinflation-flattened diaphragms

F. Clinical management
   1. Patient treated for meconium aspiration syndrome, PPHN.
   2. Oxygen saturation fell to <60% when patient agitated → started on dexmedetomidine to provide sedation without respiratory depression at 0.5 mcg/kg/h.
   3. Worsening oxygenation led to increased respiratory settings up to PIP 30 cm H_2O, FiO_2 to 0.6, pressure support of 24 cm H_2O.
   4. Arterial blood gases on these settings: pH 7.31, PCO_2 31 torr, PO_2 28 torr, BE—9.

G. Further clinical testing
   1. 2-D echocardiogram revealed normal structural heart anatomy and no righttoleft shunting
   2. Worsening chest radiograph (Fig. 99.4)
   3. Pulmonary waveform graphic analysis (Fig. 22.5)

H. Therapeutic options
   1. HFOV.
   2. Surfactant.
   3. Inhaled nitric oxide (iNO).
   4. Cardiovascular support with inotropes to improve cardiac function (although most agents increase pulmonary vascular resistance as well as systemic vascular resistance).
   5. Review pulmonary graphics: allow sedative to abate and use assist/control mode with pressure support at lower settings to normalize blood gases; wean ventilator pressures rapidly using pulmonary graphics and blood gases to monitor for gas trapping and V/Q matching.

I. Denouement
   1. Normal 2-D echocardiogram revealed normal pulmonary arterial pressure.
   2. Pulmonary graphics demonstrated iatrogenic overventilation with gas trapping.
   3. Patient allowed to breathe on her own, V/Q normalized, ventilator settings weaned quickly.
   4. Patient extubated in next 24 h and discharged home 6 days later.

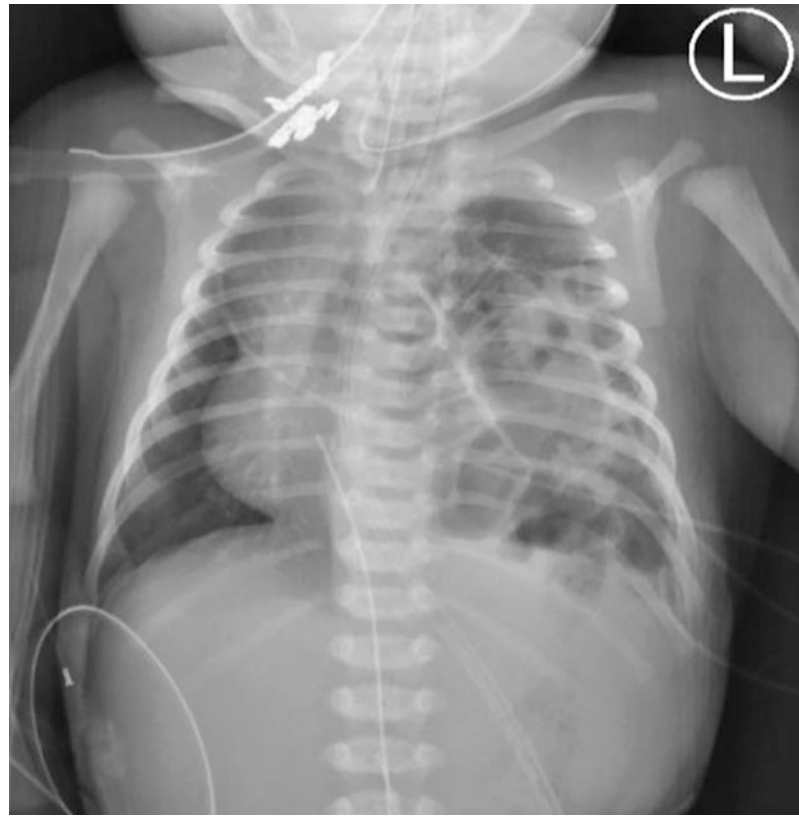

Fig. 99.5 Chest X-ray with bowel noted in left hemithorax consistent with congenital diaphragmatic hernia

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Case 3: Baby C

A. Prenatal data
   1. Mother: 37-year-old G4P3003 → 4 induced at 41 weeks' gestation
   2. Decreased fetal movement for 2 days

B. Patient data
   1. 4210 g female born vaginally, vertex presentation, assisted by vacuum extraction under epidural anesthesia.
   2. Tight nuchal cord reduced prior to shoulder delivery.

