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Preface

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# Preface

Peter J. Papadakos, MD, FCCM  Joseph Dooley, MD
*Guest Editors*

I wish to thank my many teachers and role models who instilled in me the drive to teach the noble art of medicine—the many generations of students, residents, and fellows who have allowed me to practice those skills. And most importantly the love and support of my wife and children who allow me the opportunity to care for patients. A special thanks to my friend and colleague Richard Carlson for allowing us to edit this issue of the *Clinics*.

Peter J. Papadakos, MD, FCCM

I would like to thank my wife, Barbara, and children, Bryan, Kevin, and Katie, for their love and understanding while I pursue an academic career. My wife is the foundation of our family, and I greatly appreciate her. I would also like to acknowledge my parents. Clearly, their guidance and sacrifices enabled me to achieve my career goals. Lastly, I would like to thank my colleague, Dr. P.J. Papadakos, who has been a friend and role model. I greatly appreciate his teaching and the opportunities he has given me in academic medicine.

Joe Dooley, MD

The last decade has generated a growing fund of knowledge on how ventilator management can greatly impact patient outcome. The concepts developed by ARDS Network have been broadly accepted and placed into clinical practice, not only at university centers, but has filtered down to community hospitals. We are educating our students, residents, and fellows not only on the clinical aspects of ventilation but also in the growing fund of


doi:10.1016/j.ccc.2007.02.001

knowledge of the basic science of mechanical ventilation and how it may generate not only physiologic responses in the lung but may also be part of a greater systemic inflammatory response.

It is not only our goal in the issue to review the basic aspects of mechanical ventilation, such as modes of mechanical ventilation, ventilatory monitoring, and weaning from ventilation, but we wish to also develop discussion on some of the common controversies such as alveolar recruitment and stabilization. This issue also addresses some of the cutting edge concepts of mechanical ventilation such as therapist-driven protocols to standardize our care within specific disease groups. More and more, we use the education and expertise of respiratory therapists to provide a comprehensive team approach in patient management. Introduction of computer-based closed loop ventilation will also surely change the face of critical care practice as we allow technology to aid us in the 24/7 environment of the modern ICU.

We have also started to address three major complex patient disease groups in this issue: massive chest trauma, the complex environment of the neurologic ICU, and the fast-track world of the cardiovascular patient. Aspects of each of these may have implications in the care of other less specialty-based patients. No issue of a monograph on mechanical ventilation can be complete without focusing on a major question in our society, that of end of life. We are hopeful that this issue will be useful and spur broad-based discussion on how to wean mechanical life support during that highly emotionally charged period.

The full scope of the science and technology of mechanical ventilation has grown to such an extent that no single issue of the *Clinics* can fully address the topic, but we are hopeful that this issue acts as a base for further reading and research.

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Crit Care Clin 23 (2007) 117–134

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# Physiology of Mechanical Ventilation

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Every year worldwide, millions of patients receive ventilator support during surgery. Furthermore, mechanical ventilation has become an important therapy for treating patients who have impaired pulmonary function and particularly patients suffering from acute respiratory distress syndrome (ARDS). Actually the key supportive treatment for patients who have ARDS is mechanical ventilation. The most appropriate method of mechanical ventilation in ARDS has been controversial since the syndrome was first described in 1967 [1].

Historically, a volume of 12 to 15 mL/kg has been recommended in patients with acute lung injury and ARDS, although the tidal volume (VT) in normal persons at rest is 6 to 7 mL/kg [2]. The VTs used by clinicians over the past 10 to 20 years have been decreasing progressively from greater than 12 mL/kg actual body weight (ABW) in the 1970s [3,4] to less than 9 mL/kg ABW (~10 mL/kg predicted body weight [PBW]), as confirmed by recent epidemiologic studies of ventilator practice in Europe and the Americas [5–10]. In 2000, the National Institutes of Health-sponsored Acute Respiratory Distress Syndrome (ARDS) Network showed unequivocally that lowering VTs improves patient outcome [11]. Researchers compared two ventilation strategies. The first strategy used traditional VT (12 mL/kg PBW, corresponding to about 10 mL/kg ABW) and a plateau pressure of 50 cm $H_2O$, and the second used reduced VTs (6 mL/kg PBW, corresponding to about 5 mL/kg ABW). Plateau pressures were limited to 30 cm.

This study clearly demonstrates that mechanical ventilation itself can lead to lung damage and may even be the primary factor in lung injury. Thus understanding mechanical ventilation and even more important the physiology of mechanical ventilation could help reduce this ventilator-induced lung injury (VILI).

Jack J. Haitsma is supported by the Keenan Foundation. The funding source had no role in the writing of the review or in the decision to submit the paper for publication.

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doi:10.1016/j.ccc.2006.11.016 *criticalcare.theclinics.com*

## Ventilator-induced lung injury

VILI is defined by the international consensus conference on ventilator-associated lung injury (VALI) in ARDS as acute lung injury directly induced by mechanical ventilation in animal models (Box 1) [12]. Because VILI is usually indistinguishable morphologically, physiologically, and radiologically from the diffuse alveolar damage of acute lung injury, it only can be discerned definitively in animal models. VALI is defined as lung injury that resembles ARDS, and it is thought to occur because of mechanical ventilation. VALI may be associated with pre-existing lung pathology such as ARDS. Unlike VILI, however, one cannot be sure that VALI is caused by mechanical ventilation.

Insights in the pathophysiology of VILI and VALI came from several animal studies that showed that mechanical ventilation with larger VTs rapidly results in pulmonary changes that mimic ARDS [13–15]. Injurious ventilatory settings resulted (Fig. 1) in development of diffuse alveolar damage with pulmonary edema [16,17], the recruitment and activation of inflammatory cells [18,19], local production of inflammatory mediators (eg, cytokines) [20,21], and leakage of such mediators into the systemic circulation [22,23]. The propensity to injury is related partly to the inhomogeneity in distensibility of the injured lung [24,25]. The open and thus relatively healthy lung parts will be prone to overinflation, while the injured lung areas will not be inflated. The progression of the injury to the lung will result in atelectatic lung areas and patches of still open lung tissue [26]. When this lung is ventilated, even with small VTs, air will go preferentially to these open still compliant parts. This phenomenon has been described by Gattinoni as a baby lung, and the subsequent ventilation, even with small VTs, will result in overdistension [12,24]. Depending on the amount of collapsed lung tissue, even these small VTs will increase the actual VT delivered to the open lung areas several fold.

**Box 1. Definitions of ventilator-induced lung injury and ventilator-associated**

Ventilator-induced lung injury (VILI) [12]
- Acute lung injury directly induced by mechanical ventilation in animal models

Ventilator-associated lung injury (VALI) [12]
- Acute lung injury that resembles ARDS in patients receiving mechanical ventilation
- VALI may be associated with pre-existing lung pathology such as ARDS
- VALI is associated only with mechanical ventilation

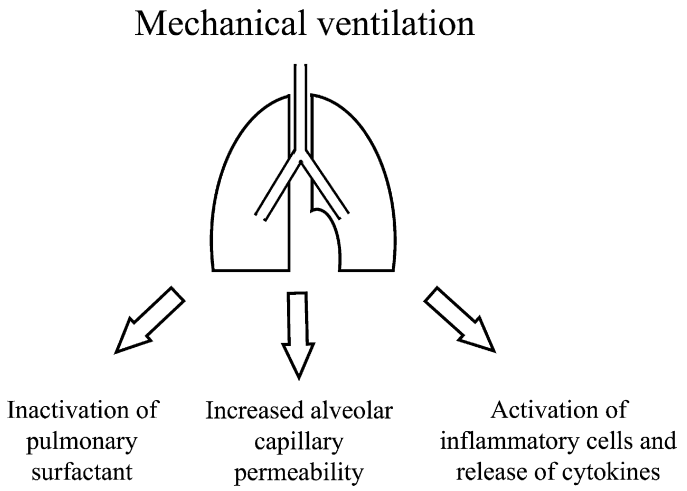


Fig. 1. Effects of injurious mechanical ventilation caused by both alveolar overdistension and repeated alveolar collapse and reopening, resulting in so-called ventilator-induced lung injury.

## Normal lung architecture

Gas exchange, the primary function of the lung, can come about only by breathing, a mechanical process that entails the cyclic application of physical stresses at the pleural surface and the transmission of those stresses throughout the lung tissue and the adherent cells. The diffusing capacity of the lung is limited structurally by the size of the alveolar surface area and the thickness of the blood–gas barrier. As a consequence, the lung's internal structure shows a gas exchange surface that is divided into a large number of small subunits connected to a branched conducting airway system, with the smallest gas exchange unit within the respiratory parenchyma being the alveolus (approximately $5 \times 10^8$ in an adult human lung) [27].

The major structural cells of the airways (epithelium, fibroblast, smooth muscle cells) all sense and respond to this highly dynamic mechanical environment. In turn, these cells cooperate to establish, maintain, and remodel the architecture and mechanical properties of the airway wall [28]. If strain is defined as the resulting length change of a structure per unit initial length, then in the course of a lifetime, the lung, and the cells within it, must withstand $10^9$ strain cycles with amplitudes that approach 4% during quiet tidal breathing and $10^7$ strain cycles with amplitudes that approach 25% during sighs, deep inspirations, or heavy exercise [29].

Formation of the air–liquid interface in the airway lumen results in surface tension, which exerts a net negative pressure on the airway (if one adopts the convention that pressures acting to collapse a tube are defined as negative and those tending to inflate a tube are defined as positive).

von Neergaard [30] was the first to suggest that surface tension plays a role in lung elasticity. He showed, in 1929, that the pressure necessary to fill the lung with liquid was less than half the pressure needed to fill the lung with air. His explanation for this remarkable difference was based on the assumption that in each alveolus there must be a barrier between air and fluid, with a tendency to reduce the size of the alveolus according to the law of LaPlace (Fig. 2) [30]. The law of LaPlace, $P = 2\gamma/r$ (P = pressure in the bubble; $\gamma$ = surface tension; r = radius of the bubble), states that a reduction of the radius of a bubble needs an equal reduction in surface tension to keep the bubble stable. When the lung was filled with fluid, the air–liquid interface was replaced by a liquid-to-liquid barrier, which eliminated the retractive forces that existed because of surface tension properties. A healthy lung (eg, alveoli) does not collapse at the end of expiration, so there must be a stabilizing force that prevents alveolar collapse. The law of LaPlace shows that when the radius of the alveolus is decreased, the surface tension has to be decreased concomitantly, which only can be accomplished by a dynamic behavior of the surface tension lowering material. In 1957, Clements [31] was the first to provide direct evidence of surface-active material in the lungs,

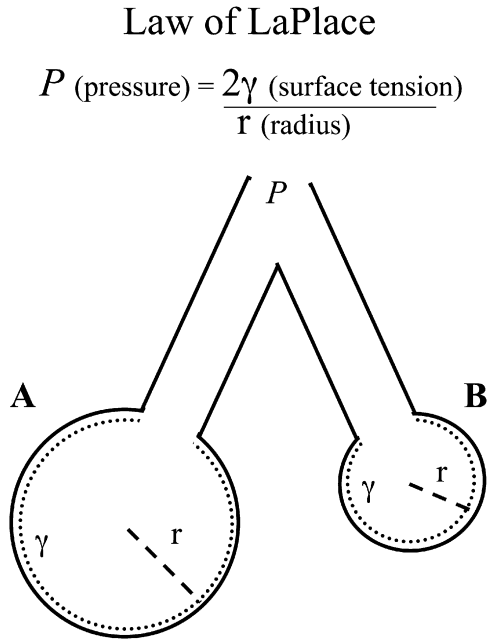


Fig. 2. According to the law LaPlace the surface tension in an alveoli has to be dynamic. When the airway pressure is similar (pressure = P) in alveoli of different sizes (difference in radius = r), the surface tension ($\gamma$) has to change accordingly. In this graph, the surface tension in alveolus A will be higher than the surface tension in B to maintain alveolar stability. Pulmonary surfactant is able to dynamically reduce the surface tension.

with a dynamic surface tension behavior. On a Wilhelmy balance, he measured the surface tension of fluid film sampled from a lung. When the film was stretched, the surface tension was relatively high (40 dynes/cm), but when the surface area was decreased, the tension fell to almost 10 dynes/cm. The fluid film from the lung now is known as surfactant, or surface active agent.

