Setting the Ventilator in the NICU

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Educational Aims

This chapter aims to give an understanding of:

- The clinical situations in which ventilation is applied in the newborn
- The approach to initiation of ventilation, including choice of mode of ventilation and first settings
- The physiological considerations and clinical evidence for adjustment of ventilator settings
- The rationale for target ranges for tidal volume, oxygen saturation and carbon dioxide

42.1 Introduction

Success in providing respiratory support to the neonate requires a clear understanding of the context in which it is being applied. Perhaps more than for any other age group, the array of different situations in which ventilation is applied to the newborn infant is extremely broad, with in each case different pathophysiological disturbances and often the need to use a specific approach to apply ventilation optimally. Table 42.1 provides a list of the more common situations in which conventional ventilation is used in the neonate and includes some considerations regarding ventilator settings for each situation. For each situation, a suggested mode of ventilation is indicated, along with target ranges for positive end-expiratory pressure (PEEP) and tidal volume (V_T). Further discussion of the physiological rationale and available evidence for ventilator settings is set out below.

42.2 Choosing the Ventilator Mode

To a significant degree, the clinician's choice of ventilator modes is limited by the equipment available in his or her NICU. Although most modern ventilators are capable of providing the basic modes of synchronised (patient-triggered) ventilation, there are a variety of hybrid modes or combinations that may be unique to each manufacturer and device. For example, some ventilators make possible the combination of synchronised intermittent mandatory ventilation (SIMV) and pressure support ventilation (PSV), and other ventilators employ PSV as a stand-alone mode with a backup rate, similar to assist/control (AC) but flow rather than time cycled. PSV eliminates the inspiratory

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Table 42.1 The context of ventilatory support in the neonate

Situation	Examples	Predominant pathophysiological disturbance(s)	Mode	PEEP*	V_T range (mL/kg)	Considerations regarding ventilator mode and settings
Apnoea	Preterm infant with apnoea of prematurity Ex-preterm infant with respiratory syncytial virus	Poor respiratory drive, physiological consequences of episodic apnoea (bradycardia and desaturation)	SIMV	Low–medium	4–5	Should only need low mandatory ventilator rate. Lungs often relatively compliant, but potential for overdistension and volutrauma if pressure settings too high
Surgery/postsurgery						
General aspects	Any infant with a painful surgical incision	Suppression of respiratory drive due to sedation. Limitation of respiratory excursion due to pain	(S)IMV	Medium	5–6	Low tidal volumes (< 5 mL/kg) may predispose to atelectasis May not trigger effectively if heavily sedated
Abdominal surgery	Term infant – gastroschisis repair Preterm infant – laparotomy for necrotising enterocolitis	Raised intra-abdominal pressure and diaphragmatic splinting	SIMV or AC	Medium–high	5–6	High PEEP needed to maintain EELV and recruitment Where intra-abdominal pressure very high, may be poor response to conventional ventilation; HFOV or HFJV preferred
Thoracic surgery	Term infant – lobectomy for congenital lobar emphysema Preterm infant – ligation of persistent ductus arteriosus	Lung compliance alterations intra-operatively; post-operative risk of air leak	SIMV or AC	Medium	4–5	Changes in both PEEP and V_T may be needed intra-operatively
Lung disease						
Diffuse alveolar disease	Preterm infant with RDS	Poor lung compliance, compliant chest wall	AC	High	4–5	Recruitment using PEEP increments may be helpful. Short T_I and fast rate well tolerated
	Term or preterm infant with haemorrhagic pulmonary oedema	Poor lung compliance	SIMV or AC	High	4–6	Recruitment using PEEP increments and fixed tidal volume may be helpful. Longer T_I needed to help recruitment
Localised or heterogeneous disease	Preterm infant with nosocomial pneumonia Term infant with meconium aspiration syndrome	Areas of low compliance with adjacent areas of relatively normal lung	SIMV or SIMV + PSV	Medium	5–6	Potential for overdistension of relatively normal lung regions. Fast ventilator rates may result in a T_E that is too short for normal lung regions. Higher V_T needed in meconium aspiration due to increased alveolar dead space

Inflammatory and/or fibrotic disease	Preterm infant with chronic lung disease	Regions of low compliance and increased resistance, especially expiratory resistance	SIMV + PSV or AC	Medium–high	5–7	Fast ventilator rates may result in a T_E that is too short for the diseased lung regions with long expiratory time constants. Sufficient PEEP is needed to prevent expiratory flow limitation at low lung volumes
Pulmonary hypoplasia	Preterm infant born after early and prolonged rupture of membranes Term infant with congenital diaphragmatic hernia	Low lung compliance related to small total lung volume. Overdistension of lungs at standard ventilator pressures	SIMV or AC	Low–medium	3–5	Hypoplastic lung is vulnerable to overdistension, stretch injury and high pulmonary vascular resistance. Avoid high V_T/PIP. Consider high-frequency ventilation if PIP > 25 cm H_2O, or if there is refractory hypoxic respiratory failure
Gas trapping/air leak	Preterm infant with pulmonary interstitial emphysema	Compression of normal airspaces by interstitial gas	SIMV	Medium	4–5	Low PEEP approach may lead to persistent hypoxaemia and respiratory acidosis. High-frequency ventilation (especially HFJV) is preferable
	Pneumothorax (after drainage)	Continued leak of gas into the pleural space	SIMV or AC	Medium	4–5	Consider high-frequency ventilation (if available) where there is a torrential gas leak
Pulmonary insufficiency of prematurity	Extremely preterm infant in room air shortly after birth, failing extubation due to inadequate respiratory effort	Global immaturity of respiratory system, with low respiratory muscle capacity	AC or SIMV + PSV for weaning	Medium	4–5	Lungs become relatively compliant once atelectasis resolved, and there is potential for overdistension and volutrauma if pressure settings too high.
Persistent pulmonary hypertension	PPHN with parenchymal lung disease	Reduced pulmonary blood flow secondary to increased pulmonary arteriolar tone, exacerbated by low alveolar pO_2 and pH	SIMV or AC	Medium	4–6	V_T and PEEP requirements depend on associated parenchymal disease
	PPHN with normal lung parenchyma	Reduced pulmonary blood flow secondary to increased pulmonary arteriolar tone	SIMV or AC	Low	4–5	Avoid hyperventilation
Cardiac disease						
Left to right shunts	Preterm infant – patent ductus arteriosus Term infant – large ventricular septal defect	Decreased lung compliance related to pulmonary engorgement and oedema	AC	High	5–6	Increasing CO_2 can help limit blood flow to some degree

(continued)

Table 42.1 (continued)

Situation	Examples	Predominant pathophysiological disturbance(s)	Mode	PEEP*	V_T range (mL/kg)	Considerations regarding ventilator mode and settings
Vulnerable pulmonary circulation	Pulmonary atresia with duct-dependent pulmonary circulation Hypoplastic left heart syndrome, post-Norwood operation	Pulmonary blood flow highly variable and under the influence of intra-alveolar pressure	SIMV	Low–medium	5–7	Lung overdistension with high-pressure settings will restrict pulmonary blood flow. Manipulation of pCO_2 can help to control pulmonary blood flow – lower CO_2 to promote blood flow, increase CO_2 to restrict blood flow
Neuromuscular disease	Term infant with myotonic dystrophy	Low FRC and V_T secondary to compromised respiratory muscle function	AC or SIMV + PSV	Medium	4–6	Appropriate to give mechanical support for each breath
Airway obstruction						
Supra-glottic airway obstruction	Severe Pierre Robin sequence	Alveolar hypoventilation, normal lung compliance	SIMV	Low–medium	4–6	
Glottic/sub-glottic airway obstruction	Term infant with oesophageal atresia and tracheomalacia	Alveolar hypoventilation, expiratory prolongation and gas trapping	SIMV	Low–medium if obstruction relieved, high otherwise	4–6	Settings influenced by whether the obstruction can be relieved by positioning of the endotracheal tube tip beyond the point of maximal narrowing

PEEP positive end-expiratory pressure, V_T tidal volume, *SIMV* synchronised intermittent mandatory ventilation, *AC* assist/control, *EELV* end-expiratory lung volume, *HFOV* high-frequency oscillatory ventilation, *HFJV* high-frequency jet ventilation, T_I inspiratory time, T_E expiratory time, *PSV* pressure support ventilation
*PEEP levels: low = 4 cm H_2O (preterm), 5 cm H_2O (term); medium = 5–6 cm H_2O (preterm), 6–8 cm H_2O (term); high = 7–8 cm H_2O (preterm), 9–12 cm H_2O (term)

hold, making for better synchronisation and automatically adjusting the effective inspiratory time (T_I) as time constants change. However, this mode may not be appropriate in extremely small premature infants in the first few days of life, in whom respiratory time constants are so short that the actual T_I may be less than 0.25 s. This duration of inspiration may be inadequate for gas mixing in the terminal air spaces and additionally may lead to excessively rapid respiratory rates.

Ventilators designed primarily for adult/paediatric patients but capable of also supporting neonates tend to have a greater variety of modes (some untested in newborn infants) and to offer volume-controlled ventilation. Unlike on the specialty neonatal ventilators, PSV on these devices does not have a backup rate and thus requires a reliable respiratory effort, not often present in preterm infants. However, when ventilating newborn infants, the clinician must be aware of the pitfalls of applying various modes to this unique population. The major limitation of volume-controlled ventilation is that the device only controls the volume delivered into the proximal (ventilator) end of the circuit, not the volume entering the patient's lungs. Because of compression of gas and stretching of the circuit, as well as leak around uncuffed endotracheal tubes (ETT), there is only a very indirect relationship between set and delivered V_T. For this reason, time-cycled, pressure-limited ventilation has been the standard ventilation mode in the NICU. There are several volume-targeted modes of pressure-limited ventilation with different operating principles and capabilities that more accurately control delivered V_T in newborn infants. Some of these modalities have been studied in considerable detail and shown to reduce the incidence of hypocapnia, excessively large V_T, duration of mechanical ventilation and to decrease levels of pro-inflammatory cytokines (Keszler 2009). Volume-targeted ventilation is discussed in detail elsewhere in this book. The more conventional modes are discussed below, and suggestions regarding the most appropriate modes for neonatal ventilation are incorporated in Table 42.1.

