Mechanical Ventilation

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Alik Kornecki and Derek S. Wheeler

Abstract

Mechanical ventilation is perhaps the cornerstone of contemporary critical care. Indeed, the history of critical care medicine, especially pediatric critical care medicine, is inextricably tied with that of mechanical ventilation. The first Pediatric Intensive Care Units (PICUs) arose during the polio epidemic with negative pressure ventilation (the so-called "iron lung"). However, while mechanical ventilation is clearly life-sustaining, one should remember that it is only a supportive modality and does not reverse the underlying disease process. Moreover, mechanical ventilation can be associated with a number of adverse effects, which in turn can be associated with significant morbidity and risk of mortality. A thorough understanding of the physiologic basis of mechanical ventilation is therefore essential to providing safe, effective care in the PICU.

Keywords

Mechanical ventilation • Pressure-control • Volume-control • Modes of ventilation • Respiratory physiology • Weaning • Cardiorespiratory interactions • PEEP

Introduction

Mechanical ventilation is perhaps the cornerstone of contemporary critical care. Indeed, the history of critical care medicine, especially pediatric critical care medicine, is inextricably tied with that of mechanical ventilation. The first Pediatric Intensive Care Units (PICUs) arose during the polio epidemic with negative pressure ventilation (the so-called "iron lung") [1]. However, while mechanical ventilation is clearly life-sustaining, one should remember that it is only a supportive modality and does not reverse the underlying disease process. Moreover, mechanical ventilation can be associated with a number of adverse effects, which in turn can be associated with significant morbidity and risk of mortality. A thorough understanding of the physiologic basis of mechanical ventilation is therefore essential to providing safe, effective care in the PICU.

A. Kornecki, MD (✉)
Department of Pediatric Critical Care,
London Health Sciences Centre, Children's Hospital,
Pediatric Critical Care, 800 Commissioners Rd. East, 5010,
London, ON N6A 5W9, Canada
e-mail: alik.kornecki@lhsc.on

D.S. Wheeler, MD, MMM
Division of Critical Care Medicine,
Cincinnati Children's Hospital Medical Center,
University of Cincinnati College of Medicine,
Cincinnati, OH, USA
e-mail: derek.wheeler@cchmc.org

Physiology of Mechanical Ventilation

Respiratory System Equation of Motion

Conceptually, the respiratory system can be modeled as a balloon that is connected to a tube. The forces required to inflate the balloon must overcome an elastic element (the balloon in the box) and a resistive element (the resistance in the tube). Classic respiratory mechanics must obey the

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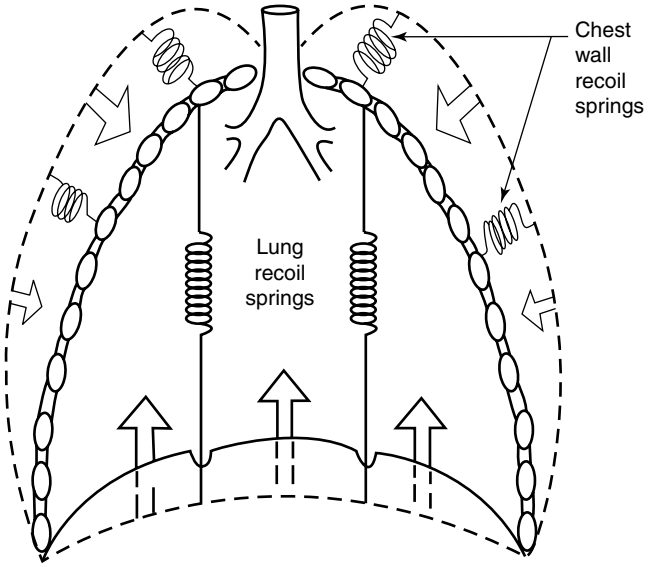

Fig. 8.1 Opposing forces in the respiratory system. Elastic recoil is the tendency of elements in the chest wall and lungs that are stretched during inspiration to snap back or recoil (*arrows*) to their original state at the end of expiration. At this point (at FRC or resting volume), the "springs" are relaxed, and the structure of the rib cage allows no further collapse. Opposing forces of the chest wall and lung balance out, and intrathoracic and airway pressures become equal (this further defines FRC) (Reprinted from Harris and Wood [2])

laws of Newtonian physics. The relationship between pressure, volume, and flow is therefore modeled by the equation of motion. Just like the balloon model, in order to "inflate" the lungs, the total pressure applied must exceed the opposing elastic ($P_{elastic}$) and resistance forces ($P_{resistance}$) of the lungs, chest wall, and conducting airways (Fig. 8.1). The total pressure applied to the respiratory system (P_{RS}) of a patient on mechanical ventilatory support is the sum of the pressure generated by the ventilator measured at the airway (P_{AWO}) and the pressure developed by the respiratory muscles (P_{MUS}).

$$P_{RS} = P_{AWO} + P_{MUS} = P_{elastic} + P_{resistance} \tag{8.1}$$

Note that during spontaneous breathing, P_{AWO} is equal to zero, as all of the pressure required to generate flow through the respiratory system is provided by the respiratory muscles. Conversely, if a patient is on full mechanical ventilatory support, P_{MUS} is equal to zero, as all of the pressure required to generate flow through the respiratory system is provided by the ventilator.

The total pressure applied to the respiratory system (P_{RS}) must exceed the opposing elastic and flow-resistive forces of the respiratory system. Recall that the normal tendency of the elastic forces of the lungs will result in lung collapse, while the normal tendency of the elastic forces of the chest wall is to expand. At functional residual capacity (FRC), these elastic forces are perfectly opposed. These elastic forces (also referred to as elastic recoil pressure, or elastance) reflect the relative stiffness of the respiratory system (i.e., the tendency of the respiratory system to return to its resting shape after deformation by an external force, in this case P_{RS}). Elastance (E) is the change in pressure (ΔP, or dP) for a given change in volume (ΔV, or dV).

$$E = dP/dV \tag{8.2}$$

The total elastance of the respiratory system is the sum of the elastance of the lungs and of the chest wall (the lungs and chest wall behave like elements in series). Elastance is the reciprocal of compliance. Practically, compliance is a measure of the distensibility of the respiratory system. It is therefore the change in volume (dV) for a given change in pressure (dP):

$$C = 1/E = dV/dP \tag{8.3}$$

Note that under most conditions, there is a linear relationship between pressure and volume (Fig. 8.2), such that compliance is the slope of the pressure-volume curve.

The resistive forces in the respiratory system include airways resistance (R), respiratory system inertance (I), and tissue resistance. Resistance is analogous to Ohm's Law of electricity, such that resistance is determined by the change in pressure (dP) over flow.

$$R = dP/\dot{V} = dP/\left(dV/dt\right) \tag{8.4}$$

where R is resistance, dP is the pressure gradient, and $\dot{V}$ is flow (i.e. the change in volume over time). Ordinarily, under most physiologic conditions, tissue resistance makes a very small contribution to these resistive forces and is therefore usually ignored. Inertance (I) is a measure of the pressure gradient required to cause a change in flow-rate with time, i.e. pressure divided by acceleration.

$$I = dP/d\dot{V} = dP/d^2\ V/dt^2 \tag{8.5}$$

where I is the inertance, dP is the change in pressure, $d\dot{V}$ is the change in flow over time (i.e., acceleration of the gas, or d^2V/dt^2). Inertance is negligible during quiet, passive breathing and during most forms of mechanical ventilation (with the notable exception, perhaps of high frequency ventilation). It is therefore frequently ignored.

Compliance therefore relates pressure to volume, resistance relates pressure to flow, and inertance relates pressure to linear acceleration. Putting all of these concepts together, the equation of motion for the respiratory system therefore becomes:

$$P_{RS} = \left(E \times V\right) + \left(R \times \dot{V}\right) + I = \left(V/C\right) + \left(R \times \dot{V}\right) + I \tag{8.6}$$

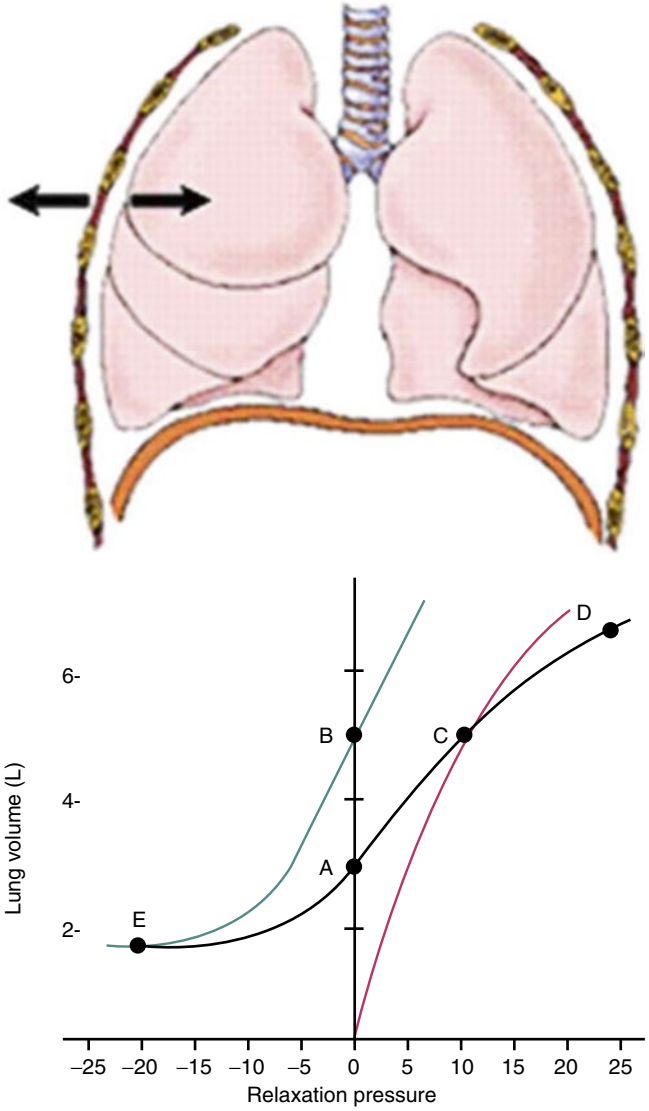

Fig. 8.2 Compliance of the lung, chest wall, and respiratory system. *Top*: diagram of the lung and chest cage. *Arrows* show the movement of the chest cage and lung. *Bottom*: Separate relaxation curves for the lung (*right*) and chest cage (*left*) along with the combined lung-chest cage relaxation curve (*middle*). The combined lung-chest cage curve is the algebraic sum of the separate lung and chest cage curves. The slope of each relaxation curve corresponds to the compliance for the structure(s). At end expiration (*point A*), recoil or relaxation pressure for the lung and chest cage alone are equal but opposite. At this point, lung volume corresponds to FRC. As additional air volume is inhaled into the lung, the lung is stretched further and exhibits a greater recoil pressure. At the same time, the chest cage is less compressed, so its negative recoil pressure diminishes as it approaches its equilibrium volume. When a slightly larger air volume is inhaled, the chest cage reaches its equilibrium volume (0-mmHg relaxation pressure, *point B*), and the lung and lung-chest relaxation curves intersect (*point C*). Thereby, at this lung volume, all measured relaxation for the lung-chest cage system is from the lung because the chest cage is at its equilibrium volume (*point B*), or the volume it would assume if the lung were not present. If an even greater air volume is inhaled (*point D*), both the lung and chest cage are stretched beyond their equilibrium volumes. Note that the compliance curve for the combined lung-chest cage becomes more flattened (less compliant) at this point because the lung and chest cage are both tending to recoil toward smaller equilibrium volumes. If the total lung-chest cage system is returned to resting end expiration (*point A*) and air is expelled, a negative relaxation pressure results for both the chest cage and combined lung-chest cage (*point E*). At this point, the chest cage is compressed as more and more air is expelled, with the negative recoil pressure resulting from the tendency of the chest to expand toward its equilibrium volume (*point B*). At the same time, the lung contributes little positive relaxation pressure because it is close to its equilibrium volume (i.e., 0-ml volume) because it is stretched very little (Reprinted from DiCarlo [3]. With permission of the American Physiological Society)

Note also that the equation of motion can be re-written as:

$$P_{RS} = E \times V + \int dV/dt + \int d^2V/dt^2 \quad (8.7)$$

Given that the inertance is negligible, the "I" term falls out. Substituting 1/C for the "E" term (compliance is the inverse of elastance), the respiratory equation of motion becomes:

$$P_{RS} = V/C + \int dV/dt \quad (8.8)$$

Children Are Not Small Adults!

While ventilation has been extensively investigated and characterized in preterm neonates and adults, there has been relatively few laboratory investigations and prospective clinical investigations of mechanical ventilation in infants and/or older children. As a result, age-based guidelines for the use of conventional mechanical ventilation in pediatric patients have not been well-established. Indeed, the recommendations for mechanical ventilation in children have been extrapolated from adult data [4]. Compared to adults, pediatric patients demonstrate a spectrum of lung and chest wall development. Maturation in the human lung continues well after the neonatal period until between 2 and 8 years of age [5]. Acute respiratory failure is one of the most common reasons that children are admitted to the PICU. The unique developmental differences between children and adults contribute to this prevalence and significantly impact the management of critically ill children [6–9]. For example, infants and young children have fewer alveoli compared to adults (approximately 20 million alveoli after birth to 300 million alveoli by the age of 8 years) [10–12]. The size of each individual alveolus is also smaller in children (150–180 μm diameter versus 250–300 μm diameter) [13]. Together, these two anatomic differences markedly decrease the surface area available for gas exchange by approximately 8 years of age.

The airways enlarge both in length and diameter with age. However, growth of the distal airways lags behind that of the

proximal airways during the first 5 years of life, accounting for the increased peripheral versus central airways resistance in children relative to adults [14]. Resistance is inversely proportional to the radius of the airway to the fourth power (by Hagen-Poiseuille's Law). Therefore, an equivalent reduction in airway caliber (e.g. by mucus, bronchospasm, edema, etc) in a child versus an adult will result in a greater relative decrease in the total cross-sectional area of the airway, as well as a greater relative increase in resistance. In addition, the cartilaginous support of the peripheral airways is less well developed, increasing the risk of dynamic compression with high expiratory flow rates (e.g. as occurs during crying, coughing, or respiratory distress). Finally, the pathways of collateral ventilation (e.g., pores of Kohn) are not fully developed in young children. These pathways allow alveoli to participate in gas exchange, even in the presence of an obstructed distal airway. Collectively, these important anatomic differences significantly increase the risk of atelectasis in children [7, 15].

The developmental influences on respiratory mechanics are also critically important [16]. The ribs are more horizontally aligned in young infants and children compared to adults, which makes it difficult to generate a greater negative intrathoracic pressure in the presence of poor lung compliance. The lung matrix of a neonate contains only small amounts of collagen. The elastin-to-collagen ratio changes during the first months and years of life and affects lung stiffness (i.e. elastance) and elastic recoil. Similarly, the infant's chest wall is soft and compliant, providing little opposition to the natural recoil (deflating tendency) of the lungs. These changes in elastic recoil pressure for both the lung and chest wall result in a lower functional residual capacity (FRC) in children versus adults [17], which may even approach the critical closing volume of the alveolus in neonates and infants (Fig. 8.3). In order to generate the same tidal volume per kg body weight, infants must perform a greater amount of work compared to adults, which is clinically manifest as severe retractions due to the highly compliant rib cage and contraction of the diaphragm during negative pressure generation [19]. Retractions represent a significant waste of energy – therefore, some infants will stop breathing from fatigue when faced with these excessive respiratory demands, which has been confirmed through electromyography performed in fatiguing infants who become apneic in the face of increased work of breathing [20, 21].

Ventilation-perfusion mismatching is one of the most common causes of hypoxemia in the PICU. As discussed in previous chapters of this textbook, due to the effects of gravitational forces, both ventilation and perfusion decrease significantly from the base (or dependent regions) of the lung to the apex (or non-dependent regions), though perfusion decreases to a greater degree compared to ventilation (Fig. 8.4). The regional differences in both ventilation and perfusion are greatly influenced by gravity. Intrapleural

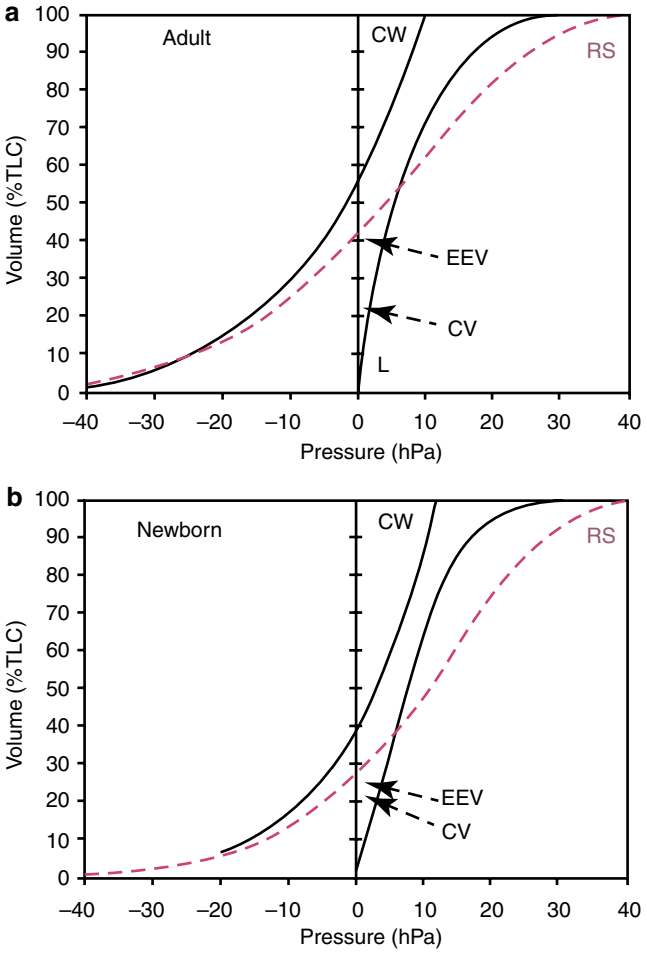

Fig. 8.3 Changes in total respiratory system compliance (*RS*), chest wall compliance (*CW*), and lung compliance (*L*) as a function of age. Two theoretical pressure-volume curves are provided for comparison – the *top curve* shows a pressure-volume curve in an adult, while the *bottom curve* shows a pressure-volume curve in a neonate. The normal elastic properties of the lung and chest wall are such that there is an inward elastic recoil of the lung (lung tends to collapse) and outward elastic recoil of the chest wall (chest wall tends to expand). At functional residual capacity (FRC) (depicted as the volume at which the airway pressure on the respiratory system pressure-volume curve is zero, EEV), these forces are in equilibrium. Note that the FRC is lower in children compared to adults. Also note that at FRC, the corresponding airway pressure on the chest wall curve is negative (i.e. at this volume, the natural tendency of the chest wall is to expand). The chest wall is in equilibrium (i.e. volume at which the corresponding airway pressure is zero) at a higher percentage of total lung capacity (TLC) in adults compared to children (due to increased chest wall compliance in children). Finally, also note that the closing volume (depicted as CV) approaches FRC in children compared to adults (Adapted from West [18]. With permission from John Wiley & Sons, Inc.)

pressure (P_{PL}) is less negative in the dependent regions of the lung (the base). Alveolar pressure (P_A) remains relatively constant. The transpulmonary pressure (P_L), or alveolar distending pressure, is therefore lower in the dependent regions of the lung:

$$P_L = P_A - P_{PL} \tag{8.9}$$

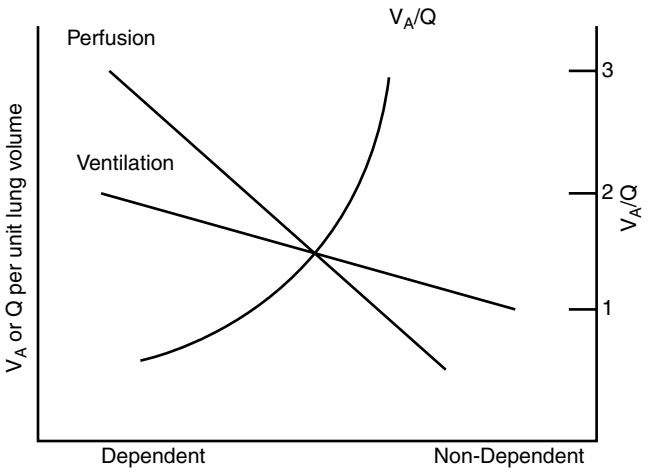

Fig. 8.4 Differential distribution of ventilation (V_A), perfusion (Q), and ventilation-perfusion ratio in the lung. The dependent lung regions preferentially receive better ventilation and perfusion compared to the non-dependent lung regions. However, the perfusion gradient is much steeper than the ventilation gradient, such that the ventilation-perfusion ratio is higher in the non-dependent (apex) regions compared to the dependent (base) regions (Adapted from West [18]. With permission from John Wiley & Sons, Inc.)

At functional residual capacity (FRC), the alveoli in the dependent regions of the lung will then tend to have a lower volume. At the apex, or non-dependent regions of the lung, the converse is true (higher transpulmonary pressure due to a more negative intrapleural pressure, leading to higher volumes). The higher volume alveoli in the non-dependent regions are therefore on a flatter portion of the compliance curve (i.e., less compliant). This creates a seeming paradox in the normal lung, where the lower volume alveoli at the base will have a greater compliance and are more easily inflated compared to the higher volume alveoli at the apex, because they are situated on the steeper segment of the pressure-volume curve [22]. These gravitational differences also result in a greater degree of lung perfusion at the base (dependent regions), compared to the apex (non-dependent regions).

Note also that the regional differences in ventilation also depend upon lung volumes. At FRC, the dependent lung regions are preferentially ventilated. At lower lung volumes (e.g., residual volume, RV, the volume left in the lungs at the end of a maximal forced expiratory effort), the converse is true. Dynamic compression of the airways, due to the effects of a maximal, forced expiratory effort (which often generates a positive P_{PL}), occurs in the lower (dependent) regions of the lung first. This leads to gas-trapping within the alveoli in the lower (dependent) regions of the lung. The alveoli in the non-dependent regions will therefore be on a much steeper portion of the compliance curve (i.e., increased compliance). Together, these two phenomena lead to preferential ventilation of the non-dependent lung regions first (in contrast to the situation at FRC).