## Surfactant

Pulmonary surfactant is produced by the alveolar type II cells in the lung and is composed of two major fractions: lipids and surfactant-specific proteins (SP-A to D) [32]. Lipids make up approximately 90% of pulmonary surfactant, and phospholipids form the bulk of the lipids. The two main surfactant phospholipids, phosphatidylcholine and phosphatidylglycerol, specifically contribute to the overall surface tension-reducing properties of surfactant [33].

The normal physiological functions of the pulmonary surfactant system include mechanical stabilization of lung alveoli, by decreasing surface tension of the interface between alveoli and air [34]. Hydrophobic surfactant proteins B and C are essential for lung function and pulmonary homeostasis after birth by enhancing the spreading, adsorption, and stability of surfactant lipids required for the reduction of surface tension in the alveolus [35,36].

Surfactant protects against lung edema by stabilizing the fluid balance in the lung, especially across the alveolo–capillary membrane. In general, alveolar flooding will not occur when the surfactant system is functioning properly. When the surface tension rises above a critical level, however, alveolar flooding will occur, leading to influx of proteins into the alveolar space, which results in further inactivation of surfactant [37–39].

Surfactant also plays an important role in the lung's defense against infection [40]. Surfactant proteins SP-A and SP-D are collagen-containing C-type (calcium-dependent) lectins called collectins, which contribute significantly to surfactant homeostasis and pulmonary immunity. These highly versatile innate immune molecules are involved in a range of immune functions including viral neutralization; clearance of bacteria, fungi, and apoptotic and necrotic cells; down-regulation of allergic reaction; and resolution of inflammation [41].

## Airway pressures; plateau pressure and transpulmonary pressure

In an animal model, Dreyfuss and colleagues [16] applied high inspiratory pressures in combination with high volumes, which resulted in increased alveolar permeability, a hallmark of lung injury. In a second group, low pressure was combined with high volume (iron lung ventilation), again resulting in alveolar permeability [16]. In the third group, the effect of high pressures

combined with low volume was studied by strapping the chest wall to reduce chest excursions. The permeability of this group (high-pressure low-volume group) did not differ from the control group [16]. Thus large VT ventilation increases alveolar permeability, whereas peak inspiratory pressures do not seem to influence the development of this type of lung injury. Similar observations were made in rabbits ventilated with high peak pressures in which thorax excursions were limited by a plaster cast [42]. Thus in injured lungs. the effect of higher volumes only aggravated the permeability, as demonstrated in animals in which the surfactant system was inactivated and which subsequently were ventilated with high VTs [17,43].

The alveolar pressure alone, however, as measured in such studies, does not provide a measure of alveolar distension. Rather than the absolute airway pressure, the absolute transpulmonary pressure (which is equal to the alveolar pressure minus pleural pressure) is responsible for injury [44,45]. Depending on the chest wall's contribution to respiratory mechanics, a given positive end-expiratory and/or end-inspiratory plateau pressure may be appropriate for one patient but inadequate or potentially injurious for another. Thus, failure to account for chest wall mechanics may affect results in clinical trials of mechanical ventilation strategies in acute respiratory distress syndrome [46]. In a consensus statement regarding the use of mechanical ventilation, a plateau pressure less than 35 cm $H_2O$ was recommended [47] based primarily on animal data [14,48,49]. Other animal studies, however, suggest that, under some circumstances, plateau pressures lower than 35 cm $H_2O$ also should be of concern.

Because of the inaccuracy of plateau pressure as a surrogate for lung distension [45,50] and given the central role of end-inspiratory transpulmonary pressure in preventing VILI during tidal ventilation, measurement of transpulmonary pressure provides physiologically more relevant information than estimates derived from plateau pressure, which do not take into account individual values of chest wall elastance. For example, Ranieri and colleagues [50] demonstrated that the optimal values for VT were substantially lower, and optimal values for positive end-expiratory pressure (PEEP) were higher when respiratory system mechanics (volume–pressure curves based on airway opening pressure) were analyzed as compared with when the physiologically more relevant lung mechanics (based on transpulmonary pressure) were analyzed in patients with high chest wall elastance caused by abdominal distension. Thus, arbitrarily limiting plateau pressure to 30 to 35 cm $H_2O$ not only may be unnecessary to prevent VILI in patients who have high chest wall elastance but may cause harm by leading to severe hypoxemia and/or insufficient ventilation. A secondary analysis of the ARDSNet data confirmed that VT reduction even benefited patients with safe plateau pressures of 31 cm $H_2O$ or less of water, meaning that pressure-limited ventilation based on plateau pressures alone, without concomitant volume limitation, may be detrimental [46].

**Alveolar repeated collapse and re-expansion**

Pioneering work of Mead and colleagues [51] demonstrated that because of the pulmonary interdependence of the alveoli, the forces acting on the fragile lung tissue in nonuniformly expanded lungs are not only the applied transpulmonary pressures, but also the shear forces that are present in the interstitium between open and closed alveoli (Fig. 3). These potentially pathogenic forces include repetitive (cyclic) strain (stretch) from overdistension and interdependence and shear stress to the epithelial cells as lung units collapse and reopen, so-called atelectrauma [52]. Based on a theoretical analysis, they predicted that a transpulmonary pressure of 30 cm $H_2O$ could result in shear forces of 140 cm $H_2O$ [51]. Shear forces, rather than end-inspiratory overstretching, may be the major reason for epithelial disruption and the loss of barrier function of the alveolar epithelium. In an ARDS lung, alveoli are subjected to opening and closing during ventilation [12,26,51]. Using in vivo video microscopy, Steinberg and colleagues [26] directly assessed alveolar stability in normal and surfactant-deactivated lungs and showed alveolar instability (atelectotrauma) during ventilation.

Important evidence for this mechanism comes from the finding that ventilation, even at low lung volumes, can augment lung injury [53,54]. Muscedere and colleagues [53] ventilated isolated, nonperfused, lavaged rat lungs with physiologic VTs (5 to 6 mL/kg) at different end-expiratory pressures (above and below Pinf). Lung injury was significantly greater in

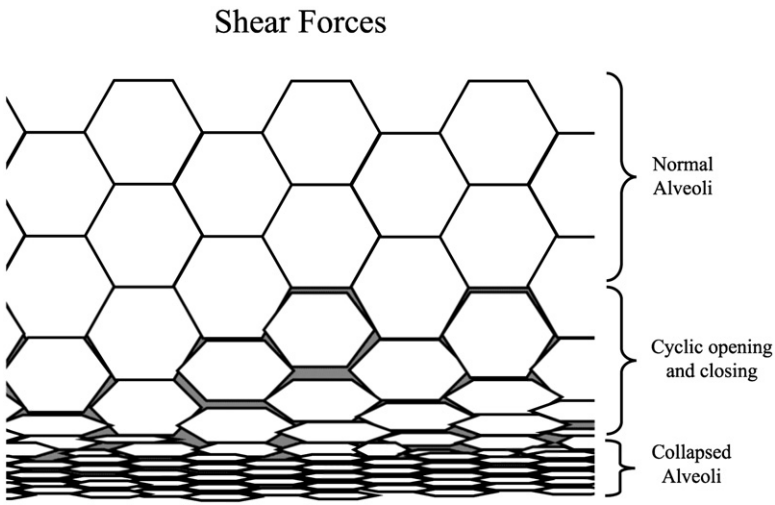


Fig. 3. The interface between collapsed and consolidated lung and normal lung units is heterogeneous and unstable. This region is prone to cyclic recruitment and collapse and localized asymmetrical stretch of lung units, causing so-called shear forces, which are a major part of atelectotrauma.

the groups ventilated with a PEEP below Pinf, and in these groups, the site of injury depended on the level of PEEP (see Fig. 3). Tsuchida and colleagues [55] showed that injurious ventilation, in an animal model with extensive atelectatic areas, resulted in alveolar injury (assessed by histology, myeloperoxidase protein expression, quantification, and localization of cytokine mRNA expression) especially in the nondependent regions. Thus, preventing repeated opening and closing of these lung areas might actually be protective against this ventilator-induced mediator release [56]. This study further confirms that ventilation of atelectatic lungs causes the baby lung effect, where VTs only will go into the nonatelectatic area, resulting in tidal overdistension of the available aerated lung [24,25] and finally release of inflammatory cytokines [52,57].

Thus in addition to high airway pressures, end-expiratory lung volume is an important determinant of the degree and site of lung injury during positive pressure ventilation. Therefore preventing repeated collapse by stabilizing lung tissue at end-expiration with PEEP can reduce lung injury [12,14,48,49].

## Positive end-expiratory pressure

Webb and Tierney [49] in 1974 demonstrated the critical role that PEEP plays in preventing/reducing lung injury. In rats ventilated with 10 cm $H_2O$ of PEEP and a peak pressure of 45 cm $H_2O$, no lung injury was present, but when using the same peak pressure and omitting PEEP, severe pulmonary edema was formed within 20 minutes [49]. Dreyfuss and colleagues [58] showed in 1985 that in rats ventilated at peak inspiratory pressure of 45 cm $H_2O$, damage caused by mechanical ventilation begins at the endothelial side after 5 minutes and rapidly progresses to the epithelium after 20 minutes. A subsequent study showed a reduction of endothelial injury and the preservation of the structure of the alveolar epithelium by use of 10 cm $H_2O$ of PEEP, which was accompanied by a lack of alveolar flooding [16].

Reducing protein influx, minimizing deterioration of lung mechanics, and other such protective effects by ventilating with higher levels of PEEP have been reported by others [59,60]. Different animal models have shown that ventilation with PEEP at lower VTs results in less edema than ventilation without PEEP and a higher VT for the same peak or mean airway pressure [16,49,61,62] and that, more specifically, PEEP prevents alveolar flooding [48,49]. Four mechanisms have been proposed to explain the improved pulmonary function and gas exchange with PEEP:

- Increased functional residual capacity
- Alveolar stabilization, especially after recruitment
- Redistribution of extravascular lung water
- Improved ventilation–perfusion matching [63]

PEEP usually decreases cardiac output, a well known fact since the classic studies of Cournand and colleagues [64] where positive pressure ventilation restricted the filling of the right ventricle, because the elevated intrathoracic pressure restricted venous flow into the thorax, thereby, reducing cardiac output. Hyperinflation compresses the heart between the expanding lungs, increasing juxtacardiac intrathoracic pressure and pericardial pressure more than lateral chest wall intrathoracic pressure [65]. This decrease in apparent left ventricular diastolic compliance previously was misinterpreted as PEEP-induced impaired left ventricular contractility. When patients are fluid resuscitated back to their original left ventricular end-diastolic volume, however, cardiac output also returns to its original levels [3] despite the continued application of PEEP [66,67].