3. Apgar scores 4 (1 min) and 6 (5 min).
4. Suction, stimulation, and oxygen administration in the delivery room
5. Retractions and grunting noted and started on CPAP + 5 cm H_2O (FiO_2 0.5).
6. Initial arterial blood gas at 1 h (FiO_2 0.5): pH 7.12, $PaCO_2$ 83 torr, PaO_2 44 torr, BE −6.
7. Intubated with 3.5 mm ET tube, placed on time-cycled ventilation using pressure support with volume guarantee.
8. 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, tachypnea, and subcostal retractions
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 cell 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 management
1. Placed on antibiotics, maintenance IV fluids at 80 mL/kg/day.
2. Received normal saline bolus ×2, then dopamine for persistent hypotension.
3. Echocardiogram: increased pulmonary vascular resistance with right-to-left shunt at foramen ovale and ductus arteriosus.
4. Repeat CXR showed flattened diaphragms, interstitial fluid, small heart, and no air leaks.
5. FiO_2 increased to 1.0, ventilatory settings increased to Pāw 16 cm H_2O; volume guarantee increased to 6 mL/kg; unable to reach targeted V_T and adequately oxygenate (PaO_2 less than 50 torr, large A-a gradient); noted to have large ET air leak and ET tube changed to 4.0 mm.
6. Started on dexmedetomidine.

F. Diagnosis
1. Persistent pulmonary hypertension of the newborn (PPHN); unable to oxygenate despite minimizing ETT leak and maximal conventional settings with adequate tidal volumes.
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. Initiate inhaled nitric oxide
3. Surfactant
4. Inhaled or continuous IV epoprostenol
5. Bosentan (endothelin receptor antagonist)
6. Sildenafil (PDE5 inhibitor)
7. Milrinone (PDE3 inhibitor)
8. Extracorporeal membrane oxygenation (ECMO)

H. Failure of mechanical ventilation
1. Inability to adequately oxygenate (unacceptably low PaO_2, large A-a gradient and/or 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. Indications for ECMO
1. Oxygenation index (OI) greater than 40 for three blood gases 30 min apart

$$OI = \left(FiO_2 \times P\bar{a}w\right) / PaO_2 \times 100$$

$P\bar{a}w$ = Mean airway pressure

2. Alveolar/arterial oxygen gradient ($AaDO_2$) > 610 mmHg × 8 h or > 605 mmHg × 4 h, if PIP > 38 cm H_2O
   $AaDO_2 = (Patm - PH_2O) - PaCO_2 - PaO_2$
   Patm = 760 mmHg; PH_2O = 47 mmHg at sea level
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 at 20 ppm.
2. OI greater than 50 for 3 h.
3. Started on continuous IV epoprostenol and milrinone.
4. Started on dopamine and hydrocortisone to increase SVR.
5. OI greater than 40 for 3 more hours.
6. Placed on veno-venous ECMO for 6 days.
7. Decannulated and extubated without difficulty.
8. Discharged with normal physical examination at 20 days of age.

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Case 4: Baby D

A. Prenatal data
1. Mother: 35-year-old G2P1001 → 2 with good prenatal care
2. 20-week ultrasound normal except 2 vessel cord noted
3. 28 week and 32-week ultrasounds also normal

4. Prenatal labs: O+, hepatitis B negative, HIV negative, and GBS negative
5. Spontaneous labor at community 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).
3. Mild retractions noted at birth; heart rate > 100.
4. Tachypnea and mild retractions noted in DR with appropriate saturation.
5. Admitted to nursery for observation of resolution of suspected transient tachypnea of the newborn.
6. Respiratory status worsened over the next 12 h.