Despite many years of daily use, no consensus has emerged regarding the relative merits of the commonly used modes of synchronised ventilation. Guidance from large prospective trials with important clinical outcomes, such as incidence of air leak, chronic lung disease or length of ventilation, is lacking. Short-term clinical trials have demonstrated less tachypnoea and less variable V_T (Mrozek et al. 2000), more rapid weaning from mechanical ventilation (Chan and Greenough 1994; Dimitriou et al. 1995) and smaller V_T with smaller fluctuations in blood pressure (Hummler et al. 1996) with AC, compared to SIMV. There are important physiological considerations suggesting that SIMV may not provide optimal support in very premature infants. SIMV supports a user-defined number of breaths synchronised with the infant's spontaneous respiratory effort. Spontaneous breaths in excess of the set rate are not supported, resulting in uneven tidal volume and high work of breathing during weaning. This is particularly important in extremely small and immature infants intubated with a narrow bore ETT (Fiastro et al. 1988). The high airway resistance of the ETT, limited muscle strength and mechanical disadvantage of the infant's excessively compliant chest wall result in small, ineffective V_T. Small breaths that largely rebreathe dead space gas will contribute little to effective alveolar ventilation. To maintain adequate alveolar minute ventilation, relatively large V_T is thus required with the limited number of mechanical inflations provided by the ventilator. In a group of ELBW infants in the recovery phase of respiratory distress syndrome (RDS) ventilated with SIMV, the V_T of mechanical inflations was about 6 mL/kg with spontaneous V_T of 2.5 mL/kg, very close to anatomical dead space (Osorio et al. 2005). However, most clinicians continue to use SIMV, particularly during the weaning phase (Sharma and Greenough 2007). This is based on the intuitive assumption that fewer mechanical inflations are less damaging and on the traditional thinking that the ventilator rate must be lowered before extubation. However, because lung injury is primarily caused by excessive V_T, irrespective of the pressure required to generate that V_T (Dreyfuss and Saumon 1993; Hernandez et al. 1989; Dreyfuss and Saumon 1998), the smaller V_T used with AC (Hummler et al. 1996) likely outweighs the faster rate. This concept is supported by the Oxford Region Controlled Trial of Artificial Ventilation

study where a ventilator rate of 60 inflations per min compared to 20–40 was shown to result in less air leak with unsynchronised IMV (OCTAVE Study Group 1991). Many clinicians also mistakenly believe that assisting every breath prevents respiratory muscle training. This concern reflects a poor understanding of the patient–ventilator interaction during synchronised ventilation. With synchronised ventilation, the V_T is generated by the combined inspiratory effort of the patient (the baby pulling air in) and the positive pressure generated by the ventilator pushing air in. The resulting transpulmonary pressure, together with the compliance of the respiratory system, determines the V_T. Thus, as ventilator inflation pressure is decreased during weaning, the infant gradually assumes a greater proportion of the work of breathing and achieves respiratory muscle training. Ultimately, the ventilator pressure is decreased to the point when it only overcomes the added resistance of the ETT and circuit, at which point the infant should be extubated.

There is little difference between the modes during the acute phase of the disease when SIMV rate is relatively high. The differences become more meaningful during weaning, especially at rates <20. The less intuitive weaning process with AC appears to be one of the reasons clinicians continue to employ SIMV during weaning from mechanical ventilation. Another reason is the anecdotal observation that sometimes infants become tachypnoeic with AC and may have mild hypocapnia. This tachypnoea may reflect the infant's response to low mean airway pressure (P_{AW}) during weaning – shortening the expiratory time (T_E) serves to maintain lung volume at end expiration. Tachypnoea appears to be infrequent when decreasing peak inspiratory pressure (PIP) is balanced by higher PEEP to avoid loss of lung volume. Low rate SIMV, especially in small infants with 2.5-mm-diameter ETT, is likely to impair the weaning process. Some ventilators offer the option of supporting spontaneous breaths with pressure support ventilation. This will compensate for the problems associated with simple SIMV but becomes a more complex process requiring the clinician to select settings for both SIMV and the level of pressure support. Nonetheless, more rapid weaning when SIMV was combined with PSV compared to SIMV alone has been demonstrated (Reyes et al. 2006). Based on these findings, it is recommended that when SIMV is used during the weaning process, PSV should be utilised to support spontaneous breathing. The alternate and less complicated approach is to use AC or PSV as a stand-alone mode to assist all spontaneous efforts and simply wean the inflations pressure, taking care to maintain adequate P_{AW}. This is most easily accomplished when using volume-targeted modes of ventilation discussed earlier in this book. Finally, the attributes of the particular ventilator may influence the choice of triggered modes. Many flow-triggered devices are susceptible to auto-triggering due to leak around the ETT. This is more problematic with AC than with SIMV, where the mechanical breath rate is limited. Devices that have a very effective leak-adapted trigger and breath termination algorithms, such as the Draeger Babylog, are virtually immune from this problem and thus facilitate the use of AC.

42.3 First Settings

This section focuses on the initial management of the ventilated infant following intubation. Overall rationale for, and evidence supporting, choice of ventilator settings in newborns is set out in Sect. 42.4.

After intubation, a period of ventilation using a portable ventilation device will usually be required until the endotracheal tube is secured, nasogastric tube inserted, and the baby positioned in readiness for ventilation. In preterm infants, bolus surfactant may also be given at this time. If the ventilation device does not allow delivery of PEEP, the infant should be connected to the ventilator as quickly as possible.

The initial ventilator settings should take into account the context in which ventilation is being applied to the neonate (Table 42.1) and the apparent response to the pressure settings being used during ventilation with a portable device. There should be a stepwise approach to setting the ventilator at the time of initiation of mechanical

Table 42.2 Stepwise approach to initial ventilator settings

These parameters to be set in the order suggested
PEEP – set according to context (see Table 42.1) and oxygen requirement
T_I – sufficient to allow complete gas inflow to occur (and longer, if tidal recruitment needed)
PIP – sufficient to produce adequate chest movement (and V_T, when measured)
T_E (or ventilator rate)[a] – set so as to allow complete gas outflow to occur and, in combination with V_T, to produce adequate minute ventilation

PEEP positive end-expiratory pressure, T_I inspiratory time, *PIP* peak inflation pressure, V_T tidal volume, T_E expiratory time

[a]In some ventilators, the rate is set directly, and in others it is determined by the combination of inspiratory and expiratory time

Table 42.3 Clinical evaluation after initiation of mechanical ventilation

Observation
Colour and circulation
Infant's spontaneous respiratory rate
Patient–ventilator interaction – evidence of triggering/autocycling
Chest rise and diaphragmatic excursion
Work of breathing
Gastric distension
Auscultation
Breath sounds to all lung areas
Adventitial sounds
Large airway sounds
Heart sounds
Ventilation parameters
Delivered tidal volume
Flow–time curve – evidence of sufficient inspiratory and expiratory time

ventilation (Table 42.2), guided in part by a thorough clinical appraisal (Table 42.3). PEEP should be considered first, with suggested PEEP levels for a range of different situations set out in Table 42.1. The T_I should be set at around 0.5 s for a term infant and 0.35 s for a preterm infant, and then further adjusted depending on the analysis of the flow–time curve, which can be displayed on most modern neonatal ventilators. For most applications of time-cycled pressure-limited ventilation, T_I should be set long enough to allow complete or near-complete inflow of gas into the lung during inspiration. If the T_I is too short, there may not be sufficient time for an adequate tidal volume to be delivered nor for alveolar recruitment to occur with each tidal inflation. Setting PIP should be guided by a visual appreciation of chest rise and preferably the measured V_T. Suggested target values for V_T are set out in Table 42.1. Finally, T_E (and thus, respiratory rate) is adjusted, with the aim of producing sufficient minute ventilation to clear CO_2 without causing dynamic hyperinflation related to inadvertent PEEP. An estimate of minute ventilation can be made using the product of measured V_T and respiratory rate, with a value of 200–300 mL/kg/min usually being an adequate starting point before the first pCO_2 reading is obtained. Note that this estimate of minute ventilation does not incorporate dead space volume, which is substantial in some infants, particularly those with hyperinflated lungs ("alveolar dead space"). Additionally, rapid shallow breathing leads to high dead space to V_T ratio and reduced alveolar ventilation. Avoidance of inadvertent PEEP can be difficult when an infant has a rapid spontaneous breathing rate and each breath is being supported by the ventilator. Examination of the flow–time curve during expiration will reveal whether gas outflow is complete before the next inflation begins and thus whether dynamic hyperinflation is likely to occur. If so, further adjustment to the mode of ventilation, respiratory rate and even inspiratory time may be necessary, as discussed below.

42.3.1 Assessment After Going onto the Ventilator

A thorough clinical re-evaluation after initiation of ventilation is essential (Table 42.3), with the expectation that further adjustments to ventilator settings may be necessary. Careful note of the rate of spontaneous ventilation, and the effectiveness of triggering, should be made as the infant recovers from the intubation and the effects of any sedative and muscle relaxant drugs used prior to it. The need for further sedation/analgesia should be assessed. Muscle relaxation is rarely indicated in

the era of effective synchronised ventilation. Narcotic analgesia should be used judiciously; clinical trial evidence suggests morphine administration relieves pain in ventilated neonates but may increase the risk of adverse neurological outcomes (Anand et al. 2004). If spontaneous breathing is to continue, the trigger sensitivity may need to be altered to optimise patient–ventilator interaction. In general, the trigger threshold should be as low as possible without causing autocycling, because higher trigger threshold is associated with higher work of breathing and longer trigger delay. An attempt should always be made to confirm whether "triggered" inflations are actually preceded by spontaneous respiratory effort or, alternatively, whether the ventilator is autocycling. The latter situation is more likely when there is a significant tube leak (despite "tube compensation") (Bernstein et al. 1995), or with condensed water collecting in the ventilator tubing, and can lead to very significant hyperventilation particularly in AC mode.

Observation of the chest rise and abdominal motion will give some guide to the delivered V_T, although this is a clinical skill that requires some time to learn (Aufricht et al. 1993), and may underestimate the actual V_T (Schmolzer et al. 2010). High residual work of breathing may reflect inadequate tidal volume or inadequate minute ventilation, and ventilator settings should be adjusted appropriately. In the immediate post-intubation period, respiratory system compliance may be transiently decreased due to gaseous abdominal distension, especially after prolonged face mask ventilation. Venting of the stomach with a tube should occur soon after intubation to overcome any impairment of respiratory system compliance related to gastric distension with gas (Heldt 1988). Airway obstruction or ETT malposition should also be ruled out if the infant appears to be struggling.

Auscultation of the chest gives vital information in the intubated patient (Table 42.3) and should be conducted thoroughly and carefully after mechanical ventilation has been initiated. The intensity and distribution of breath sounds within the thorax gives information about the nature of the respiratory pathology and the effectiveness of ventilation. Uneven breath sounds (lower intensity over left hemithorax) suggest the possibility of tube malposition with the tip in the right main bronchus. The presence of a large airway noise which abates when the tube is pulled out a small distance adds further support. Large airway noise (low-pitched inspiratory noise) can relate to a build-up of secretions in the intrathoracic conducting airways and may also be transmitted from the glottic level in the presence of an endotracheal tube leak. If caused by tube leak, the noise will be of similar intensity (or louder) on auscultation with the stethoscope applied over the forehead (due to its extrathoracic origin). Applying cricoid pressure to ablate the leak provides additional confirmation.

The final component of the initial clinical assessment after commencing ventilation is an analysis of available ventilator data. Observation should be made over a number of inflations of the delivered V_T for a set PIP or, conversely, the PIP required to deliver a set V_T. If in a volume-targeted mode, the PIP limit may need to be increased if the desired V_T is not being delivered. Analysis of the flow waveform will allow refinements of T_I and expiratory time (T_E).

After intubation and commencement of mechanical ventilation, a chest X-ray should always be performed to confirm the position of the endotracheal tube, to assess the state of the lung parenchyma and to gain an appreciation of the degree of lung inflation. Given that chest X-rays are taken at peak inflation, the degree of lung inflation will be a reflection of end-inspiratory lung volume (EELV plus V_T), and thus does not help significantly in titrating PEEP. For this reason, some investigators have chosen to perform chest X-rays at end expiration (Pohlandt et al. 1992), but this is not currently a widespread practice.