Pulmonary edema and lung inflammation in critically ill children (and adults, for that matter) will exaggerate the gravitational effects on the intrapleural pressure gradient discussed above. As P_{PL} exceeds P_A, closure of lung units in dependent lung regions will occur during normal breathing. This inverts the normal distribution of ventilation causing the apex (or non-dependent region) of the lung to receive improved ventilation. These effects are compounded by the fact that the patients have a lower lung volume (recall the discussion above). While there are significant changes in the distribution of alveolar ventilation, perfusion is less affected. In other words, perfusion continues to be greatest at the base (or dependent region) of the lungs, leading to significant ventilation/perfusion mismatch in the dependent regions of the lungs. Chest CT and electrical impedance tomography (EIT) studies have elegantly shown the regional differences in lung consolidation in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [23–31].

There appears to be some important differences in children versus adults with regards to regional differences in ventilation (note that these studies were performed in spontaneously breathing patients). For example, in adults with unilateral lung collapse, ventilation and perfusion are better matched if patients are positioned with the "good lung" in a dependent position ("good lung down"). Conversely, in children with unilateral lung collapse, ventilation and perfusion are better matched if patients are positioned with the "good lung" in a non-dependent position ("bad lung down") [32–35].

Finally the ratio of lung volume to body weight is not constant and varies with development. In humans this ratio increase significantly with age in the first 2 years of life; therefore, when V_T is corrected to body weight, a smaller fraction of lung volume is inflated in young infant compared to older child. On this basis alone, adult guidelines for lung protective ventilation are unlikely to be applicable to the infant and young child.

The aforementioned developmental differences in lung pathophysiology may have significant implications on the management of critically ill children with acute respiratory failure. As an example, based upon the ARDS Network trial of low tidal volume ventilation [36], the current recommendation is to target a tidal volume of (V_T) of 6 mL/kg predicted body weight in critically ill adults with ALI/ARDS. There have been few studies on low tidal volume ventilation in critically ill children, though most authorities recommend such an approach [4, 37], based largely upon extrapolation from adult data. In addition, a low tidal volume ventilation strategy has been used in several multi-center, randomized, controlled trials in critically ill children with acute lung injury with acceptable results [38–40]. Adkins and colleagues [41] reported that the lungs of young, newborn rabbits were more susceptible to the development of ventilator-induced lung injury (VILI) due to increased lung and chest wall compliance and larger distending volumes at high peak airway pressures compared to adult rabbits.

However, several studies using a rodent model of VILI suggest that newborns may not be as susceptible to the adverse effects of VILI compared to adults [42–44].

A single center, retrospective study compared the mortality between critically ill children with ALI from a time period before low V_T ventilation was prevalent (1988–1992) with the current era, when the use of low V_T ventilation has become more established (2000–2004) [45]. Children in the more recent era had a lower mean V_T/kg (8.1 ± 1.4 vs. 10.2 ± 1.7, $p < 0.001$) and higher positive end-expiratory pressure (PEEP) (7.1 ± 2.4 vs. 6.1 ± 2.7, $p = 0.007$), with resultant lower peak inspiratory pressure (PIP) (27.8 ± 4.2 vs. 31.5 ± 7.3, $p < 0.001$) and higher $PaCO_2$ (47.2 ± 11.8 vs. 37.0 ± 5.0, $p < 0.001$). More importantly, children in the more recent era had a significantly lower mortality (21 % vs. 35 %, $p = 0.04$) and more ventilator-free days (16.0 ± 9.1 vs. 12.7 ± 10, $p = 0.03$). A recently published study in China also suggested that the use of lower tidal volumes are associated with better outcomes [46]. Conversely, a follow-up study failed to show a relationship between the tidal volume in the first 7 days and mortality [47]. Erickson and colleagues [48] published the results of a prospective, observational study of ALI which included nearly all of the PICUs in Australia and New Zealand. In contrast to the results above, increased tidal volumes were associated with decreased mortality. Finally, a single-center, retrospective study showed an association between higher V_T and increased ventilator-free days. In this study, 85 % of the children were ventilated with a target VT between 6 and 10 mL/kg, though a higher VT within this range was associated with increased ventilator-free days [49]. Regardless of what conclusions are to be made from these discrepant data, the main point that must be emphasized is that heedless extrapolation of adult data to critically ill children should be avoided, given the differences in respiratory physiology in children versus adults.

Indications for Mechanical Ventilation

The need for mechanical ventilatory support is one of the most common reasons for admission to the PICU, and acute respiratory failure is by far the most common indication for mechanical ventilation [50–53]. Although explicit indications exist (Table 8.1), they are not well validated. Thus, the decision to institute mechanical ventilation is made by the physician at the bedside on clinical grounds, and takes into consideration the underlying condition, the likely course of the disease, and the potential response to medical treatment. The indications for tracheal intubation (e.g. airway protection, relief of airway obstruction) are not the same as for mechanical ventilation and are discussed elsewhere in this textbook. However, children who require tracheal intubation will usually require mechanical ventilatory support, because of reduction in respiratory drive associated with sedation, the perceived benefits of positive end-expiratory pressure (PEEP), and the need to counter the resistance to airflow offered by the tracheal tube. In general, institution of mechanical ventilation is indicated when the patient's spontaneous ventilation is threatened or not adequate to sustain life.

Table 8.1 Indications for mechanical ventilation

Respiratory failure
Pump failure
Chest wall dysfunction (*e.g.* flail chest)
Neuromuscular disease
Central nervous dysfunction (decrease in respiratory drive)
Congenital (*e.g.* Ondine's course)
Acquired (*e.g.* trauma, drugs, infectors)
Pulmonary disease
Ventilation/perfusion mismatch (*e.g.* pneumonia)
Pulmonary shunt (*e.g.* acute respiratory distress syndrome)
Reduction in functional residual capacity
Others
Support an intubated patient (*e.g.* patient intubated for airway protection)
Decrease work of breathing and afterload
Optimized carbon dioxide levels (*e.g.* head trauma with increase in intracranial pressure)

Children usually require mechanical ventilation because of acute respiratory failure (or impending respiratory failure), which occurs when the system fails to meet the body's requirements in terms of oxygenation (acute hypoxemic respiratory failure) and/or elimination of carbon dioxide (acute ventilator failure). Acute respiratory failure may occur as a result of primary lung disease (e.g. reduction in functional residual capacity or compliance, worsened ventilation-perfusion mismatch) or pump dysfunction (e.g. reduced central drive, muscle disease). Beyond these pulmonary indications, mechanical ventilation may also be instituted in order to improve left ventricular function in case of heart failure or to optimize CO_2 in the case of increased intracranial pressure. As mechanical ventilation is not without complications, the goal should be to apply it only when necessary and with minimal injury to the lungs and maximal comfort to the patient. In other words, the goals of mechanical ventilation are to provide adequate oxygenation and ventilation (which necessarily includes maintaining alveolar recruitment and patient-ventilator synchrony), while minimizing alveolar overdistension, auto-PEEP (see below), and oxygen toxicity (i.e., using the lowest possible F_{IO2}).

Non-invasive Mechanical Ventilation

The interface between the ventilator and the patient may be classified into two categories: invasive and non-invasive. Invasive ventilation uses a tracheal or a tracheostomy tube, or for a limited period of time during a general anesthetic, a

Table 8.2 Adverse effects of invasive positive pressure mechanical ventilation

Respiratory
Upper airways
Nasal trauma
Nasopharyngeal and pharyngeal trauma
Laryngeal trauma – vocal cord fixation/paralysis
Subglottic edema/stenosis
Lower airways
Air-leak
Pneumothorax
Pneumomedistinum
Pulmonary interstitial emphysema
Atelectasis
Ventilation-associated Respiratory Infections (VARI)
Ventilator-associated Pneumonia (VAP)
Ventilator-associated Tracheobronchitis (VAT)
Nosocomial Sinusitis
Ventilation associated lung injury
Cardiovascular
Decrease venous return
Increase pulmonary vascular resistance
Central nervous system
Increase intracranial pressure
Renal
Decrease urine output (direct and indirect effect)

Table 8.3 Potential applications for noninvasive positive pressure ventilation (NIPPV) in children

More common
Nocturnal central hypoventilation
Chronic lung disease
Neuromuscular disease
Cystic fibrosis – bridge for transplant
Cardiac failure
Less common
Acute respiratory failure – likely to reverse within 24 h
Transient post-extubation upper airway obstruction
Pneumonia
Asthma – bronchiolitis
Pulmonary edema
Patients that refuse tracheal intubation

laryngeal mask airway (LMA). Non-invasive ventilation, on the other hand, does not require a tracheal device. Non-invasive ventilation may be administered with a positive pressure ventilator, sometimes termed non-invasive positive pressure ventilation (NIPPV), or as negative pressure ventilation. The main advantages of non-invasive ventilation are the avoidance of tracheal intubation or tracheotosmy, with the associated complications (Table 8.2). The presence of a tracheal tube increases the risk of airway trauma and ventilator-associated respiratory infections (VARI, which includes ventilator-associated tracheobronchitis, sinusitis, or ventilator-associated pneumonia), as well as an increased propensity for immobilization and need for sedation and/or neuromuscular blockade. In addition, important physiological functions such as speech, cough, and swallowing are impaired. Furthermore, non-invasive ventilation may be applied outside the critical care setting and outside the hospital as an optimal home ventilation solution.

Non-invasive Positive Pressure Ventilation (NIPPV)

Non-invasive positive pressure ventilation (NIPPV) refers to the delivery of positive airway pressure *via* a conduit other than a tracheal device, i.e. via either a facemask or nasal mask. It was first introduced to provide home ventilation for children with nocturnal hypoventilation caused by neuromuscular disease. Since the early 1990s, NIPPV has gained increased popularity for extended acute and chronic indications. For example, NIPPV is becoming a commonly used modality in the neonatal ICU for managing premature lung disease, with mixed results [54–56]. However, as with other modalities of ventilation there are fewer studies in critically ill children than in adults [57–69]. As a result, selection guidelines regarding the use of NIPPV in children are extrapolated from the adult literature (Table 8.3). While there are few randomized, controlled studies regarding the efficacy of NIPPV in critically ill children, there are several case series that describe its application in children with mild to moderate acute respiratory failure (e.g. bronchiolitis, asthma, pneumonia) and for chronic home ventilation (e.g. neuromuscular disease) [54, 58, 59]. The application of CPAP has been shown to increase FRC, improve lung mechanics, and increase arterial oxygenation in patients with ALI [70]. NIPPV in the early phase of ALI may reverse the disease process and prevent tracheal intubation in selected patients; however NIPPV is limited by difficulties in effectively applying high airway pressures, controlling airway secretions, and avoiding patient discomfort when utilized for prolonged periods. A trial of NIPPV should be attempted in any stable child with early or impending respiratory failure. However, one should not persist with its use if it becomes clear that the approach is only deferring the inevitable need for tracheal intubation [55, 71, 72]. The major contraindications for the use of NIPPV are clinical conditions in which upper airway protective reflexes are compromised, especially with reduced level of consciousness, or recent gastrointestinal surgeries in which increased bowel gas may compromise repair and/or recovery.

Non-invasive positive pressure ventilation may be administered through a nasal mask or an oro-nasal mask. The oro-nasal mask covers both the nose and the mouth. It may be less comfortable than the nasal mask; however, it abolishes the potential air leak through the mouth that commonly occurs during nasal mask ventilation. Controlled trials in adults

comparing nasal and oro-nasal masks show inconsistent results regarding the efficacy of gas exchange; however, the nasal mask is generally better tolerated. Another type of mask is called the helmet [60]. The helmet covers the patient's entire head, is similar to an over-sized hockey helmet, and is sealed using straps under the shoulder. The patients can better interact with the environment and it can be applied to any patient regardless of facial contour [58, 59, 73].

A relatively newer device that is being used with more frequency in the PICU is the high-flow nasal cannula (HFNC) system [74]. HFNC use higher gas flow rates compared to standard nasal cannula, and there is some evidence to suggest that HFNC does deliver some degree of continuous positive airway pressure [75–79]. There are reports that the increased use of HFNC in certain conditions (e.g. bronchiolitis) have led to a decrease in the number of children requiring invasive mechanical ventilation compared to historical experience [80–82]. However, HFNC has not been shown to be superior (or for that matter, equivalent) to either NIPPV in a prospective trial, so further studies are recommended.

NIPPV may be applied as continuous positive pressure airway pressure (CPAP) or combination of CPAP with pressure support ventilation (PSV). Any ventilator with high flow may be used to provide NIPPV. It can be delivered by volume or pressure-preset modes, or with a bi-level controlled or continuous positive pressure (CPAP) device. The more commonly used devices are portable bi-level ventilators that are designed for NIPPV and can operate successfully with a relatively large leak, providing high continuous flow. Pressure support ventilation is the most common mode of ventilation used with these devices. With bi-level devices (often erroneously referred to as BiPAP®, Respironics, Corporation, Murrysville, PA, which is one of several commercially available devices that can deliver bi-level positive airway pressure), the nomenclature may vary, but the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) are preset. The patient's spontaneous inspiration triggers the machine and the difference between IPAP and EPAP is the magnitude of the pressure support delivered with each breath. Because of the potential leak around the mask with high pressures, 15–25 cm H_2O is generally the highest pressure that usually can be achieved reliably and consistently. As certain ventilators do not have an inspiratory time limit, the preset pressure may be not attained in the presence of a significant air leak and the device will not therefore cycle *off* to expiration. In certain circumstances, only constant continuous positive airway pressure (CPAP) is provided throughout inspiration and expiration.

The key factor for effective initiation of NIPPV is a cooperative and relaxed patient. Patient coaching and gradual titration of the pressure may improve the rate of success. As a result, initiation of NIPPV is time consuming for the team as compared to conventional ventilation; this may be the major reason why some clinicians are reluctant to apply it. NIPPV is safe and can be delivered in any number of settings beyond the PICU. However, it can be associated with complications, such that it is generally the common practice to initiate NIPPV in the PICU setting where increased personnel and monitoring can provide constant attention to titrating adjustments to the patient's needs. Principle complications include skin ulceration and erosion in the area of contact between the mask and the skin, and once the skin has become eroded, application of the mask is extremely difficult. Drying of the nasal and pharyngeal mucosa, aspiration, and abdominal distension with gastric dilatation have all been reported as well.

Non-invasive Negative Pressure Ventilation

Until the mid-1900's negative pressure ventilation was almost the only method available to provide ventilation for the management of respiratory failure. Today, it is used only on rare occasions. It works by intermittently applying negative (i.e. sub-atmospheric) pressure to the chest, or to the chest and abdomen. This causes expansion of the chest, and decreases pleural and alveolar pressure, thereby creating a pressure gradient for inspired gas to move into the alveoli during inspiration. The expiration in most of the ventilators occurs passively by elastic recoil of the lungs, but in some the option of active expiration exists. The main two types of ventilators are the traditional *iron lung* where the torso (i.e. chest and abdomen, but not the head) are enclosed in a sealed solid cylinder and the Cuirass system, wherein a plastic shell is placed around the chest.

At present, negative pressure ventilation delivers negative pressure by four modes – cyclic negative pressure, so-called *negative-positive* pressure (*where expiration is actively assisted*), continuous negative pressure, and negative pressure with an oscillator. Most ventilators have the capacity to independently control the pressure and time during inspiration and during expiration. The role of such ventilation is not well established in either adults or children [83, 84]. Nonetheless, negative pressure ventilation is routinely applied in certain centers for chronic home ventilation when the non-invasive positive pressure is either unavailable or is not tolerated. The main factors that limit its widespread application include large unit size, noise, and potential upper airway collapse during inspiration [85].

When the entire body is exposed to negative pressure as occurs with the tank ventilators, non-invasive negative pressure ventilation has similar hemodynamic effects to conventional positive pressure ventilation. However, when the negative pressure is confined to the chest alone (e.g. using the cuirass-type, Hayek Oscillator) this modality of ventilation closely mimics the physiological dynamics of spontaneous ventilation and may have potential hemodynamic advantages

over conventional positive pressure ventilation (PPV). The deleterious effect on PPV on venous return is not present with negative pressure ventilation. On the contrary, negative pressure ventilation augments venous return, as in spontaneous inspiration. An appealing indication for non-invasive negative pressure ventilation was suggested by Shekerdemian and colleagues in a number of clinical studies [86–90]. During inspiration the right atrial pressure decreases, increasing the gradient for venous return. These investigators showed that following the Fontan operation or repair of tetralogy of Fallot, children had a significantly greater pulmonary blood flow and cardiac output when ventilated using negative versus positive pressure [86, 88, 90]. In summary then, while non-invasive negative pressure ventilation is a potentially attractive mode of ventilation, there are not enough physiological and clinical data to support its use as a first line approach. It may be applied on individual basis when venous return or pulmonary blood flow is especially tenuous.

Invasive Mechanical Ventilation

Since the 1960s, when negative pressure ventilation was almost completely abandoned (with the notable exceptions discussed briefly above), nearly all mechanical ventilators have employed the principal of intermittent positive pressure ventilation, where the lungs are inflated by applying a positive pressure to the airways. Most modern ventilators are equipped with a piston bellows system or use a high pressure gas source to drive the gas flow to the lungs. Ventilators used to be classified according to the termination of active inspiration and initiation of passive exhalation. Accordingly, the inspiratory phase may be terminated when a preset pressure is achieved (*pressure-cycled ventilators*), a preset volume is achieved (*volume-cycled ventilators*), or when a preset inspiratory time is reached (*time-cycled ventilators*). This classification has become somewhat irrelevant with time, as with nearly all modern ventilators currently in use, the clinician may separately control the tidal volume, the pressure delivered, and the inspiratory time (or indirectly with the flow). Some ventilators that are used for transport or for home ventilation are pure *pressure-cycled ventilators,* where the ventilator produces gas flow to the lungs until it reached a preset pressure, then inspiration is terminated and thereafter, the expiration valve opens, and expiration begins. The duration of inspiration and tidal volume varies according to the total respiratory system compliance (*chest and lung*) and the airway resistance. When lung or chest wall compliance is low or inspiratory time short, then the delivered tidal volume will be smaller. Furthermore, in case of an air leak, the preset airway pressure may not be reached thereby preventing the termination of inspiration. The above limitations restrict the use of these ventilators to children with relatively healthy lungs (e.g. neuromuscular disease, central hypoventilation).

Pressure Control Versus Volume Control

Mechanical ventilation is often classified by whether the ventilator is set to deliver a pre-determined tidal volume (volume limited, volume pre-set ventilation, volume-cycled ventilation, or volume control ventilation, VCV) or to achieve a pre-determined peak pressure (pressure limited, pressure pre-set ventilation, pressure-cycled, or pressure control ventilation, PCV) [91–93]. During Pressure Control Ventilation (PCV), the breath is delivered at a set rate with a decelerating flow pattern (Fig. 8.5). The tidal volume is determined by the preset pressure, inspiratory time and respiratory system mechanics. During the Volume Control Ventilation (VCV), a preset volume is delivered by the ventilator with each breath using a constant flow pattern (Fig. 8.5). The breath is terminated by a preset time (*time-cycled*) or after the delivery of the preset tidal volume (*volume-cycled*). During time-cycled, volume-preset ventilation, the inspiratory flow is regulated in order to deliver the preset tidal volume and the tidal volume and minute ventilation are guaranteed (regardless of resistance or compliance).

PCV has been associated with decreased patient work of breathing [94, 95], improved oxygenation at lower peak pressures [96, 97], and better outcomes (in terms of number of extrapulmonary organ failures and duration of mechanical ventilation) in critically ill adults with ALI/ARDS [98, 99]. In addition, in otherwise healthy children undergoing general anesthesia, PCV is associated with lower peak pressures [100–102]. Regardless of these studies, the choice of PCV or VCV is often dictated by institutional bias and/or physician preference.

Pressure Control Ventilation

During Pressure Control Ventilation (PCV), the breath is delivered at a set rate with a decelerating flow pattern and is terminated when a preset peak inspiratory pressure (PIP) is achieved (Fig. 8.5). The tidal volume is determined by the preset PIP and respiratory system mechanics. The inspiratory time is usually set by the operator. PCV is usually recommended in patients with leakage around an uncuffed tracheal tube, in cases of obstructive lung disease (e.g. status asthmaticus), neonates or small infants where measurement of the tidal volume is inherently inaccurate, or rarely, in the presence of a bronchopleural fistula. When the tidal volume is measured at the ventilator, instead of at the end of the tracheal tube, then changes in circuit compliance significantly influence the accuracy of the measurement. This is particularly the case with neonates and infants, where the tidal volumes are far smaller compared with the volume of the ventilator circuit. The main drawback of PCV is that tidal volume and minute ventilation are directly influenced by the respiratory system mechanics, and as these change, so too does the delivered tidal volume. As a result, in cases of rapidly changing respiratory

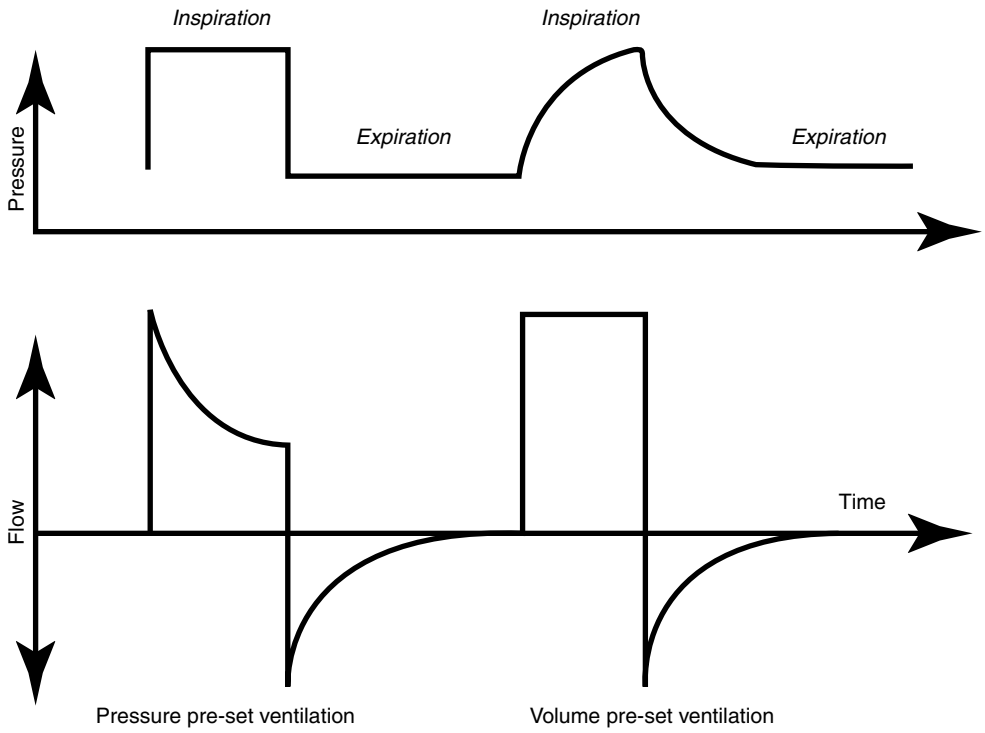

Fig. 8.5 Pressure limited breath (*left*) vs. volume limited breath (*right*). The same tidal volume is delivered in both modes. However, with a decelerating flow in limited pressure (*left*) or square wave flow in volume limited mode (*right*)

system mechanics (e.g. administration of surfactant), the patient may be at risk of inappropriate levels of ventilation. However, the same argument can be made about volume-preset ventilation and the potential risk of barotrauma with rapid changes in respiratory mechanics (see below).