## Recruitment maneuvers

Recruitment maneuvers have been suggested to open up collapsed lung tissue to improve ventilation in patients who have ARDS [68]. To exploit the potential for recruitment, a transpulmonary pressure greater than the opening pressure must be applied to the lung (Fig. 4). To do so, chest

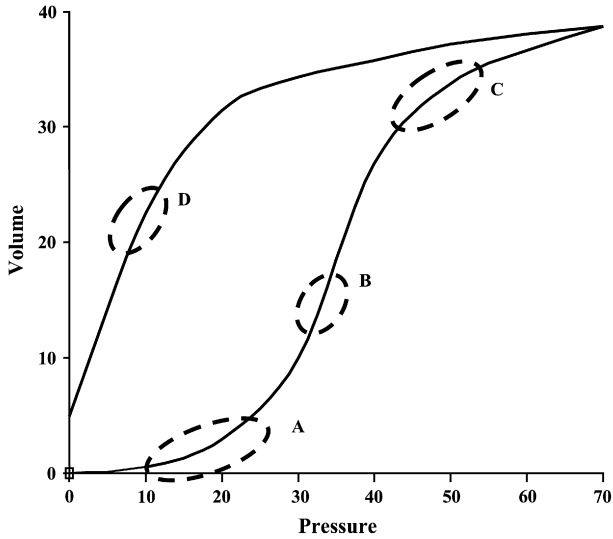


Fig. 4. Pressure volume diagram of a lung with acute lung injury. Points A–D depict different areas of ventilation. At point A, there is cyclic opening and closing of alveoli. At point B, only open alveoli will be ventilated (closed units stay closed), where as at point C, overdistension of ventilated alveoli will occur. At point D, after recruitment, more alveoli have been opened, and all of these alveoli will participate in ventilation. Of note, although more alveoli participate in ventilation at point D, the airway pressure needed to accomplish ventilation is much lower compared with point B.

wall elastance must be measured or estimated. To avoid collapse after recruitment, a PEEP greater than the compressive forces operating on the lung and alveolar ventilation sufficient to prevent absorption atelectasis must be provided. Indeed, avoidance of stretch (low airway plateau pressure) and prevention of cyclic collapse and reopening (adequate PEEP and alveolar ventilation) are the physiologic cornerstones of mechanical ventilation in acute lung injury/acute respiratory distress syndrome [69]. In animal studies, the beneficial effect of recruitment maneuvers translates into improved oxygenation, reduction of airway pressures and VTs, and reduced lung injury [70–75].

In patients, however, the use of recruitment maneuvers remains very controversial. Recently, Gattinoni and colleagues [76] showed that the percentage of potentially recruitable lung is extremely variable and strongly associated with the response to PEEP in patients who have ARDS. Although several studies in patients with or at risk for ARDS have demonstrated improvement in oxygenation [67,77] and some studies also improved outcome [78–81], other studies, especially the ARDS Network ALVEOLI trial, failed to demonstrate improved outcome [82,83]. Understanding how recruitment maneuvers differ, and why lungs are less or more susceptible for collapse can help improve lung recruitment.

Grasso and colleagues [77] classified patients who had ARDS after recruitment maneuvers with continuous positive airway pressure 40 cm $H_2O$ for 40 seconds into responders and nonresponders according to the occurrence (or not) of a 50% increase in $PaO_2/FiO_2$ after the recruiting maneuver. After 2 minutes, the researchers observed a 20 plus or minus 3% increase in $PaO_2/FiO_2$ in the nonresponder group ($n = 11$) and a 175 plus or minus 23% increase in the responder group. The responder group had a lower lung and chest wall elastance and had been ventilated for a shorter period of time with less hemodynamic impairment than the nonresponder group [77]. Patroniti and colleagues [84] also observed that recruitment potential in early ARDS is high. Using the setting from the ALVEOLI trial Grasso and colleagues [85] used the higher PEEP strategy from the AVEOLI trial and observed significant alveolar recruitment ($587 \pm 158$ mL), improvement in arterial oxygen partial pressure/inspired oxygen fraction ratio (from $150 \pm 36$ to $396 \pm 138$), and reduction in static lung elastance (from $23 \pm 3$ to $20 \pm 2$ cm $H_2O$/l), in nine responders. In 10 nonrecruiters, alveolar recruitment was minimal; oxygenation did not improve, and static lung elastance significantly increased (from $26 \pm 5$ to $28 \pm 6$ cm $H_2O$/L), suggesting that the protocol used by the ARDS Network, lacking solid physiologic basis, frequently fails to induce alveolar recruitment and may increase the risk of alveolar overinflation [85].

Recruitment maneuvers also seem to work better in extrapulmonary ARDS, but a lung protective strategy alone without adjusting at the PEEP level does not provide full lung recruitment and best oxygenation [86]. Similar observations were made by Foti and colleagues [87] in patients

who had ARDS, demonstrating that recruitment maneuvers can improve oxygenation even at relatively low PEEP, but are less effective than a continuous high PEEP level. Monitoring patients up to 6 hours after a recruitment maneuver, Borges and colleagues [88] showed that recruitment maneuvers reversed the hypoxemia present in most patients who had early primary or secondary ARDS. This resulted in sustained recruitment of more than 95% of airspace on CT analysis; the proposed maximum-recruitment strategy (P/F ratio > 400 mm Hg) was applied only after intensive fluid resuscitation and after excluding patients who were deteriorating rapidly [88]. Therefore, one should be cautious about its application to patients not intensively monitored and resuscitated. Amato and colleagues [78,79] demonstrated that recruitment maneuvers in limited studies can improve outcome. Whether this will improve outcome or reduce VALI in other patients, however, are matters for future study [88]. Current guidelines for recruitment procedure are: apply as early as possible in the disease process (extra pulmonary ARDS is often easier), make sure that the patient is as hemodynamically stable as possible, and apply intensive fluid resuscitation before the recruitment procedure and maintain recruited lung tissue by adjusting the PEEP pressure. Specific guidelines include:

- Recruitment maneuvers should be applied as early as possible during the disease process.
- Extra pulmonary ARDS is in general easier to recruit.
- Apply intensive fluid resuscitation before the recruitment maneuver to minimize hemodynamic adverse effects.
- Maintain recruited lung tissue by adjusting ventilation (adjust PEEP levels and apply low VTs 6 mL/kg).

## Mechanical ventilation in patients who have adult respiratory distress syndrome—how far are we, and what can we improve?

Hickling and colleagues [89] in a retrospective analysis, demonstrated that ARDS patients ventilated with a low VT, and permissive hypercapnia had decreased mortality compared with historical controls. Three subsequent controlled trials using low VT strategies were started simultaneously, but all failed to demonstrate improved patient outcomes [90–92]. These studies used a VT of approximately 7 mL/kg in their low VT arms and a VT of 10 mL/kg in their control arms [90–92]. In contrast, using a VT of 6 mL/kg in their treatment arm and a VT of 12 mL/kg in their control arm (VT calculated by using PBW) the ARDS Network was able to reduce mortality [11]. In the ARDS Network study, PBW was approximately 20% lower than measured body weight, resulting in a VT of approximately 10 mL/kg measured body weight for the control arm [93]. The explanation given by the ARDS Network trial for the beneficial effect on mortality

was the greater difference in VT between the two arms of the study, the power of the study (ARDS Network studied 861 patients, while the other three studied a maximum of 120 patients), and the aggressive treatment/prevention of acidosis [11]. Other studies performed since then have demonstrated that higher VTs increase VILI and lead to the development of ALI [94,95]. Amato and colleagues [78] 2 years earlier reported a significantly reduced mortality in 53 patients by applying a protective ventilation strategy. In their study, VT also was reduced to below 6 mL/kg in the low VT group compared with 12 mL/kg VT in the control arm. Villar and colleagues [96] also showed a reduction in ICU mortality in patients who had severe and persistent ARDS. In their conventional ventilated arm (VT 9 to 11 mL/kg PBW, PEEP $\geq$ 5 cm $H_2O$), mortality was 53.3% and 32% in their lung-protective arm (VT 5 to 8 mL/kg PBW, and PEEP was set on day 1 at 2 cm $H_2O$ above the inflection point on the pressure–volume curve) [96].

These studies demonstrate that improving ventilation by reducing VT reduces mortality. Can one optimize ventilation further, however, by adhering to the physiology of mechanical ventilation? Although PEEP levels remain controversial, these studies showed that higher PEEP levels seem to be beneficial. In contrast to the three negative studies [90–92], the PEEP level in the low VT group of Amato and colleagues [78] was higher, almost 17 cm $H_2O$, and 14 cm $H_2O$ in the study by Villar and colleagues [96], compared with 8 to 10 cm $H_2O$ PEEP in the studies by Brochard and colleagues [90], Brower and colleagues [91], and Stewart and colleagues [92]. In the ARDS Network trial, the low VT group had a slightly higher set PEEP of 9 cm $H_2O$ compared with a set PEEP of 8 cm $H_2O$ in the control group [11]. The increased respiratory rate (to help prevent acidosis) used in the low VT group, however, may have resulted in intrinsic PEEP that contributed to a higher total PEEP (16 cm $H_2O$) in this group [97,98] compared with 12 cm $H_2O$ in the traditional VT group. This higher total PEEP could help explain the decrease in mortality observed in this group, although the data addressing this issue are somewhat contradictory. The follow-up study in 2004 by the ARDS Network addressed whether increased PEEP levels would decrease mortality [82] further. Mean PEEP values on days 1 through 4 were 8.3 cm $H_2O$ in the lower PEEP group and 13.2 cm $H_2O$ in the higher PEEP group. Although in this study no benefit in outcome was observed between the patient groups (the study was stopped early after enrolment of 549 patients), the mortality rate in both study arms was relatively low (24.9% lower PEEP and 27.5% higher PEEP) [82], providing supportive data that adjusting the ventilatory settings decreases mortality in ARDS/ALI patients. Unfortunately, patients randomized to the higher PEEP group also had at baseline more characteristics that predict a higher mortality. Adjustment for these differences in baseline covariates did not alter the final outcome but did favor the higher PEEP group [82].

## Summary

The main conclusion to draw concerning improving ventilation in patients who have ARDS is the need to use lower tidal volumes of 6 mL/kg PBW, and although a maximum mean airway pressure should be used as a guideline, lowering VTs also should be done below this maximum. Numerous recent studies further strengthen this message, because they suggest that the use of ventilatory strategies with relatively large VTs is associated with the secondary acquisition of ALI/ARDS [9,94,95], particularly in patients at risk for development of this syndrome.

Unfortunately a wide variation in application of low VT ventilation exists, and the proportion of patients receiving VTs within recommended limits ($VT \leq 8$ mL/kg) remains modest at 16% [99]. Implementation of feedback and education concerning lung-protective mechanical ventilation with special attention to the importance of closely adjusting VTs to PBW can help in improve physician compliance in the use of lung-protective ventilation [100,101].

To further improve ventilation according to physiological principals, recruitment procedures can be performed to increase oxygenation, but further studies are needed to optimize this procedure.