42.3.2 Monitoring and Documentation During Mechanical Ventilation

With the need for mechanical ventilation comes the need for intensive monitoring and careful charting of physiological and ventilatory

Table 42.4 Monitoring of the ventilated infant

Physiological monitoring
Essential
Cardiorespiratory monitoring (numeric display of heart rate and respiratory rate, with preferably a real-time display of 3-lead ECG wave and respiratory impedance tracing)
Transcutaneous SpO_2 (numeric display with preferably a plethysmographic SpO_2 tracing)
Temperature
Desirable
Intra-arterial catheter placement for continuous blood pressure monitoring and intermittent arterial blood gas sampling
Transcutaneous pCO_2 (+/− pO_2)
End-tidal CO_2 (infants beyond term)
Ventilation parameters to be monitored and recorded
Essential
Delivered ventilator pressures (PEEP, PIP and P_{AW})
T_I
Respiratory rate (mechanically assisted and total)
V_T (breath by breath, preferably the expired V_T measured at the airway opening)
%leak (difference between inspired and expired V_T, expressed as a percentage of the inspired V_T)
Humidifier temperature
Desirable
Ventilator waveforms (time scalars of pressure and flow)
Compliance and resistance measurements
Tidal pressure–volume curves

PEEP positive end-expiratory pressure, *PIP* peak inspiratory pressure, P_{AW} mean airway pressure, T_I inspiratory time, V_T tidal volume

parameters. All mechanically ventilated infants should have, at the very least, cardiorespiratory monitoring, continuous measurement of oxygen saturation (SpO_2) via a transcutaneous pulse oximetry probe and temperature monitoring (Table 42.4). An intra-arterial catheter to continuously monitor blood pressure and allow periodic arterial blood gas sampling is essential in the unstable and critically ill infant and highly desirable in any infant requiring mechanical ventilation. A continuous estimate of pCO_2 derived from transcutaneous monitoring or end-tidal gas sampling is also valuable, whether or not an arterial line is in place. Because ET CO_2 monitoring adds significantly to the instrumental dead space and is often inaccurate in small infants whose rapid respiratory rates do not allow an end-tidal plateau to be reached, transcutaneous monitoring is to be preferred in most ventilated neonates.

Ventilation parameters that should be monitored and recorded include ventilator pressures and timing and the total breath number and number of mechanically assisted breaths per minute (Table 42.4). The delivered V_T (and the target V_T, if set) should be noted, along with the proportion of leak. To be accurate, V_T must be measured at the airway opening, not at the ventilator end of the circuit. Whilst some devices offer a compliance compensation feature that corrects for the loss of V_T in the circuit, this feature does not function well in the presence of ETT leak. The humidifier temperature should be regularly checked and recorded. Most modern ventilators also provide continuous display of waveforms and/or tidal ventilation loops, and these, along with breath-by-breath compliance and resistance measurements, can be very helpful in fine-tuning ventilator settings, as described in this and other chapters in this text.

42.4 Ventilator Settings and Strategies: Pathophysiological Rationale, Meta-analytic Evidence and Therapeutic End Points

42.4.1 Manipulating End-Expiratory Lung Volume

Physiological first principles, and a large body of experimental and clinical evidence, point to the importance of manipulating EELV during mechanical ventilation of the diseased lung. It has become clear that to apply ventilation optimally requires a well-recruited lung with adequate end-expiratory volume (Rimensberger 2002; Clark et al. 2000). Such an approach is dependent on the application of sufficient PEEP, and the physiological considerations that guide PEEP setting are discussed in this section.

Clinical and experimental data point to a clear relationship between PEEP and EELV and, thus, oxygenation. Changes in other ventilator settings may, however, potentially lead to alterations in EELV. A long-held belief was that an increase in P_{AW} by alteration of any combination of ventilator settings would have a similar impact on oxygenation and thus that there should be an optimal P_{AW} at which to apply ventilation (Boros et al. 1977). It is now becoming accepted that the components that make up the P_{AW} (PIP, PEEP, T_I, rate and gas flow) should be considered separately. As stated by Monkman and Kirpalani:

> In retrospect, the simplifying but reductionist elegance that focused upon a single unitary number [P_{AW}] may have misled the field. (Monkman and Kirpalani 2003)

Thus, an improvement in oxygenation after a PEEP increase should not be viewed as having occurred simply because the P_{AW} is higher but rather because EELV has increased and $\dot{V}/Q$ matching has improved. Despite also producing P_{AW} changes, alteration in other ventilator parameters does not have the same effect on EELV (Fig. 42.1) (Thome et al. 1998) nor on oxygenation (Stewart et al. 1981). The inextricable linkage between PEEP, EELV and oxygenation dictates that it is PEEP that is the first, and arguably the

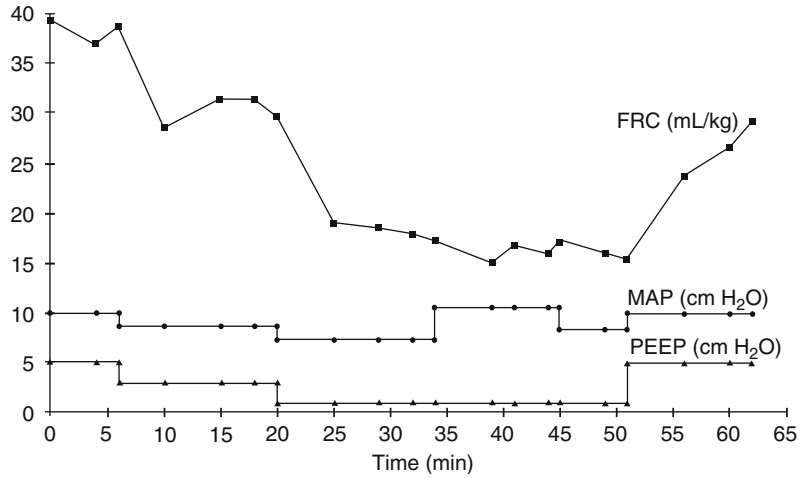

Fig. 42.1 Effect of ventilation changes on end-expiratory lung volume. Changes in end-expiratory lung volume (EELV, denoted as functional residual capacity, FRC) during programmed manipulation of ventilator settings in a ventilated infant. EELV is seen to reduce with stepwise reductions in positive end-expiratory pressure (PEEP) and thus mean airway pressure (P_{AW}, denoted as MAP) during the first 30 min. At minute 34, inspiratory time is lengthened from 0.3 to 0.6 s, leading to an increase in P_{AW}, but no significant change in EELV. Conversely, when PEEP is increased (minute 52), there is a substantial improvement in EELV (Reproduced from Thome et al. (1998) with permission)

most important, ventilatory parameter to be considered in the continuing management of the ventilated neonate.

An important difficulty in manipulating EELV in the ventilated subject is that the available methods to measure EELV at the bedside are imprecise and in some cases impractical (Dargaville and Rimensberger 2010). Whole-body plethysmography (Stocks et al. 2001) and gas dilution (Sivan et al. 1990; Vilstrup et al. 1992), both of which give absolute values for EELV, are not appropriate for repeated measurements in a clinical setting. Other methods, including respiratory inductance plethysmography (Adams 1996; Emeriaud et al. 2010), fibre-optic plethysmography (Davis et al. 1999) and electrical impedance tomography (Frerichs et al. 2001), allow measurement not of absolute volume but of change in EELV relative to a baseline condition, and only with prior calibration can a gas volume change in mL be derived. Despite these limitations, a great deal of information has been obtained from experimental studies in which EELV has been measured, either at the bedside or in the laboratory, as alterations in PEEP have been made. The key findings of this work are set out below. This knowledge can be used by clinicians to set and titrate PEEP in ventilated subjects, aided by indirect measures of EELV, in particular oxygenation and tidal breath compliance.

42.4.1.1 Relationships Between PEEP, EELV and Recruitment

An understanding of what can potentially be achieved through manipulation of lung volume using PEEP comes from firstly examining the changes in EELV and recruitment during stepwise PEEP manoeuvres. Such information is derived from lung modelling, studies in experimental animals and in humans with lung disease. An example is shown in Fig. 42.2. With stepwise PEEP increments and a constant inflating pressure (PIP–PEEP), a surfactant-depleted lung starting at residual volume follows the path of the inflation limb of the pressure–volume (PV) relationship (Fig. 42.2), with an improvement in tidal breath compliance as more non-aerated lung units are recruited, followed by a fall in compliance as more lung units become overdistended near total lung capacity. During PEEP decrements (Fig. 42.2), the property of hysteresis is demonstrated with a different PV trajectory than during PEEP increments, following a path closer to the deflation limb of the PV relationship. There is preservation of recruitment through a large proportion of this trajectory, and the open tidal ventilation loops reflect the marked improvement in compliance during PEEP decrements, as has been predicted by lung modelling (Hickling 2001). At the point of maximal curvature of the deflation limb ("closing pressure"), the lung is still well inflated, recruitment is largely preserved and tidal ventilation at this point is associated with minimal overdistension and a peak in compliance. This is the point of "optimal PEEP", at which the lung is ventilated with the best possible oxygenation and compliance and with the least

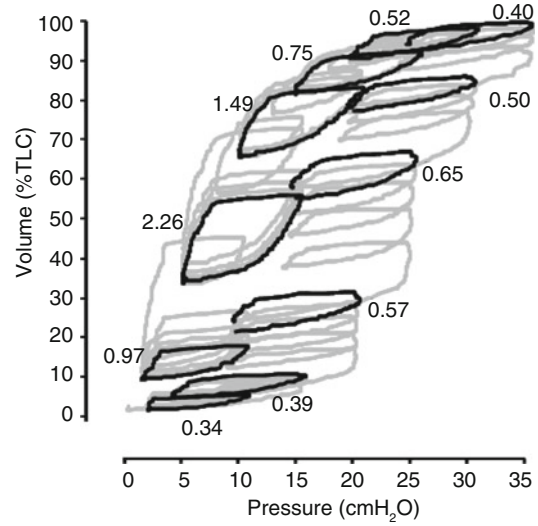

Fig. 42.2 Stepwise vital capacity manoeuvre in the injured lung. Pressure–volume curve during a stepwise vital capacity manoeuvre using positive end-expiratory pressure (PEEP) increments and decrements in a mechanically ventilated 2.1 kg piglet after repeated saline lavage. Each PEEP level was held for 15 s. Inflating pressure (peak inspiratory pressure – PEEP) remained at 10 cm H_2O throughout. *Y*-axis shows lung volume measured by respiratory inductance plethysmography and scaled to total lung capacity (TLC). Complete tracing is shown in *grey* and the final breath at each PEEP level in *black*, and the tidal breath compliance (mL/cm H_2O/kg) for each of the final breaths is indicated in *italics* (Data derived from same experimental series as reference (Dargaville et al. 2010))

Table 42.5 The benefits of positive end-expiratory pressure (PEEP) optimisation in the diseased lung

Maintenance of lung recruitment
Defence against absorption atelectasis in high FiO_2
Improved lung compliance and thus a reduction in peak inflation pressure to achieve the same tidal volume
Better oxygenation and a reduction in FiO_2
More efficient CO_2 removal
More even distribution of ventilation
Preservation of surfactant
Reduction in lung injury

possible pressure (Rimensberger et al. 1999a). Additional advantages of optimising PEEP in this way are shown in Table 42.5. In the experimental animal with recruitable lungs, PEEP set in relation to the point of maximal curvature of the deflation limb is often at or below the PEEP value predicted from the lower inflection point of the inflation limb (Rimensberger et al. 1999a).