Volume Control Ventilation

During Volume Control Ventilation (VCV), a preset volume is delivered by the ventilator with each breath using a constant flow pattern (Fig. 8.5). The breath is terminated by a preset time (*time-cycled*) or after the delivery of the preset tidal volume (*volume-cycled*). During time-cycled, volume-preset ventilation, the inspiratory flow is regulated in order to deliver the preset tidal volume and the tidal volume and minute ventilation are guaranteed (regardless of resistance or compliance). This mode of ventilation is commonly used in larger infants and children, but it is not generally recommended for neonates or small infants. The main drawback is variation in tidal volume delivery, due to either leaks in the system or inaccurate volume measurement. If compliance worsens, higher peak pressures will be delivered, which can be associated with areas of overdistension (e.g., areas of normal lung compliance) and ventilator-associated lung injury. In modern ventilators, the peak pressure can be limited during volume control ventilation (see next mode, below).

Adaptive Pressure Control Ventilation

Most of the newer ventilators have an additional mode of ventilation that combines the purported advantages of a decelerating flow pattern characteristic of the pressure-limited mode [94], as well as the guaranteed tidal volume associated with volume-preset ventilation. A preset tidal volume is delivered with the lowest pressure possible, using a decelerating flow pattern. After the first volume-limited breath, the plateau pressure measured by the ventilator is used for the next breath; this pattern is continued for each successive breath (Fig. 8.6). For each subsequent breath, the ventilator automatically adjusts the minimal inspiratory pressure required to guarantee the preset tidal volume. If the tidal volume increases above the preset value, the next breath is delivered with a lower pressure. This mode, called adaptive pressure-control ventilation, goes by a number of different names, depending upon the commercial brand of ventilator used: Pressure-regulated Volume Control (PRVC) (Servo-I, Maquet, Solna, Sweden), AutoFlow (Dräger, Telford, PA), adaptive pressure ventilation (Hamilton Galileo, Hamilton Medical AG, Bonaduz, Switzerland), Volume control plus (Puritan Bennet, Covidien, Dublin, Ireland), and volume-targeted pressure control or pressure controlled volume guaranteed (GE Healthcare, Cleveland, OH). Limited clinical trials have shown that lower levels of peak airway pressure are required to deliver the same tidal volumes using adaptive pressure control compared to classic volume control modes [94, 103, 104], though it is unclear whether this represents a meaningful advantage in the prevention of ventilator-induced lung injury (VILI). However, based upon what is known about the relationship between higher ventilatory pressures and worse outcomes [45, 48, 105, 106], it may be reasonable to hypothesize that this mode may be a better mode of ventilation for critically ill patients with ALI/ARDS.

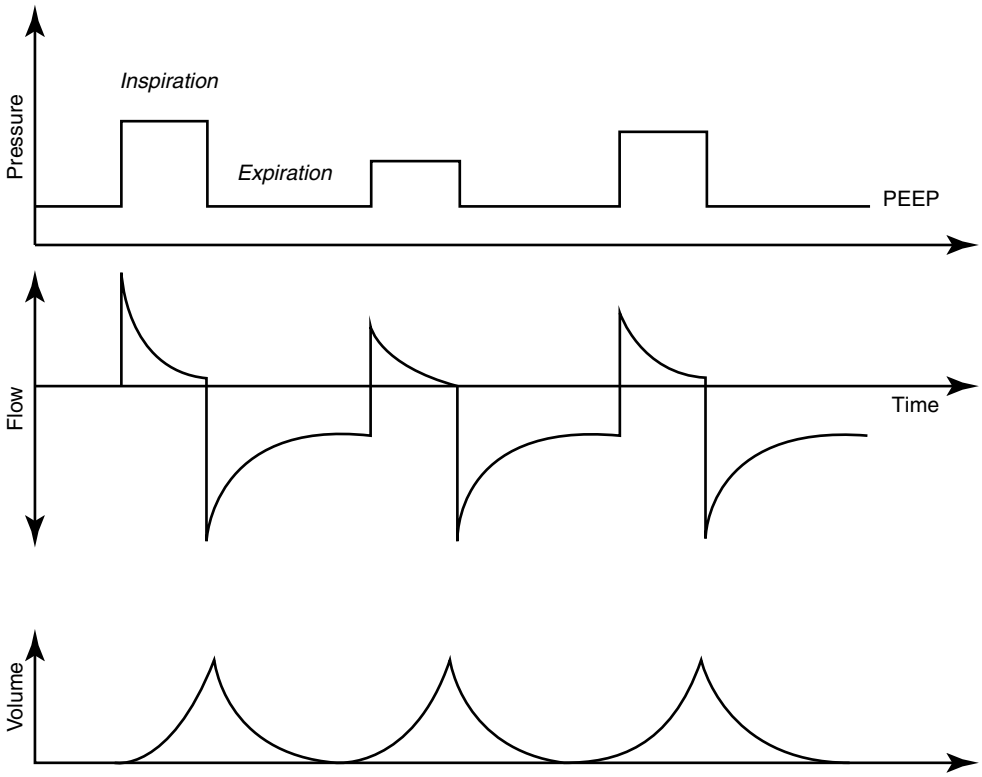

Fig. 8.6 Pressure regulated volume control (PRVC). A control mode in which the ventilator delivered a preset tidal volume, with preset frequency, and inspiratory time. The ventilator automatically adapts the optimal inspiratory pressure (lowest) in order to deliver the preset tidal volume

Ventilator Modes

The ventilatory cycle during mechanical ventilation is divided into an inspiratory and an expiratory phase. The different modes of mechanical ventilation are further classified according to the mechanism of the so-called patient-ventilator interaction during inspiration. This ranges from full ventilator control of the tidal volume and frequency, to provision of partial support only during a spontaneous breathing where the patient determines both the tidal volume and the respiratory rate. A classification of common modes of mechanical ventilation follows:

Control Mode Mechanical Ventilation (CMV)

In this mode of ventilation, the ventilator delivers a mechanical breath at a preset interval, irrespective of the patient's spontaneous effort (Fig. 8.7). The breath is either *volume-limited* or *pressure-limited*. In this mode of ventilation, the patient's spontaneous effort to breathe may interfere with the mandatory breath delivered by the ventilator. In order to prevent this, the patient's spontaneous breathing may be inhibited by decreasing the respiratory drive, either by administering sedative drugs or by hyperventilation to induce respiratory alkalosis. This mode of ventilation has almost been completely abandoned in children. It may be used rarely when a high rate of ventilation is required and the specific ventilator is unable to provide synchronized intermittent mandatory ventilation (SIMV) at such respiratory rates.

Assist/Control Mechanical Ventilation

This is a form of ventilation in which the ventilator provides a mechanical breath at a preset interval with a preset tidal volume or pressure in response to each spontaneous breath, regardless of the tidal volume desired by the patient (Fig. 8.8). Where the patient doesn't trigger the ventilator within the specified time interval, the ventilator will provide the preset tidal volume or pressure breath at the preset respiratory rate.

Synchronized Intermittent Mandatory Ventilation (SIMV)

This mode of ventilation was originally developed as a weaning mode but was quickly adopted as the main-stream mode of ventilation because of its apparent advantages over the control mode. It is a mixed ventilatory mode that allows both mandatory and spontaneous breathing (Fig. 8.9). The mandatory breaths can be pressure- or volume-regulated and the spontaneous breaths can be pressure-supported (or not). The SIMV algorithm is designed to deliver a mandatory breath in each SIMV breathe cycle, where the breath cycle is 60/[number of breaths per minute], in seconds. The mandatory breath is either patient- or ventilator-initiated. The SIMV cycle has two periods. The first period is the mandatory period that is reserved for the mandatory breath. If the patient doesn't trigger the ventilator during the mandatory period, then the machine will deliver the preset mandatory breath at the end of this period. When the patient triggers the ventilator during

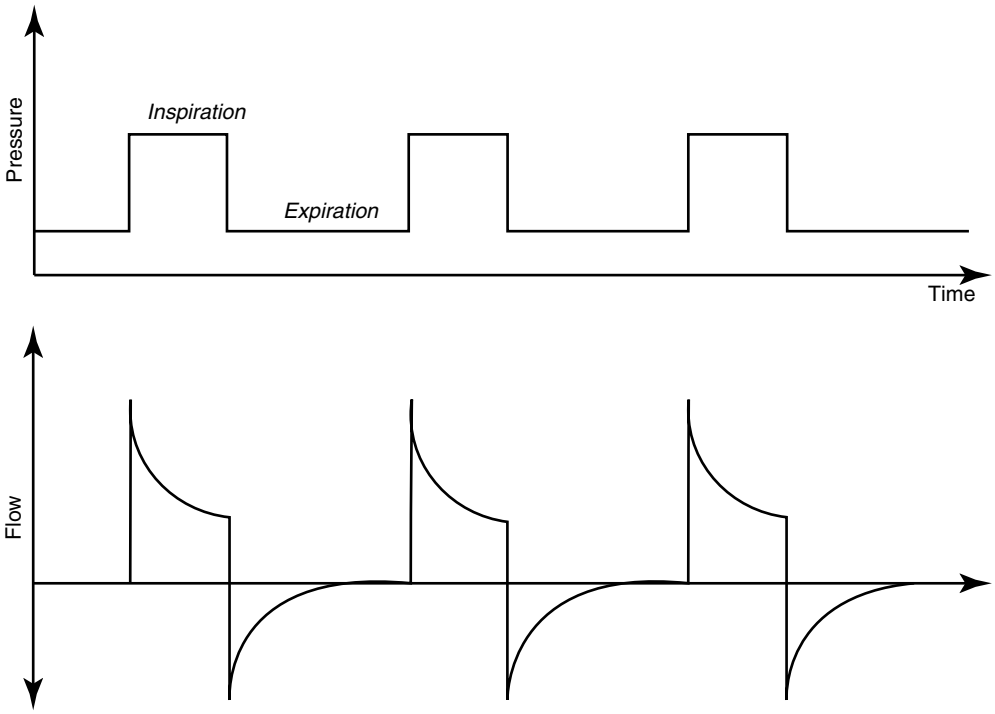

Fig. 8.7 Control ventilation mode. The ventilator delivers preset tidal volume or pressure with a preset inspiratory time and respiratory rate. End expiratory pressure (PEEP) may be kept over zero

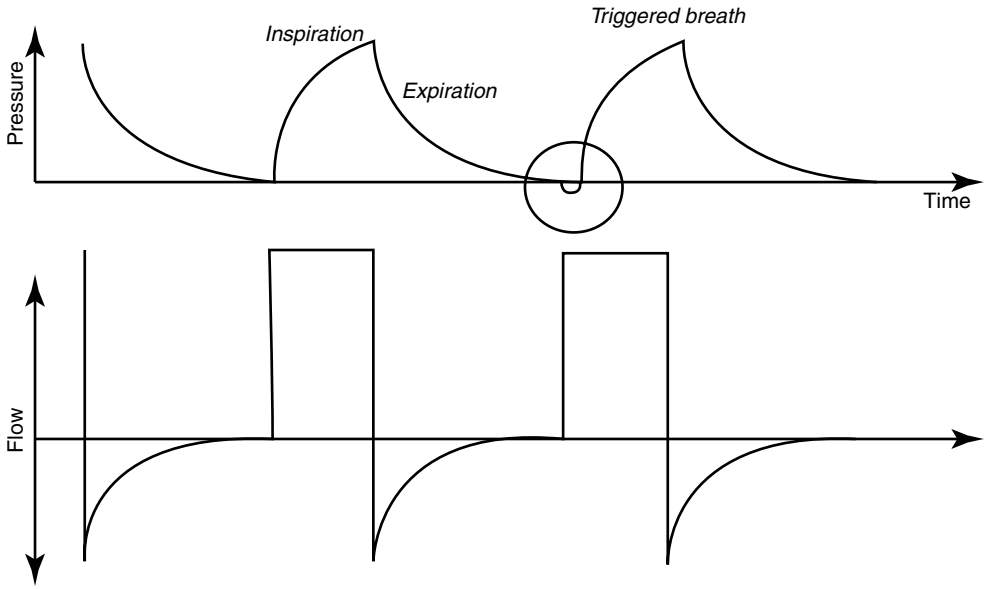

Fig. 8.8 Assist/control ventilation. When the patient doesn't trigger the ventilator within the specified time interval, the ventilator will provide the preset tidal volume at the preset respiratory rate (*left*). When the patient triggered the ventilator, a preset tidal volume in response to each spontaneous breath is delivered by the ventilator (*right*)

this period, a preset mandatory breath is delivered and the mandatory period is terminated. The second period is a spontaneous period which is reserved for the spontaneous breaths. The spontaneous period starts each time a mandatory period terminates. The main advantages of SIMV over CMV are maintenance of spontaneous respiratory activity which results in continuous use of the respiratory muscles and improved patient-ventilator synchronization. The result of the latter may be a reduction in the use of excessive sedation and neuromuscular blockade.

Pressure Support Ventilation

Pressure Support was designed as a spontaneous mode of ventilation that augments only spontaneous breaths (Fig. 8.10). The idea is that by doing so, the work of breathing imposed on the patient is reduced. It is a patient-triggered, pressure-limited, flow-cycled mode of ventilation. During pressure support ventilation, the ventilator delivers flow in order to provide a constant preset inspiratory pressure with each spontaneous breath. The patient controls the respiratory rate, inspiratory time, and the tidal volume (unless the preset

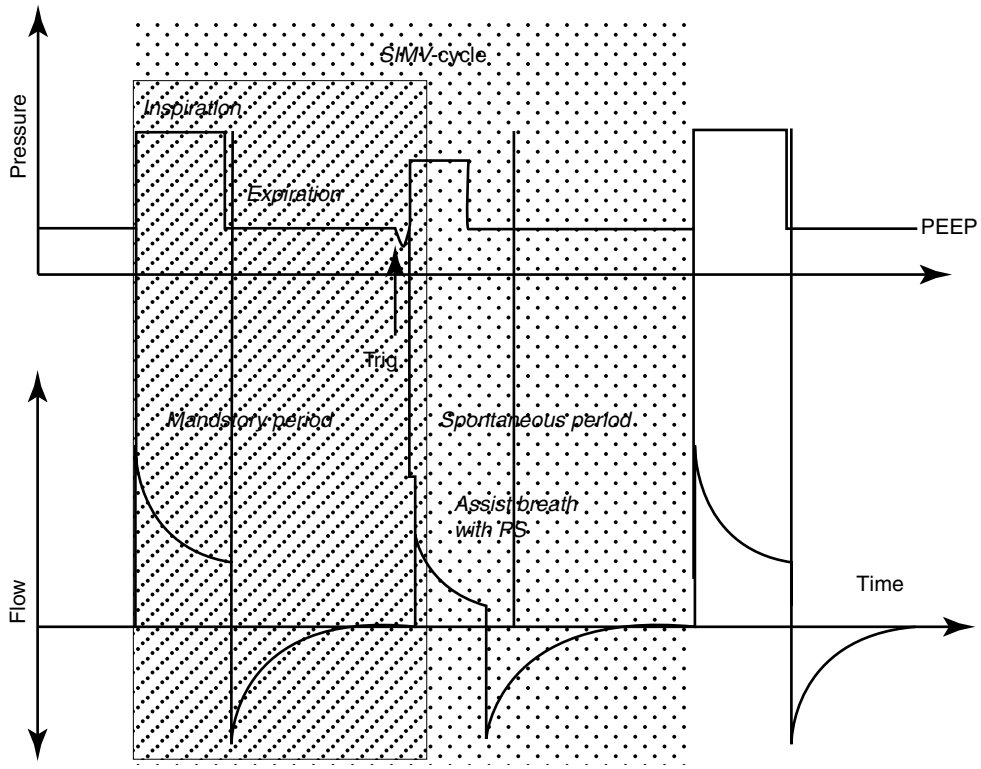

Fig. 8.9 Synchronized intermittent mandatory ventilation (*SIMV*). The SIMV cycle consist of a mandatory period and spontaneous period. A breath effort during the SIMV mandatory period will deliver a breath with a preset volume or pressure. A breath effort during the spontaneous period will delivered spontaneous breath in the absence of pressure support, or pressure/volume supported breath. In case the patient doesn't take a breath during the mandatory period the ventilator delivers a mandatory breath (volume limited or pressure limited)

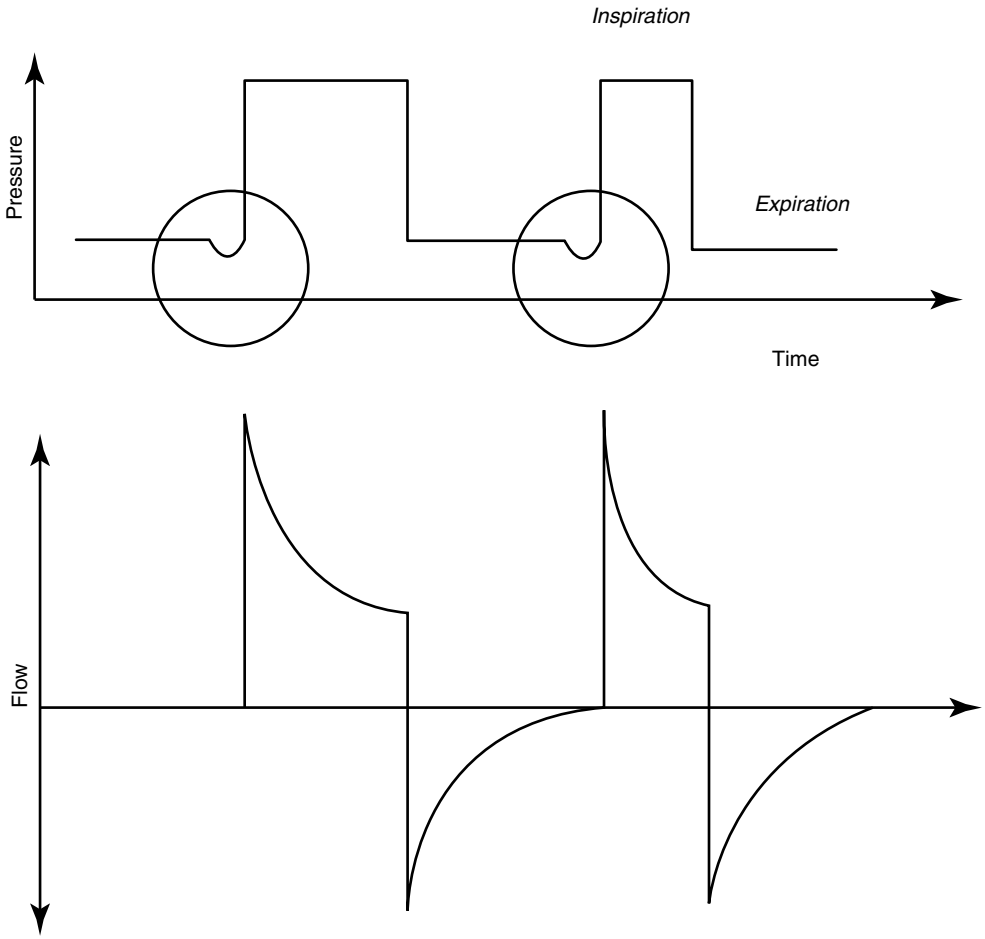

Fig. 8.10 A combination of control and pressure support ventilation

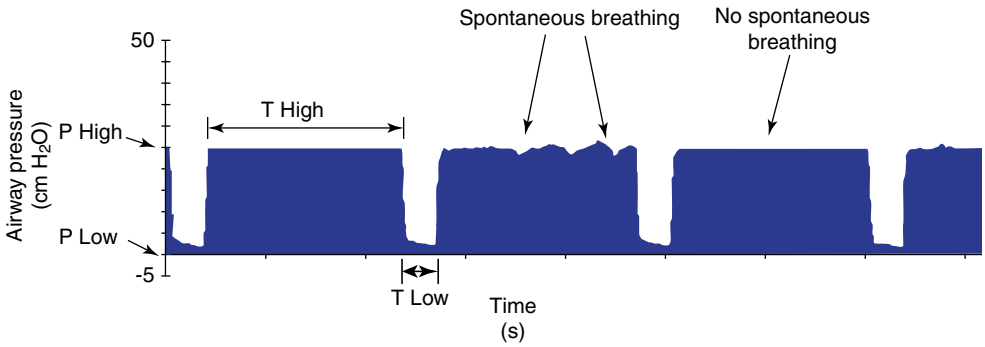

Fig. 8.11 Airway pressure release ventilation (APRV)

pressure is extremely high). To trigger the ventilator, the patient has to develop a minimum negative inspiratory effort that exceeds in magnitude the preset sensitivity (based on either pressure or flow). In order to reduce the effort of triggering to a minimum, most modern ventilators are equipped with very sensitive pressure or flow transducers that have a fast demand valve and a continuous flow. Since support ventilation is completely dependent on patient capacity to develop an inspiratory effort when this mode is used in isolation, the patient must have sufficient respiratory drive and muscle strength in order to trigger the ventilator. Furthermore, pressure support ventilation *per se* doesn't prevent apnea; however, virtually all modern ventilators have an alarm and backup mechanical support in the event of apnea.

The basis for determining or choosing the optimal preset pressure levels is not well established. In addition, neither the appropriate pulmonary disease states nor the use of adjunct SIMV have been determined for pressure support ventilation [107]. However, in practice, pressure support is usually used in combination with SIMV in order to improve patient comfort, or simply because practice has evolved that way. In addition, pressure support is commonly used during the weaning process.

One approach in implementing pressure support ventilation is to adjust the preset pressure to a level appropriate to achieve the desire tidal volume, and/or to achieve apparent patient comfort. The major drawback in this mode of ventilation, as with any pressure-preset mode, is that tidal volume is not guaranteed. The delivered tidal volume in pressure support ventilation depends on patient effort, which of course may continuously change. Changes in neurologic status (e.g. increased sedation which may reduce respiratory drive) or alteration in respiratory mechanics may affect the delivered tidal volume. Furthermore, oxygen demand (i.e. the requirement for O_2 due to fever, stress or pain) may change over time, and as a result, minute ventilation may change correspondingly while the preset pressure remains constant.