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Crit Care Clin 23 (2007) 135–148

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# Laboratory Monitoring of Mechanical Ventilation

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A patient's respiratory status and the effectiveness of mechanical ventilation are assessed in many ways. Available methods for determining this information include clinical assessment, pulse oximetry, end tidal carbon dioxide ($CO_2$) monitoring, pressure volume loops, and laboratory tests. This article examines the use of laboratory tests for managing mechanical ventilation. Blood gas analysis is a common test widely used for this purpose, and this is evaluated in detail. Other tests, however, provide valuable insight into the management of patients receiving mechanical ventilation. These include serum electrolytes, thyroid function tests, and adrenal function tests.

## Arterial blood gas analysis

Mechanical ventilation controls two basic components of a patient's physiology: ventilation and oxygenation. Through arterial blood gas analysis, one can determine the patient's pH, arterial partial pressure of $CO_2$ ($P_aCO_2$), and arterial partial pressure of oxygen ($P_aO_2$). In the most basic terms, the minute ventilation (tidal volume multiplied by respiratory rate) is adjusted to achieve a physiologic appropriate pH and $P_aCO_2$. Both the fraction of inspired oxygen ($F_IO_2$) and mean airway pressure can be adjusted to achieve an acceptable $P_aO_2$. This section reviews the mechanics of blood gas analysis. The use of blood gas analysis for managing specific patient conditions then is explored.

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doi:10.1016/j.ccc.2006.11.013

*Mechanics*

Blood gas analyzers report a range of results, but the only parameters directly measured are the partial pressures of $O_2$ ($PO_2$) and $CO_2$ ($PCO_2$) and blood pH.

*Oxygen electrode*

In late 1954, Leland C. Clark, Jr., PhD, designed a blood $O_2$ electrode, also known as a Clark cell or polarographic electrode [1]. The polarographic $O_2$ electrode measures the $PO_2$ in a blood or gas sample. It is composed of a glass-coated platinum cathode and a silver/silver chloride reference electrode, which are immersed in an electrolyte solution of potassium chloride. The necessary reactions occur under a polarizing voltage of 600 to 800 mV, and the total current is limited by the very small exposed area on the platinum cathode. At the anode, electrons are provided by the oxidation reaction of the silver with the chloride ions of the potassium chloride electrolyte solution to give silver chloride and electrons.

$$Ag^+ + Cl^- \rightarrow AgCl + e^-$$

At the cathode, $O_2$ combines, by means of a reduction reaction, with the electrons and water, giving rise to hydroxyl ions.

$$O_2 + 2H_2O + 2e^- \rightarrow H_2O_2 + 2OH^-$$

This equation shows that the number of $O_2$ molecules available determines the number of electrons that can be taken up at the cathode. The more electrons taken up, the greater the current flow. Thus the current, having been determined by the availability of the $O_2$ molecules, is directly proportional to the $PO_2$. A membrane, usually polypropylene, separates the electrode from the blood, preventing deposition of protein but allowing the $O_2$ tension in the blood to equilibrate with the electrolyte solution. The electrode is kept at a constant temperature of 37°C, and regular checks of the membrane are required to ensure it is not perforated or coated with proteins.

*Carbon dioxide electrode*

In early 1954 Richard Stow, MD, described his $CO_2$ electrode, but failed to develop it further. Later that same year, Severinghaus [2] improved upon the Stow-type $CO_2$ electrode to create the $CO_2$ electrode in use today. The Severinghaus or $CO_2$ electrode is a modified pH electrode in contact with sodium bicarbonate solution and separated from the blood specimen by a rubber or Teflon semipermeable membrane. The Severinghaus $CO_2$ electrode provides a direct method of $PCO_2$ measurement from the hydrogen ion change associated with the reaction of $CO_2$ with water.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3$$

Hydrogen ions are produced in proportion to the $PCO_2$ and are measured by the pH-sensitive glass electrode. $CO_2$, but not hydrogen ions, diffuses from the blood sample across the membrane into the sodium bicarbonate solution, producing hydrogen ions and a change in pH. At the tip of the electrode, $CO_2$ diffuses through the plastic membrane into the mesh impregnated with the bicarbonate solution and combines with the water present, producing the hydrogen ions and bicarbonate. The resulting change of hydrogen ion concentration is measured by the glass electrode. The analyzer then calculates the $PCO_2$.

$$PCO_2 = CO_2 \text{ concentration}/100 \times \left(\text{barometric pressure water vapour pressure}\left[37^{\circ}\text{C}\right]\right)$$

As with the Clark electrode, the Severinghaus electrode must be maintained at 37°C and calibrated with gases of known $PCO_2$. Additionally, the integrity of the membrane is essential.

*pH electrode*

The pH electrode is an ion-selective electrode dependent on the hydrogen ion-sensitive glass at its tip. A measuring silver/silver chloride electrode is encased in a bulb of special pH-sensitive glass. and it contains a buffer solution that maintains a constant pH. This glass electrode is placed in the blood sample, and a potential difference is generated across the glass that is proportional to the difference in hydrogen ion concentration. The potential is measured between a reference electrode (in contact with the blood by means of a semipermeable membrane) and the measuring electrode. Both electrodes must be kept at 37°C, clean and calibrated with buffer solutions of known pH.

When obtaining a sample for blood gas analysis, a heparinized, freshly drawn, bubble-free arterial blood sample is required. Heparin is acidic, and if too much is present in the sample, the measured $PCO_2$ and calculated bicarbonate are reduced. A freshly drawn sample is important, as delay in measurement allows continued metabolism by the erythrocytes, thus reducing pH and $PO_2$ and increasing $PCO_2$. If a delay in analysis is expected, keeping the specimen on ice allows accurate measurement to be postponed for up to 1 hour. A bubble-free sample is necessary, as air bubbles introduce error by causing a fall in $PCO_2$ and an increase in $PO_2$.

## Cases

Blood gas analysis is a tool used commonly by clinicians for managing mechanical ventilation. Like any clinical tool, the appropriate use and evaluation of blood gas analysis are necessary for the proper management

of patients receiving mechanical ventilation. The inappropriate interpretation of blood gas results can lead to unnecessarily prolonged mechanical ventilation and ICU care, increased morbidity, and perhaps, increased mortality. This section examines common clinical scenarios in which blood gas analysis is used to determine patient management. The cases examined are of varying levels of complexity, but will provide a general overview of the management of patients receiving mechanical ventilation. Many of the issues explored in this section are described in detail in other sections of this issue, including lung protection strategies in acute respiratory distress syndrome (ARDS) (permissive hypercapnea, positive end-expiratory pressure [PEEP], inverse ratio ventilation, and $O_2$ toxicity). This section describes these issues in the context of the use of blood gas analysis for managing mechanical ventilation, but not in detail. Before examining specific cases, it is important to know normal values for arterial blood gas analysis. On room air, they are as follows (from the University of Rochester of Rochester Medical Center Laboratory):

1. pH: 7.35 to 7.43
2. $P_aCO_2$: 36 to 46 mm Hg
3. $P_aO_2$: 80 to 100 mm Hg
4. Bicarbonate: 19 to 23 mmol/L
5. Base Excess: $-3$ to $+1$ mmol/L
6. $O_2$ saturation: 94% to 100%

*Case 1—the previously healthy patient receiving mechanical ventilation*

Previously healthy patients require mechanical ventilation in various situations. Anesthesiologists commonly manage previously healthy patients undergoing mechanical ventilation as part of a general anesthetic. In this case, blood gas analysis usually is not required, as pulse oximetry and end-tidal $CO_2$ monitoring provide the information needed to adjust the patient's minute ventilation, inspired $O_2$ concentration, and mean airway pressure. Depending on the situation, these patients may have an arterial catheter. In this case, blood gas analysis could then be used to adjust these parameters. At times, such a patient may require mechanical ventilation in the ICU for varying periods of time. Examples include patients who suffer large blood losses as a result of trauma, obstetric catastrophes, or other causes. Another example may be marked airway or facial edema in which premature extubation and withdrawal from mechanical ventilation could prove risky. Occasionally surgeons will request several days of paralysis and mechanical ventilation for patients who have undergone complex plastic surgery procedures or those who, for various reasons, have abdominal fascia that was unable to be closed. If such a patient was to arrive in the ICU, initial blood gas analysis may reveal the following values:

pH 7.26, $PCO_2$ 60 mm Hg, $PO_2$ 62 mm Hg, and an $O_2$ saturation of 90%.

Assuming normal values of pH 7.4 and $PCO_2$ 40, the patient has a pure respiratory acidosis and mild hypoxia. The goal is to achieve a pH and $PCO_2$ near normal and an $O_2$ saturation of 92% or better. Recall that there is a 0.08 change in pH for every 10 mm Hg change in $PCO_2$ from the normal value of 40 mm Hg. Hypercapnea will cause a respiratory acidosis and, thus, a negative change in pH. In this case, the predicted change in pH is determined as follows:

$$\text{Predicted pH} = 7.4 - (.08)(PCO_2 - 40 \text{ torr})/10 \text{ torr}$$
$$\text{Predicted pH} = 7.4 - (.08)(60 - 40)/10$$
$$\text{Predicted pH} = 7.4 - 0.16$$
$$\text{Predicted pH} = 7.26$$

The predicted pH is the same as the measured pH, which is consistent with a pure respiratory acidosis. Ventilator adjustments made to improve this patient's respiratory status would include increasing the minute ventilation (respiratory rate and/or tidal volume), increasing the $F_IO_2$ (recognizing the risks associated with $O_2$ toxicity when $O_2$ concentrations are greater than 60%), and increasing the mean airway pressure (by increasing the PEEP and/or adjusting the I:E ratio). Assuming the patient weighs 70 kg and is on controlled ventilation with a tidal volume of 400 cc, respiratory rate (RR) = 10, I:E ratio = 1:3, and an $F_IO_2$ = 40% with PEEP of 0 cm $H_2O$, adjustments may include increasing the tidal volume ($V_T$) to 500 cc (maintaining $V_T$ in the 6 to 8 cc/kg range), increasing the RR to 16, increasing the PEEP to 5 cm $H_2O$, changing the I:E ratio to 1:2, and increasing the $F_IO_2$ to 50%. In almost all cases, at least 3 to 5 cm $H_2O$ of PEEP should be used to prevent alveolar collapse. The use of PEEP limits the risk of worsening lung injury and improves oxygenation by decreasing the shunt fraction.

*Case 2—the septic patient*

Sepsis is the cause for many ICU admissions. Early in the disease process, septic patients may be febrile, hypotensive, tachycardic, tachypnic, and are often hypoxic. They are often hypovolemic and have a metabolic acidosis. The tachypnea seen is most often compensatory for a metabolic acidosis. These patients usually are intubated and ventilated to protect their airway and treat respiratory failure. Management also includes aggressive intravenous fluid resuscitation and antibiotics. A typical arterial blood gas (ABG) in such a scenario would be:

pH 7.20, $PCO_2$ 50 mm Hg, $PO_2$ 80 mm Hg, and an $O_2$ saturation of 95%.

This patient has a mixed metabolic and respiratory acidosis. This is evident, because one would expect a patient who has this degree of respiratory acidosis to have a pH of 7.32 if this was a pure respiratory acidosis.

$$pH = 7.4 - (0.08)(50 \text{ torr} - 40 \text{ torr})/10 \text{ torr}$$
$$pH = 7.4 - 0.08$$
$$pH = 7.32$$

The measured pH of 7.20 is lower, or more acidic, than the predicted pH, which accounts for the mixed respiratory and metabolic acidosis.