Finding optimal PEEP as described above is not difficult in experimental animals, as long as the lung is recruitable and can withstand brief inflation to total lung capacity. The technique has also been applied to adult subjects with acute respiratory distress syndrome (Amato et al. 1998; Suarez-Sipmann and Bohm 2009), allowing confirmation of many of the physiological features noted in the laboratory. A limiting factor is that if the lung has few recruitable units, there will be minimal hysteresis and the PEEP at the point of maximal curvature of the deflation limb may actually be higher than the PEEP at the lower inflection point on the inflation limb, with minimal benefit in compliance, and the risk of overdistension with each tidal breath (Albaiceta et al. 2005).

In mechanically ventilated newborn infants, there have been few attempts to find optimal PEEP using stepwise increments and decrements as described above. The PV relationship of the lung has, however, been mapped in ventilated infants on high-frequency oscillatory ventilation (HFOV), allowing definition of hysteresis and a point of maximal curvature (closing pressure) on the deflation limb (Tingay et al. 2006). Similar PV tracing during HFOV, using oxygenation as in indicator of lung volume, is routinely used in some institutions to identify optimal P_{AW} (De Jaegere et al. 2006). The deflation limb of the PV relationship has also been traced in preterm infants using a quasistatic technique performed over a maximum of 10 s (Vilstrup et al. 1996). A point of maximal curvature appears to be identifiable in each recording, but in this early study, no attempt was made to use this landmark for PEEP setting. In parallel with adult studies, there has been some attempt to set PEEP in newborn infants based on the shape of the inspiratory PV curve, traced over 30 s after a 5 s disconnection to ambient pressure (Mathe et al. 1987). An inflection point was identifiable in each infant, with greater concavity in those with more severe disease (indicating potential for recruitment). Change in the position of the inflection point, and the concavity of the inflation limb, was noted with resolution of disease (Fig. 42.3). Setting PEEP by this method improved oxygenation in infants at the height of disease, but not those in the recovery phase (Mathe et al. 1987).

With the exception of these more penetrating studies, the investigation of PEEP and PEEP setting in ventilated neonates has been limited to studies of short-lived PEEP adjustments, in some cases with stepwise PEEP increments analogous to the titration of CPAP described in the very earliest reports of this therapy (Gregory et al. 1971). Increases in PEEP universally lead to an increase in EELV (Thome et al. 1998; Dinger et al. 2001; Bose et al. 1986) and an improvement in oxygenation (Stewart et al. 1981; Dinger et al. 2001; Bose et al. 1986). In the diseased lung, the oxygenation response to increasing EELV is related to both decreased venoarterial shunting due to recruitment of non-aerated lung units and improvement of $\dot{V}$ / Q matching with better gas aeration. The potential for PEEP to induce change in EELV in the ventilated neonate is significantly greater than for isolated changes in PIP or T_I (Thome et al. 1998). PEEP increases were most usually associated with a fall in tidal compliance suggesting overdistension (Dinger et al. 2001; Alegria et al. 2006). Infants with more severe lung disease may, however, demonstrate an improvement in compliance with PEEP increments indicating lung recruitment (Dinger et al. 2001). The level of applied PEEP also has the potential to impact upon cardiac function, but it is clear that the adverse effects of PEEP on cardiac output are much more prominent in the normal lung (Holzman and

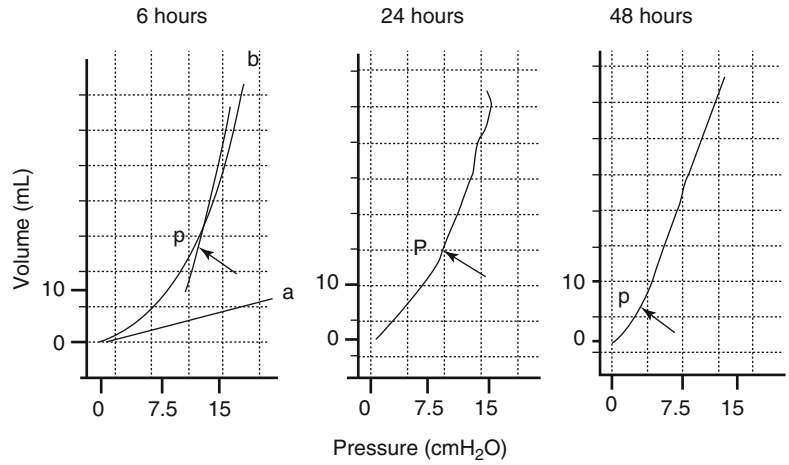

Fig. 42.3 Inflation limb of the pressure–volume relationship in an infant with respiratory distress syndrome. Sequential inflation limb pressure–volume curves from a newborn with respiratory distress syndrome recorded at 6, 24, and 48 h. *X*-axis, applied pressure; *Y*-axis, volume of insufflated oxygen. The initial slope (*a*) and slope in the linear portion of the pressure–volume curve (*b*) are shown at 6 h. *Black arrows* and point *P* indicate the lower inflection point, at which positive end-expiratory pressure was then set. Note the shift in position of this point with improvement in lung function (Redrawn from Mathe et al. (1987), with permission)

Scarpelli 1979). This relates to the transmission of intra-alveolar pressure to the pleural and mediastinal compartment, which is substantially greater in a recruited lung. Indeed, one study in the pre-surfactant era used rise in pleural pressure (as indicated by oesophageal pressure) to indicate the point at which lung recruitment had occurred during PEEP increments (Bonta et al. 1977).

The findings of these studies are heavily influenced by the severity of lung disease in the subjects under study and the starting point and span of PEEP settings used. There has also been considerable reluctance to keep the driving pressure constant with PEEP adjustments, in part related to a misconception that PEEP by itself produces lung recruitment. Recruitment is an inspiratory phenomenon; the value of PEEP is in maintaining recruitment of open lung units at end expiration (Gattinoni et al. 2003). None of the PEEP-titration studies in neonates have until recently emulated the "open lung" concept of lung recruitment followed by titration of PEEP using small pressure decrements (Suarez-Sipmann and Bohm 2009; Lachmann 1992). The only study designed to maintain stable pressure amplitude during PEEP increments investigated the effect of a lung recruitment maneuver (LRM) with incremental PEEP adjustments in infants with mean GA of 25 wk ventilated for RDS with AC+VG in a small randomized trial (Lista et al. 2011). LRM consisted of 0.2 cm H_2O increments in PEEP every 5 minutes, until FiO_2 reached 0.25, followed by reduction of PEEP until oxygenation began to deteriorate. If FiO_2 rose, PEEP was increased again to re-recruit the lung and then reduced again to situate the lungs on the deflation limb of the pressure/volume curve. Initial FiO_2 was 56±24 versus 52±21, in the two groups. The full LRM lasted for 61±18 minutes. The infants appeared to have only mild lung disease, with maximum PEEP reaching only 6.1±0.3 cm H_2O. LRM lead to faster weaning of FiO_2 (94±24 versus 435±221 minutes; $p=0.000$) and shorter O_2 dependency (29±12 versus 45±17 days; $p=0.04$). No adverse events and no differences in the outcomes were observed. Though limited by the modest severity of illness and small sample size, the study suggests that LRM with incremental PEEP adjustments is feasible during conventional ventilation.

42.4.1.2 Guiding Principles for PEEP Setting in the Neonate

1. There is no universal PEEP setting that is correct for all lung diseases, or even for one disease, or even for one individual through the

course of their disease. Units that choose to mandate a PEEP level for reasons of simplicity or the need to protocolise ventilator settings are missing opportunities to manage respiratory failure optimally and according to sound physiological reasoning. Suggested ranges for PEEP are given in Table 42.1; these should be considered in the light of the individual circumstances, with further adjustment according to the physiological response and the course of the disease. The PEEP setting should be re-evaluated whenever there is an alteration to pulmonary mechanics, for example, after surfactant administration (Goldsmith et al. 1991).

2. Unquestionably, very low PEEP (and zero PEEP) is inappropriate in the diseased lung (Monkman and Kirpalani 2003), predisposing to low EELV, poor oxygenation, impaired pulmonary mechanics, greater turnover of surfactant and a risk of greater lung injury.
3. Conversely, a PEEP level that is set too high for too long leads to overdistension of the lung, impairment of venous return and cardiac output and predisposition to pneumothorax.
4. PEEP is not, of itself, a recruitment tool, and PEEP increments will not recruit the lung optimally without an adequate inflating pressure (PIP-PEEP) to reinflate non-aerated lung units. Once the lung is recruited, the PEEP (and PIP) must then be turned down.
5. PEEP is effective in maintaining lung volume in circumstances predisposing to atelectasis, for example, during anaesthesia (Easa et al. 1995) and/or after administration of muscle relaxants (von Ungern-Sternberg et al. 2006). PEEP also helps to minimise absorption atelectasis associated with ventilation using 100 % oxygen (von Ungern-Sternberg et al. 2007).

42.4.2 Inspiratory Time

As described elsewhere in this text, the respiratory time constants that determine how rapidly lung volume re-equilibrates after a pressure change are determined by the compliance and resistance of the respiratory system (Bancalari 1986). Infants with poorly compliant lungs secondary to RDS have very short time constants and thus require only a very short T_I for equilibration to occur (as low as 0.15 s). This may, however, be insufficient time for tidal recruitment to occur during the inspiratory phase. Setting T_I in the diseased lung must therefore find a balance between the wish to minimise the duration of plateau pressure at peak inflation and the need to provide adequate time for the recruiting effect of the pressure plateau.

Early ventilation strategies in ventilated neonates evolved to the use of a long T_I, in part because of the lack of PEEP, and the observation that longer T_I and slower ventilator rates improved oxygenation in infants with RDS (Reynolds 1971). With further, and more probing, clinical observations, it became clear that this pattern of ventilation was contrary to the spontaneous respiratory efforts of a preterm infant (South and Morley 1986), unless muscle-relaxed. Clinical trials comparing long T_I (0.66–1.0 s) with short T_I (0.33–0.5 s) subsequently demonstrated an advantage in the shorter T_I group, including a slight reduction in mortality and a clear decrease in the risk of air leak, particularly in infants with RDS (OCTAVE Study Group 1991; Kamlin and Davis 2004).

With the advent of synchronised ventilation has come a further imperative to match the ventilator T_I to that of the infant. Inappropriately long set T_I may lead to dyssynchrony, with the infant exhaling against the ventilator inflation pressure. Conversely if T_I is too short (or lung volume loss too rapid), the infant may interrupt expiration with a further inspiratory effort during the ventilator expiratory cycle (McCallion et al. 2005). From the suggested first T_I settings (0.5 s in the term infant, 0.35 s in the preterm infant, see above), adjustments should be made based on the appearance of the flow waveform. T_I should be prolonged if there is clearly insufficient time for flow to enter the lung. Shortening of the T_I should be considered if there is a prolonged period of zero flow with an inflation pressure plateau; a suggested maximum for this period is one-third of the total inflation time. Recommended ranges for within which to set T_I in the ventilated newborn are 0.25–0.4 s in preterm infants and 0.4–0.6 s in those at full term.