Volume Support Ventilation

In order to overcome the major drawbacks of pressure support ventilation (i.e. tidal volume is not guaranteed), some recent models have introduced the concept of volume support ventilation. Basically, this is a pressure support mode where the inflation pressure changes in order to maintain a constant (i.e. preset) tidal volume. Using a closed-loop control system, the ventilator alters the pressure level to deliver a preset tidal volume. The delivered tidal volume is used as a feedback control for continuous adjustment of the level of pressure. This way the ventilator continuously adapts to the changes in patient effort, respiratory system mechanics and oxygen requirement. The operator sets the desired tidal volume and also, by choosing the respiratory rate, the minute ventilation. Volume support ventilation is a commonly used weaning mode of ventilation (see further discussion below) [38].

Airway Pressure Release Ventilation (APRV)

Airway pressure release ventilation (APRV) is a modality that was first described in 1987, though it has had somewhat of a renaissance in the past few years [108–112]. Conceptually, APRV is really just the application of a relatively high CPAP (called P_{HIGH}) for a set period of time (called T_{HIGH}) to maintain adequate alveolar recruitment, with an intermittent release phase to a lower pressure (called P_{LOW}) for a set period of time (called T_{LOW}) to allow for expiration (Fig. 8.11). Inspiration can occur via one of two ways. Inspiration can occur via a mechanical breath (essentially the movement from P_{HIGH} to P_{LOW} generates a "breath"). Rather than producing a tidal volume by increasing the airway pressure above a preset PEEP, as in the conventional modes of positive pressure ventilation, the tidal volume is generated when airway pressure is reduced from the preset pressure. T_{HIGH} is usually much longer than T_{LOW}, such that in the absence of spontaneous ventilation, APRV is essentially pressure-controlled inverse ratio ventilation (see below). However, one of the major advantages to APRV is the ability to breathe spontaneously at either P_{HIGH} or P_{LOW}. Theoretically, spontaneous breathing (resulting from diaphragmatic contraction) during APRV results in preferential recruitment of the dependent lung regions (recall from the discussion above that the main of areas of consolidation in patients with ALI/ARDS are in the dependent lung regions). Therefore, overdistension of the better aerated (and more compliant) non-dependent regions is avoided [113]. Ventilation (i.e.

Table 8.4 Initial ventilator settings for APRV

1. Set P_{HIGH} at the desired plateau pressure (typically 20–30 cm H_2O), usually the plateau pressure obtained by an end-inspiratory hold maneuver if the patient was in VCV or the PIP if the patient was in PCV
2. Set P_{LOW} at 0 cm H_2O
3. Set T_{HIGH} at 3–5 s
4. Set T_{LOW} at 0.2–0.8 s

Adapted from Habashi [114, 115]
In order to improve oxygenation (i.e. increase SpO_2) – increase P_{HIGH} (usually in 2 cm H_2O increments) or both P_{HIGH} and T_{HIGH} (usually in 0.2 s increments)
In order to improve ventilation (i.e. decrease $PaCO_2$) – decrease T_{HIGH} or increase T_{LOW}
During weaning, decrease P_{HIGH} and increase T_{HIGH}

removal of CO_2) is also improved during the release phase of APRV [114, 115]. In addition, because spontaneous breaths do not trigger the ventilator (just as in CPAP), spontaneous inspiration during any phase of APRV results in lower pleural pressure and can therefore augment right ventricular filling [116]. The majority of the time is spent at P_{HIGH} (80–95 % of the "cycle"). The time spent at P_{LOW} must be short enough to prevent derecruitment, yet long enough to prevent air-trapping and auto-PEEP. Recommendations for initial ventilator settings and adjustments for APRV are listed in Table 8.4. Clinical studies demonstrate improved patient comfort, gas exchange, and cardiac output during spontaneous breaths with APRV [109, 114, 115, 117]. The theoretical benefits of APRV, however, have not been shown to be superior (or even equal) to any other ventilator strategy in critically ill children with acute respiratory failure.

Inverse Ratio Ventilation

Pressure-controlled Inverse Ratio Ventilation (IRV) uses inspiratory times which exceed expiratory times, usually resulting in I:E ratios of 2:1 or even 3:1 during otherwise conventional mechanical ventilation. IRV is thought to enhance alveolar recruitment, though at the expense of a significant increase in mean airway pressure (and the potential of auto-PEEP – see below). To date, there are no studies showing that IRV is superior (or even equivalent) to any other mode of mechanical ventilator support in the PICU [118]. This mode of mechanical ventilation has largely fallen out of favor [119].

Automatic Tube Compensation (ATC)

Although not technically a mode of ventilation, some ventilators offer the option of automatic tube compensation (ATC) in which the ventilator assists a spontaneous breath by delivering positive pressure, the degree of which is proportional to the inspiratory flow and tracheal tube resistance. This pressure compensates for the estimated flow-resistive work of breathing via a closed loop control of the calculated tracheal tube resistance [120–122]. The theoretical advantage of the system is that the work of breathing imposed by the artificial airway (e.g. tracheal tube, tracheostomy) is overcome. The system uses a known resistive coefficient of the tube, measures the flow through the tube, and then applies a pressure (during inspiration) or reduce the PEEP during expiration) proportional to the resistance throughout the respiratory cycle (inspiration and expiration).. Kinks or bends in the tube as it traverses the upper airway and secretions in the inner lumen may change the tube resistance and result in imperfect compensation. Some investigators have reported that ATC improves patient comfort and helps to eliminate dynamic hyperinflation [123]. There is very little data on the effect of automatic tube compensation on work of breathing, oxygenation, ventilation, or outcomes in critically ill children [124].

Proportional Assist Ventilation (PAV)

In the conventional mode of pressure support or assist control ventilation, the support delivered by the ventilator is fixed. In contrast, PAV is governed by the equation of motion that identifies the necessary pressure to be applied to the respiratory system in order to overcome opposing elastance and resistance forces that exist in proportion to the volume and flow, respectively [125]. During PAV, the ventilator output (i.e. flow and pressure) changes according to changes in the patient's effort (that is, the more the patient pulls, the more pressure the machine generates), which in turn reflects the resistance and elastance of the respiratory system [126]. There is limited experience with this type of mechanical ventilatory support in the PICU. In addition, there are no clinical trials to suggest that this mode of ventilation is superior or equivalent to any other modes of ventilation.

Neurally Adjusted Ventilatory Assist (NAVA)

In the NAVA mode of ventilation, continuous detection of the electrical activity of the diaphragm muscles are used as an index of inspiratory drive and the amount of support provided by the ventilator corresponds to the ventilatory demand. NAVA is currently only available with one type of ventilator (Servo-i, Maquet, Solna, Sweden). NAVA requires placement of an esophageal catheter that measures the diaphragm muscle electrical activity (EA_{di}), which is a measure of the patient's neurally-mediated respiratory effort. The degree of ventilator support provided by the ventilator is proportional to the EA_{di} signal. The ventilator is equipped with a safety mechanism, such that in the event of loss of the EA_{di} signal (e.g. dislocation or disruption of the catheter), the ventilator switches to a back-up pressure support ventilation mode. If the patient does not have a spontaneous respiratory drive (e.g. oversedation, brain injury, phrenic nerve damage, neuromuscular blockade, etc), the ventilator switches to a back-up pressure control ventilation mode. The level of

inspiratory pressure delivered by the ventilator is determined by the following equation:

$$P_{aw} = \text{NAVA Level} \times EA_{di} \quad (8.10)$$

where the EAdi is the instantaneous integral of the diaphragmatic electrical activity signal (measured in μV) and the NAVA level (measured in cm $H_2O/\mu V$) is set by the clinician. While NAVA is relatively new, there are several studies suggesting that NAVA improves patient-ventilator synchrony and is generally well-tolerated [127–134], even in premature infants [135, 136]. NAVA has also been used non-invasively. However, as yet there are no studies in either children or adults that demonstrate that NAVA is superior compared to other modes of ventilation, in terms of clinical outcomes [137, 138]. Given the potential and theoretical benefits, this is certainly a promising area for further research.

Determining Initial Ventilator Settings

The overall goal of mechanical ventilation is to provide acceptable gas exchange while causing the least amount of lung injury. Generally speaking, *aggressive* ventilation in terms of airway pressure, tidal volume, and FiO_2 results in better gas exchange but with a higher risk for the development of lung damage. Thus, one should always weigh the benefits of gas exchange against the injury caused to the lung in order to achieve oxygenation and ventilation targets [119, 139–141]. The definition of acceptable gas exchange is complex, and there are no validated values for $PaCO_2$ and SaO_2 towards which one should aim. In terms of $PaCO_2$, there has been a gradual acceptance of higher values as clinicians treating neonates with acute respiratory failure [142–148], children and adults with either asthma [149, 150] or ARDS have historically practiced [151, 152]. In these contexts, the higher levels of $PaCO_2$ are tolerated or *permitted* by the clinician, hence the term *permissive hypercapnia*. Such tolerance is not accepted where elevated $PaCO_2$ could be directly harmful, such as in the presence of intracranial hypertension or acute pulmonary hypertension. In addition, recent experimental work suggests that elevated $PaCO_2$ might be directly beneficial in certain situations, although these concepts have not been well tested outside the laboratory [153–155]. Although the risks associated with hypercapnia have received a lot of attention, the risks of hypocapnia are less well appreciated. While in some circumstances hypocapnia is valuable (e.g. evolving brainstem herniation), in many situations it is either of no benefit or potentially harmful [154, 156]. The lowest acceptable level of oxygenation is even more difficult to define. Although there is no consensus regarding how low one might aim with arterial oxygen saturation (SaO_2), a lower target level of SaO_2 >90–92 % ($PaO_2 \approx 55$ mmHg) appears physiologically safe. Indeed when high levels of PEEP, plateau pressure, and/or FiO_2 are required, clinicians will commonly accept lower target levels of SaO_2 (i.e. 85–88 %) [157, 158] (some clinicians have referred to this as *permissive hypoxemia*) [159–162].

As stated previously, in cases of parenchymal lung disease, lung compliance and the functional residual capacity (FRC) are usually reduced. Unfortunately, the parenchymal lung disease is usually heterogeneous in nature and different regions of the lung are differently affected – as a result the mechanical properties are inhomogenous. The gas delivered will preferentially go to the regions with lower resistance and higher lung compliance. The rationale behind the setting of the ventilator is to homogenize the otherwise inhomogeneous disease (recruitment), to keep the lung open throughout the respiratory cycle (with use of PEEP), and to avoid over distension (limited V_T and/or plateau pressure) of the relatively healthy lung regions.

At this stage the ventilator settings should be tailored to each patient and there are no proven formulaic guidelines. The basic principles for applying mechanical ventilation in a child with acute respiratory failure include:

1. Hemodynamic status should be optimized by assuring intravascular volume and inotrope support in order to tolerate relatively high levels of PEEP
2. The proportion of non-aerated lung should be minimized by recruitment
3. The transpulmonary pressure and tidal volume should not be excessive
4. Patient comfort must be ensured and some ventilatory effort ideally maintained.

The choice of Pressure Control (PCV) versus Volume Control Ventilation (VCV) is not well established and often depends more on the type of ventilator, physician preference, or institutional bias. Historically, VCV has been used in most adult critical care units, while PCV was the preferred mode in pediatric critical care units (largely due to the lack of available ventilators that could deliver such low tidal volumes to neonates and young infants and children) [163]. However, VCV has been used safely even in premature, low birth-weight neonates with hyaline membrane disease, and no study has demonstrated the clear superiority of PCV over VCV, or vice versa, even in this unique population [164–167]. The choice of PCV versus VCV will further dictate whether peak inspiratory pressures (PIPs) or tidal volumes are set by the clinician.

Tidal Volume (V_T)

The mortality associated with ALI/ARDS has declined steadily up to about 10 years ago. While it is likely that the

reasons for improved patient survival are multifactorial, the limitation of delivered V_T and airway pressure (see below) are the only interventions that have been demonstrated in prospective, randomized, controlled trials to improve outcome. Specifically the studies performed by Amato [168] and the ARDS network [169] comparing a protective ventilator strategy (V_T <6 mL/kg ideal body weight, plateau pressure <30–35 cm H_2O) *vs*. ventilation with high V_T (12 mL/kg) showed improved patient outcome. This outcome benefit was not reported in studies in which intermediate levels of V_T were employed [170, 171]. Although the clinical implementation of the ARDS network protocol in adults has been shown to be effective and to result in reduced mortality among adults ARDS patients [172] there is still much controversy over the extent to which V_T and airway pressures should be limited and whether low V_T, low Pplat or both are necessary in order to improve outcome [173]. While the optimal tidal volume in critically ill children has not been well established, it is generally accepted that high tidal volumes associated with high end-inspiratory pressures have a negative impact on outcome [37, 45, 46, 158, 174], as described in the sections above. Therefore, it seems reasonable to use the lowest V_T necessary to achieve acceptable gas exchange, without predisposing to atelectasis (i.e. derecruitment). Most clinicians target tidal volumes in the range of 5–8 mL/kg predicted body weight [158, 175]. While it is difficult to base recommendations in critically ill children from adult clinical data, the anecdotal experience and current literature would at least suggest that this is a rational and safe starting practice. Considerable difficulty may arise in the accurate measurement of delivered V_T, and this is especially the case with small children. Ideally circuit flow (hence volume, which is measured as the integral of the flow) should be measured as close to the airway opening as possible. In many ventilators the V_T is determined from the gas flow measured at the expiratory valve, i.e. on the ventilator. Measurement of V_T at the ventilator is inaccurate (up to 90 % measurement error in small infants). The magnitude of error varies between ventilators and is also affected by respiratory system compliance, the modality of ventilation employed and the circuit type. Stand-alone respiratory monitors which can measure V_T accurately are available and appear to be more accurate than using the exhaled tidal volume at the expiratory valve of the ventilator [176–178].

The administration of low V_T is not without drawbacks. Low V_T ventilation may promote atelectasis, increase intrapulmonary shunting, and promote VALI. It results in hypercapnia which predisposes to raised intracranial pressure, pulmonary hypertension and impaired myocardial contractility. Further, hypercapnia may increase the patient's work of breathing, and promote patient-ventilator dyssynchrony (described further below).

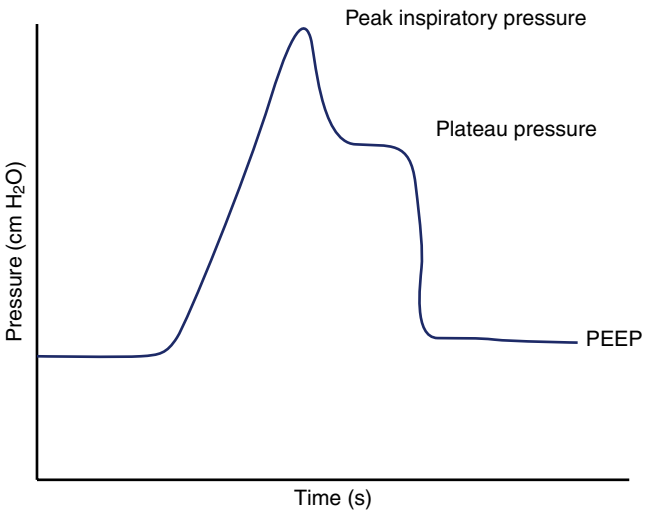

Fig. 8.12 Airway pressure waveform during volume control ventilation (VCV). An end-inspiratory hold maneuver is performed to measure plateau pressure (P_{PLAT}). The difference between PIP and P_{PLAT} is determined by the flow setting on the ventilator, as well as the resistance in the airways. An increase in the PIP–P_{PLAT} difference would (in the absence of other changes in ventilator settings) therefore suggest an increase in airways resistance

Inspiratory Pressures

With PCV, the clinician sets the peak inspiratory pressure (PIP), while in VCV, the PIP is determined by the patient's respiratory mechanics. The transpulmonary pressure (P_L) (by Eq. 8.9 alveolar pressure, P_A minus intrapleural pressure, P_{PL}) is the true alveolar distending pressure. However, P_L is not normally monitored in the clinical setting and its measurable analog may be the plateau pressure (static, i.e. no flow, end-inspiratory pressure (Fig. 8.12). Theoretically, in children because of the higher chest wall compliance, there is a better correlation between the PIP, plateau pressure (P_{PLAT}), and P_L than in the adult. The PIP is the pressure measured by the ventilator in the major airways and thus reflects airway resistance. Conversely, P_{PLAT} is the pressure that reflects the alveolar pressure and may be measured in most modern ventilators using an end-inspiratory hold maneuver for 0.5–1.5 s. In PCV, the inspiratory flow decreases to zero at the end of inspiration, such that P_{PLAT} and PIP are essentially the same. Importantly, P_{PLAT} can only be measured accurately when the patient is not exerting any respiratory effort and there is no leak around the tracheal tube. The difference between the PIP measured by the ventilator and P_{PLAT} is due predominately to airway resistance. Patients with a significant component of airway resistance (e.g. status asthmaticus) may have a large gradient between P_{PLAT} and PIP. The P_L is theoretically 10–30 % lower than P_{PLAT}. A P_L of 20 cm H_2O is generally safe and unless chest wall compliance is very poor (e.g. morbid obesity, ascites, fluid

Table 8.5 Setting PEEP based upon FIO_2

FIO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	6	8	8	10	10	10	12	14	14	14	16	18	≥18

Adapted from Curley et al. [182]. With permission from Elsevier
Summary of PEEP titration used in a pediatric prone positioning trial. Goal PaO_2 50–80 mmHg, SpO_2 88–92 %

overload, abdominal compartment syndrome), P_{PLAT} should probably be <30 cm H_2O [36, 105, 119, 175, 179, 180].

Positive End-Expiratory Pressure (PEEP)

The peak expiratory pressure (i.e. PEEP) has a pivotal role in maintaining the unstable lung units open throughout the respiratory cycle and increasing FRC. The overall effect here may be to limit the risk of VILI and improve oxygenation, thereby allowing the use of a lower FiO_2 and P_L. However, simultaneously high levels of PEEP have the potential to cause hemodynamic instability, and by increasing P_L and lung volume, may in turn contribute to overdistension and VILI. For example, a clinical trial in adults with ARDS that were ventilated with low V_T (6 mL/kg) and limited plateau pressure (≤ 30 cm H_2O) failed to show differences in mortality or length of ventilation between ventilation with high (13.2 ± 3.5 cm H_2O) and low (8.3 ± 3.2 cm H_2O) PEEP [181]. In this particular trial, PEEP was set based upon the FIO_2 required to maintain acceptable oxygenation levels (SpO_2 88–95 % or PaO_2 55–80 mmHg) (Table 8.5). There is no clear consensus, however, on the ideal method to set an optimal PEEP.

Some experts recommend determining the optimal PEEP by plotting the semi-static pressure-volume curve and setting the PEEP between the lower and higher inflection points. In this case, the lower inflection point (LIP) represents the pressure at which a large number of alveoli are recruited, while the upper inflection point (UIP) represents the pressure at which a large number of alveoli are overdistended [183–186]. With this in mind, the ideal PEEP would be just above the LIP. Unfortunately, there have been no studies assessing this particular method in critically ill children with acute respiratory failure.

Another method of setting PEEP is to start with a relatively normal PEEP (~5 cm H_2O) and increasing PEEP by a series of 2 cm H_2O incremental steps and watching for improvement in oxygenation and lung mechanics (compliance). The period of time required to observe clinically meaningful and sustained changes in oxygenation after a PEEP change is debatable, but most studies suggest it is on the order of 20–30 min after each change [187–189]. Alternatively, ideal PEEP could be determined by starting high and gradually lowering PEEP in 2 cm H_2O decrements, as derecruitment may occur faster than recruitment [189]. In addition, it has been shown that there is hysteresis in the pressure-volume curve (difference between inspiration and expiration) and that the ideal PEEP setting should be determined on the deflation limb [190, 191].

The stress index is another potential method of setting optimal PEEP [185, 192–195]. With this method, the shape of the pressure-time curve during constant-flow (i.e. classic) VCV is used to detect optimal recruitment versus overdistension (Fig. 8.13). With this method, worsening compliance (stress index > 1) suggests that the lungs are overdistended and the PEEP is too high. Conversely, improving compliance (stress index < 1) suggests there is further potential for lung recruitment and the PEEP is too low [193]. Importantly, the presence of a pleural effusion has been shown to impact the accuracy of this particular method [196].

The dead-space fraction (V_D/V_T) may also be used to determine optimal PEEP and is commonly measured using the Bohr equation:

$$V_D/V_T = \left(PaCO_2 - PeCO_2\right)/PaCO_2 \qquad (8.11)$$

where $PeCO_2$ is the mean partial pressure of expired CO_2 (expired gas is collected and compared) and $PaCO_2$ is the partial pressure of CO_2 obtained from an arterial blood gas. A normal V_D/V_T is 0.3 or less. Increased V_D/V_T has been shown to correlate with outcomes in both critically ill children [197] and adults [198–201] with ARDS. The optimal PEEP is defined as the pressure level with the highest compliance in conjunction with the lowest VD/VT [202, 203].

The use of esophageal pressure monitoring has recently been proposed to determine the optimal PEEP (as well as for detecting auto-PEEP). Esophageal pressure (P_{ES}) is measured using a thin-walled balloon which contains a small amount of air at the end of a catheter placed into the lower esophagus. P_{ES} is a surrogate measure for pleural pressure (P_{PL}). Indeed, P_{ES} has been used to estimate P_{PL} in the laboratory setting for many years [204]. However, it has only been within the last few years that P_{ES} has been used as a surrogate for P_{PL} in the clinical setting [205–208]. There are no studies currently in children using this method.