Again assume a 70 kg patient, this time with ventilator settings of $V_T$ = 400 cc, RR = 14, I:E ratio 1:2, $F_IO_2$ = 40%, and PEEP = 5 cm $H_2O$. In this case, the patient has demonstrated good lung compliance with peak inspiratory pressures of 25 cm $H_2O$. The patient is oxygenating adequately and is on an appropriate level of PEEP. One strategy would be to increase the minute ventilation to correct the pH. This would require increasing the $V_T$ to 500 to 550 cc and/or increasing the RR to achieve a respiratory alkalosis. The problem with this approach is that correcting the pH by hyperventilating the patient does not address the etiology of the metabolic acidosis. The metabolic acidosis is likely caused by excess lactic acid production. Recall that lactic acid is produced during anaerobic metabolism. In sepsis, this usually occurs as a result of end organ hypoperfusion as a consequence of hypovolemia. Some clinicians would elect to administer sodium bicarbonate at this point to correct the metabolic acidosis. This approach, however, fails to address the end organ hypoperfusion. In this case, a more logical strategy would be to correct the respiratory acidosis component of the disorder while correcting the patient's intravascular volume deficit. The pH then is monitored frequently to assess for resolution of the metabolic component of the acidosis. This helps guide intravenous fluid volume management, the use of inotropes and vasopressors, and the administration of blood products. Although the usual goal is pH correction to the normal value of 7.35 to 7.45, there may be some theoretical benefit to accepting mild acidemia. Recall that the oxygen–hemoglobin dissociation curve (Fig. 1) is shifted to the right during acidosis.

This allows greater oxygen release from the capillaries to the tissues. Because shock, by definition, is the inadequate delivery of oxygen at a cellular level, initial tolerance of a lower-than-normal pH, by allowing mild-to-moderate $CO_2$ retention (permissive hypercapnea), may be beneficial for $O_2$ delivery.

### *Case 3—the septic patient with ARDS*

In the scenario described previously, how would the situation be approached if the patient had ARDS in addition to sepsis? In this scenario, the patient may have the following ABG:

pH 7.20, $PCO_2$ 50 mm Hg, $PO_2$50 mm Hg, and an $O_2$ saturation of 85%.

With ventilator settings of $F_IO_2$ = 70%, $V_T$ = 500 cc, RR = 14, I:E ratio = 1:2, and PEEP = 5 cm $H_2O$, the patient has a peak inspiratory pressure of 55 cm $H_2O$. In this situation, the patient has several problems. Similar to the

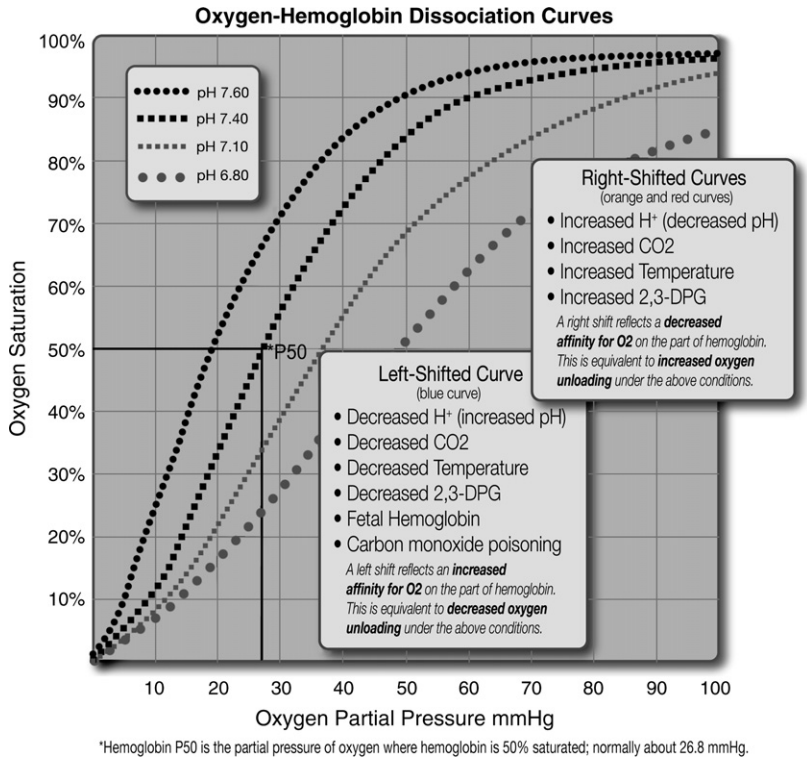


Fig. 1. Oxygen–hemoglobin dissociation curves. (Courtesy of David Grimes, DO).

last patient, he has a mixed metabolic and respiratory acidosis. He is also hypoxic, and his lungs are noncompliant.

$$\text{Compliance} = \Delta \text{ volume}/\Delta \text{ pressure}$$

The patient's airway pressures are high and a potentially toxic level of inspired oxygen is being administered ($F_IO_2 > 60\%$), both which can lead to further lung injury. One approach to this patient would be to increase the minute ventilation and increase the $F_IO_2$. The minute ventilation could be increased by increasing the $V_T$, increasing the RR, or increasing both. Both maneuvers, however, would increase the peak inspiratory pressure and likely would contribute to worsening barotrauma. Increasing the already high $F_IO_2$ would increase the potential for the formation of reactive oxygen species and free radicals. Barotrauma and oxygen toxicity can increase the severity of the patient's ARDS.

An alternative approach to this case would be to accept the respiratory acidosis and use permissive hypercapnea as a lung protective strategy. Increasing the mean airway pressure by increasing the PEEP or decreasing the I:E ratio from 1:2 to 1:1.5 or 1:1 usually will result in improved

oxygenation by means of alveolar recruitment (inflating collapsed alveoli). A combination of both strategies could be used, as this may allow decreasing the $F_IO_2$ to a less-than-toxic level. Increasing the PEEP not only improves oxygenation, but also may improve lung compliance. Improving lung compliance decreases the difference between peak pressure and PEEP ($\Delta P$). It is the $\Delta P$, not the peak pressure, which is the primary determinant of shear forces, and high shear forces lead to further injury of the lung. The improved compliance leads to less pressure needed to properly inflate the lung, reducing barotrauma.

Another lung protection strategy is to accept low-normal oxygen saturations. Specifically, accepting an oxygen saturation of about 92% (with a $PO_2$ in the 60 mm Hg range) can minimize the $F_IO_2$ required. It is important to remember that the primary determinant of $O_2$ delivery is hemoglobin $O_2$ saturation. There is little improvement in oxygen delivery by increasing the oxygen saturation to 96% or 98% from 92%. By increasing the $F_IO_2$ to levels greater than 60%, however, there is a much greater potential for lung injury because of $O_2$ toxicity.

In summary, a sound approach to ventilator management for this patient with both sepsis and systemic inflammatory response syndrome (SIRS) would include increasing the PEEP, decreasing the I:E ratio, accepting a mild-to-moderate respiratory acidosis, and accepting an $O_2$ saturation of approximately 92%. This would minimize the potential for further lung injury while providing adequate oxygen delivery and adequate removal of $CO_2$. As with the prior patient, addressing the patient's metabolic acidosis with an appropriate fluid resuscitation would be necessary. The initial approach (increasing the minute ventilation and inspired oxygen concentration) could have led to worsening lung injury, resulting in worsening lung compliance and worsening hypoxia.

### *Case 4—weaning the previously healthy patient from mechanical ventilation*

A common problem faced in the ICU is weaning patients from mechanical ventilation. Inappropriate use or incorrect analysis of ABG data can lead to unnecessarily prolonged periods of mechanical ventilation and ICU stay. In weaning patients, critical care physicians typically use weaning modes of ventilation such as pressure support or continuous positive airway pressure and, decreasing the amount of support a patient receives as he or she improves. In addition to mechanical ventilation, these patients also commonly receive some degree of sedation to tolerate endotracheal intubation, mechanical ventilation, and wound pain. A fairly common ABG for this type of patient on a weaning mode of ventilation such as pressure support (PS) with settings of PS of 12 cm $H_2O$, $F_IO_2 = 40\%$ and PEEP of 5 cm $H_2O$ would be as follows:

pH 7.36, $PCO_2$ 50 mm Hg, $PO_2$ 95 mm Hg, and an $O_2$ saturation of 96%.

This ABG is consistent with a respiratory acidosis with metabolic compensation. Approaches to a patient who has these ABG results may be to increase his or her pressure support or switch to a controlled mode of ventilation. It is important to make decisions such as these based on the patient's clinical condition and vital signs, however. If such a patient had a RR of 16 with good tidal volumes and appeared comfortable, the etiology for his or her respiratory acidosis likely would be mild respiratory depression caused by sedation. Placing this patient on increased pressure support is unnecessary and would only increase both the time requiring mechanical ventilation and the potential for associated morbidity such as ventilator-associated pneumonia and decubitus ulcers. A better approach would be to continue the patient's weaning by decreasing pressure support or making no ventilator setting changes and simply observing his or her ongoing clinical course.

*Case 5—weaning the patient with pre-existing lung disease from mechanical ventilation*

This scenario is similar to Case 4. In this case, however, the patient had chronic obstructive pulmonary disease (COPD) with a $PCO_2 = 60$ mm Hg and $PO_2 = 60$ mm Hg on 21% $O_2$ (room air) before perforating his or her bowel. This injury required surgical intervention, resulting in prolonged mechanical intervention and several weeks of ICU care. Before the perforation (ie, in the patient's baseline condition), the patient would be expected to have a bicarbonate level of 32 mmol/L.

$$\begin{aligned}\text{Bicarbonate correction} &= 4\ \text{mmol/L for each 10 torr change in } PCO_2 \\ &\quad + \text{``normal bicarbonate level''} \\ \text{Bicarbonate correction} &= (4\ \text{mmol/L})(60\ \text{torr} - 40\ \text{torr})/10 \\ &\quad + 24\ \text{mmol/L} \\ \text{Bicarbonate correction} &= 8\ \text{mmol/L} + 24\ \text{mmol/L} \\ \text{Bicarbonate correction} &= 32\ \text{mmol/L}\end{aligned}$$

The pH is calculated using the Henderson-Hasselbach equation as follows:

$$\begin{aligned}\text{pH} &= 6.1 + \log([HCO_3]/[(.03)(PCO_2)]) \\ \text{pH} &= 7.35\end{aligned}$$

This patient's lung disease will not be corrected by his or her ICU stay, and, if anything, it may worsen. In this case, the ABG during weaning may be:

pH 7.32, $PCO_2$ 65, $PO_2$ 78, $HCO_3$ 34 on $F_IO_2$ of 40%.

This patient has baseline lung disease and $CO_2$ retention. This patient has metabolic compensation for his or her chronic respiratory acidosis that is worse than baseline because of a combination of sedative medications and

deconditioning caused by prolonged ventilatory support. If the patient appeared comfortable with no clinical evidence of respiratory insufficiency, there would be no indication to increase ventilatory support. Furthermore, efforts to correct the patient's bicarbonate to normal (eg, by administering acetazolamide) would make weaning more difficult or impossible by forcing the patient to produce an unobtainable minute ventilation to correct his or her pH. One caveat of this approach is that most patients do not arrive in the ICU with baseline ABGs, especially with emergent admissions. In this case, a best guess of the patient's baseline ABG based on the patient's history is made.