An alternative to making manual adjustments to T_I is to use a flow-cycled mode with expiratory triggering (PSV) (Scopesi et al. 2007). This mode is not

recommended in the diseased lung prone to atelectasis (Keszler 2009) but may be a sensible alternative during the weaning phase. If there is the option to adjust the percentage of peak inspired flow at which inflation terminates (termination sensitivity), a value no higher than 10 % is recommended.

42.4.3 Choosing the Appropriate Tidal Volume

Since its inception, for a variety of reasons neonatal ventilation has largely been conducted using pressure-limited ventilatory modes. This remains so up until the present day (van Kaam et al. 2010). Until recently, it has been difficult to measure tidal volumes, but the latest generation of neonatal ventilators allows accurate measurement of V_T, including expired V_T measured at the airway opening. Monitoring and recording of V_T is now routine in most neonatal intensive care units (van Kaam et al. 2010), and with the availability of volume-targeted modes or volume-controlled ventilation, there has been a shift of focus away from the PIP applied and towards the V_T that results. Suggested V_T settings for neonatal ventilation are shown in Table 42.1, and the physiological rationale and clinical evidence in relation to setting or targeting V_T are set out below.

42.4.3.1 Physiological Rationale for Targeting Tidal Volume

Even in the normal lung, tidal ventilation is important not only for gas exchange but also for maintaining lung recruitment, with very low and/or monotonous V_T contributing to atelectasis (Suki et al. 1998; Mutch et al. 2000). For the lung compromised by immaturity, disease or both, maintenance of an adequate V_T during conventional ventilation is of paramount importance. There is compelling evidence for the need to monitor, target and limit tidal volumes in the ventilated neonate, with the clear message that both high and low V_T settings can be dangerous (Keszler 2009).

By virtue of the resultant stretch injury, ventilation with excessive V_T in the neonate has the potential to cause long-standing damage. The combination of immature lung architecture and a highly compliant chest wall renders the newborn lung, and especially the preterm lung, uniquely vulnerable to overdistension and stretch injury (Clark et al. 2000). Laboratory investigations have highlighted the danger of ventilation with high tidal volumes (Dreyfuss and Saumon 1998; Dreyfuss et al. 1988) with even a few large tidal inflations causing extensive lung injury in the immature lung (Bjorklund et al. 1997). It is also clear that the severity and distribution of injury in this setting depend not only on the magnitude of V_T but also on the state of the lung at end expiration, including the degree of recruitment and residual aeration of lung units (Clark et al. 2000; Chiumello et al. 2008). Application of high V_T to an atelectatic lung causes significant alveolar injury maximal in the nondependent regions, i.e. those areas that remain expanded at end expiration (Tsuchida et al. 2006). Prior reversal of atelectasis by surfactant treatment substantially attenuates the lung injury related to high V_T in the preterm lung (Wada et al. 1997), presumably because the gas delivered with each inflation is more evenly distributed, with less resultant regional overdistension (Dargaville et al. 2010).

Clinical studies in ventilated newborn infants support a role for high V_T in the pathogenesis of lung injury, although the evidence is largely circumstantial. Early clinical trials of rapid versus slow respiratory rates by necessity involved ventilation with different levels of V_T to achieve similar minute ventilation, although the actual V_T was not measured. In comparison to ventilation of infants with RDS with rates of at least 60/min, ventilation at slow rates of 30–40/min (and therefore higher V_T) was associated with a marked increase in pulmonary interstitial emphysema (Pohlandt et al. 1992) and pneumothorax (OCTAVE Study Group 1991). Other markers of over-ventilation in early life, such as hypocapnia, are known to increase the risk for the development of chronic lung disease (Garland et al. 1995; Kraybill et al. 1989), with one putative mechanism being volutrauma related to high V_T (Rimensberger 2002).

Whilst acknowledging the pivotal role of volutrauma in the development of ventilator-induced injury, it must be recognised that ventilation at inappropriately low V_T also has consequences, both in the short and long term. Ventilation of the atelectatic lung at relatively low V_T is associated

with insufficient alveolar recruitment and EELV, poor gas exchange (Probyn et al. 2004) and considerable lung injury (Muscedere et al. 1994), with a predilection for the small airways. If, and only if, the lung is adequately recruited can the benefits of "gentle ventilation" with relatively small tidal volumes be realised. The combination of an "open lung" (Lachmann 1992) and low V_T provides adequate gas exchange and markedly reduces the risk of lung injury during mechanical ventilation (Rimensberger 2002; Rimensberger et al. 1999a, b; van Kaam et al. 2004). Studies of this approach in ventilated adults with acute respiratory distress syndrome have shown reduced mortality and more rapid weaning from ventilation (Amato et al. 1998; ARDS Network 2000). Controlled clinical trials of an open lung approach have yet to be conducted in ventilated newborns (van Kaam and Rimensberger 2007).

42.4.3.2 What Is the Safe Upper Limit of V_T in the Ventilated Neonate?

In parallel with studies in adults showing the benefit of a V_T of 6 mL/kg over a V_T of 12 mL/kg (ARDS Network 2000), limiting tidal volume to <10 mL/kg in ventilated newborns seems appropriate, and most neonates are now ventilated with a V_T of between 4 and 7 mL/kg (van Kaam et al. 2010). Given the vulnerability of the preterm lung in the early days of life, an upper acceptable limit of 6–7 mL/kg is suggested in infants less than 32 weeks. There are particular circumstances in which a V_T as low as 5 mL/kg may still induce injury. Infants with diaphragmatic hernia have immature and underdeveloped lungs which are exquisitely sensitive to volutrauma and by virtue of the reduced total lung capacity tend to respire with V_T values less than 5 mL/kg (Te Pas et al. 2009). For these infants the safe upper limit for V_T may be below 5 mL/kg. Similar considerations apply for neonates with pulmonary hypoplasia from other causes, including preterm infants born after early and prolonged rupture of membranes.

42.4.3.3 What Is the Safe Lower Limit of V_T in the Ventilated Neonate?

Many preterm infants on synchronised ventilation using AC mode supporting every detected patient effort can achieve adequate gas exchange with V_T values as low as 3–3.5 mL/kg (Scopesi et al. 2007). The concern is that such low values of V_T may over time be insufficient to maintain alveolar recruitment, in particular when low PEEP settings are used (Keszler 2006). A clinical trial comparing V_T targets of 3 and 5 mL/kg found the lower value to be associated with an increase in pro-inflammatory cytokines in bronchoalveolar lavage fluid (Castoldi et al. 2011). V_T targets below 5 mL/kg may be inappropriate in chronically ventilated preterm infants, in whom the V_T required to maintain normocapnia was noted to increase to 6 mL/kg by the third week of ventilation (Keszler et al. 2009). Additionally, there is a small but significant effect of the fixed instrumental dead space of the flow sensor necessary to measure VT. This additional dead space becomes proportionally larger in the smallest infants, resulting in the need for tidal volume of about 6 ml/kg to maintain normocapnia in infants around 500g, compared to larger preterm infants (Nassabeh-Montazami 2009).

42.4.4 Respiratory Rate

Selection of respiratory rate is a function of the mode of ventilation (SIMV vs AC, ±volume targeting) as well as the clinical scenario and degree of compromise of CO_2 clearance. Some of the pioneering work on neonatal ventilation arrived at low ventilator rates and long T_I as an appropriate strategy for neonatal ventilation. The technical limitations of the ventilators used, including the inability to directly provide PEEP, influenced this choice. Several clinical trials have found rapid respiratory rates (≥60/min), along with shorter T_I, to be less injurious to the lung than slower rates (OCTAVE Study Group 1991; Pohlandt et al. 1992). Additionally the use of a rapid ventilator rate allows more opportunity for synchrony given the rapid respiratory rate and short T_I of most infants with lung disease (South and Morley 1992). Suggestions for setting of respiratory rate are shown in Table 42.6.

The combination of a rapid ventilator rate and a relatively long T_I may lead to dynamic hyperinflation related to the development of inadvertent PEEP (Simbruner 1986). Whilst some investigators have looked upon this as a way to improve lung recruitment, physiological first principles and experimen-

Table 42.6 Setting respiratory rate

Mode	Gestation	Context	Suggested set ventilator rate (inflations per minute)	Comments
SIMV (or IMV if muscle-relaxed)	Term	Height of disease	40 (30–50)[a]	Consider adding pressure support if there is high work of breathing with unassisted breaths
		Weaning	Reduce in decrements of 5–10	
	Preterm	Height of disease	60 (40–80)[a]	Consider changing to AC mode if there is high work of breathing with unassisted breaths
		Weaning	Reduce in decrements of 5	
Assist/control	Term	Height of disease	Backup rate 30–40	Ensure as many inflations as possible are triggered
		Weaning	Backup rate to remain below spontaneous breathing rate	
	Preterm	Height of disease	Backup rate 40–60	Ensure as many inflations as possible are triggered
		Weaning	Backup rate to remain below spontaneous breathing rate	

SIMV synchronised intermittent mandatory ventilation, *AC* assist/control
[a]Starting point (range)

tal evidence would suggest that it is better to apply sufficient PEEP at the airway opening rather than rely on the generation of an unknown and variable amount of inadvertent PEEP to improve lung volume (Yanos et al. 1998). Avoidance of dynamic hyperinflation is thus an important goal of neonatal ventilation, in particular in the context of an increased resistance to airflow. The flow waveform should be examined to ensure there is sufficient expiratory time for complete exhalation. A more definitive test for measurement of inadvertent PEEP has been described, which involves insertion of a T-piece in the ventilator circuit, brief interruption of ventilation by clamping and measurement of equilibrium pressure distal to the clamp (Simbruner 1986). If there is suspicion of incomplete exhalation, available options to prolong expiratory time include (a) reduction of ventilator rate with T_I kept constant or (b) shortening of T_I, if appropriate, whilst keeping ventilator rate constant. A combination of both of these may be the best solution.

42.4.5 Fractional Inspired Oxygen Concentration

Oxygen was first administered to newborns within 6 years of its discovery in 1774, and its administration to the premature neonate has continued in various forms thereafter (Silverman 2004). Use of "liberal" oxygen therapy, with an FiO_2 above 0.5, first became widespread in preterm infants in the late 1940s, and its impact on the developing retinal vasculature was soon apparent in the form of a large number of infants (more than 10,000) blinded by retinopathy of prematurity (Silverman 2004; Askie et al. 2009). In the aftermath of this disaster of iatrogenesis, there was the recognition of the need to restrict oxygen therapy (Askie et al. 2009), with measurement of both the FiO_2 and the oxygenation response of the infant now considered essential. Unrestricted and/or inadequately regulated oxygen therapy, and the retinopathy following from it, is now a significant concern in developing and newly industrialised countries (Gilbert 2008; Maida et al. 2008), and a "third epidemic" of retinopathy has emerged in these nations coincident with the increase in preterm survivors (Gilbert 2008; Maida et al. 2008).