FIO_2

Levels of FiO_2 lower than 0.5 are usually consider safe. The initial FiO_2 should be 0.6 unless SaO_2 <92 %. After setting the PEEP, FiO_2 should be set to the lowest level required to

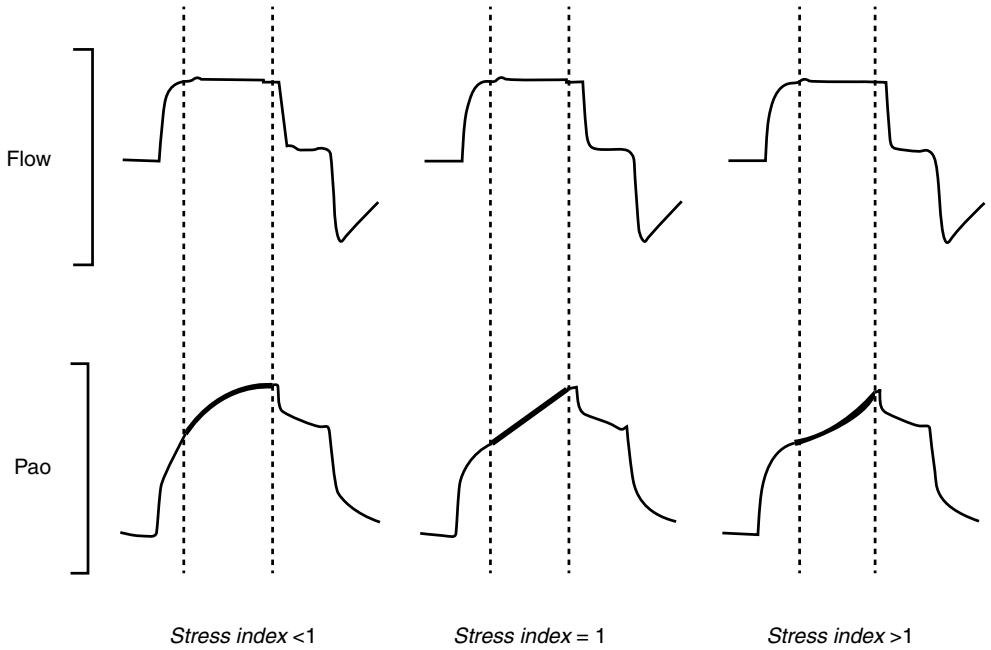

Fig. 8.13 Graphic representation of the stress index concept during constant-flow volume control ventilation. In this method, the shape of the pressure-time curve is used to determine and set optimal PEEP. If the compliance worsens as the lungs are inflated, the stress index will be >1 (shown as an upward concavity on the far right of the Figure). In this case, PEEP should be decreased. If the compliance is improving as the lungs are inflated, the stress index will be <1 (shown as a downward concavity on the far left of the Figure). In this case, PEEP should be increased further. The middle curve depicts ideal lung recruitment, when the stress index = 1 (there is a linear increase in pressure with constant-flow lung inflation) (Reprinted from Grasso et al. [193]. With permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Official journal of the American Thoracic Society)

attain a SaO_2 >88–92 %. In a sick patient, FiO_2 <0.3 is not recommended for safety reasons (e.g. inadvertent extubation). When FiO_2 >0.6 is required despite high levels of PEEP, the tolerated SaO_2 limit may be reduced to 85–88 % (permissive hypoxemia) and/or additional methods for improving oxygenation considered (e.g., extracorporeal membrane oxygenation, a trial of prone positioning, etc) [160, 162, 209].

Rate (Frequency)

The ventilator rate is selected according the patient age and nature of the disease and is then adjusted according to the $PaCO_2$ and patient comfort. Recall that $PaCO_2$ is inversely proportional to minute ventilation (V_E).

$$V_E = V_T \times f \tag{8.12}$$

where f is the frequency or respiratory rate. The initial respiratory rate setting is ~40 breaths per minute in a neonate, ~20–25 breaths per minute in an infant and decreases further with age. The inspiratory time may be selected in order to provide a certain inspiratory: expiratory (I:E) ratio (usually 1:1.5 or 1:2) or to provide a preset inspiratory time. In neonates, the inspiratory time is usually set to 0.3–0.4 s and this usually increases with age. In heterogeneous lung disease with low compliance and variable time constants, the inspiratory time is usually longer in order to allow sufficient inflation. In contrast, in the case of obstructive lung disease (e.g. asthma, bronchiolitis), the expiratory time is set longer in order to allow the lung to fully empty, thereby avoiding air trapping and over inflation which can be confirmed by auscultation, time-flow loops, and auto-PEEP determinations using an expiratory pause (see further discussion below).

Triggering the Ventilator

In order to deliver a triggered breath the ventilator has to sense the patient's inspiratory effort. There are two principle mechanisms by which such sensing occurs – through either changes in pressure or changes in flow. In all modern ventilators designated for pediatric use, a continuous base flow exists in the circuit. Sensors measure the delivered flow and the exhaled flow and continuously calculate the difference between the two. If no leak exists in the system or around the tracheal tube, the flow measured is identical in both sensors unless the patient makes an inspiratory effort. As the patient inspires from the baseline flow, the delivered flow remains

unchanged, but the exhaled flow is reduced. When the differences between the delivered and exhaled flow equal or are greater than the preset flow sensitivity, the ventilator commences an inspiration. With pressure sensitivity, a drop in pressure below the preset baseline end-expiratory pressure is the signal to commence a ventilator breath.

Since a non-cuffed tube is commonly used in neonates, a leak may exist around the tracheal tube. The leak causes a drop in flow and pressure in the circuit, and may be detected as an inspiration; this will cause the ventilator to commence an inspiration commonly called *auto-cycling* or *auto-triggering*. In order to compensate for a leak, the operator may attempt to increase the sensitivity to flow or pressure. The differences between flow and pressure sensitivity are subtle. With flow-triggering, flow is experienced during the short interval between the start of the effort and the beginning of gas delivery. In contrast, with pressure triggering, a brief isometric effort is experienced. In clinical practice, there may be little significant differences between the two systems.

Patient-Ventilator Dyssynchrony

Suboptimal patient ventilator interaction (dyssynchrony) may adversely affect the comfort, work of breathing, gas exchange of the ventilated patient and if severe it can exacerbate lung injury. Patient-ventilator dyssynchrony is defined as a mismatch between a patient's underlying neurally mediated respiratory drive and the ventilator's inspiratory and expiratory times [137, 138, 210–213]. It occurs in up to 25 % of all patients on assisted mechanical ventilation in the ICU [214]. When patient-ventilator dyssynchrony is severe and frequent, it is associated with a higher risk of VILI, as well as a longer duration of mechanical ventilation (and all its associated complications) [215, 216]. In addition, patient-ventilator dyssynchrony contributes to disruption of sleep-wake cycles, higher sedation requirements, and delirium [210, 214, 216, 217]. While patient-ventilator dyssynchrony is a common problem in adults (25 %), its prevalence in pediatric practice is unknown. Clinical manifestations of patient-ventilator dyssynchrony include tachypnea, tachycardia, diaphoresis and sternal or costal retractions. Patient-ventilator interaction is determined by the success of the physician in reconciling the respiratory drive and lung mechanics of the ventilated patient with the design limitations of the ventilator. Two areas are of particular importance. First is the ability of the patient to initiate support from the ventilator, i.e. triggering. Second, is his or her ability to signal that support should be terminated so that expiration may occur (i.e. cycling). In addition, the support offered by the ventilator should be tailored to the patient's ventilatory demands. The evolution of ventilators has seen the emergence of support modes which utilize alterations in circuit gas flow to indicate the state of the respiratory cycle in the patient and by his effort determine the level of ventilatory support to be applied during inspiration.

The most common impediments to patient-ventilator synchronization are failure of patient inspiratory effort to trigger support from the ventilator and the development of intrinsic positive end expiratory pressure (auto-PEEP) through the use of ventilator patterns characterized by high respiratory rate and/or inadequate short expiratory time. The use of alteration in circuit gas flow to indicate a patient inspiratory effort (i.e. flow trigger; '*flow by*') has largely replaced the traditional *pressure* trigger in most ventilators. As discussed below, auto-PEEP can be detected with the end expiratory airway occlusion maneuver (expiratory hold in certain ventilators), but this particular maneuver requires a cooperative or paralyzed patient. It can be detected by analysis of flow-time curve, although the simplest method is by auscultation over the trachea for breath sounds that persist and do not stop for a short period of time before the next inspiration.

Patient-ventilator dyssynchrony is subclassified into trigger dyssynchrony, flow dyssynchrony, and cycle dyssynchrony. Trigger dyssynchrony is perhaps the most common and occurs when the patient is unable to trigger a supported breath or when the ventilator auto-triggers (i.e. auto-cycling or auto-triggering – see above). The ventilator trigger sensitivity should be set to be as sensitive as possible, without causing auto-cycling or auto-triggering. Aside from the wrong trigger sensitivity on the ventilator, failure to trigger a supported breath is usually due to a respiratory muscle weakness (which is especially common in patients on prolonged mechanical ventilatory support), auto-PEEP (see below), excessive condensation in the ventilator circuit, or leaks in the circuit or around the tracheal tube. Cardiac oscillations have also been shown to occasionally cause trigger asynchrony (auto-cycling) [218]. Flow dyssynchrony occurs when the inspiratory flow is set too low for the patient's demand. Clinical manifestations of flow dyssynchrony include tachypnea, retractions, and paradoxical breathing. Increasing the inspiratory flow or changing from VCV to either PCV or Adaptive Pressure Control mode (e.g. PRVC, Servo-i, Maquet, Solna, Sweden) should help alleviate some of these signs and symptoms [94–96, 213, 219, 220]. Alternatively, if the patient is already in PCV, increasing the rise time setting may help. Finally, cycle dyssynchrony occurs when the neurally mediated inspiratory time of the patient does not match the ventilator's inspiratory time. If the inspiratory time is too short, the patient may double-trigger the ventilator, leading to breath stacking. If the inspiratory time is too long, the patient will actively exhale while the ventilator continues to deliver a breath. Patient-ventilator dyssynchrony can be detected by clinical manifestations of respiratory distress or by examining the respiratory graphics on the ventilator [212, 213, 221–224].

Adjuncts to Mechanical Ventilation

Recruitment Maneuvers

A recruitment maneuver (RM) is performed in an attempt to re-open collapsed alveoli, thereby promoting better ventilation-perfusion matching. There are several ways of performing a RM that are described in the literature – however, to date there are no studies showing that RM improve outcome [225–227]. In addition, among the different approaches, there haven't been any studies showing the superiority of one RM method over another. In general, RM's have been shown to be safe and at least transiently improve oxygenation in critically ill children [228–232], though there are some studies that have demonstrated a transient and systemic release of pro-inflammatory cytokines after performing a RM [233, 234]. The significance of this latter finding is unknown. However, until there are studies showing that RM's improve outcome in critically ill children and/or adults, we suggest that RM's are probably best reserved for those children with refractory hypoxemia, as more of a rescue maneuver to improve oxygenation [235]. In addition, it is probably more important to maintain lung recruitment, once a RM has been performed, by setting an appropriate level of PEEP (see above).

Prone Positioning

Prone positioning has been shown to improve oxygenation transiently in both critically ill children and adults in multiple studies performed over the last decade. However, the effects of this improvement in oxygenation on mortality have been inconsistent [236–242]. Analysis of previously published trials suggest that there is a population of critically ill patients with severe ARDS who could benefit from prone positioning [241, 242]. Based on these data, a multicenter, prospective, randomized, controlled trial performed in critically ill adults with severe ARDS (defined as a PaO_2/FIO_2 ratio <150 mmHg with FIO_2 of at least 0.6) showed that early (meeting ARDS criteria for less than 36 h) and prolonged (at least 16 h per day) significantly reduced 28- and 90-day mortality [243]. Therefore, it would seem reasonable to keep prone positioning in the armamentarium for management of critically ill children with severe ARDS, at least as a rescue therapy for those patients with refractory hypoxemia.

Nitric Oxide

Inhaled nitric oxide (iNO), a potent short acting selective vasodilator, has been shown to have short-term effects on oxygenation in selected patients with ALI/ARDS. Unfortunately, these short-term improvements have no resulted in significant improvements in clinical outcomes, such as the duration of ventilatory support or mortality [244]. Therefore, iNO is generally reserved for patients with refractory hypoxemia with FiO_2 >0.6 and a significant pulmonary shunt in which a trial of iNO shows improvement in oxygenation. Inhaled nitric oxide is discussed elsewhere in this textbook.

Surfactant Administration

The role of surfactant administration in patient with ALI/ARDS has not been established. Several studies have been performed in adults and children with conflicting results. A prospective, multi-center, randomized, placebo-controlled trial in children showed that surfactant may improve outcome (i.e., ventilator-free days, mortality) of selected group of children with ALI [245]. However, a more recent trial was stopped early due to futility [246]. Based on these studies, exogenous surfactant administration cannot be recommended outside the context of a clinical trial.

Complications of Mechanical Ventilation

Mechanical ventilation is a lifesaving therapy in many circumstances. However, as mentioned briefly above (and discussed further in subsequent chapters of this textbook), mechanical ventilation is not a natural way of breathing and is associated with numerous complications and adverse physiological side effects which for the most part.

Respiratory Complications

Injury to the respiratory system can involve either (or both) the upper airways and lungs. Airway injury may be due to laryngoscopy, insertion of the tracheal tube, or the presence of the tracheal tube for a prolonged period of time. Lung injury is due to mechanical stretch caused by the continuous pressure and volume changes associated with positive pressure ventilation. Such injury may be macroscopic (i.e. extra-alveolar air leak) or microscopic. The latter is functionally and histologically similar to that observed in ARDS and is termed Ventilator-Induced Lung Injury (VILI). Additional pulmonary complications include Ventilator-Associated Respiratory Infections (VARI) and atelectasis.

Upper Airway Injury

Early complications related to tracheal intubation are mostly due to traumatic intubation and include tooth avulsion or damage, laryngeal trauma, and pharyngeal injury ranging from mild edema to laceration with severe bleeding. Tissue injury secondary to prolonged tracheal intubation is likely due to the pressure and shearing forces the tube exerts on the surrounding tissues which may be exacerbated by movement

of the head or neck. Nasotracheal intubation may cause pressure sores or necrosis of the ala nasi or nasal septum, and oral intubation may cause similar ulceration at the angle of the mouth. Prolonged ventilation in the neonate may cause grooves in the palate, and in extreme cases, a traumatic cleft.

Clinically apparent laryngeal injury is relatively rare and ranges from mild edema to ulceration of the mucosa. Significant vocal cord injury may be minimal, or in extreme cases, involve subluxation of the arytenoid cartilages with subsequent vocal cord fixation. The more frequent and clinically significant complications occur in the subglottic region (i.e. below the vocal cords). This region is a narrower region in children as compared with adults, and it is the only region with a complete circumferential cartilaginous ring that doesn't afford for expansion under pressure. Infection and ischemic necrosis may develop over time, and during healing granulation tissue, or in the absence of resolution, an organized scar may develop and evolve causing subglottic stenosis and clinically significant upper airway obstruction. Similar injury may develop deeper in the trachea at the tip of the tracheal tube or at the carina as a result of continuous epithelial injury from the suction catheter. Some of the injuries may be prevented by skillful tracheal intubation, with a proper size tube, and taking care with tube repositioning, taping and carefully measured suctioning lengths. When a cuffed tracheal tube is being used, the cuff should be deflated daily for assessment of a leak, and then inflated to a maximal pressure no greater than 25 cm H_2O.

Air Leak

Macroscopic air leak has been reported in up to 40 % of children receiving mechanical ventilation [247]. However, more contemporary studies suggest that with the open-lung approach to mechanical ventilation with the use of low tidal volumes and permissive hypercapnia, the incidence of air leak is much lower [45, 248]. Excessive transpulmonary pressure and overdistension leads to alveolar rupture and escape into the pulmonary interstisium (i.e. Pulmonary Interstitial Emphysema, PIE). Extension of this injury may involve the mediastinum (i.e. pneumomediastinum), the pleural space (i.e. pneumothorax) or pericardium (i.e. pneumopericardium), or it may propagate into the subcutaneous space (i.e. subcutaneous emphysema). Subcutaneous emphysema, pneumopericardium and PIE are usually not clinically significant, although the former may cause discomfort. Pneumothorax is generally the most important type of air leak. If continuous, air may enter the pleural space with each inspiration, and because it cannot exit the space, a net accumulation occurs, with steadily increasing pressure (i.e. tension pneumothorax). Over time, the volume of air and the pressure in the pleural space increase significantly causing collapse of the ipsilateral lung, shift of the mediastinum, obstruction of the venous return, and compromise of the cardiac output. Tension pneumothorax should be immediately suspected in any mechanically ventilated child who unexpectedly experiences an acute deterioration in oxygenation or cardiac output. Unless it is rapidly diagnosed and drained it may cause death. Air leak is rare in otherwise healthy lungs, in the absence of excessive airway pressures. Retrospective studies have shown the association of occurrence or air leak with high levels of PIP, PEEP, or tidal volume [45, 248–250]. Application of a protective ventilation strategy that limits plateau pressure and tidal volume may decrease the risk of air leak.

Ventilation Associated Respiratory Infections (VARI)

Nosocomial infections that are associated with tracheal intubation and mechanical ventilation include ventilator-associated tracheobronchitis (VAT), ventilator-associated pneumonia (VAP), and nosocomial sinusitis. VAP is a significant problem in the PICU and has been associated with significant increases in duration of mechanical ventilation, PICU length of stay (LOS), hospital LOS, costs, and mortality [251–260]. VAP is principally a clinical diagnosis based on the appearance of new infiltrates on chest radiography, purulent endotracheal secretions, and the presence of fever or leukocytosis. The microbiologic diagnosis can be confirmed by obtaining a tracheal aspirate for culture during suction, bronchoalveolar lavage (BAL), or bronchoscopic-protected specimen brush sampling, though the latter is rarely performed in children. When the diagnosis of VAP is established on clinical grounds, microbiological confirmation (i.e. BAL) should be sought, and therapy (directed by the local microbial sensitivity profile) commenced pending microbiologic confirmation. The antibiotics should be tailored according to the response and the subsequent microbiologic data. It is important to recognize the local resistance patterns when making empiric choices about initial antibiotic therapy. A bundle of measures that may reduce the risks of VAP include the following placing patients in semi-recumbent position (elevating the head of the bed), changing heat-moister exchangers, and maintenance of oral hygiene [256, 259, 261, 262].

Ventilator-associated tracheobronchitis (VAT) may be a precursor to VAP [263–266], and preliminary data has suggested that it also increases the duration of stay in the PICU (Wheeler, *unpublished data*). The diagnostic criteria for VAT are similar to those used for VAP, with the exception of a change in infiltrates on chest radiograph or worsening ventilator status. The use of VAP as a quality metric has been questioned [267–269], primarily due to the low specificity of the diagnostic criteria. For this reason, some authors have suggested that VAT and VAP should be considered in aggregate.

There have only been a few studies about nosocomial sinusitis in the PICU [270–272]. However, these studies suggest that sinusitis is likely underappreciated and underrecognized in this population.

Atelectasis

Injured lungs have a low compliance and a tendency to collapse [273, 274]. Mechanical ventilation increases the risk by direct lung injury, retention of secretions, de-nitrogenation during ventilation with 100 % oxygen, endobronchial placement of the tracheal tube, and intermittent suctioning. Furthermore, neuromuscular blockade, commonly used during mechanical ventilation, abolishes diaphragmatic tone and further decreases FRC. Because infants have a relatively lower FRC and less collateral ventilation than adult, they may be at even greater risk of developing atelectasis. It mainly occur in the left lower and right upper lobe Principi T et al. [248]). Atelectasis is important because it may compromise oxygenation, increase pulmonary artery pressure, and contribute to VILI by over-distension of the ventilated lung regions. It may be treated with positioning, physiotherapy, increasing the PEEP, and the use of routine, short recruitment maneuvers. Prolonged ventilation may contribute to *disuse atrophy* of the diaphragm, which has been demonstrated in animal studies, but not in humans. However, it seems that maintenance of spontaneous respiratory effort may mitigate against this problem.

Ventilator-Induced Lung Injury (VILI)

VILI is discussed in great detail in a subsequent chapter. Suffice it to say that positive pressure ventilation is not a natural form of breathing and can cause lung injury that is virtually indistinguishable from that of ALI/ARDS. Several types of VILI are relevant in the PICU. *Volutrauma* (lung injury induced by excessive tidal volumes, leading to repetitive stretch injury) can be minimized by avoiding the use of excessive tidal volumes (generally defined as tidal volume ≥10 mL/kg predicted body weight) and transpulmonary pressures – the so-called lung-protective strategy [36, 105]. *Barotrauma* (lung injury induced by excessive pressures, leading to alveolar overdistension and air leak) can be minimized by avoiding the use of excessive plateau pressures (see discussion below), generally less than 30 cm H_2O [105]. These high pressures cause injury by virtue of the fact that higher transpulmonary pressures cause excessive stretching and alveolar distension. Numerous animal models have shown, however, that limiting alveolar expansion, even in the face of very high transpulmonary pressures (e.g. with chest strapping) does not cause injury [275]. Therefore, patients with poor chest wall compliance (e.g. obesity, significant abdominal distension) may require increased transpulmonary pressures which can be done relatively safely as long as excessive tidal volumes are avoided [276, 277]. Atelectrauma (lung injury induced by the cyclical opening of alveoli during the inspiratory phase and closure/collapse during the expiratory phase) can be minimized with the so-called "open lung approach," which combines a lung-protective strategy of low tidal volume ventilation with optimal lung recruitment (using PEEP). Biotrauma (lung injury induced by the local production and systemic release of proinflammatory cytokines) can lead to a systemic inflammatory response and multiple organ dysfunction syndrome (MODS) [278]. Finally, a fractional inspired oxygen concentration (FIO_2) approaching 1.0 can lead to oxidative injury to the lung (oxygen toxicity). The safe range of FIO_2 is not exactly known, but most authorities suggest that FIO_2 ≤0.6 is preferable.

Auto-PEEP

Auto-PEEP (also known as intrinsic PEEP, inadvertent PEEP, endogenous PEEP, occult PEEP) is measured using an end-expiratory pause for 0.5–1.5 s during either VCV or PCV [279]. The measurement of auto-PEEP is only accurate when the patient is not exerting a significant respiratory effort. Auto-PEEP is caused by air-trapping (hyperinflation) in the alveoli at the end of expiration, which exerts a positive pressure, and it is usually due to an incomplete expiration prior to the initiation of the next breath [280–282]. The incomplete expiration is usually due to the presence of severe airflow limitation (e.g. increased airways resistance, as in children with asthma), though auto-PEEP can be present even in the absence of airflow limitation [283]. For example, setting the inspiratory time too high (e.g. inverse ratio ventilation) will result in too short of an expiratory time. Patients with dynamic hyperinflation and dynamic compression of the airways are also at risk. Dynamic hyperinflation is present when the end-expiratory lung volume exceeds FRC, usually as a result of airflow limitation (resulting in incomplete emptying of the alveoli during exhalation), but also from ventilation with high tidal volumes, use of short expiratory times, or presence of lung units with long time constants (resistance x compliance).

There are several other clues to the presence of auto-PEEP. The breathing pattern and respiratory graphics are particularly useful. If the patient is still exhaling when the next breath is delivered (observed directly or on the respiratory waveform), auto-PEEP is likely present (Fig. 8.14). Similarly, inspiratory efforts that fail to trigger a breath (i.e. trigger asynchrony – see above) also suggest the presence of auto-PEEP. Finally, signs and symptoms of increased work of breathing (tachypnea, nasal flaring, retractions) can also suggest the presence of auto-PEEP. Finally, an esophageal pressure monitor can also detect the presence of auto-PEEP [280].