## Other laboratory tests

As previously mentioned, arterial blood gas analysis is the primary modality for monitoring respiratory status. There are other clinically useful laboratory tests, however. Venous blood gas analysis is useful for ventilator management if arterial blood samples are not easily available and there is an alternate way to measure a patients oxygenation. Monitoring serum electrolytes also gives information about respiratory issues. Finally, if patients are failing to wean from the ventilator, checking adrenal and thyroid function may identify relatively easy-to-treat etiologies for persistent respiratory failure.

### *Venous blood gas*

In the ICU, access to arterial blood usually is accomplished through the use of an arterial catheter. As a patient's clinical status improves, the risks associated with an arterial line such as infection and vascular injury often outweigh the benefits. Without an arterial catheter, obtaining an arterial blood sample would require a skin puncture, which is uncomfortable, and, after a prolonged ICU course, could prove difficult. Most patients admitted to an ICU for a prolonged period of time, however, have a central venous catheter. The information obtained from a venous blood gas (VBG), specifically the pH and the $PCO_2$, can be very useful. Because a VBG provides little information about a patient's arterial blood oxygenation, the patient's $O_2$ saturation must be available from an alternate source such as a pulse oximeter. Normal values for venous pH and $PCO_2$ at the University of Rochester Medical Center are pH: 7.32 to 7.42 and $P_vCO_2$: 40 mm Hg to 50 mm Hg.

Kelly and colleagues [3] compared arterial and venous samples on 246 patients admitted to the emergency department and found that the difference in pH values ranged from $-0.16$ to $+0.06$ units, with the average being $-0.04$ units. The $P_vCO_2$ will vary somewhat depending on the sample site, determined by the metabolic activity of the area of venous drainage. It is for this reason that a mixed venous sample will give the most reliable $PCO_2$ for the whole body. A mixed venous sample is obtained from the

pulmonary artery and represents a mixing of all of the blood returning to the heart. A normal mixed venous $PCO_2$ is 46 mm Hg. Clearly, needing a pulmonary artery catheter adds risk to the patient. In general, the $PCO_2$ should be about 4 to 8 mm Hg higher than the arterial $PCO_2$. An example using the VBG is described in the following section.

*Serum electrolytes*

Serum electrolytes, particularly serum bicarbonate, are also of use in monitoring ventilation. Patients recovering from sepsis or SIRS often will have significant edema. If these patients also have concomitant lung disease, they may require significant diuresis in order the successfully wean from the ventilator. Unfortunately, a forced diuresis can lead to a significant metabolic alkalosis. It is important to determine whether a patient is alkalemic for two reasons. First, because of the shift of the $O_2$–hemoglobin dissociation curve seen with alkalemia, $O_2$ will be bound more tightly to hemoglobin, making $O_2$ delivery to the tissues more difficult (see Fig. 1). This may result in tissue hypoxia. Second, failure to recognize that this is a metabolic compensation for a respiratory acidosis could result in the wrong therapy. This situation could be determined by obtaining the blood pH by means of a VBG. An acidotic pH would indicate a respiratory acidosis with metabolic compensation, and no pharmacologic correction of the bicarbonate would be necessary. An alkalemic pH, however, would indicate a contraction alkalosis that should be treated. In this case, the metabolic alkalosis is treated commonly with a carbonic anhydrase inhibitor such as acetazolamide.

*Serum cortisol level*

Adrenal insufficiency is relatively common in critically ill patients, with one study reporting an incidence as high as 36% [4]. The adrenal insufficiency usually represents relative dysfunction of the adrenals as opposed to true adrenal failure. Nevertheless, it can cause significant problems for affected patients, including respiratory failure and vasopressor-resistant hypotension and shock.

Huang and Lin [5] performed a prospective, randomized, placebo-controlled double-blinded study on 93 patients requiring mechanical ventilation in a tertiary care teaching hospital. They started with 472 patients and excluded those successfully extubated within 72 hours, those with hemodynamic instability, those already receiving steroids, and those with a severe neurologic injury. Out of the 93 remaining patients, 70 met the criteria for adrenal insufficiency and were randomized to receive either stress-dose steroids or placebo. They then compared three groups: patients with adequate adrenal reserve, patients with inadequate adrenal reserve receiving steroid replacement, and patients with inadequate adrenal reserve but receiving

no replacement (placebo group). Successful ventilator weaning was significantly higher in the adequate adrenal function (88.4%) and stress-dose treatment (91.4%) groups than in the placebo group (68.8%).

Despite these results, the diagnosis and treatment of adrenal insufficiency in the ICU are somewhat controversial. Most would agree that a morning cortisol level less than 25 μg/dL and failure to elicit at a 9 μg/dL rise in cortisol level in response to high-dose cosyntropin stimulation represents adrenal insufficiency. Some would argue that these criteria are too strict and may exclude patients with treatable adrenal insufficiency. Nonetheless, using these criteria, most patients with adrenal insufficiency should be identified. Huang's study provides good evidence that treating these patients can improve the chances of success of weaning them from mechanical ventilation.

*Thyroid function tests*

In the ICU, hypothyroidism can result in respiratory failure, congestive heart failure, central nervous system (CNS) dysfunction, and hyponatremia. For patients who have hypothyroidism on mechanical ventilation, respiratory failure may be attributed to decreased hypoxic and hypercapnic ventilatory drive. Respiratory muscles also are noted to be weak. For patients not yet intubated and requiring mechanical ventilation, an enlarged tongue and obstructive sleep apnea can contribute to respiratory failure. Rarely, a large goiter can cause upper airway obstruction and subsequent respiratory compromise [6]. Other contributing factors include alveolar hypoventilation and pleural effusion.

Martinez and colleagues [7] studied three patients who had confirmed hypothyroidism and respiratory failure and found that all three had diaphragmatic dysfunction corrected with adequate hormone replacement. Datta and Scalise [8] performed a retrospective study on 173 patients admitted to a regional weaning facility for failure to wean from mechanical ventilation. Of those 173 patients, 140 had screening thyroid-stimulating hormone (TSH) levels obtained on admission. Seventeen patients (12%) were found to have elevated TSH levels, and low serum tri-iodothyronine (T3) and/or low thyroxine (T4) levels confirmed the diagnosis of hypothyroidism in four (3%) patients. With the addition of thyroid replacement therapy, three patients were weaned from mechanical ventilation successfully. The fourth patient died from unrelated causes. The authors concluded that hypothyroidism is an uncommon cause of failure to wean from mechanical ventilation, but because it is an easily treatable cause, it should be considered in all patients who fail to wean from mechanical ventilation.

Laboratory tests used to make the diagnosis of hypothyroidism include T4 and TSH levels as noted previously and the free thyroxine level (FT4). Classically, decreased T4 and FT4 levels with an elevated TSH level are seen in primary hypothyroidism, and decreased T4 and FT4 levels with a low or normal TSH level are seen in secondary hypothyroidism. Making

the diagnosis of secondary hypothyroidism, however, can be difficult. Many severely ill patients are found to have low serum T4 concentrations with normal or low TSH concentrations, and the FT4 concentration may be low, normal, or high. In these cases, most patients have nonthyroidal illness (euthyroid sick syndrome) and should have follow-up thyroid function tests after recovery from their acute illness. If there is other evidence of pituitary or hypothalamic disease, the diagnosis of secondary hypothyroidism should be considered [6].

*Phosphate level*

Phosphate is the most abundant intracellular anion. It is necessary for ATP production, and it is a component of DNA, RNA, and 2,3-diphosphoglycerate (2,3-DPG). The normal serum phosphate range is 2.5 to 4.5 mg/dL (0.81 to 1.45 mmol/L) in adults. Hypophosphatemia is defined as mild (2 to 2.5 mg/dL or 0.65 to 0.81 mmol/L), moderate (1 to 2 mg/dL or 0.32 to 0.65 mmol/L), or severe ($<$1 mg/dL or 0.32 mmol/L) [9]. Mild hypophosphatemia has nonspecific manifestations such as myalgias, weakness, and anorexia. Severe hypophosphatemia may cause tetany, seizures, coma, rhabdomyolysis, and ventricular tachycardia [10]. Severe hypophosphatemia is also a clear cause for acute respiratory failure. Less clear is whether moderate or mild hypophosphatemia can contribute to respiratory failure and inability to wean from the ventilator. Respiratory insufficiency and failure to wean likely can be attributed to weakness caused by insufficient ATP production. Furthermore, inadequate 2,3-DPG production can hinder respiratory function by shifting the $O_2$–hemoglobin dissociation curve to the left (see Fig. 1). It should be noted that serum phosphate levels may not reflect phosphate content in respiratory muscles accurately. Fiaccadori and colleagues [11] demonstrated significant phosphorus depletion in the respiratory muscles of COPD patients when compared with patients with normal lung function. No correlation with serum phosphorus levels was demonstrable in these patients, however.

When confronted with a patient with an unclear etiology for his or her respiratory failure, it is logical to rule out hypophosphatemia as a cause. Although it is unclear how relevant a mild or moderate serum phosphorus level may be, it is reasonable to correct deficiencies regardless of severity, especially if the etiology for the respiratory failure is unclear.

## Summary

Laboratory analysis is clearly necessary for the effective management of most patients receiving mechanical ventilation in the ICU. Blood gas analysis, using either arterial or venous samples, is the mainstay of management. Serum bicarbonate levels noted on serum electrolyte analysis are often useful in ventilator management. When patients have persistent, unexplained

respiratory failure, however, it is also prudent to check adrenal function, thyroid function, and phosphate levels.

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Crit Care Clin 23 (2007) 149–159

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# Therapist Driven Protocols: A Look Back and Moving into the Future

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For nearly three decades, the author and colleagues have tried to define the best methods of discontinuing mechanical ventilation (MV) in patients recovering from respiratory failure [1]. In just the past decade, respiratory care has had an increasingly proactive role in achieving this. There have been many articles written in the last decade attempting to determine the best method to initiate and improve ventilatory weaning [2]. Therapist-driven protocols (TDPs) have been shown to decrease the duration of MV, reduce cost, length of stay (LOS), and improve the rate of weaning [3,4] when compared with physician-directed weaning.

Before the author and colleagues could start, they had to define what TDPs are. They defined them as a patient care plan, which are initiated and implemented by credentialed respiratory care practitioners. These plans were constructed with the assistance of the physicians and are approved by medical staff at the author's institution. TDPs allow the therapist the ability to evaluate the patient, initiate therapy, adjust, discontinue, or even restart respiratory care treatments or procedures on an as-needed basis once the protocols are ordered by the physician. They allow the therapist to work in a goal-oriented, rather than task-oriented, environment.

Before showing the best methods for weaning, one must take a look back. The author and colleagues have defined persistent MV as a patient who has been mechanically ventilated for more than 21 days [5]. They have developed improved modalities of ventilation and learned that when protective strategies are used, the author and colleagues have improved survival even past 28 days of MV and shown to reduce barotraumas and ventilator-induced lung injury (VILI) [6]. One must look at the pathophysiology of patients' ventilator dependency, criteria to wean patients when they are ready, strategies to maximize their own spontaneous breathing efforts, and the role for tracheotomy

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0749-0704/07/$ - see front matter 
doi:10.1016/j.ccc.2006.11.012 *criticalcare.theclinics.com*

if needed [7,8]. Most of the time when patients are on MV for greater than 28 days, they have had an injury or disease process that puts strain on the respiratory muscles, so therapists try to decrease the work of breathing to let their lung tissue and muscles heal. Eliminating their respiratory effort, however, is not always desirable, as it causes deconditioning and atrophies of the respiratory muscles [9]. One can see this deconditioning sometimes in less than 48 hours. As such, if at all possible the author and colleagues try to have the patient breath as possible, even if it is in a control mode. With this in mind, when it is determined to begin weaning, patients have lesser-diminished muscles and do not strain their oxygen reserves from using their respiratory muscles from a low starting point. It is also important to note that if the patient goes into acute respiratory distress syndrome (ARDS), then one may want to use a lung-protective strategy, and wait until the patient's outlook improves before considering weaning [10].