Notwithstanding the above, titration of FiO_2 remains arguably the most neglected and least precise element of neonatal ventilation. Indwelling arterial oxygen sensors are no longer in use, and pO_2 readings in blood taken from an arterial line give only a snapshot in time. For this reason, moment by moment adjustments in FiO_2 are usually made on the basis of SpO_2 readings,

and it is clear that many infants, in particular preterm infants, spend considerable amounts of time with SpO_2 readings (and therefore PaO_2 levels) outside the desired or target range (Hagadorn et al. 2006; Laptook et al. 2006; Claure et al. 2011). Given the shortages of nursing personnel in many neonatal units, very significant changes in SpO_2 may go unnoticed and uncorrected for some time, putting a patient at risk of the effects of hypoxia or hyperoxia (Claure et al. 2011; Bolivar et al. 1995). Automated control of FiO_2, discussed elsewhere in this text, offers the possibility of better targeting of SpO_2 ranges and less hyperoxia (Claure et al. 2011) but remains largely unavailable at present.

Frequent adjustments to FiO_2 are required in many ventilated newborns, in particular those with episodes of frequent apnoea or chest splinting in expiration (Bolivar et al. 1995). Prolonged periods of high FiO_2 may be necessary in infants with very significant parenchymal disease, pulmonary hypertension or both. In general, every opportunity should be taken to reduce FiO_2, both by choosing the lowest acceptable SpO_2 target and by optimising lung volume and recruitment at every juncture.

42.5 Acceptable Oxygen Saturation in Premature Infants

Oxygen saturation monitoring has been a routine part of neonatal intensive care for several decades, but until recently there has been a dearth of information concerning the correct target ranges (upper and lower limits) for SpO_2 in preterm infants receiving supplemental oxygen. In recent years, however, there has been an accumulation of clinical trial evidence regarding oxygen therapy and appropriate oxygen saturation targets in premature infants (STOP-ROP Multicenter Study Group 2000; Askie et al. 2003; Carlo et al. 2010; Schmidt et al. 2013; Stenson et al. 2013; Stenson 2013), overcoming at least in part a great deal of uncertainty (Tin and Wariyar 2002). This information has been taken into account in formulating the recommendations for SpO_2 target ranges indicated in Table 42.7.

Table 42.7 Suggested target ranges for oxygen saturation

Preterm < 28 weeks gestation at birth	
Before 36 weeks CGA[a]	90–94 %
≥36 weeks CGA	92–96 %
Preterm 28–36 weeks gestation at birth	
Before 36 weeks CGA	90–94 %
≥36 weeks CGA	92–96 %
Term	
Parenchymal lung disease	92–96 %
Persistent pulmonary hypertension	94–98 %[a]
Cyanotic congenital heart disease	70–85 %[b]

CGA corrected gestational age

[a]Appropriate pO_2 target at least 50 mmHg

[b]Where there is a duct-dependent pulmonary blood flow, supplemental oxygen may constrict or close the ductus arteriosus

42.5.1 What Is the Safe Upper Limit for SpO_2 in the Preterm Infant?

The association of hyperoxia with adverse pulmonary, neurological and retinal effects in the preterm infant is well understood and is discussed elsewhere in this book. In the era of saturation monitoring, relative hyperoxia (SpO_2 ≥95 %) from 32 weeks corrected gestation or beyond has been associated with progression of chronic lung disease (STOP-ROP Multicenter Study Group 2000; Askie et al. 2003), without altering the outcome of retinopathy (STOP-ROP Multicenter Study Group 2000). More recently, a number of clinical trials, conducted in the USA, Canada, UK, Australia and New Zealand, have compared target SpO_2 ranges of 85–89 % and 91–95 % commenced soon after birth in preterm infants <28 weeks gestation. These target ranges remained in force up until 36 weeks corrected gestation, as long as the infant is receiving supplemental oxygen. An initial report from each of these studies has now been published (Carlo et al. 2010; Schmidt et al. 2013; Stenson et al. 2013), and an individual patient meta-analysis combining data from all trials (the NeOProM collaboration) is awaited (Stenson 2013). Three methodological issues in these trials bear consideration. The first is that for both high (91–95 %) and low (85–89 %) target groups, the actual SpO_2 readings when in supplemental oxygen were at the high end of the

intended range, likely a reflection of a well-documented tendency for bedside staff to target the high end of an SpO_2 range (Clucas et al. 2007). Moreover, the upward shift in actual SpO_2 readings was more prominent in the lower target group, with a median SpO_2 value of around 90–91 %, and on average only a 3 % separation between readings in the two groups, rather than the 6 % that would have been expected. The second methodological consideration is that while the trials were being conducted, the SpO_2 calibration curve within the oximeters being used was found to under-represent SpO_2 values of 87–90 % (Stenson 2013). Installation of a revised algorithm in the UK and Australian trials led in to a clearer separation in SpO_2 readings between the groups, and appeared to affect the outcomes (see below). The final methodological issue is that in only one of the studies (the COT study, Schmidt et al. 2013) were both upper and lower alarms limits clearly stipulated and enforced, which may have affected the proportion of extreme SpO_2 values, and thus potentially the results.

Overall the findings of the recent clinical trials of SpO_2 targeting were (a) that a lower target range (85–89 %) was associated with an increased risk of mortality (the exception being the COT study (Schmidt et al. 2013)), with the relative risk of in-hospital mortality being 1.3 to 1.4 (Carlo et al. 2010; Stenson et al. 2013); (b) that a lower target range also appeared to predispose to necrotising enterocolitis; and (c) that a higher target range (91–95 %) was associated with an increase in retinopathy of prematurity (relative risk 1.3–2.0) with again the COT study being the exception. The COT study investigators commented that strict enforcement of alarm limits, and in particular the upper limit, may have contributed to the lack of association between the high target group and retinopathy noted in their study.

The SpO_2 targeting trials performed to date have not examined multiple SpO_2 ranges, and thus recommendations about the safe upper and lower limits can only be based on the information at hand. Nevertheless, balancing the risks of mortality and necrotising enterocolitis on the one hand, against the risk of retinopathy on the other, an upper SpO_2 limit of 94 % would seem prudent, with an alarm set at 96 % and active at all times when in supplemental oxygen (Table 42.7). A higher upper limit (96 %) is appropriate for preterm infants beyond 36 weeks corrected gestation. The upper limit of 96 % can also be applied from the outset to term infants with parenchmal lung disease, in whom the risk of retinopathy is negligible. A higher target range (and thus upper limit) is recommended for infants with pulmonary hypertension (Table 42.7).

42.5.2 What Is the Safe Lower Limit for SpO_2 in the Preterm Infant?

The combined results of the SpO_2 targeting trials point to an increase in mortality and probably necrotising enterocolitis where an SpO_2 below 90 % is targeted. For this reason, a lower SpO_2 limit at or above 90 % has been recommended for preterm infants <36 weeks corrected age (Table 42.7). A lower SpO_2 limit at or above 92 % is appropriate for term infants in most clinical contexts (Table 42.7), with the exception being cyanotic congenital heart disease.

42.6 Safe CO_2 Limits

There are good experimental data in support of the role of permissive hypercapnia in lung injury protection (as discussed elsewhere in this book). These effects go beyond the reduced minute ventilation that goes hand in hand with permissive hypercapnia; elevated $FiCO_2$ appears to offer protection independent of minute ventilation (Peltekova et al. 2010). The need for lower minute ventilation should in itself reduce lung injury in the preterm infant, although this hypothesis, whilst supported in a small single-centre trial (Mariani et al. 1999), was not clearly validated in the large clinical trial conducted by the Neonatal Research Network (Carlo et al. 2002).

The safe limits of $PaCO_2$ are difficult to determine from available literature. Despite decades of use of mechanical ventilation of newborn infants,

the number and quality of studies specifically addressing this critical question is surprisingly low. There is unequivocal evidence that low $PaCO_2$ is associated with increased risk of severe intraventricular haemorrhage (IVH) and periventricular leukomalacia (Graziani et al. 1992; Fujimoto et al. 1994; Wiswell et al. 1996; Okumura et al. 2001; Collins et al. 2001) and that very high levels, especially in preterm infants during the first few days of life, may also increase the risk of IVH (Kaiser et al. 2006; Fabres et al. 2007). The data of Fabres et al. indicated that even modestly decreased $PaCO_2$ (<39 mmHg) was associated with a twofold increase in IVH, as was a maximal $PaCO_2$ over 60 mmHg and prolonged exposure to a $PaCO_2$ greater than 52 mmHg. However, safe lower and upper limits remain an open question. The postnatal age of the infant, the degree of prematurity and coexisting morbidities, such as asphyxia, hypotension and sepsis, which are known to impair cerebral blood flow autoregulation, all affect the vulnerability of the patient to high or low levels of CO_2. The studies showing association of hypercapnia and IVH focussed on the early postnatal period. The only large prospective clinical trial of permissive hypercapnia suggests safety of mild permissive hypercapnia, but the mean $PaCO_2$ remained between 45 and 50 mmHg for the first 7 days of life in the "hypercapnia" group (Carlo et al. 2002). This study does not, therefore, refute the retrospective data suggesting increased risk of adverse outcomes with maximal $PaCO_2$ values above 60 mmHg during the first week of life (Fabres et al. 2007). Whilst there are very plausible pathophysiological mechanisms which link hypercapnia to IVH, it must be recognised that the retrospective studies cannot establish causation. It is possible that high CO_2 values are a marker for other events or a reflection of the severity of illness rather than the cause of the IVH. A relatively small prospective trial targeting $PaCO_2$ values between 55 and 65 from birth enrolled only one-third of the projected sample size (65 infants) before being stopped early because target PCO_2 values could not be reached (Thome et al. 2006). This study found no difference in pulmonary outcomes but an increase in the composite outcome of death or neurological impairment at 18–22 months from 42 to 62 % in the hypercapnia group, despite a difference of only 6 mmHg in $PaCO_2$ values between the groups.

Data on safety of permissive hypercapnia beyond the first week of life are lacking. It is generally believed that because of metabolic compensation and less vulnerability to IVH, higher levels of $PaCO_2$ can be tolerated safely, but neither the validity of the assumption nor the safe upper limits of $PaCO_2$ during this period have been established.

Although clinical studies have focussed on $PaCO_2$, whether $PaCO_2$ or pH should be our primary concern is still subject to debate; clinical studies have not specifically addressed the question of whether compensated respiratory acidosis is safe or whether the infant with metabolic acidosis compensated by hyperventilation is at similar risk as one who has an uncompensated alkalosis. Experimental studies clearly show, however, that local tissue pH, not pCO_2, is the primary determinant of cerebral vasoconstriction or dilatation (Fencl et al. 1968; Kontos et al. 1977). Rapid changes in $PaCO_2$ are also dangerous and should be avoided, because they lead to rapid changes in cerebral blood flow (Raichle et al. 1970; Gleason et al. 1989). A large retrospective study of 849 preterm infants concluded that not only both extremes of CO_2 but also fluctuations in $PaCO_2$ are associated with severe IVH (Fabres et al. 2007).