C. Physical findings at 12 h of age
1. Severe respiratory distress, deep retractions, and decreased breath sounds on the left. Cyanotic requiring FiO_2 of 100%.
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. CBC, blood culture obtained, and antibiotics started
2. CXR obtained (Fig. 99.5)—bowel in left hemithorax consistent with congenital diaphragmatic hernia
3. Intubated after diagnosis
4. Replogle tube placed for decompression
5. Transferred to level III NICU via helicopter
6. Placed on HFOV on admission to NICU
7. Required 1.0 FiO_2, iNO started at 20 ppm with improvement of FiO_2 to 0.4
8. Surgery consulted

E. Differential diagnosis
1. Left congenital diaphragmatic hernia (Diagnosis)
2. Cystic lesions of the lung
   (a) Congenital lobar emphysema
   (b) Congenital pulmonary alveolar malformation

F. Respiratory management:
1. Gentle ventilation
   (a) HFOV with Pāw to maintain adequate chest expansion (8–9 ribs on CXR). HFJV is an acceptable alternative.
   (b) Can also use SIMV PC/PS if PIP able to be maintained <25 cm H_2O and reasonable spontaneous breathing.
   (c) Attempt to maintain pH (7.30–7.35) but allow permissive hypercapnia as long as pH >7.25.
   (d) Goal PaO_2 of 40–60 torr, with goal of pre-ductal saturation >90%.
2. ECMO—if HFOV in conjunction with iNO unable to achieve adequate gas exchange, although a statistical benefit from ECMO is unclear since the major determining factor in outcome may be pulmonary hypoplasia. Use of iNO is also controversial in CDH.
3. Elective surgical repair of defect once patient stabilized on ventilator and preferably off ECMO (controversial); delayed surgical repair of the defect until after decannulation is preferred.

G. Denouement
1. Maintained with gentle ventilation on HFOV and iNO.
2. No need for ECMO.
3. CDH repaired at 1 week of life.

4. Extubated to nasal CPAP at 2 weeks.
5. On room air at 3 weeks.
6. Discharged on full feeds at 1 month of age.

Suggested Reading

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Case 5: Baby E

A. Prenatal data
   1. 28-year-old G4P1112 → 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 5 (10 min)
   3. Intubated and ventilated in delivery room; no medications or chest compressions required
   4. Transported to level III NICU
C. Physical examination on admission to level III NICU
   1. Hypotonic and depressed reflexes
   2. Minimal respiratory effort with moderate distress: retractions and grunting, rales noted at the base of lungs bilaterally.
   3. Liver palpated 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
   2. Normal basic metabolic and hepatic panels
   3. Normal arterial blood gases despite minimal ventilatory support
      ($P\bar{a}w$ = 7 cm H_2O)
F. Clinical management
   1. Met encephalopathy and blood gas criteria for therapeutic hypothermia and placed on cooling blanket for 72 h.

2. Numerous technical problems with endotracheal tube thought to result from plugging, displacement.
3. Weaned from hypothermia on day 3, rewarmed over 12 h; attempts to extubate from day 4–7 unsuccessful despite appropriate low PIP, rate, and small V_T on pressure support with conventional ventilator.

G. Extubation failure: Differential diagnosis (Table 99.1)
H. Repeat CXR and CT at 7 days of age
   1. Severe hyperinflation
   2. Volume loss in both upper lobes
I. Adjuncts to successful weaning and extubation
   1. Transition to noninvasive positive pressure ventilation or nasal CPAP (prefer bubble)
   2. Diuretics and bronchodilators
   3. Methylxanthines, racemic epinephrine
   4. Systemic or inhaled peri-extubation steroids (usually only used after several failed extubation attempts and other causes of extubation failure have been excluded)
J. Denouement
   1. Barium esophagoscopy, cardiac catheterization → true vascular ring with double aortic arch
   2. Surgical division of vascular ring and ductus arteriosus ligation accomplished without complication
   3. Patient successfully extubated on first postoperative day