Ideally, auto-PEEP should be as low as possible (preferably 0 mmHg), as there several associated adverse effects. First and foremost, auto-PEEP effectively acts as a threshold

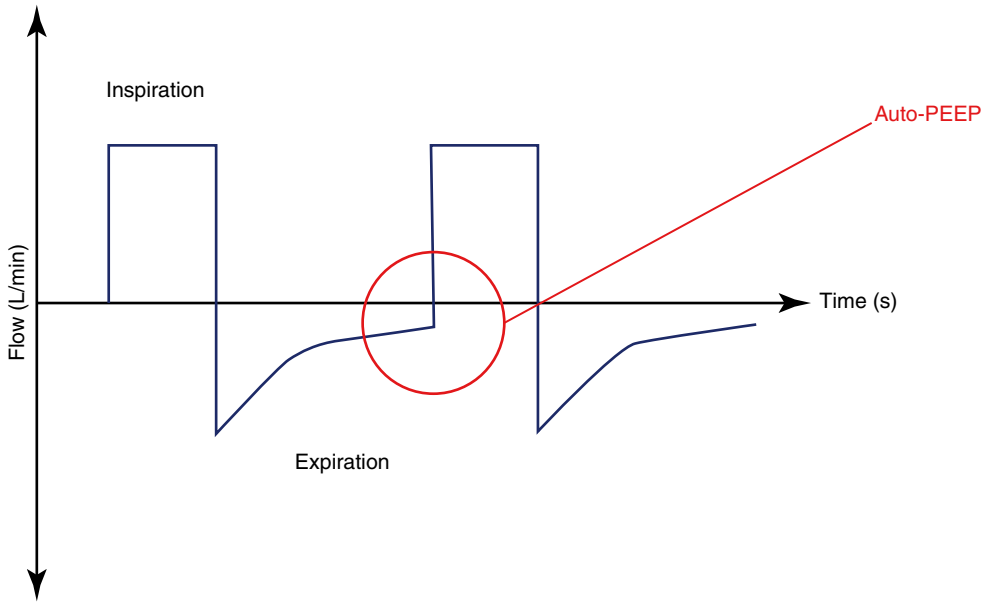

Fig. 8.14 Detection of auto-PEEP. Flow-time waveform in a patient showing persistence of airflow at the end of expiration, as well as an incomplete return to the baseline

pressure that the patient must overcome to trigger the ventilator, leading to patient-ventilator asynchrony (trigger asynchrony). Auto-PEEP represents an additional inspiratory load, as shown by the modified equation of motion below:

$$P_{RS} = V/C + (R \times V) + PEEP_i \quad (8.13)$$

where $PEEP_i$ is the auto-PEEP (intrinsic PEEP). In the presence of auto-PEEP, a negative intrapleural pressure equal to the level of auto-PEEP and the ventilator sensitivity threshold must be generated in order to generate inspiratory flow (Fig. 8.15). The application of extrinsic PEEP (set by the clinician) will improve the patient's ability to trigger the ventilator, by raising the trigger level closer to the total PEEP (so-called *waterfall effect*) [284]. Auto-PEEP also increases the risk of VILI (through overdistension) and worsens hemodynamics (through the cardiorespiratory interactions discussed below).

Central Nervous System Effects

The effects of positive pressure ventilation have been extensively studied in the context of head trauma, but the effects on intracranial pressure (ICP) and cerebral perfusion pressure are complicated. Some issues are apparent from several studies. The application of PEEP may directly increase ICP by transmission of pleural pressure through vertebral veins towards the cranium. Indirectly, PEEP may increase ICP by increasing the right ventricular afterload, decreasing right ventricular output, and decreasing venous return – including the venous return from the skull. These effects are more prominent in patients with normal ICP, and are minimal in the context of modestly elevated ICP [285–287]. Furthermore, increased PEEP may decrease cardiac output and systemic arterial pressure, and thereby reduce cerebral perfusion pressure.

There is a growing interest in the effects of sedation and neuromuscular blockade, which are frequently used in critically ill children on mechanical ventilation, on delirium and sleep [288]. The alarms on the ventilator, the need for suctioning, and poor patient-ventilator synchrony also contribute to the adverse effects of mechanical ventilation on sleep [217]. This is a relatively new area for research, and there will likely be more studies devoted to this issue.

Cardiovascular Effects

The heart is a pressure chamber within another pressure chamber, the thorax. Since the pulmonary vasculature, right ventricle, and the left atrium all exist in the same pressure chamber (i.e. thorax), the changes in pleural or intrathoracic pressure affects them identically. However, intrathoracic pressure will affect the pressure gradient for both blood draining into the heart (i.e. venous return) as well as for the blood flow leaving the heart (i.e. left ventricle ejection), independent of cardiac function. The overall effects of mechanical ventilation on cardiovascular function are discussed in much greater detail in the chapter on Cardiorespiratory Interactions. However, they will be reviewed in brief here as well.

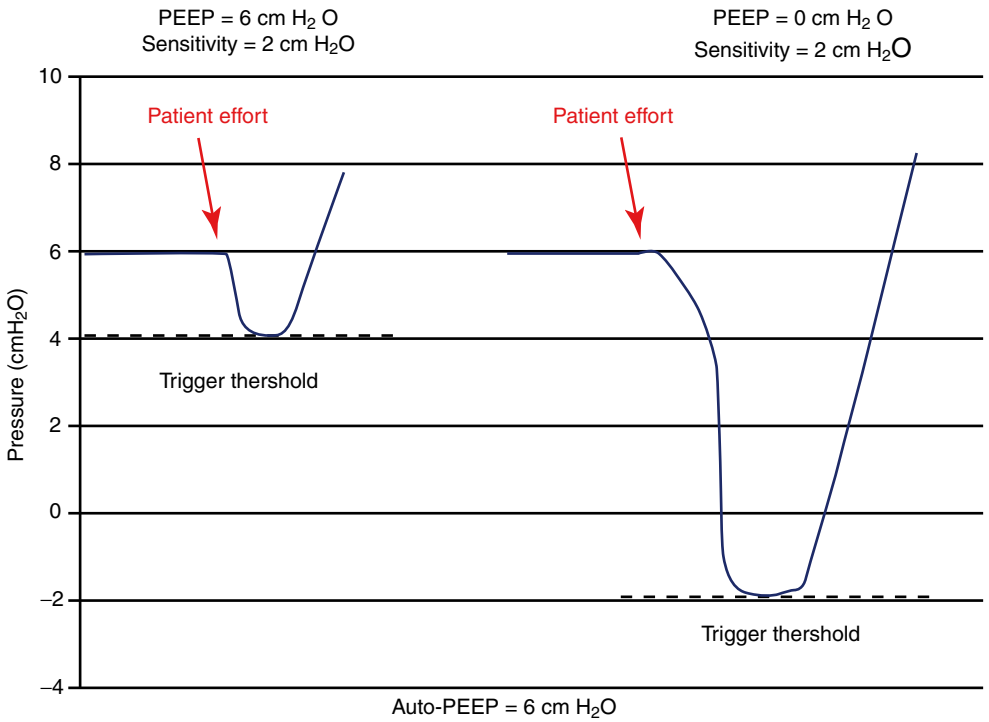

Fig. 8.15 Pressure-triggering in a child with auto-PEEP 6 cm H_2O. On the *left-hand side* of the graph, the trigger sensitivity is set at 2 cm H_2O and the extrinsic PEEP is set at 6 cm H_2O. The ventilator is triggered when the patient's own spontaneous inspiratory effort reduces the airway pressure to the set threshold level (in this case, 2 cm H_2O below PEEP, or 4 cm H_2O). On the *right-hand side* of the graph, the trigger sensitivity is set at 2 cm H_2O, but this time the extrinsic PEEP is set at zero. Now the patient must reduce the airway pressure to 2 cm H_2O below auto-PEEP, which requires a negative pressure of 8 cm H_2O

During inspiration with positive pressure ventilation, the thorax expands and the lung volume and intrathoracic pressure increase. In contrast, with a negative pressure (or spontaneous) inspiration, the changes are in the opposite direction – the volume of the thorax and lung increase, but the intrathoracic pressure decreases. It is important to understand that the pressure that the clinician usually observes during mechanical ventilation is the airway pressure, which is that pressure in the proximal trachea, not the pressure transmitted to the lung. During positive pressure ventilation, the volume of the lung increases only by increasing the airway pressure, only part of this pressure is transmitted to the lung. The pleural pressure may be monitored with an esophageal probe, but this is not routine in most centers. In cases where lung compliance is reduced (as in ALI/ARDS) or lung resistance is increased (as in asthma), the percentage of airway pressure transferred to pleural pressure is lower than when chest wall compliance is reduced. Generally, when tidal volume is kept constant, the changes in airway pressure reflect mostly the changes in mechanics of the lung and will not reflect changes in intrathoracic pressure [289, 290].

Venous Return

When intrathoracic pressure increases, right atrial atmospheric pressure also increases. The systemic venous return, which is the principal determinate of cardiac output in the normal heart, depends on the gradient between the upstream mean systemic pressure and the downstream pressure in the right atrium. An increase in the right atrial pressure therefore decreases the venous return to the right atrium, decreasing the filling pressure and stroke volume of the right ventricle. The reduction in venous return due to an elevation in right atrial pressure may be of a lower magnitude than the increases seen with a reduction in right atrial pressure. This occurs because during positive pressure ventilation the intra-abdominal pressure increases, increasing the mean systemic pressure. The hemodynamic effects of increased intrathoracic pressure are, under normal conditions, not clinically significant. However, in certain clinical conditions, the effect of elevated intrathoracic pressure may compromise cardiac output. These include hyopvolemia, relative hyopvolemia (e.g. septic shock), and obstructive right heart lesions and/or right ventricle failure. Often this effect is countered by effects on left ventricular afterload.

Left Ventricular Afterload

The left ventricle and thoracic aorta are also in the thorax and both are affected by changes in intrathoracic pressure. The pressure that left ventricular work is directed against is the transmural pressure and not the pressure measured outside the thorax. The transmural pressure of the aorta is the difference between the intravascular pressure (positive) and the intrathoracic pressure (negative during spontaneous respiration). During spontaneous inspiration, the intrathoracic pressure decreases (becomes more negative) and as a result the transmural pressure increases, thereby increasing the afterload of the left ventricle. Conversely, during positive pressure ventilation, the intrathoracic pressure becomes positive and as a result the transmural pressure decreases, thereby decreasing the afterload of the left ventricle. Thus, the application of positive pressure ventilation with PEEP (or just CPAP) has been shown to improve significantly cardiac output in patient with heart failure [291]. Most commonly these swings in intra-thoracic pressure are not clinically significant in otherwise healthy children under normal conditions. However, they may become clinically significant in extremes, such as the case of severe upper-airway obstruction where the intra-thoracic pressure significantly decreases, resulting in a substantial increase in the afterload of the left ventricle and contributing to the development of acute pulmonary edema (so-called negative pressure or post-obstructive pulmonary edema).

Cardiovascular Effects of Change in Lung Volume

A key effect of altered lung volume is on the pulmonary circulation, a low-resistance, low-pressure system. The pulmonary vessels can be classified as either alveolar or extra-alveolar vessels. The alveolar vessels are small vessels (i.e. capillaries, arterioles and venules) that are adjacent to the alveolar wall. The extra-alveolar vessels are the larger vessels in the interstitium. The total pulmonary vascular resistance (PVR) is the sum of the resistance in both the alveolar and the extra-alveolar vessels. A change in lung volume has different effect on both systems. In normal lung mechanics, ventilation around FRC is associated with the nadir of PVR. However, when the lung is inflated above FRC, the distended alveoli may compress the alveolar vessels and increase the PVR. Similarly, as lung volume falls below FRC, the extra-alveolar vessels become more tortuous, the transmural pressure increases, and the vessels tend to collapse, resulting in increased PVR. Thus, at least in the isolated perfused lung (although never conclusively demonstrated in humans), maintenance of the lung volume at physiologic FRC will yield optimal PVR. Furthermore, in case of ventilation with small tidal volumes, certain areas of the lung tend to collapse, causing alveolar hypoxia which in turn may activate hypoxic pulmonary vasoconstriction. Indeed, in contrast to the traditional beliefs outlined above, newer *in vivo* data suggests that during atelectasis, alveolar hypoxia, not volume loss, may be the key determinant of increased PVR [292].

Ventricular Interdependence

The right and left ventricles pump in series and share a common intraventricular septum. If the right ventricular volume increases, it shifts the septum to the left, reducing left ventricle filling volume and compromising left ventricle diastolic function. Ventricular interdependence is not a significant factor in positive pressure ventilation unless pulmonary vascular resistance is increased significantly. Some suggest that this phenomenon may become clinical significant in patients with acutely injured lungs where echo-cardiographic studies have revealed leftward shift with the application of PEEP, most probably because of the increase in pulmonary vascular resistance and right ventricle afterload.

Renal Effects

Mechanical ventilation with positive pressure induces a reduction in renal water and sodium excretion. This effect appears to be exacerbated by PEEP. The rise in intrathoracic pressure, administration of sedatives and analgesic drugs, and immobility reduce venous return, cardiac output, and may eventually lower mean arterial pressure. As a result, renal perfusion decreases, and the renin–angiotensin system is stimulated. Angiotensin II formation stimulates aldosterone production resulting in increased reabsorption of water and sodium. Low systemic blood pressure increases the secretion of antidiuretic hormone which also decreases urinary output Reduced venous return and decreased right atrial pressure results in reduced levels of atrial natriuretic peptide to further reduce diuresis [293–295]. These issues are particularly important when discontinuing mechanical ventilation, as in the presence of good cardiac function, a large diuresis may occur. Recently, the biotrauma hypothesis suggests that non-protective ventilation may release inflammatory mediators into the systemic circulation that potentially cause renal dysfunction [296].

Hepatic Effects

Blood flow to the liver represents the balance of flow through the hepatic artery and portal circulation. The reduction of cardiac output associated with positive pressure ventilation may reduce flow through the hepatic artery. In addition, positive pressure ventilation increases intra-abdominal pressure which may decrease portal vein flow [249, 297]. Indeed, positive pressure ventilation has been shown to reduce splanchnic blood flow in some [249, 297], but not all studies [298]. Many patients receiving positive pressure ventilation

demonstrate some degree of hepatic dysfunction; it is not clear whether positive pressure ventilation is causative here, or whether the dysfunction represents systemic underlying systemic disease. The precise clinical significance of the positive pressure on liver function in the critically ill is not clear.

Weaning from Mechanical Ventilation

Weaning is the usual word to describe termination of mechanical ventilation, because in most cases in adults it is a gradual and sometimes long process. However, in children the more appropriate description would be liberation or termination of mechanical ventilation, because in most children the process is short without either delay or significant problems [38]. Only small groups of children, usually those with underlying chronic pulmonary diseases required weaning. However, in those children with neuromuscular diseases, weaning as commonly practiced in adult ICU's may actually be counter-productive and potentially disadvantageous.

Premature termination of tracheal intubation and mechanical ventilation may result in the re-intubation of the patient and introduction of a second period of mechanical ventilation that is often associated with clinical deterioration and increased morbidity and mortality. There is no established strategy for successful termination of ventilation, though, it has been shown that faster and more successful weaning may be achieved with the implementation of weaning protocols designed to offer objective clinical parameters associated with successful extubation and complement of clinical judgment.

The gradual transition from full or almost full mechanical support to spontaneous breathing may be accomplished by gradually decreasing the mandatory breath rate with SIMV, the level of PEEP and/or the degree of pressure or volume support. Sedation should be reduced carefully in order not to compromise the respiratory drive, while at the same time not compromising patient comfort or precipitating drug withdrawal. Although objective measurements for successful termination of ventilation and extubation do not exist, patients should be evaluated daily to determine whether they still required mechanical ventilation. A spontaneous breathing trial as an extubation readiness test (Pressure support ventilation with PS 10 cm H_2O and PEEP 5 cm H_2O for 2 h) was associated with a reduction in the duration of mechanical ventilation by 24 h [299], though this requires further study before it can be universally recommended [300]. One should consider the following before termination of ventilation and extubation: evidence of recovery from the cause of respiratory failure, minimal O_2 or PEEP requirement (e.g. FiO_2 <0.4, PEEP <6 cmH_2O), absence of significant acidosis (e.g. pH >7.25), hemodynamic stability, good respiratory drive and ability to protect the airway.

Conclusion

Mechanical ventilation plays a pivotal role in the treatment of critically ill children. The knowledge of childhood physiology and ventilation techniques may be among the most important skills a physician practices in critical care. Over time, mechanical ventilators have become more sophisticated and new modes of ventilation have been introduced and monitoring techniques have undergone dramatic improvements. With the recognition of the complications associated with PPV and the advances in monitoring, it is possible that in the near future we will be able to tailor, in real-time, the modality of ventilation to a specific patient with a specific disease.

References

1. Downes JJ. Development of pediatric critical care medicine – how did we get here and why? In: Wheeler DS, Wong HR, Shanley TP, editors. Pediatric critical care medicine: basic science and clinical evidence. London: Springer London Limited; 2007. p. 3–30.
2. Harris TR, Wood BR. Physiologic principles. In: Goldsmith JP, Karotkin EH, editors. Assisted ventilation of the neonate. 3rd ed. Philadelphia: W.B. Saunders Company; 1996. p32.
3. DiCarlo SE. Teaching alveolar ventilation with simple, inexpensive models. Adv Physiol Educ. 2008;32(3):185–91.
4. Cheifetz IM. Management of acute lung injury: sharing data between adults and children. Respir Care. 2011;56:1258–72.
5. Dunnill MS. Postnatal growth of the lung. Thorax. 1962;17:329–33.
6. Stocks J. Respiratory physiology during early life. Monaldi Arch Chest Dis. 1999;54:358–64.
7. Bateman ST, Arnold JH. Acute respiratory in children. Curr Opin Pediatr. 2000;12:233–7.
8. Chase M, Wheeler DS, editors. The pediatric chest. London: Springer London Limited; 2007.
9. Wheeler DS, Zingarelli B, Wong HR. Children are not small adults. Open Inflamm J. 2011;4:4–15.
10. Boyden EA, Tompsett DH. The changing patterns in the developing lungs of infants. Acta Anat (Basel). 1965;61:164–92.
11. Reid L. Influence of the pattern of structural growth of lung on susceptibility to specific infectious diseases in infants and children. Pediatr Res. 1977;11:210–5.
12. Thurlbeck WM. Postnatal growth of the lung and its significance in disease. Hum Pathol. 1978;9:492–3.
13. Zeman KL, Bennett WD. Growth of the small airways and alveoli from childhood to the adult lung measured by aerosol-derived airway morphometry. J Appl Physiol. 2006;100:965–71.
14. Hogg JC, Williams J, Richardson JB, Macklem PT, Thurlbeck WM. Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. N Engl J Med. 1970;282:1283–7.
15. Peroni DG, Boner AL. Atelectasis: mechanisms, diagnosis, and management. Paediatr Respir Rev. 2000;1:274–8.
16. Muller NL, Bryan AC. Chest wall mechanics and respiratory muscles in infants. Pediatr Clin North Am. 1979;26:503–16.
17. Thorsteinsson A, Jonmarker C, Larsson A, Vilstrup C, Werner O. Functional residual capacity in anesthetized children: normal values and values in children with cardiac anomalies. Anesthesiology. 1990;73:876–81.
18. West JB. Ventilation/blood flow and gas exchange. 3rd ed. Oxford: Blackwell; 1977. p. 33–52.