In the past, respiratory therapists have used different techniques to determine if a patient was ready to wean and subsequently extubate. Measurements like maximum airway pressure, negative inspiratory force, and forced vital capacity (FVC) have been used for decades to determine if a patient likely has the ability to be weaned. As more has been learned more about lung physiology, it has been shown that these measurements are not as accurate as once thought [11]. Work done by Tobin in the 1990s [4] has shown that looking at the patient's tidal volume (VT) and respiratory rate (RR) is the best indicator, not just to see if the patient can be extubated, but also to see how well the patient can breathe spontaneously. He had put that into an equation called the rapid shallow breathing index (RSBi) which is the RR divided by the VT (measured in liters). Patients who had an RSBi of less than 105 were considered for weaning (Fig. 1).

When starting to wean patients off MV, the author and colleagues started to do this in conventional fashion, by using synchronized intermittent mandatory ventilation and decreasing the rate until patients were strong enough to breathe enough on their own, do the measurements, and try to extubate them. As the author and colleagues found out, using the traditional measurements was not the best predictor to evaluate if a patient could be extubated [3,12]. The reintubation rate by using this method was around 28% to 33%, nearly a third of all patients [13]. The task at hand was a technique that would allow one to better predict patients who could be extubated, and determine when the patients had enough effort tolerance to breathe on their own and maintain their airway [7].

When coming up with a protocol to improve weaning, respiratory therapy wanted a protocol to involve therapists in daily checks of patients on MV for weaning [1]. To start, the author and colleagues came up with a method wherein the therapist would set the patient up on the vent. They found that using pressure ventilator modes and incorporating lung-protective strategies [10] worked best to decrease the incidence of VILI. This included using 6 to 8 mL/kg VT on all patients whom the author

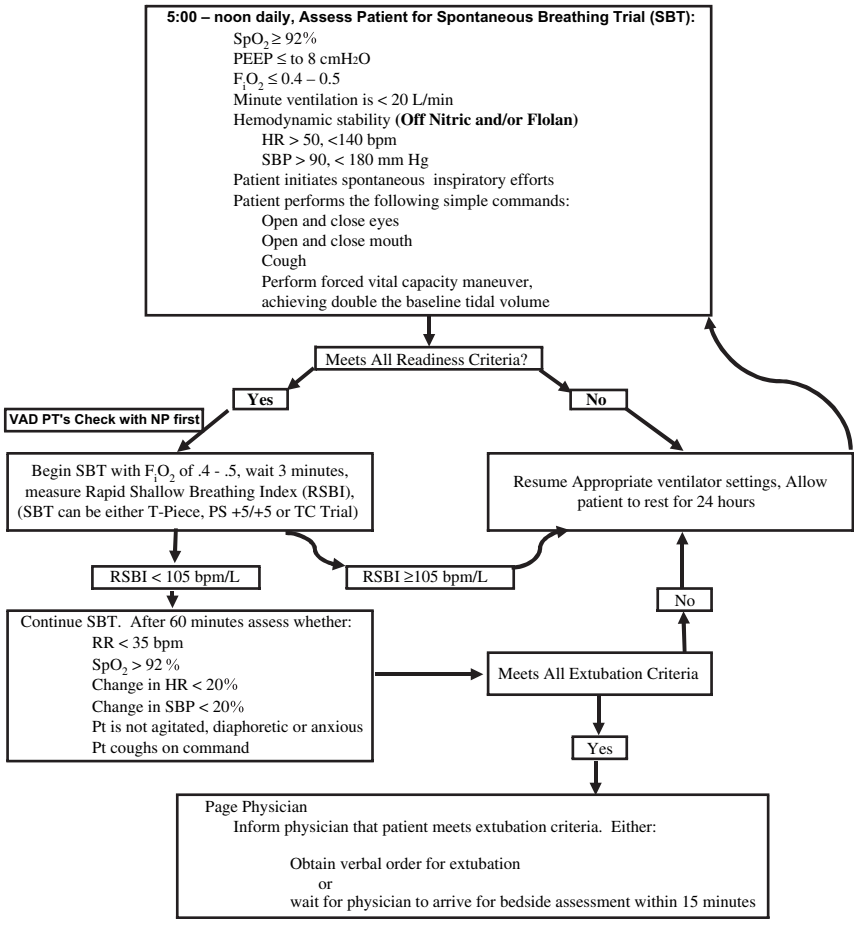


Fig. 1. Protocol for liberating patients from mechanical ventilation.

and colleagues ventilate. The respiratory therapist also uses best positive end-expiratory pressure (PEEP), where he or she finds the opening and closing pressures on a pressure loop, and increases to PEEP up to 2 cm $H_2O$ over that point. With this technique of using lung-protective strategies, the therapist is able to use the least amount of $FIO_2$ for the patient and protect the lung for when the patient is deemed ready for weaning. This is all done in conjunction with the physician and nurse. If the patient is postoperative with no acute injuries or disease process, the therapist attempts to evaluate the patient to be weaned expeditiously. Studies have show that weaning patients within 48 hours can reduce complications by as much as 50%, and decrease the percentage of patients who need reintubation [2]. The author and colleagues also screened patients who they felt were entering

an ARDS picture. They have four categories in use: (1) The $P_{CO_2}/FIO_2$ ratio less than 200, (2) an oxygen index greater than 16, (3) a plateau pressure greater than 30 cm $H_2O$, and (4) new onset of patchy infiltrates on chest x-ray. If patients fit three out these four categories, they are considered in ARDS, and the author and colleagues continue using lung-protective techniques and do not consider weaning. When patients improve, and the ventilator settings can be lowered, the author and colleagues will try to wean them.

Once patients have overcome their lung injury, and their ventilator settings have been decreased to a point where they are starting to breathe more on their own, the therapist can consider them able to wean. In reality one would like to wean patients within 48 hours of the start of MV. Patients extubated within this time have 50% fewer complications and decreased length of stay (LOS) [2]. Once patients have fit parameters [1,2,7,14–18] to be considered in the author's protocol (see Fig. 1), the therapist will inform the registered nurse that they fit the protocol, and a spontaneous breathing trial (SBT) can be tried. A patient can be placed on a pressure support (PsV) trial of 5 cm $H_2O$ with a PEEP of 5 cm $H_2O$. Patients are left on these settings for 5 to 10 minutes. The therapist then calculates an RSBi; if the RSBi is less than 105, the therapist will inform the registered nurse and the physician that the patient has passed the initial part of the protocol. Then the patient is left on those settings for 30 to 60 minutes. If the patient does not show any adverse signs (increased heart rate [HR], blood pressure [BP], RR, signs of hypoxia, or increased work of breathing), he or she is evaluated for extubation by the ICU team. Exceptions to this would be in the cardiovascular intensive care unit (CVICU) unit. If the patient is on nitric oxide or Flolan, he or she is excluded from the protocol. Also the author and colleagues make sure to check with the CVICU surgeons if patients who are on ventricular assisted devices can be placed on the protocol. The CVICU also has it own fast-track program, which is separate from the author's protocol. If patients are not able to be extubated within 24 hours, they are considered to be on the author's protocol. If patients have a tracheotomy tube at this point, after they are evaluated on the PsV trial, they are evaluated for a further SBT, which would be a continuation of the PsV trail. Alternatively, a tracheotomy collar trial may be attempted. In either case, if a patient's RSBi increases during the SBT, one can increase the amount of pressure support for his or her comfort [5]. If this happens, the patient still is considered to be doing an SBT but a separate order to control the patient's VT is needed. Then the patient will continue to do his or her SBT, and when fatigued will be placed back on resting settings. If the patient has a history or potential of going into congestive heart failure (CHF), the author and colleagues then consider placing the patient on a T-piece trial for 30 minutes rather than a PsV trial, to make sure that the lack of PEEP does not cause a flooding into the lungs, thereby decreasing the chance of reintubation [15]. Additionally, the respiratory therapist, before extubation, will check for presence of a cuff leak, as 5% of the patients who need

reintubation need it because of laryngeal edema [3]. If the patients do not have a cuff leak, the chance of reintubation increases to about 33% because of postextubation stridor. If there is no leak, the ICU team must consider why there is no leak, perhaps because of neck trauma (by external trauma or difficult intubation), fluid overload, or the endotracheal tube being too large for that patient.

As the patients perform their SBT (either by PsV or tracheotomy collar), the therapist observes that they maintain certain parameters, such as RR less than 35 breaths per minute (bpm), SpO2 greater than 92%, changes over 20% of either HR or RR, and that patients are not agitated, diaphoretic, or anxious. It is also important to make sure that patients have a strong spontaneous cough. If patients fall out of any of these parameters, the therapists place them back on their resting settings and attempt to do another SBT the next day. The author and colleagues always make sure that they rest the patients only when they are fatigued from their SBT, not when they have failed. If patients severely fail their SBT, it may take over 24 hours for their respiratory muscles to get back to baseline. The therapist then will assess patients for signs of respiratory failure. There has always been discourse on what is considered the best resting mode. Many doctors and therapists believe that SIMV is a resting mode, but with lower rates if the patient's own rate is over that of the ventilator, then the patient is not resting. Usually control modes are considered best, because the patient does need to expend much energy to breathe, and therefore is able to rest to perform SBT the following day. Some hospitals still use the assist-control mode, but when using pressure-limited volume modes, such as pressure regulated volume control or continuous mandatory ventilation, using an auto flow device is desired. When the author and colleagues first started their therapist driven patients (TDPs), they used the SIMV as resting and weaning, they had a small success then hit a plateau. They reduced their ventilator days slightly but not enough to declare success. When the therapists started to use SBTs, along with resting patients on a controlled mode, the author and colleagues started to see a significant difference. They started to get the patients off MV sooner, cutting ventilator LOS by nearly 50% (Fig. 2). From this early work, respiratory care was able to come up with the TDP that in use today. When the author and colleagues first started doing this study, they placed patients into three categories:

- True trauma patients who had injuries or lung injuries from their traumas
- A group for postoperative and vascular patients (this was a large group that excluded coronary artery bypass grafts (CABGs) and solid organ transplants
- Miscellaneous, these included burn victims, necrotizing fasciitis, and any others that were not traumas and surgeries

The author and colleagues later found that most of the patients in the third group were the hardest to extubate over a short time, mainly because

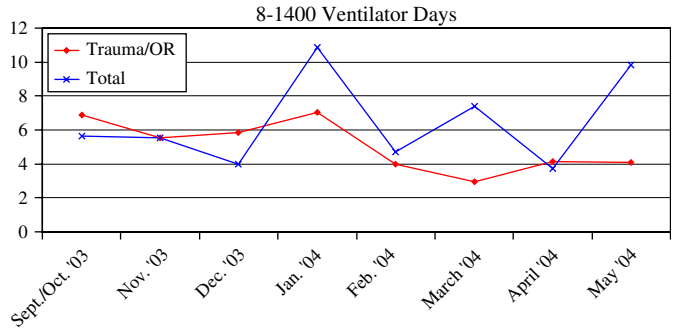


Fig. 2. Trauma/OR and other ventilator wean days using therapist protocols.

the burns needed to be intubated over a longer period of time for repeated trips to the operating room for grafting. When looking at the original data, it showed almost no change in the ventilator days from using the TDPs. When the author and colleagues took out the data that included the third group, they saw that cut the ventilator days were cut almost in half. Thus from these data and parameters, the author and colleagues derived the therapist-driven protocols in use today.