Table 99.1 Causes of extubation failure

I. Pulmonary
(a) Unresolved primary lung disease
(i) Respiratory distress syndrome
(ii) Pulmonary hypertension
(iii) Chronic lung disease of prematurity
(b) Atelectasis
(c) Pneumonia
(d) Diaphragm dysfunction
II. Cardiovascular/pulmonary edema
(a) Left-to-right shunt, PDA or VSD
(b) Congenital heart disease with increase pulmonary blood flow
(c) Fluid overload
III. Airway
(a) Subglottic stenosis
(b) Laryngomalacia
(c) Vascular ring
IV. Nervous system
(a) Central apnea
(b) Intraventricular hemorrhage sequelae
(c) Seizures
(d) White matter injury
(e) Sedative medication
(f) Meningitis
V. Other
(a) Sepsis
(b) Abdominal process causing significant distention
(c)Electrolyte disturbances
(d) Metabolic disorder
(e) Nerve palsy
(f) Myasthenia gravis

Suggested Reading

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Sant'Anna G, Keszler M: Weaning from mechanical ventilation (Chapter 24). In: Goldsmith JP, Karotkin EH, Keszler M, Suresh GK, editors. Assisted ventilation of the neonate. 6th ed. Philadelphia: Elsevier; 2017. p. 229–42.

Case 6: Baby F

A. Prenatal data
   1. Mother: 21-year-old G1P0000 → 2 with no prenatal care at 27 weeks' gestation
   2. Presents in active labor, fully dilated, and ready to deliver at level III hospital
B. Patient data
   1. 890 g male, vertex presentation, spontaneous vaginal delivery
   2. Apgar scores: 4 (1 min) and 6 (5 min)
   3. Respiratory distress at birth
C. Physical findings
   1. Adequate ventilatory drive with respiratory distress: deep retractions, poor air exchange, and wet rales
   2. Bruising of scalp, trunk
D. Respiratory management
   1. Placed initially on CPAP in the delivery room to establish functional residual capacity
   2. Progressive respiratory distress and increased work of breathing
   3. Intubated at 1 h of age; exogenous surfactant given twice 12 h apart
   4. Poor response to CMV in pressure support, volume guarantee; switched to HFOV secondary to CO_2 retention/acidosis
   5. Patent ductus arteriosus (PDA) murmur heard at 3 days, confirmed on 2D-echocardiogram
   6. Indomethacin tried, two courses → no effect
   7. Unable to wean from ventilator despite adequate nutrition, blood transfusions, and caffeine; requiring continuous sedation
   8. CXR at 28 days (Fig. 23.6): Areas of atelectasis alternating with cystic areas and interstitial edema consistent with early BPD
   9. 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 < 96% have BPD

(2) Infants receiving <30% oxygen or ≥ 30% oxygen with SpO_2 > 96%, test 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 pulmonary 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 respiratory drive secondary to chronic inadequate nutrition, low methylxanthine level
   (c) CNS intact—cranial US negative for IVH/PVL
   (d) Infection
   (e) Anemia
   (f) Electrolyte abnormalities
   (g) Pressure support ventilation with low SIMV rate and patient-driven inspiratory time
2. Goal is to extubate; may use nasal bubble CPAP or non-invasive ventilation to prevent atelectasis/apnea
3. Ligate PDA (controversial)
4. Permissive hypercapnia
5. Permissive hypoxemia (goal SpO_2 88–92%)
6. Bronchodilators (controversial)
7. Adequate calories with fluid restriction (130 mL–140 mL/kg/day) and/or diuretics (not a good longterm solution and unsupported by evidence)
8. Corticosteroids: short course
   (a) Pros: Very efficient in weaning from ventilator
   (b) Cons: Short term—infection, hypertension, hyperglycemia, and adrenocortical suppression. Long term-associated with impaired brain and somatic growth and increased incidence of cerebral palsy

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 mL–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 NIPPV within 48 h.
5. Patient discharge at 76 days of age on oxygen by nasal cannula.

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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

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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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