What then is the clinician to do in the face of such uncertainty? First, it should be recognised that low $PaCO_2$ values are clearly more dangerous than moderately high values and that targeting mildly hypercapnic values decreases the risk of inadvertent hypocapnia. Second, it is important to avoid rapid changes in $PaCO_2$. On balance, available evidence suggests that keeping $PaCO_2$ values in the range of 45–50 mmHg during the first week of life is appropriate and safe. As a practical matter, because very preterm infants have a low renal threshold for bicarbonate and tend to have a modest metabolic acidosis, it is difficult to achieve significant hypercapnia during the first few days of life without unacceptable degree of acidosis. With time, the vulnerability of the brain to IVH decreases, and metabolic compensation develops, allowing $PaCO_2$ to rise to levels of 50–60 mmHg with relatively normal pH by the second and third

week of life. Permissive hypercapnia with $PaCO_2$ values of 60–70 mmHg is widely practised and not clearly associated with adverse outcomes. The safety of this approach is in need of urgent study.

Essentials to Remember

- Ventilator settings in the neonate should be individualised, taking into account the context in which respiratory failure has occurred, the effects on lung volume and compliance and the vulnerability of the lung to injury.
- Where possible, ventilation should be in synchrony with spontaneous respiratory effort.
- PEEP is the most important determinant of end-expiratory lung volume and oxygenation.
- Delivery of each tidal breath is important not only for gas exchange but also recruitment.
- Premature neonates are more vulnerable to oxygen toxicity, and the target SpO_2 range in these infants is thus lower than for term infants.
- Hypocapnia is significantly more dangerous than hypercapnia in ventilated neonates.

References

Adams JA (1996) Respiratory inductive plethysmography. In: Stocks J, Sly PD, Tepper RS, Morgan WJ (eds) Infant respiratory function testing. Wiley-Liss, New York, pp 139–163

Albaiceta GM, Luyando LH, Parra D, Menendez R, Calvo J, Pedreira PR, Taboada F (2005) Inspiratory vs. expiratory pressure-volume curves to set end-expiratory pressure in acute lung injury. Intensive Care Med 31:1370–1378

Alegria X, Claure N, Wada Y, Esquer C, D'Ugard C, Bancalari E (2006) Acute effects of PEEP on tidal volume and respiratory center output during synchronized ventilation in preterm infants. Pediatr Pulmonol 41:759–764

Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354

Anand KJ, Hall RW, Desai N, Shephard B, Bergqvist LL, Young TE, Boyle EM, Carbajal R, Bhutani VK, Moore MB, Kronsberg SS, Barton BA (2004) Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. Lancet 363:1673–1682

ARDS Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 342:1301–1308

Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM (2003) Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 349:959–967

Askie LM, Henderson-Smart DJ, Ko H (2009) Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochrane Database Syst Rev (1):CD001077

Aufricht C, Huemer C, Frenzel C, Simbruner G (1993) Respiratory compliance assessed from chest expansion and inflation pressure in ventilated neonates. Am J Perinatol 10:139–142

Bancalari E (1986) Inadvertent positive end-expiratory pressure during mechanical ventilation [editorial]. J Pediatr 108:567–569

Bernstein G, Knodel E, Heldt GP (1995) Airway leak size in neonates and autocycling of three flow-triggered ventilators. Crit Care Med 23:1739–1744

Bjorklund LJ, Ingimarsson J, Curstedt T, John J, Robertson B, Werner O, Vilstrup CT (1997) Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. Pediatr Res 42:348–355

Bolivar JM, Gerhardt T, Gonzalez A, Hummler H, Claure N, Everett R, Bancalari E (1995) Mechanisms for episodes of hypoxemia in preterm infants undergoing mechanical ventilation. J Pediatr 127:767–773

Bonta BW, Uauy R, Warshaw JB, Motoyama EK (1977) Determination of optimal continuous positive airway pressure for the treatment of IRDS by measurement of esophageal pressure. J Pediatr 91:449–454

Boros SJ, Matalon SV, Ewald R, Leonard AS, Hunt CE (1977) The effect of independent variations in inspiratory-expiratory ratio and end expiratory pressure during mechanical ventilation in hyaline membrane disease: the significance of mean airway pressure. J Pediatr 91:794–798

Bose CL, Lawson EE, Greene A, Mentz W, Friedman M (1986) Measurement of cardiopulmonary function in ventilated neonates with respiratory distress syndrome using rebreathing methodology. Pediatr Res 20: 316–320

Carlo WA, Stark AR, Wright LL, Tyson JE, Papile LA, Shankaran S, Donovan EF, Oh W, Bauer CR, Saha S, Poole WK, Stoll B (2002) Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. J Pediatr 141:370–374

Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID

III, Piazza AJ, Sanchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD (2010) Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 362: 1959–1969

Castoldi F, Daniele I, Fontana P, Cavigioli F, Lista G (2011) Lung recruitment maneuver during volume guarantee ventilation of preterm infants with acute respiratory distress syndrome. Am J Perinatol 28:521–528

Chan V, Greenough A (1994) Comparison of weaning by patient triggered ventilation or synchronous intermittent mandatory ventilation in preterm infants. Acta Paediatr 83:335–337

Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ, Gattinoni L (2008) Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 178: 346–355

Clark RH, Slutsky AS, Gerstmann DR (2000) Lung protective strategies of ventilation in the neonate: what are they? Pediatrics 105:112–114

Claure N, Bancalari E, D'Ugard C, Nelin L, Stein M, Ramanathan R, Hernandez R, Donn SM, Becker M, Bachman T (2011) Multicenter crossover study of automated control of inspired oxygen in ventilated preterm infants. Pediatrics 127:e76–e83

Clucas L, Doyle LW, Dawson J, Donath S, Davis PG (2007) Compliance with alarm limits for pulse oximetry in very preterm infants. Pediatrics 119: 1056–1060

Collins MP, Lorenz JM, Jetton JR, Paneth N (2001) Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. Pediatr Res 50:712–719

Dargaville PA, Rimensberger PC (2010) Lung volume measurement in the neonate-throwing light on the subject. Pediatr Res 67:9–10

Dargaville PA, Rimensberger PC, Frerichs I (2010) Regional tidal ventilation and compliance during a stepwise vital capacity manoeuvre. Intensive Care Med 36:1953–1961

Davis C, Mazzolini A, Mills J, Dargaville P (1999) A new sensor for monitoring chest wall motion during high-frequency oscillatory ventilation. Med Eng Phys 21:619–623

De Jaegere A, van Veenendaal MB, Michiels A, van Kaam AH (2006) Lung recruitment using oxygenation during open lung high-frequency ventilation in preterm infants. Am J Respir Crit Care Med 174:639–645

Dimitriou G, Greenough A, Griffin F, Chan V (1995) Synchronous intermittent mandatory ventilation modes compared with patient triggered ventilation during weaning. Arch Dis Child Fetal Neonatal Ed 72:F188–F190

Dinger J, Topfer A, Schaller P, Schwarze R (2001) Effect of positive end expiratory pressure on functional residual capacity and compliance in surfactant-treated preterm infants. J Perinat Med 29:137–143

Dreyfuss D, Saumon G (1993) Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis 148:1194–1203

Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323

Dreyfuss D, Soler P, Basset G, Saumon G (1988) High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159–1164

Easa D, Finn KC, Balaraman V, Sood S, Wilkerson S, Takenaka W, Mundie TG (1995) Preservation of pulmonary function in the ventilated neonatal piglet with normal lungs. Pediatr Pulmonol 19:174–181

Emeriaud G, Baconnier P, Eberhard A, Debillon T, Calabrese P, Benchetrit G (2010) Variability of end-expiratory lung volume in premature infants. Neonatology 98:321–329

Fabres J, Carlo WA, Phillips V, Howard G, Ambalavanan N (2007) Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. Pediatrics 119:299–305

Fencl V, Vale JR, Broch JR (1968) Cerebral blood flow and pulmonary ventilation in metabolic acidosis and alkalosis. Scand J Clin Lab Invest Suppl 102:VIII

Fiastro JF, Habib MP, Quan SF (1988) Pressure support compensation for inspiratory work due to endotracheal tubes and demand continuous positive airway pressure. Chest 93:499–505

Frerichs I, Schiffmann H, Hahn G, Hellige G (2001) Non-invasive radiation-free monitoring of regional lung ventilation in critically ill infants. Intensive Care Med 27:1385–1394

Fujimoto S, Togari H, Yamaguchi N, Mizutani F, Suzuki S, Sobajima H (1994) Hypocarbia and cystic periventricular leukomalacia in premature infants. Arch Dis Child 71:F107–F110

Garland JS, Buck RK, Allred EN, Leviton A (1995) Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory distress syndrome. Arch Pediatr Adolesc Med 149:617–622

Gattinoni L, Vagginelli F, Chiumello D, Taccone P, Carlesso E (2003) Physiologic rationale for ventilator setting in acute lung injury/acute respiratory distress syndrome patients. Crit Care Med 31:S300–S304

Gilbert C (2008) Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 84:77–82

Gleason CA, Short BL, Jones MD Jr (1989) Cerebral blood flow and metabolism during and after prolonged hypocapnia in newborn lambs. J Pediatr 115:309–314

Goldsmith LS, Greenspan JS, Rubenstein SD, Wolfson MR, Shaffer TH (1991) Immediate improvement in lung volume after exogenous surfactant: alveolar recruitment versus increased distention. J Pediatr 119:424–428

Graziani LJ, Spitzer AR, Mitchell DG, Merton DA, Stanley C, Robinson N, McKee L (1992) Mechanical ventilation in preterm infants: neurosonographic and developmental studies. Pediatrics 90:515–522

Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK (1971) Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med 284:1333–1340

Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, Cole CH (2006) Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. Pediatrics 118:1574–1582

Heldt GP (1988) The effect of gavage feeding on the mechanics of the lung, chest wall, and diaphragm of preterm infants. Pediatr Res 24:55–58

Hernandez LA, Peevy KJ, Moise AA, Parker JC (1989) Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol 66:2364–2368

Hickling KG (2001) Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. Am J Respir Crit Care Med 163:69–78

Holzman BH, Scarpelli EM (1979) Cardiopulmonary consequences of positive end-expiratory pressure. Pediatr Res 13:1112–1120

Hummler H, Gerhardt T, Gonzalez A, Claure N, Everett R, Bancalari E (1996) Influence of different methods of synchronized mechanical ventilation on ventilation, gas exchange, patient effort, and blood pressure fluctuations in premature neonates. Pediatr Pulmonol 22:305–313

Kaiser JR, Gauss CH, Pont MM, Williams DK (2006) Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol 26:279–285

Kamlin CO, Davis PG (2004) Long versus short inspiratory times in neonates receiving mechanical ventilation. Cochrane Database Syst Rev (4):CD004503

Keszler M (2006) Volume guarantee and ventilator-induced lung injury: Goldilock's rules apply. Pediatr Pulmonol 41:364–366

Keszler M (2009) State of the art in conventional mechanical ventilation. J Perinatol 29:262–275

Keszler M, Nassabeh-Montazami S, Abubakar K (2009) Evolution of tidal volume requirement during the first 3 weeks of life in infants <800 g ventilated with Volume Guarantee. Arch Dis Child Fetal Neonatal Ed 94:F279–F282

Kontos HA, Raper AJ, Patterson JL (1977) Analysis of vasoactivity of local pH, PCO2 and bicarbonate on pial vessels. Stroke 8:358–360

Kraybill EN, Runyan DK, Bose CL, Khan JH (1989) Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr 115:115–120