19. Guslits BG, Gaston SE, Bryan MH, England SJ, Bryan AC. Diaphragmatic work of breathing in premature human infants. J Appl Physiol. 1987;62:1410–5.
20. Muller N, Volgyesi G, Calle D, Whitton J, Froes AB, Bryan MH, et al. Diaphragmatic muscle fatigue in the newborn. J Appl Physiol. 1979;46:688–95.
21. Muller N, Volgyesi G, Bryan MH, Bryan AC. The consequences of diaphragmatic muscle fatigue in the newborn infant. J Pediatr. 1979;95:793–7.
22. West JB. Respiratory physiology: the essentials. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2000.
23. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med. 1994;149:8–13.
24. Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanisms of positive end-expiratory pressure in early adult respiratory distress syndrome. JAMA. 1993;269:2122–7.
25. Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med. 1995;151:1807–14.
26. Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Intensive Care Med. 2000;26:1215–27.
27. Rouby JJ, Puybasset L, Cluzel P, Richecoeur J, Lu Q, Grenier P. Regional distribution of gas and tissue in acute respiratory distress syndrome. II. Physiologic correlations and definition of an ARDS Severity Score. CT Scan ARDS Study Group. Intensive Care Med. 2000;26:1046–56.
28. Puybasset L, Cluzel P, Gusman P, Grenier P, Preteux F, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology. CT Scan ARDS Study Group. Intensive Care Med. 2000;26:857–69.
29. Grychtol B, Wolf GK, Arnold JH. Differences in regional pulmonary pressure-impedance curves before and after lung injury assessed with a novel algorithm. Physiol Meas. 2009;30: S137–48.
30. Wolf GK, Grychtol B, Frerichs I, Zurakowski D, Arnold JH. Regional lung volume changes during high-frequency oscillatory ventilation. Pediatr Crit Care Med. 2010;11:610–5.
31. Gomez-Laberge C, Rettig JS, Smallwood CD, Boyd TK, Arnold JH, Wolf GK. Interaction of dependent and non-dependent regions of the acutely injured lung during a stepwise recruitment manoeuvre. Physiol Meas. 2013;34:163–77.
32. Heaf DP, Helms P, Gordon I, Turner HM. Postural effects on gas exchange in infants. N Engl J Med. 1983;308:1505–8.
33. Davies H, Kitchman R, Gordon I, Helms P. Regional ventilation in infancy. Reversal of adult pattern. N Engl J Med. 1985;313: 1626–8.
34. Bhuyan U, Peters AM, Gordon I, Davies H, Helms P. Effects of posture on the distribution of pulmonary ventilation and perfusion in children and adults. Thorax. 1989;44:480–4.
35. Davies H, Helms P, Gordon I. Effect of posture on regional ventilation in children. Pediatr Pulmonol. 1992;12:227–32.
36. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
37. Hanson JH, Flori H. Application of the acute respiratory distress syndrome network low-tidal volume strategy to pediatric acute lung injury. Respir Care Clin N Am. 2006;12:349–57.
38. Randolph AG, Wypij D, Venkataraman ST, Hanson JH, Gedeit RG, Meert KL, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized controlled trial. JAMA. 2002;288:2561–8.
39. Randolph AG, Forbes PW, Gedeit RG, Arnold JH, Wetzel RC, Luckett PM, et al. Cumulative fluid intake minus output is not associated with ventilator weaning during or extubation outcomes in children. Pediatr Crit Care Med. 2005;6:642–7.
40. Curley MA, Hibberd PL, Fineman LD, Wypij D, Shih MC, Thompson JE, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. JAMA. 2005;294:229–37.
41. Adkins WK, Herndon LA, Coker PJ, Buchanan B, Parker JC. Age effects susceptibility to pulmonary barotrauma in rabbits. Crit Care Med. 1991;19:390–3.
42. Copland IB, Martinez F, Kavanagh BP, Engelberts D, McKerlie C, Belik J, et al. High tidal volume ventilation causes different inflammatory responses in newborn versus adult lung. Am J Respir Crit Care Med. 2004;169:739–48.
43. Kornecki A, Tsuchida S, Ondiveeran HK, Engelberts D, Frndova H, Tanswell AK, et al. Lung development and susceptibility to ventilator-induced lung injury. Am J Respir Crit Care Med. 2005;171:743–52.
44. Martinez F, Lewis J, Copland I, Engelberts D, Kavanagh BP, Post M, et al. Mechanical ventilation effect on surfactant content, function, and lung compliance in the newborn rat. Pediatr Res. 2004;56:19–25.
45. Albuali WH, Singh RN, Fraser DD, Seabrook JA, Kavanagh BP, Parshuram CS, et al. Have changes in ventilation practice improved outcome in children with acute lung injury? Pediatr Crit Care Med. 2007;8:324–30.
46. Hu X, Qian S, Xu F, Huang B, Zhou D, Wang Y, et al. Incidence, management, and mortality of acute hypoxemic respiratory failure and acute respiratory distress syndrome from a prospective study of Chinese paediatric intensive care network. Acta Paediatr. 2010;99:715–21.
47. Zhu YF, Lu XL, Wang Y, Chen JL, Chao JX, Zhou XW, et al. Mortality and morbidity of acute hypoxemic respiratory failure and acute respiratory distress syndrome in infants and young children. Chin Med J (Engl). 2012;125:2265–71.
48. Erickson S, Schibler A, Numa A, Nuthall G, Yung M, Pascoe E, et al. Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study. Pediatr Crit Care Med. 2007;8:317–23.
49. Khemani RG, Conti D, Alonzo TA, Bart 3rd RD, Newth CJ. Effect of tidal volume in children with acute hypoxemic respiratory failure. Intensive Care Med. 2009;35:1428–37.
50. Farias JA, Frutos F, Esteban A, Flores JC, Retta A, Baltodano A, et al. What is the daily practice of mechanical ventilation in pediatric intensive care units? A multicenter study. Intensive Care Med. 2004;30:918–25.
51. Khemani RG, Markovitz BP, Curley MA. Characteristics of children intubated and mechanically ventilated in 16 PICUs. Chest. 2009;136:765–71.
52. Wolfler A, Calderoni E, Ottonello G, Conti G, Baroncini S, Santuz P, et al. Daily practice of mechanical ventilation in Italian pediatric intensive care units: a prospective survey. Pediatr Crit Care Med. 2011;12:141–6.
53. Farias JA, Fernandez A, Monteverde E, Flores JC, Baltodano A, Mechaca A, et al. Mechanical ventilation in pediatric intensive care units during the season for acute lower respiratory infection: a multicenter study. Pediatr Crit Care Med. 2012;13:158–64.
54. Mesiano G, Davis GM. Ventilatory strategies in the neonatal and paediatric intensive care units. Paediatr Respir Rev. 2008;9: 281–9.
55. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008;358:700–8.

56. Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010;362:1970–9.
57. Fortenberry JD, Del Toro J, Jefferson LS, Evey L, Haase D. Management of pediatric acute hypoxemic respiratory insufficiency with bilevel positive pressure (BiPAP) nasal mask ventilation. Chest. 1995;108:1059–64.
58. Teague WG. Noninvasive ventilation in the pediatric intensive care unit for children with acute respiratory failure. Pediatr Pulmonol. 2003;35:418–26.
59. Cheifetz IM. Invasive and noninvasive pediatric mechanical ventilation. Respir Care. 2003;48:442–53.
60. Piastra M, Antonelli M, Chiaretti A, Polidori G, Polidori L, Conti G. Treatment of acute respiratory failure by helmet-delivered noninvasive pressure support ventilation in children with acute leukemia: a pilot study. Intensive Care Med. 2004;30:472–6.
61. Katz S, Selvadurai H, Keilty K, Mitchell M, MacLusky I. Outcome of non-invasive positive pressure ventilation in paediatric neuromuscular disease. Arch Dis Child. 2004;89:121–4.
62. Bernet V, Hug MI, Frey B. Predictive factors for the success of noninvasive mask ventilation in infants and children with acute respiratory failure. Pediatr Crit Care Med. 2005;6:660–4.
63. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. Pediatr Crit Care Med. 2006; 7:329–34.
64. Piastra M, Antonelli M, Caresta E, Chiaretti A, Polidori G, Conti G. Noninvasive ventilation in childhood acute neuromuscular respiratory failure: a pilot study. Respiration. 2006;73:791–8.
65. Pancera CF, Hayashi M, Fregnani JH, Negri EM, Deheinzelin D, de Camargo B. Noninvasive ventilation in immunocompromised pediatric patients: eight years of experience in a pediatric oncology intensive care unit. J Pediatr Hematol Oncol. 2008;30:533–8.
66. Yanez LJ, Yunge M, Emilfork M, Lapadula M, Alcantara A, Fernandez C, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med. 2008;9:484–9.
67. Piastra M, De Luca D, Pietrini D, Pulitano S, D'Arrigo S, Mancino A, et al. Noninvasive pressure-support ventilation in immunocompromised children with ARDS: a feasibility study. Intensive Care Med. 2009;35:1420–7.
68. Dohna-Schwake C, Stehling F, Tschiedel E, Wallot M, Mellies U. Non-invasive ventilation on a pediatric intensive care unit: feasibility, efficacy, and predictors of success. Pediatr Pulmonol. 2011;46:1114–20.
69. Mayordomo-Colunga J, Medina A, Rey C, Concha A, Menendez S, Los Arcos M, et al. Non invasive ventilation after extubation in paediatric patients: a preliminary study. BMC Pediatr. 2010;10:29.
70. L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, et al. Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med. 2005;172:1112–8.
71. Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive pressure ventilation for postextubation respiratory distress: a randomized controlled trial. JAMA. 2002;287:3238–44.
72. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apeztequia C, Gonzalez M, et al. Noninvasive positive pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004;350:2452–60.
73. Kavanagh BP, Roy L. Pediatric ventilation – towards simpler approaches for complex diseases. Paediatr Anaesth. 2005;15:627–9.
74. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. Intensive Care Med. 2013;39:247–57.
75. Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. J Perinatol. 2007;27:772–5.
76. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? Pediatrics. 2008;121:82–8.
77. Finer NN, Mannino FL. High-flow nasal cannula: a kinder, gentler CPAP? J Pediatr. 2009;154:160–2.
78. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanism of action. Respir Med. 2009;103: 1400–5.
79. Arora B, Mahajan P, Zidan MA, Sethuraman U. Nasopharyngeal airway pressures in bronchiolitis patients treated with high-flow nasal cannula oxygen therapy. Pediatr Emerg Care. 2012;28:1179–84.
80. McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannula therapy in infants with bronchiolitis. J Pediatr. 2010;156:634–8.
81. Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med. 2011; 37:847–52.
82. Ganu SS, Gautam A, Wilkins B, Egan J. Increase in use of noninvasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade. Intensive Care Med. 2012;38:1177–83.
83. Hartmann H, Jawad MH, Noyes J, Samuels MP, Southall DP. Negative extrathoracic pressure ventilation in central hypoventilation syndrome. Arch Dis Child. 1994;70:418–23.
84. Samuels MP, Raine J, Wright T, Alexander JA, Lockyer K, Spencer SA, et al. Continuous negative extrathoracic pressure in neonatal respiratory failure. Pediatrics. 1996;98:1154–60.
85. Corrado A, Gorini M, Villella G, De Paola E. Negative pressure ventilation in the treatment of acute respiratory failure: an old noninvasive technique reconsidered. Eur Respir J. 1996;9: 1531–44.
86. Shekerdemian LS, Shore DF, Lincoln C, Bush A, Redington AN. Negative-pressure ventilation improves cardiac output after right heart surgery. Circulation. 1996;94:II49–55.
87. Shekerdemian LS, Schulze-Neick I, Redington AN, Bush A, Penny DJ. Negative pressure ventilation as haemodynamic rescue following surgery for congenital heart disease. Intensive Care Med. 2000;26:93–6.
88. Shekerdemian LS, Bush A, Shore DF, Lincoln C, Redington AN. Cardiorespiratory responses to negative pressure ventilation after tetralogy of Fallot repair: a hemodynamic tool for patients with a low-output state. J Am Coll Cardiol. 1999;33:549–55.
89. Shekerdemian LS, Bush A, Lincoln C, Shore DF, Petros AJ, Redington AN. Cardiopulmonary interactions in healthy children and children after simple cardiac surgery: the effects of positive and negative pressure ventilation. Heart. 1997;78:587–93.
90. Shekerdemian LS, Bush A, Shore DF, Lincoln C, Redington AN. Cardiopulmonary interactions after Fontan operations: augmentation of cardiac output using negative pressure ventilation. Circulation. 1997;96:3934–42.
91. Chatburn RL. Understanding mechanical ventilators. Expert Rev Respir Med. 2010;4:809–19.
92. Mireles-Cabodevila E, Hatipoglu U, Chatburn RL. A rational framework for selecting modes of ventilation. Respir Care. 2013;58:348–66.
93. Chatburn RL. Classification of ventilator modes: update and proposal for implementation. Respir Care. 2007;52:301–23.
94. Campbell RS, Davis BR. Pressure-controlled versus volume-controlled ventilation: does it matter? Respir Care. 2002;47: 416–26.
95. Kallet RH, Campbell AR, Alonso JA, Morabito DJ, Mackersie RC. The effects of pressure control versus volume control assisted ventilation on patient work of breathing in acute lung injury and acute respiratory distress syndrome. Respir Care. 2000;45: 1085–96.

96. Davis KJ, Branson RD, Campbell RS, Porembka DT. Comparison of volume control and pressure control ventilation: is flow waveform the difference? J Trauma. 1996;41:808–14.
97. Prella M, Feihl F, Domenighetti G. Effects of short-term pressure-controlled ventilation on gas exchange, airway pressures, and gas distribution in patients with acute lung injury/ARDS: comparison with volume-controlled ventilation. Chest. 2002;122:1382–8.
98. Rappaport SH, Shpiner R, Yoshihara G, Wright J, Chang P, Abraham E. Randomized, prospective trial of pressure-limited versus volume-controlled ventilation in severe respiratory failure. Crit Care Med. 1994;22:22–32.
99. Esteban A, Alia I, Gordo F, de Pablo R, Suarez J, Gonzalez G, et al. Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. Chest. 2000;117:1690–6.
100. Keidan I, Berkenstadt H, Segal E, Perel A. Pressure versus volume-controlled ventilation with a laryngeal mask airway in paediatric patients. Paediatr Anaesth. 2001;11:691–4.
101. Bordes M, Semjen F, Degryse C, Bourgain JL, Cros AM. Pressure-controlled ventilation is superior to volume-controlled ventilation with a laryngeal mask airway in children. Acta Anaesthesiol Scand. 2007;51:82–5.
102. Seet MM, Soliman KM, Sbeih ZF. Comparison of three modes of positive pressure mask ventilation during induction of anaesthesia: a prospective, randomized, crossover study. Eur J Anaesthesiol. 2009;26:913–6.
103. Guldager H, Nielsen SL, Carl P, Soerensen MB. A comparison of volume control and pressure-regulated volume control ventilation in acute respiratory failure. Crit Care. 1997;1:75–7.
104. Kocis KC, Dekeon MK, Rosen HK, Bandy KP, Crowley DC, Bove EL, et al. Pressure-regulated volume control vs volume control ventilation in infants after surgery for congenital heart disease. Pediatr Cardiol. 2001;22:233–7.
105. Hager DN, Krishnan JA, Hayden DL, Brower RG. Tidal volume reduction in patients with acute lung injury when plateau pressures are high. Am J Respir Crit Care Med. 2005;172:1241–5.
106. Villar J, Perez-Mendez L, Basaldua S, Blanco J, Aguilar G, Toral D, et al. A risk tertiles model for predicting mortality in patients with acute respiratory distress syndrome: age, plateau pressure, and P(aO(2))/F(IO(2)) at ARDS onset can predict mortality. Respir Care. 2011;56:420–8.
107. Wetzel RC. Pressure-support ventilation in children with severe asthma. Crit Care Med. 1996;24:1603–5.
108. Jenkins JK, Gebergzabher YD, Island ER, Habashi N, Hauser GJ. Use of airway pressure release ventilation in a child with refractory hepatopulmonary syndrome after liver transplantation. Pediatr Transplant. 2013;17:E81–7.
109. Kamath SS, Super DM, Mhanna MJ. Effects of airway pressure release ventilation on blood pressure and urine output in children. Pediatr Pulmonol. 2010;45:48–54.
110. Krishnan J, Morrison W. Airway pressure release ventilation: a pediatric case series. Pediatr Pulmonol. 2007;42:83–8.
111. Foland JA, Martin J, Novotny T, Super DM, Dyer RA, Mhanna MJ. Airway pressure release ventilation with a short release time in a child with acute respiratory distress syndrome. Respir Care. 2001;46:1019–23.
112. Dominquez T, Lin R, Helfaer M. Airway pressure release ventilation in pediatrics. Pediatr Crit Care Med. 2001;2:243–6.
113. Neumann P, Wrigge H, Zinserling J, Hinz J, Maripuu E, Andersson LG, et al. Spontaneous breathing affects the spatial ventilation and perfusion distribution during mechanical ventilatory support. Crit Care Med. 2005;33:1090–5.
114. Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. Crit Care Med. 2005;33:S228–40.
115. Frawley PM, Habashi NM. Airway pressure release ventilation: theory and practice. AACN Clin Issues. 2001;12:234–46.
116. Hedenstierna G, Lichtwarck-Aschoff M. Interfacing spontaneous breathing and mechanical ventilation. Minerva Anestesiol. 2006; 72:183–98.
117. Putensen C, Wrigge H. Clinical review: biphasic positive airway pressure and airway pressure release ventilation. Crit Care. 2004;8:492–7.
118. Goldstein B, Papadakos PJ. Pressure-controlled inverse-ratio ventilation in children with acute respiratory failure. Am J Crit Care. 1994;3:11–5.
119. Esan A, Hess DR, Raoof S, George L, Sessler CN. Severe hypoxemic respiratory failure. Part 1 – ventilatory strategies. Chest. 2010;137:1203–16.
120. Guttman J, Haberthur C, Mols G, Lichtwarck-Aschoff M. Automatic tube compensation (ATC). Minerva Anestesiol. 2002;68:369–77.
121. Haberthur C, Mols G, Elsasser S, Bingisser R, Stocker R, Guttman J. Extubation after breathing trials with automatic tube compensation, T-tube, or pressure support ventilation. Acta Anaesthesiol Scand. 2002;46:973–9.
122. Figueroa-Casa JB, Montoya R, Arzabala A, Connery SM. Comparison between automatic tube compensation and continuous positive airway pressure during spontaneous breathing trials. Respir Care. 2010;55:549–54.
123. Fabry B, Haberthur C, Zappe D, Guttman J, Kuhlen R, Stocker R. Breathing pattern and additional work of breathing in spontaneously breathing patients with different ventilatory demands during inspiratory pressure support and automatic tube compensation. Intensive Care Med. 1997;23:545–52.
124. El-Beleidy AS, Khattab AA, El-Sherbini SA, Al-Gebaly HF. Automatic tube compensation versus pressure support ventilation and extubation outcome in children: a randomized controlled study. ISRN Pediatr. 2013;2013:871376.
125. Younes M. Proportional assist ventilation, a new approach to ventilatory support. Theory. Am Rev Respir Dis. 1992;145: 114–20.
126. Ambrosino N, Rossi A. Proportional assist ventilation (PAV): a significant advantage or a futile struggle between logic and practice? Thorax. 2002;57:272–6.
127. Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP. A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med. 2010;11: 7–11.
128. Bengtsson JA, Edberg KE. Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med. 2010; 11:253–7.
129. Clement KC, Thurman TL, Holt SJ, Heulitt MJ. Neurally triggered breaths reduce trigger delay and improve ventilator response times in ventilated infants with bronchiolitis. Intensive Care Med. 2011;37:1826–32.
130. Liet JM, Dejode JM, Joram N, Gaillard-Le Roux B, Betremieux P, Roze JC. Respiratory support by neurally adjusted ventilatory assist (NAVA) in severe RSV-related bronchiolitis: a case series report. BMC Pediatr. 2011;11:92.
131. Alander M, Peltoniemi O, Pokka T, Kontiokari T. Comparison of pressure-, flow-, and NAVA-triggering in pediatric and neonatal ventilatory care. Pediatr Pulmonol. 2012;47:76–83.
132. de la Oliva P, Schuffelmann C, Gomez-Zamora A, Villar J, Kacmarek RM. Asynchrony, neural drive, ventilatory variability, and COMFORT: NAVA versus pressure support in pediatric patients: a non-randomized cross-over trial. Intensive Care Med. 2012;38:838–46.
133. Bordessoule A, Emeriaud G, Morneau S, Jouvet P, Beck J. Neurally adjusted ventilatory assist improves patient-ventilator interaction in infants as compared with conventional ventilation. Pediatr Res. 2012;72:194–202.

134. Duyndam A, Bol BS, Kroon A, Tibboel D, Ista E. Neurally adjusted ventilatory assist: assessing the comfort and feasibility of use in neonates and children. Nurs Crit Care. 2013;18:86–92.
135. Lee J, Kim HS, Sohn JA, Lee JA, Choi CW, Kim EK, et al. Randomized crossover study of neurally adjusted ventilatory assist in preterm infants. J Pediatr. 2012;161:808–13.
136. Stein H, Alosh H, Ethington P, White DB. Prospective crossover comparison between NAVA and pressure control ventilation in premature neonates less than 1500 grams. J Perinatol. 2013;33:452–6.
137. Verbrugghe W, Jorens PG. Neurally adjusted ventilatory assist: a ventilation tool or a ventilation toy? Respir Care. 2011;56: 327–35.
138. Terzi N, Piquilloud L, Roze H, Mercat A, Lofaso F, Delisle S, et al. Clinical review: update on neurally adjusted ventilatory assist – report of a round-table conference. Crit Care. 2012;16:225.
139. Kavanagh BP. Goals and concerns for oxygenation in acute respiratory distress syndrome. Curr Opin Crit Care. 1998;4:16–20.
140. Prodhan P, Noviski N. Pediatric acute hypoxemic respiratory failure: management of oxygenation. J Intensive Care Med. 2004;19: 140–53.
141. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA. 2008;299:637–45.
142. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. Pediatrics. 1985;76:488–94.
143. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. Pediatrics. 1999;104:1082–8.
144. Varughese M, Patole S, Shama A, Whitehall J. Permissive hypercapnia in neonates: the case of the good, the bad, and the ugly. Pediatr Pulmonol. 2002;33:56–64.
145. Ambalavanan N, Carlo WA. Ventilatory strategies in the prevention and management of bronchopulmonary dysplasia. Semin Perinatol. 2006;30:192–9.
146. Hagen EW, Sadek-Badawi M, Carlton DP, Palta M. Permissive hypercapnia and risk of brain injury and developmental impairment. Pediatrics. 2008;122:e583–9.
147. Guidry CA, Hranjec T, Rodgers BM, Kane B, McGahren ED. Permissive hypercapnia in the management of congenital diaphragmatic hernia: our institutional experience. J Am Coll Surg. 2012;213:640–7.
148. Ryu J, Haddad G, Carlo WA. Clinical effectiveness and safety of permissive hypercapnia. Clin Perinatol. 2012;39:603–12.
149. Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis. 1984;129:385–7.
150. Downey P, Cox R. Update on the management of status asthmaticus. Curr Opin Pediatr. 1996;8:226–33.
151. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med. 1994;22:1568–78.
152. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypecapnia in severe adult respiratory distress syndrome. Intensive Care Med. 1990;16:372–7.
153. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill – too little of a good thing? (hypothesis paper). Lancet. 1999;354:1283–6.
154. Laffey JG, Kavanagh BP. Biological effects of hypercapnia. Intensive Care Med. 2000;26:133–8.
155. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. Crit Care. 2010;14:220.
156. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. Crit Care Med. 2010;38:1348–59.
157. Mao C, Wong DT, Slutsky AS, Kavanagh BP. A quantitative assessment of how Canadian intensivists believe they utilize oxygen in the intensive care unit. Crit Care Med. 1999;27: 2806–11.
158. Santschi M, Randolph AG, Rimensberger PC, Jouvet P. Mechanical ventilation strategies in children with acute lung injury: a survey on stated practice pattern. Pediatr Crit Care Med. 2013;14:e332–7.
159. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med. 2013;41:423–32.
160. Cheifetz IM, Hamel DS. Is permissive hypoxemia a beneficial strategy for pediatric acute lung injury? Respir Care Clin N Am. 2006;12:359–69.
161. Capellier G, Panwar R. Is it time for permissive hypoxaemia in the intensive care unit? Crit Care Resusc. 2011;13:139–41.
162. Abdelsalam M, Cheifetz IM. Goal-directed therapy for severely hypoxic patients with acute respiratory distress syndrome: permissive hypoxemia. Respir Care. 2010;55:1483–90.
163. Morley CJ. Volume-limited and volume-targeted ventilation. Clin Perinatol. 2012;39:513–23.
164. Sinha SK, Donn SM, Gavey J, McCarty M. Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed. 1997;77:F202–5.
165. Cheema IU, Ahluwalia JS. Feasibility of tidal volume-guided ventilation in newborn infants: a randomized, crossover trial using the volume guarantee modality. Pediatrics. 2001;107:1323–8.
166. Singh J, Sinha SK, Clarke P, Byrne S, Donn SM. Mechanical ventilation of very low birth weight infants: is volume or pressure a better target variable? J Pediatr. 2006;149:308–13.
167. Singh J, Sinha SK, Alsop E, Gupta S, Mishra A, Donn SM. Long term follow-up of very low birthweight infants from a neonatal volume versus pressure mechanical ventilation trial. Arch Dis Child Fetal Neonatal Ed. 2009;94:F360–2.
168. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338:347–54.
169. 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. 2000;342:1301–8.
170. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White Jr P, Wiener CM, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med. 1999;27:1492–8.
171. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med. 1998;158:1831–8.
172. Kallet RH, Jasmer RM, Pittet JF, Tang JF, Campbell AR, Dicker R, et al. Clinical implementation of the ARDS network protocol is associated with reduced hospital mortality compared with historical controls. Crit Care Med. 2005;33:925–9.
173. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev. 2007;(3):CD003844.
174. Kneyber MC, Rimensberger PC. The need for and feasibility of a pediatric ventilation trial: reflections on a survey among pediatric intensivists. Pediatr Crit Care Med. 2012;13:632–8.
175. Lopez-Fernandez Y, Azagra AM, de la Oliva P, Modesto V, Sanchez JI, Parrilla J, et al. Pediatric Acute Lung Injury Epidemiology and Natural History study: incidence and outcome