Lachmann B (1992) Open up the lung and keep the lung open. Intensive Care Med 18:319–321

Laptook AR, Salhab W, Allen J, Saha S, Walsh M (2006) Pulse oximetry in very low birth weight infants: can oxygen saturation be maintained in the desired range? J Perinatol 26:337–341

Lista G, Castoldi F, Fontana P, Reali R, Reggiani A, Bianchi S, Compagnoni G (2011) Lung inflammation in preterm infants with respiratory distress syndrome: effects of ventilation with different tidal volumes. Pediatr Pulmonol 41:357–363

Maida JM, Mathers K, Alley CL (2008) Pediatric ophthalmology in the developing world. Curr Opin Ophthalmol 19:403–408

Mariani G, Cifuentes J, Carlo WA (1999) Randomized trial of permissive hypercapnia in preterm infants. Pediatrics 104:1082–1088

Mathe JC, Clement A, Chevalier JY, Gaultier C, Costil J (1987) Use of total inspiratory pressure-volume curves for determination of appropriate positive end-expiratory pressure in newborns with hyaline membrane disease. Intensive Care Med 13:332–336

McCallion N, Lau R, Dargaville PA, Morley CJ (2005) Volume guarantee ventilation, interrupted expiration, and expiratory braking. Arch Dis Child 90:865–870

Monkman S, Kirpalani H (2003) PEEP–a "cheap" and effective lung protection. Paediatr Respir Rev 4: 15–20

Mrozek JD, Bendel-Stenzel EM, Meyers PA, Bing DR, Connett JE, Mammel MC (2000) Randomized controlled trial of volume-targeted synchronized ventilation and conventional intermittent mandatory ventilation following initial exogenous surfactant therapy. Pediatr Pulmonol 29:11–18

Muscedere JG, Mullen JB, Gan K, Slutsky AS (1994) Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 149:1327–1334

Mutch WA, Harms S, Lefevre GR, Graham MR, Girling LG, Kowalski SE (2000) Biologically variable ventilation increases arterial oxygenation over that seen with positive end-expiratory pressure alone in a porcine model of acute respiratory distress syndrome. Crit Care Med 28:2457–2464

Nassabeh-Montazami S, Abubakar K and Keszler M (2009) The impact of instrumental dead-space in volume targeted ventilation of the extremely low birth weight infant. Pediatr Pulmonol 44:128–133

OCTAVE Study Group (1991) Multicentre randomised controlled trial of high against low frequency positive pressure ventilation. Oxford Region Controlled Trial of Artificial Ventilation OCTAVE Study Group. Arch Dis Child 66:770–775

Okumura A, Hayakawa F, Kato T, Itomi K, Maruyama K, Ishihara N, Kubota T, Suzuki M, Sato Y, Kuno K, Watanabe K (2001) Hypocarbia in preterm infants with periventricular leukomalacia: the relation between hypocarbia and mechanical ventilation. Pediatrics 107:469–475

Osorio W, Claure N, D'Ugard C, Athavale K, Bancalari E (2005) Effects of pressure support during an acute reduction of synchronized intermittent mandatory ventilation in preterm infants. J Perinatol 25:412–416

Peltekova V, Engelberts D, Otulakowski G, Uematsu S, Post M, Kavanagh BP (2010) Hypercapnic acidosis in

ventilator-induced lung injury. Intensive Care Med 36:869–878
Pohlandt F, Saule H, Schroder H, Leonhardt A, Hornchen H, Wolff C, Bernsau U, Oppermann HC, Obladen M, Feilen KD (1992) Decreased incidence of extra-alveolar air leakage or death prior to air leakage in high versus low rate positive pressure ventilation: results of a randomised seven-centre trial in preterm infants. Eur J Pediatr 151:904–909
Probyn ME, Hooper SB, Dargaville PA, McCallion N, Crossley K, Harding R, Morley CJ (2004) Positive end expiratory pressure during resuscitation of premature lambs rapidly improves blood gases without adversely affecting arterial pressure. Pediatr Res 56:198–204
Raichle ME, Posner JB, Plum F (1970) Cerebral blood flow during and after hyperventilation. Arch Neurol 23:394–403
Reyes ZC, Claure N, Tauscher MK, D'Ugard C, Vanbuskirk S, Bancalari E (2006) Randomized, controlled trial comparing synchronized intermittent mandatory ventilation and synchronized intermittent mandatory ventilation plus pressure support in preterm infants. Pediatrics 118:1409–1417
Reynolds EO (1971) Effect of alterations in mechanical ventilator settings on pulmonary gas exchange in hyaline membrane disease. Arch Dis Child 46:152–159
Rimensberger PC (2002) Neonatal respiratory failure. Curr Opin Pediatr 14:315–321
Rimensberger PC, Cox PN, Frndova H, Bryan AC (1999a) The open lung during small tidal volume ventilation: concepts of recruitment and "optimal" positive end-expiratory pressure. Crit Care Med 27:1946–1952
Rimensberger PC, Pristine G, Mullen BM, Cox PN, Slutsky AS (1999b) Lung recruitment during small tidal volume ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. Crit Care Med 27:1940–1945
Schmidt B, Whyte RK, Asztalos EV, Moddemann D, Poets C, Rabi Y, Solimano A, Roberts RS (2013) Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. JAMA 309:2111–2120
Schmolzer GM, Kamlin OC, O''Donnell CP, Dawson JA, Morley CJ, Davis PG (2010) Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room. Arch Dis Child Fetal Neonatal Ed 95:F393–F397
Scopesi F, Calevo MG, Rolfe P, Arioni C, Traggiai C, Risso FM, Serra G (2007) Volume targeted ventilation (volume guarantee) in the weaning phase of premature newborn infants. Pediatr Pulmonol 42:864–870
Sharma A, Greenough A (2007) Survey of neonatal respiratory support strategies. Acta Paediatr 96:1115–1117
Silverman WA (2004) A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. Pediatrics 113:394–396
Simbruner G (1986) Inadvertent positive end-expiratory pressure in mechanically ventilated newborn infants: detection and effect on lung mechanics and gas exchange. J Pediatr 108:589–595
Sivan Y, Deakers TW, Newth CJ (1990) Functional residual capacity in ventilated infants and children. Pediatr Res 28:451–454
South M, Morley CJ (1986) Synchronous mechanical ventilation of the neonate. Arch Dis Child 61:1190–1195
South M, Morley CJ (1992) Respiratory timing in intubated neonates with respiratory distress syndrome. Arch Dis Child 67:446–448
Stenson BJ (2013) Oxygen targets for preterm infants. Neonatology 103:341–345
Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, Battin M, Bowler U, Broadbent R, Cairns P, Davis PG, Deshpande S, Donoghoe M, Doyle L, Fleck BW, Ghadge A, Hague W, Halliday HL, Hewson M, King A, Kirby A, Marlow N, Meyer M, Morley C, Simmer K, Tin W, Wardle SP, Brocklehurst P (2013) Oxygen saturation and outcomes in preterm infants. N Engl J Med 368:2094–2104
Stewart AR, Finer NN, Peters KL (1981) Effects of alterations of inspiratory and expiratory pressures and inspiratory/expiratory ratios on mean airway pressure, blood gases, and intracranial pressure. Pediatrics 67:474–481
Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R (2001) Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/American Thoracic Society. Eur Respir J 17:302–312
STOP-ROP Multicenter Study Group (2000) Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. Pediatrics 105:295–310
Suarez-Sipmann F, Bohm SH (2009) Recruit the lung before titrating the right positive end-expiratory pressure to protect it. Crit Care 13:134
Suki B, Alencar AM, Sujeer MK, Lutchen KR, Collins JJ, Andrade JS Jr, Ingenito EP, Zapperi S, Stanley HE (1998) Life-support system benefits from noise. Nature 393:127–128
Te Pas AB, Kamlin CO, Dawson JA, O'Donnell C, Sokol J, Stewart M, Morley CJ, Davis PG (2009) Ventilation and spontaneous breathing at birth of infants with congenital diaphragmatic hernia. J Pediatr 154:369–373
Thome U, Topfer A, Schaller P, Pohlandt F (1998) The effect of positive end expiratory pressure, peak inspiratory pressure, and inspiratory time on functional residual capacity in mechanically ventilated preterm infants. Eur J Pediatr 157:831–837
Thome UH, Carroll W, Wu TJ, Johnson RB, Roane C, Young D, Carlo WA (2006) Outcome of extremely preterm infants randomized at birth to different PaCO2 targets during the first seven days of life. Biol Neonate 90:218–225
Tin W, Wariyar U (2002) Giving small babies oxygen: 50 years of uncertainty. Semin Neonatol 7:361–367
Tingay DG, Mills JF, Morley CJ, Pellicano A, Dargaville PA (2006) The deflation limb of the pressure-volume relationship in infants during high-frequency ventilation. Am J Respir Crit Care Med 173:414–420

Tsuchida S, Engelberts D, Peltekova V, Hopkins N, Frndova H, Babyn P, McKerlie C, Post M, McLoughlin P, Kavanagh BP (2006) Atelectasis causes alveolar injury in nonatelectatic lung regions. Am J Respir Crit Care Med 174:279–289

van Kaam AH, Rimensberger PC (2007) Lung-protective ventilation strategies in neonatology: what do we know – what do we need to know? Crit Care Med 35:925–931

van Kaam AH, Haitsma JJ, De Jaegere A, van Aalderen WM, Kok JH, Lachmann B (2004) Open lung ventilation improves gas exchange and attenuates secondary lung injury in a piglet model of meconium aspiration. Crit Care Med 32:443–449

van Kaam AH, Rimensberger PC, Borensztajn D, De Jaegere AP (2010) Ventilation practices in the neonatal intensive care unit: a cross-sectional study. J Pediatr 157:767–771

Vilstrup CT, Bjorklund LJ, Larsson A, Lachmann B, Werner O (1992) Functional residual capacity and ventilation homogeneity in mechanically ventilated small neonates. J Appl Physiol 73:276–283

Vilstrup CT, Bjorklund LJ, Werner O, Larsson A (1996) Lung volumes and pressure-volume relations of the respiratory system in small ventilated neonates with severe respiratory distress syndrome. Pediatr Res 39:127–133

von Ungern-Sternberg BS, Hammer J, Schibler A, Frei FJ, Erb TO (2006) Decrease of functional residual capacity and ventilation homogeneity after neuromuscular blockade in anesthetized young infants and preschool children. Anesthesiology 105:670–675

von Ungern-Sternberg BS, Regli A, Schibler A, Hammer J, Frei FJ, Erb TO (2007) The impact of positive end-expiratory pressure on functional residual capacity and ventilation homogeneity impairment in anesthetized children exposed to high levels of inspired oxygen. Anesth Analg 104:1364–1368, table

Wada K, Jobe AH, Ikegami M (1997) Tidal volume effects on surfactant treatment responses with the initiation of ventilation in preterm lambs. J Appl Physiol 83:1054–1061

Wiswell TE, Graziani LJ, Kornhauser MS, Stanley C, Merton DA, McKee L, Spitzer AR (1996) Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with high-frequency jet ventilation. Pediatrics 98:918–924

Yanos J, Watling SM, Verhey J (1998) The physiologic effects of inverse ratio ventilation. Chest 114: 834–838