of the acute respiratory distress syndrome in children. Crit Care Med. 2012;40:3238–45.
176. Cannon ML, Cornell J, Tripp-Hamel DS, Gentile MA, Hubble CL, Meliones JN, et al. Tidal volumes for ventilated infants should be determined with a pneumotachometer placed at the end of the endotracheal tube. Am J Respir Crit Care Med. 2000;162: 2109–12.
177. Castle RA, Dunne CJ, Mok Q, Wade AM, Stocks J. Accuracy of displayed tidal volume in the pediatric intensive care unit. Crit Care Med. 2002;30:2566–74.
178. Neve V, Leclerc F, Noizet O, Vernoux S, Leteurtre S, Forget P, et al. Influence of respiratory system impedance on volume and pressure delivered at the Y piece in ventilated infants. Pediatr Crit Care Med. 2003;4:418–25.
179. Hess DR. Approaches to conventional mechanical ventilation of the patient with acute respiratory distress syndrome. Respir Care. 2011;56:1555–72.
180. Cornfeld DN. Acute respiratory distress syndrome in children: physiology and management. Curr Opin Pediatr. 2013;25:338–43.
181. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT, National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressure in patients with the acute respiratory distress syndrome. N Engl J Med. 2004;351: 327–36.
182. Curley MA, Arnold JH, Thompson JE, Fackler JC, Grant MJ, Fineman LD, et al. Clinical trial design – effect of prone positioning on clinical outcomes in infants and children with acute respiratory distress syndrome. J Crit Care. 2006;21:23–37.
183. Rouby JJ, Lu Q, Vieira S. Pressure/volume curves and lung computed tomography in acute respiratory distress syndrome. Eur Respir J Suppl. 2003;42:27s–36.
184. Kallet RH. Pressure-volume curves in the management of acute respiratory distress syndrome. Respir Care Clin N Am. 2003;9: 321–41.
185. Terragni PP, Rosboch GL, Lisi A, Vitale AG, Ranieri VM. How respiratory system mechanics may help in minimising ventilator-induced lung injury in ARDS patients. Eur Respir J Suppl. 2003;42:15s–21.
186. Albaiceta GM, Blanch L, Lucangelo U. Static pressure-volume curves of the respiratory system: were they just a passing fad? Curr Opin Crit Care. 2008;14:80–6.
187. Thome U, Topper A, Schaller P, Pohlandt F. Effect of mean airway pressure on lung volume during high-frequency oscillatory ventilation of preterm infants. Am J Respir Crit Care Med. 1998;157: 1213–8.
188. Tugrul S, Cakar N, Akinci O, Ozcan PE, Disci R, Esen F, et al. Time required for equilibration of arterial oxygen pressure after setting optimal positive end-expiratory pressure in acute respiratory distress syndrome. Crit Care Med. 2005;33:995–1000.
189. Chiumello D, Coppola S, Froio S, Mietto C, Brazzi L, Carlesso E, et al. Time to reach a new steady state after changes of positive end expiratory pressure. Intensive Care Med. 2013;39:1377–85.
190. Rimensberger PC, Cox PN, Frndova H, Bryan AC. The open lung during small tidal volume ventilation: concepts of recruitment and "optimal" positive end-expiratory pressure. Crit Care Med. 1999; 27:1946–52.
191. Hickling KG. 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. 2001;163:69–78.
192. Grasso S, Terragni P, Mascia L, Fanelli V, Quintel M, Hermann P, et al. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental lung injury. Crit Care Med. 2004;32:1018–27.
193. Grasso S, Stripoli T, DeMichele M, Bruno F, Moschetta M, Angelelli G, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. Am J Respir Crit Care Med. 2007;176:761–7.
194. Huang Y, Yang Y, Chen Q, Liu S, Liu L, Pan C, et al. Pulmonary acute respiratory distress syndrome: positive end-expiratory pressure titration needs stress index. J Surg Res. 2013;185:347–52.
195. Terragni PP, Filippini C, Slutsky AS, Birocco A, Tenaglia T, Grasso S, et al. Accuracy of plateau pressure and stress index to identify injurious ventilation in patients with acute respiratory distress syndrome. Anesthesiology. 2013;119:880–9.
196. Formenti P, Graf J, Santos A, Gard KE, Faltesek K, Adams AB, et al. Non-pulmonary factors strongly influence the stress index. Intensive Care Med. 2011;37:594–600.
197. Coss-Bu JA, Walding DL, David YB, Jefferson LS. Dead space ventilation in critically ill children with lung injury. Chest. 2003;123:2050–6.
198. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med. 2002; 346:1281–6.
199. Kallet RH, Alonso JA, Pittet JF, Matthay MA. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. Respir Care. 2004;49:1008–14.
200. Lucangelo U, Bernabe F, Vatua S, Degrassi G, Villagra A, Fernandez RL, et al. Prognostic value of different dead space indices in mechanically ventilated patients with acute lung injury and ARDS. Chest. 2008;133:62–71.
201. Raurich JM, Vilar M, Colomar A, Ibanez J, Ayestaran I, Perez-Barcena J, et al. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. Respir Care. 2010;55:282–7.
202. Maisch S, Reissmann H, Feuellekrug B, Weismann D, Rutkowski T, Tusman G, et al. Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. Anesth Analg. 2008;106:175–81.
203. Fengmei G, Chen J, Songqiao L, Congshan Y, Yi Y. Dead space fraction changes during PEEP titration following lung recruitment in patients with ARDS. Respir Care. 2012;57:1578–85.
204. Cortes GA, Marini JJ. Two steps forward in bedside monitoring of lung mechanics: transpulmonary pressure and lung volume. Crit Care. 2013;17:219.
205. Talmor D, Sarge T, O'Donnell CR, Ritz R, Malhotra A, Lisbon A, et al. Esophageal and transpulmonary pressures in acute respiratory failure. Crit Care Med. 2006;34:1389–94.
206. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359:2095–104.
207. Loring SH, O'Donnell CR, Behazin N, Malhotra A, Sarge T, Ritz R, et al. Esophageal pressure in acute lung injury: do they represent artifact or useful information about transpulmonary pressure, chest wall mechanics, and lung stress? J Appl Physiol. 2010;108:515–22.
208. Gulati G, Novero A, Loring SH, Talmor D. Pleural pressure and optimal positive end-expiratory pressure based on esophageal pressure versus chest wall elastance: incompatible results. Crit Care Med. 2013;41:1951–7.
209. Hayes DJ, Tobias JD, Kukreja J, Preston TJ, Yates AR, Kirkby S, et al. Extracorporeal life support for acute respiratory distress syndrome. Ann Thorac Med. 2013;8:133–41.
210. Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. Am J Respir Crit Care Med. 2001;163:1059–63.
211. Kondili E, Akoumianaki E, Alexopoulou C, Georgopoulos D. Identifying and relieving asynchrony during mechanical ventilation. Expert Rev Respir Med. 2009;3:231–43.
212. Pierson DJ. Patient-ventilator interaction. Respir Care. 2011;56: 214–28.

213. MacIntyre NR. Patient-ventilator interactions: optimizing conventional ventilation modes. Respir Care. 2011;56:73–84.
214. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med. 2006;32:1515–22.
215. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK. Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med. 2009;37:2740–5.
216. Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? Respir Care. 2011;56:25–38.
217. Ranallo CD, Heulitt MJ. Sleep and mechanical ventilation in the intensive care unit. J Pediatr Intensive Care. 2013;2:5–10.
218. Imanaka H, Nishimura M, Takeuchi M, Kimball WR, Yahagi N, Kumon K. Autotriggering caused by cardiogenic oscillation during flow-triggered mechanical ventilation. Crit Care Med. 2000; 28:402–7.
219. MacIntyre NR, McConnell R, Cheng KG, Sane A. Patient-ventilator dyssynchrony: flow-limited versus pressure-limited breaths. Crit Care Med. 1997;25:1671–7.
220. Kallet RH, Campbell AR, Dicker RA, Katz JA, Mackersie RC. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated breathing modes. Respir Care. 2005;50:1623–31.
221. Kallet RH, Luce JM. Detection of patient-ventilatory asynchrony during low tidal volume ventilation, using ventilator waveform graphics. Respir Care. 2002;47:183–5.
222. Nilsestuen JO, Hargett KD. Using ventilator graphics to identify patient-ventilator asynchrony. Respir Care. 2005;50:202–34.
223. Gentile MA. Cycling of the mechanical ventilator breath. Respir Care. 2011;56:52–60.
224. Dhand R. Ventilator graphics and respiratory mechanics in the patient with obstructive lung disease. Respir Care. 2005;50:246–61.
225. Valente Barbas CS. Lung recruitment maneuvers in acute respiratory distress syndrome and facilitating resolution. Crit Care Med. 2003;31:S265–71.
226. Kacmarek RM, Kallet RH. Respiratory controversies in the critical care setting: should recruitment maneuvers be used in the management of ALI and ARDS? Respir Care. 2007;52:622–35.
227. Rocco PR, Pelosi P, de Abreu MG. Pros and cons of recruitment maneuvers in acute lung injury and acute respiratory distress syndrome. Expert Rev Respir Med. 2010;4:479–89.
228. Tusman G, Bohm SH, Tempra A, Melkun F, Garcia E, Turchetto E, et al. Effects of recruitment maneuver on atelectasis in anesthetized children. Anesthesiology. 2003;98:14–22.
229. Duff JP, Rosychuk RJ, Joffe AR. The safety and efficacy of sustained inflations as a lung recruitment maneuver in pediatric intensive care unit patients. Intensive Care Med. 2007;33:1778–86.
230. Boriosi JP, Sapru A, Hanson JH, Asselin J, Gildengorin G, Newman V, et al. Efficacy and safety of lung recruitment in pediatric patients with acute lung injury. Pediatr Crit Care Med. 2011;12:431–6.
231. Wolf GK, Gomez-Laberge C, Kheir JN, Zurakowski D, Walsh BK, Adler A, et al. Reversal of dependent lung collapse predicts response to lung recruitment in children with early acute lung injury. Pediatr Crit Care Med. 2012;13:509–15.
232. Kheir JN, Walsh BK, Smallwood CD, Rettig JS, Thompson JE, Gomez-Laberge C, et al. Comparison of 2 lung recruitment strategies in children with acute lung injury. Respir Care. 2013; 58:1280–90.
233. Halbertsma FJ, Vaneker M, Pickkers P, Neeleman C, Scheffer GJ, Hoeven van der JG. A single recruitment maneuver in ventilated critically ill children can translocate pulmonary cytokines into the circulation. J Crit Care. 2010;25:10–5.
234. Samransamruajkit R, Jiraratanawong K, Siritaniwat S, Chottanapan S, Deelodejanawong J, Sritippayawan S, et al. Potent inflammatory cytokine response following lung recruitment maneuvers with HFOV in pediatric acute respiratory distress syndrome. Asian Pac J Allergy Immunol. 2012;30:197–203.
235. Fan E, Wilcox ME, Brower RG, Stewart TE, Mehta S, Lapinsky SE, et al. Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med. 2008;178:1156–63.
236. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. Crit Care Med. 2008;36:603–9.
237. Abroug F, Ouanes-Besbes L, Elatrous S, Brochard L. The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty and recommendations for research. Intensive Care Med. 2008;34:1002–11.
238. Sud S, Sud M, Friedrich JO, Adhikari NK. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. CMAJ. 2008;178:1153–61.
239. Kopterides P, Siempos II, Armaganidis A. Prone positioning in hypoxemic respiratory failure: meta-analysis of randomized controlled trials. J Crit Care. 2009;24:89–100.
240. Gattinoni L, Carlesso E, Taccone P, Polli F, Guerin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual meta-analysis. Minerva Anestesiol. 2010;76:448–54.
241. Sud S, Friedrich JO, Taccone P, Adhikari NK, Latini R, Pesenti A, et al. Prone ventilation reduced mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med. 2010;36:585–99.
242. Abroug F, Ouanes-Besbes L, Dachraoui F, Brochard L. An updated study-level meta-analysis of randomised controlled trials on proning in ARDS and acute lung injury. Crit Care. 2011;15:R6.
243. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159–68.
244. Afshari A, Brok J, Moller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. Anesth Analg. 2011;112:1411–21.
245. Willson DF, Thomas NJ, Markovitz BP, Bauman LA, DiCarlo JV, Pon S, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. JAMA. 2005;293:470–6.
246. Willson DF, Thomas NJ, Tamburro R, Truemper E, Truwit J, Conaway M, et al. Pediatric calfactant in acute respiratory distress syndrome trial. Pediatr Crit Care Med. 2013;14:657–65.
247. Pfenninger J, Gerber A, Tschappeler H, Zimmerman A. Adult respiratory distress syndrome in children. J Pediatr. 1982;101: 352–7.
248. Principi T, Fraser DD, Morrison GC, Farsi SA, Carrelas JF, Maurice EA, et al. Complications of mechanical ventilation in the pediatric population. Pediatr Pulmonol. 2010 [epub ahead of print].
249. Mutlu GM, Factor P. Complications of mechanical ventilation. Respir Care Clin N Am. 2000;6:213–52.
250. Woodside KJ, van Sonnenberg E, Chon KS, Loran DB, Tocino IM, Zwischenberger JB. Pneumothorax in patients with acute respiratory distress syndrome: pathophysiology, detection, and treatment. J Intensive Care Med. 2003;18:9–20.
251. Tang CW, Liu PY, Huang YF, Pan JY, Lee SS, Hsieh KS, et al. Ventilator-associated pneumonia after pediatric cardiac surgery in southern Taiwan. J Microbiol Immunol Infect. 2009;42:413–9.
252. Taira BR, Fenton KE, Lee TK, Meng H, McCormack JE, Huang E, et al. Ventilator-associated pneumonia in pediatric trauma patients. Pediatr Crit Care Med. 2009;10:491–4.
253. Sharma H, Singh D, Pooni P, Mohan U. A study of profile of ventilator-associated pneumonia in children in Punjab. J Trop Pediatr. 2009;55:393–5.

254. Roeleveld PP, Gujit D, Kuijper EJ, Hazekamp MG, de Wilde RB, de Jonge E. Ventilator-associated pneumonia in children after cardiac surgery in The Netherlands. Intensive Care Med. 2011;37: 1656–63.
255. Morrow BM, Argent AC. Ventilator-associated pneumonia in a paediatric intensive care unit in a developing country with high HIV prevalence. J Paediatr Child Health. 2009;45:104–11.
256. Morinec J, Iacaboni J, McNett M. Risk factors and interventions for ventilator-associated pneumonia in pediatric patients. J Pediatr Nurs. 2012;27:435–42.
257. Gautam A, Ganu SS, Tegg OJ, Andresen DN, Wilkins BH, Schell DN. Ventilator-associated pneumonia in a tertiary paediatric intensive care unit: a 1-year prospective observational study. Crit Care Resusc. 2012;14:283–9.
258. Brilli RJ, Sparling LW, Lake MR, Butcher J, Myers SS, Clark MD, et al. The business case for preventing ventilator-associated pneumonia in pediatric intensive care unit patients. Jt Comm J Qual Patient Saf. 2008;34:629–38.
259. Bigham MT, Amato R, Bondurrant P, Fridrikkson J, Krawczeski CD, Raake J, et al. Ventilator-associated pneumonia in the pediatric intensive care unit: characterizing the problem and implementing a sustainable solution. J Pediatr. 2009;154:582–7.
260. Awasthi S, Tahazzul M, Ambast A, Govil YC, Jain A. Longer duration of mechanical ventilation was found to be associated with ventilator-associated pneumonia in children aged 1 month to 12 years in India. J Clin Epidemiol. 2013;66:62–6.
261. Rosenthal VD, Alvarez-Moreno C, Villamil-Gomez W, Singh S, Ramachandran B, Navoa-Ng JA, et al. Effectiveness of a multidimensional approach to reduce ventilator-associated pneumonia in pediatric intensive care units of 5 developing countries: International Nosocomial Infection Control Consortium findings. Am J Infect Control. 2012;40:497–501.
262. Brierley J, Highe L, Hines S, Dixon G. Reducing VAP by instituting a care bundle using improvement methodology in a UK paediatric intensive care unit. Eur J Pediatr. 2012;171:323–30.
263. Tamma PD, Turnbull AE, Milstone AM, Lehmann CU, Sydnor ER, Cosgrove SE. Ventilator-associated tracheitis in children: does antibiotic duration matter? Clin Infect Dis. 2011;52: 1324–31.
264. Mhanna MJ, Elsheikh IS, Super DM. Risk factors and outcome of ventilator-associated tracheitis (VAT) in pediatric trauma patients. Pediatr Pulmonol. 2013;48:176–81.
265. Simpson VS, Bailey A, Higgerson RA, Christie LM. Ventilator-associated tracheobronchitis in a mixed medical/surgical pediatric ICU. Chest. 2013;144:32–8.
266. Muszynski JA, Sartori J, Steele L, Frost R, Wang W, Khan N, et al. Multidisciplinary quality improvement initiative to reduce ventilator-associated tracheobronchitis in the PICU. Pediatr Crit Care Med. 2013;14:533–8.
267. Uckay I, Ahmed QA, Sax H, Pittet D. Ventilator-associated pneumonia as a quality indicator for patient safety? Clin Infect Dis. 2008;46:557–63.
268. Thomas BW, Maxwell RA, Dart BW, Hartmann EH, Bates DL, Mejia VA, et al. Errors in administrative-reported ventilator-associated pneumonia rates: are never events really so? Am Surg. 2011;77:998–1002.
269. Novosel TJ, Hodge LA, Weireter LJ, Britt RC, Collins JN, Reed SF, et al. Ventilator-associated pneumonia: depends on your definition. Am Surg. 2012;78:851–4.
270. Moore BM, Blumberg K, Laguna TA, Liu M, Zielinski EE, Kurachek SC. Incidental sinusitis in a pediatric intensive care unit. Pediatr Crit Care Med. 2012;13:e64–8.
271. Brook I. Microbiology of nosocomial sinusitis in mechanically ventilated children. Arch Otolaryngol Head Neck Surg. 1998;124:35–8.
272. Bos AP, Tibboel D, Hazebroek FW, Hoeve H, Meradji M, Molenaar JC. Sinusitis: hidden source of sepsis in postoperative pediatric intensive care patients. Crit Care Med. 1989;17:886–8.
273. Kavanagh BP. Perioperative atelectasis. Minerva Anestesiol. 2008;74:285–7.
274. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005;102:838–54.
275. Dreyfuss D, Savmon G. Ventilator induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med. 1998;157:294–323.
276. O'Brien JMJ, Welsh CH, Fish RH, Ancukiewicz M, Kramer AM. Excess body weight is not independently associated with outcome in mechanically ventilated patients with acute lung injury. Ann Intern Med. 2004;140:338–45.
277. Suwanvanichkij V, Curtis JR. The use of high positive end-expiratory pressure for respiratory failure in abdominal compartment syndrome. Respir Care. 2004;49:286–90.
278. Slutsky AS, Trembly L. Multiple organ failure: is mechanical ventilation a contributing factor? Am J Respir Crit Care Med. 1998;157:1721–5.
279. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. Am Rev Respir Dis. 1982;126:166–70.
280. Rossi A, Polese G, Brandi G, Conti G. Intrinsic positive end-expiratory pressure (PEEPi). Intensive Care Med. 1995;21: 522–36.
281. Brochard L. Intrinsic (or auto-) positive end-expiratory pressure during spontaneous ventilation. Intensive Care Med. 2002;28: 1552–4.
282. Brochard L. Intrinsic (or auto-) PEEP during controlled mechanical ventilation. Intensive Care Med. 2002;28:1376–8.
283. Gay PC, Rodarte JC, Hubmayer RD. The effects of expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. Am Rev Respir Dis. 1989;139:621–6.
284. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. Chest. 1989;96:449–51.
285. McGuire G, Crossley D, Richards J, Wong D. Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. Crit Care Med. 1997;25: 1059–62.
286. Zhang XY, Yang ZJ, Wang QX, Fan HR. Impact of positive end-expiratory pressure on cerebral injury patients with hypoxemia. Am J Emerg Med. 2011;29:699–703.
287. Lou M, Xue F, Chen L, Xue U, Wang K. Is high PEEP ventilation strategy safe for acute respiratory distress syndrome after severe traumatic brain injury? Brain Inj. 2012;26:887–90.
288. Bennet M. Sleep and rest in the PICU. Paediatr Nurs. 2003; 15:III–VI.
289. Pinsky MR. The hemodynamic consequences of mechanical ventilation: an evolving story. Intensive Care Med. 1997;23: 493–503.
290. Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. Arch Dis Child. 1999;80:475–80.
291. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheynes-Stokes respiration. Circulation. 2000;102:61–6.
292. Duggan M, McNamara PJ, Engelberts D, Pace-Asciak C, Babyn P, Post M, et al. Oxygen attenuates atelectasis-induced injury in the in vivo rat lung. Anesthesiology. 2005;103:522–31.
293. Annat G, Viale JP, Bui Xuan B, Hadj Aissa O, Benzoni D, Vincent M, et al. Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology. 1983;58:136–41.

294. Kaczmarczyk G. Pulmonary-renal axis during positive-pressure ventilation. New Horiz. 1994;2:512–7.
295. Dehne MG, Meister M, Rohrig R, Katzer C, Mann V. Effects of inverse ratio ventilation with PEEP on kidney function. Ren Fail. 2010;32:411–6.
296. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA. 1999;282:54–61.
297. Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. Chest. 2001;119:1222–41.
298. Kiefer P, Nunes S, Kosonen P, Takala J. Effect of positive end-expiratory pressure on splanchnic perfusion in acute lung injury. Intensive Care Med. 2000;26:376–83.
299. Foronda FK, Troster EJ, Farias JA, Barbas CS, Ferraro AA, Faria LS, et al. The impact of daily evaluation and spontaneous breathing test on the duration of pediatric mechanical ventilation: a randomized controlled trial. Crit Care Med. 2011;39:2526–33.
300. Ferguson LP, Walsh BK, Munthall D, Arnold JH. A spontaneous breathing trial with pressure support overestimates readiness for extubation in children. Pediatr Crit Care Med. 2011;12:e330–5.