In some cases, even if patients pass all their measurements and their SBT; they still can be reintubated. Studies show that if an institution is not reintubating at least 10% to 15% of its patients, then it is not extubating enough patients. Sometimes the reasons are not caused by true respiratory factors. Electrolyte imbalance, metabolism, blood volume loss, and other factors can cause respiratory failure indirectly [7]. Direct causes can be upper airway obstruction or strider, aspiration, increased pulmonary secretions, CHF, and even pain. Patients requiring reintubation can have up to 40% increased mortality rates [18]. Also, while the need for reintubation is important, just before reintubation, the patient can exhibit worse distress and can display further injury. So another part of the author's TDP is a way to prevent reintubation. This may include use of incentive spirometry, chest physiotherapy, and intermittent positive pressure breathing to augment pulmonary toilet. Another method is to place the patient on noninvasive positive-pressure ventilation (NIPPV) such as continuous positive airway pressure or bi-level positive airway pressure. Using NIPPV in patients showing some signs of respiratory failure, either direct or indirect after extubation, shows a reduction in the rate of reintubation and decreased mortality [4]. NIPPV cannot be an endpoint for respiratory failure. If there is no improvement over 24 to 48 hours after NIPPV is initiated, reintubation must be considered. One also must consider any contraindications for placing someone on NIPPV. These may include confusion without hypercapnia, if the patient's respiratory rate is already exceeding 40 bpm, if there is vomiting for any reason, or if the patient has a very high FiO2 requirement in excess of 80%. This is important for the therapist to detect

when a patient using NIPPV is going into respiratory distress or failure. The sooner a patient can be detected in respiratory distress and is intubated, presumably the shorter that patient will be on the ventilator.

Another part of the TDP is in the floor treatment areas of the hospital that the respiratory service covers. In the author's hospital, the three places that the respiratory service covers are the CVICU step-down, surgical step-down and the pulmonary/weaning units. In the CVICU step-down unit, the author and colleagues evaluate postoperative CABG and thoracic patients. First CABG patients are assessed in the unit and instructed on incentive spirometry, then restarted after they are extubated. Postoperative thoracic patients are evaluated when they return from the operating room; the therapist evaluates the breath sounds, oxygen requirement, pulmonary history, and procedures that patients have had done. Respiratory therapy works closely with nurse practitioners and surgeons, assessing treatments, radiographs, and laboratory results. Together a decision is made on the best method to perform pulmonary toilet, either by incentive spirometry or by use of a flutter valve, which vibrates the lung tissue internally and is patient-driven. If patients have a consolidation on chest radiograph, the author and colleagues may perform CPT to that area, along with ambulation with physical therapy. In finding in their pulmonary history that patients take respiratory medications, those medications will be continued. If a patient cannot take a deep-enough breath, medication nebulizers will be used. Once a patient can breathe deeply enough, the author and colleagues will try to switch to metered-dose inhalers. The therapist can initiate change this in part of the author's protocol. In evaluating the patient using the incentive spirometry, the author and colleagues test for his or her vital capacity. The respiratory therapist will work with the patient to achieve at least 50% of that number. So if a patient's vital capacity is 2 L, one would like to see that patient achieve between 1 and 2 L. The therapist will work with patients for 48 hours, and if they remain in that area, they are signed off to the nurses in the unit. If patients have any other respiratory difficulties during their course, the therapist will reassess that patient, and if needed, restart appropriate pulmonary toilet. If patients cannot reach their goals (excluding surgery, ie, lobectomy or pnuemectomy), the therapist determines the best means by which he or she can help them to reach that goal. The respiratory therapist may start bronchodilators or add a flutter valve to that treatment. The author and colleagues have made entirely separate protocol for this part of the hospital (Box 1) and have had great success in decreasing the LOS for those patients. The author and colleagues also strive to keep those patients out of the ICUs, thereby leaving more beds open for other critically ill patients. The author's TDPs are also used in the pulmonary unit. This unit has both pulmonary patients (chronic obstructive pulmonary disease [COPD], asthma) and patients who have had a prolonged ventilatory wean. These patients generally have been ventilated in excess of 30 days and have tracheotomy tubes. The respiratory care service has a very good rapport with the doctors and nurse practitioners (NPs) in this unit. The author and colleagues attend rounds with the

**Box 1. Therapist-driven protocols**

*Daily priorities*
Morning
- Check with charge registered nurse to get the day's surgery schedule and discuss any overnight issues.
  In patients scheduled for surgery should be evaluated preoperatively.
- Round with thoracic team at 0730 (0830 on Mondays)

Give nebulizer (neb)/metered dose inhaler (MDI) treatments after rounds (see treatment times).
- Assess other patients who need to be followed by the respiratory therapy service.
- Assess any preoperative patients.
- Communicate any treatment updates with NP.

Afternoon
- Give afternoon treatments as needed.
- Assess postoperative patients (registered nurse will notify the respiratory therapy service when patients return from the operating room).
- Note respiratory therapy orders on cork board (registered nurses will write new orders on cork board).
- Equipment changes (as per respiratory protocol)
- Remember to rinse out medication neb with normal sterile saline and place in bag per infection control protocols.

*New Items*
IS protocol
- Former incentive spirometry (IS) protocol remains the same for cardiac patients (four times daily for 1 day).
- All thoracotomy patients started on IS will be seen every 4 w/a $\times$ 2 days until they can achieve 50% of predicted.
  If patients meet full predicted value in the first day, may be signed off.

Assessments
- All patients on the thoracic service must be evaluated by the respiratory therapy service (coded in green on board and patient rooms)
- Cardiac patients will be followed the same as before (coded in red on the board and in patients room), but because the cardiac team performs rounds earlier, respiratory therapy team members are not expected to round with it.

- Patients coded in black are off-service/medical patients. May have treatment orders, but will not be followed routinely.
- Fill out respiratory assessment form on first evaluation (white/yellow form). This must include:
  - Current diagnosis (eg, empyema, or lung contrast angiography [CA], not thoracotomy or video assisted thoracoscopic surgery [VATS])
  - Surgical procedure performed (eg, VATS, thoracotomy, or lobectomy)
  - Predicted IS value from nomogram
  - Pertinent pulmonary history (eg, asthma or smoking history)
  - Any home respiratory medication or home oxygen use
- Any updates to respiratory therapy treatment plans or assessments will be documented in the progress notes and on the Kardex.
- Patients receiving MDIs/nebs or other respiratory treatments will have their need for treatments re-evaluated no less than every 3 days.
  - Note changes to treatments on the 375 sheet.
  - Include date and order number, and full treatment information, and place on information sheet for 712.
  - Remember to sign off order in the patient's chart.
  - If patients are receiving med nebs, and can take a deep breath and hold it for several seconds, they may be switched to MDIs, unless they take med nebs at home. If they take MDIs at home, they may be switched to self-administered MDI, unless they still are receiving IS and/or flutter valve treatments.
  - If treatments are discontinued, note in Kardex or sign-off patient from respiratory therapy service as applicable.

Thorocotomy sign-off criteria

- The patient may be ''signed off'' from the respiratory therapy service if: Patient is meeting IS goal (>50% of predicted)
  - Patient does not require nebs/MDIs or is able to self-administer without assistanceand is able to mobilize secretions.

Document ''Patient signed off from respiratory therapy service'' on the assessment or in the progress notes.

Other respiratory treatments

- Thoracotomy patients who are unable to meet their IS goal should be evaluated for further therapy.

- Therapists should consult with the team/NP about adding nebs/MDIs, positive expiratory pressure/flutter valve, or CPT treatments for patients who cannot meet their IS goals.
- The need for additional therapies will be re-evaluated no less than every 3 days.

Treatment times

- Morning rounds take priority; nebs/MDIs can and should be delayed until after rounds are done. Rounds generally will be completed by 8:30 a.m.
- Assessments on patients who are not receiving MDI/neb treatments should be done after treatments are completed.

Other

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Because of the significant increase in morning activity on 712, the 712 respiratory therapist will not be expected to help 716 with 0800 rounds. But will be able to help out later in the day. The charge person will determine who will help out in the morning.

wean team to determine the different levels on which a patient can be weaned. These levels are from 4 hours of weaning up to 24 hours off the ventilator. Patients continue to be evaluated for use of bronchodilators, as most patients in this unit have had some damage or disease process to their lungs and are usually appropriate candidates for bronchodilators. Just as in CVICU step-down, the therapist evaluates patients for the use of CPT, flutter valves, and other devices. Respiratory therapy also will assist in the physical therapy of the patient in ambulation, and in speech pathology with swallow evaluation and the use of Passy Muir valve for evaluating speech. Another part of the author's TDPs that is expanding is the evaluation of tracheotomy patients on the floor. One of the primary places this happens is in the surgical step-down unit. These are mostly liver transplant and other general surgery patients who have been ventilated for lengthy periods of time. They have been weaned in the surgical unit by the author's wean protocol; the therapist then assists the doctors in evaluating patients to downsize their tracheotomy tubes. The author's institution has a policy that no patient outside the ICU can have a cuffed tracheotomy. Once patients are off the ventilator for 48 hours, the therapist will evaluate with the doctors to downsize their tracheotomy tube. The author and colleagues either use a smaller Shiley tracheotomy tube with no cuff or a metal tracheotomy tube. Once they are in the surgical step-down, the author and colleagues perform assessments on those patients in the same fashion as CVICU/pulmonary step-down units. The therapist will ensure patients are stable on their tracheotomy collar to see if it possible for them to use a Passy Muir valve. The author and colleagues also will assist with ambulation, if needed.

In sum, over the past several years' research, the author and colleagues have found that using the TDPs not only reduces the time the patient is on a ventilator, but also his or her overall LOS in the hospital. With these protocols in place, the author and colleagues are decreasing the amount of VILIs and decreasing the mortality of patients with ARDS in the ICU. The author and colleagues are finding with the increasing number of sicker patients coming to the hospital, by using the TDPs, they can assess the patients on the floors hoping to prevent them from being intubated and sent to the ICU. This can save the hospital money, and more importantly keep the patients healthier and get them home earlier. It also helps the therapist to work on goals for the patient, rather than just doing tasks, which keeps the therapist learning and gives him or her a greater sense of accomplishment. This expands the therapist's knowledge base and overall effectiveness of respiratory care.

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Crit Care Clin 23 (2007) 161–167

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# Mode of Mechanical Ventilation: Volume Controlled Mode

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It is important to understand the goals of mechanical ventilation (MV). The primary goal of ventilator support is the maintenance of adequate, but not necessarily normal, gas exchange, which must be achieved with minimal lung injury and the lowest possible degree of hemodynamic impairment, while avoiding injury to distant organs such as the brain.

Modes of MV are described by the relationships between the various types of breaths and by the variables that can occur during the inspiratory phase of ventilation. Each mode of ventilation is distinguished by how it initiates a breath (trigger), how it sustains a breath (limit), and how it terminates a breath (cycle); these are referred to as phase variables. There are two basic modes of ventilation: ventilation limited by a pressure target and ventilation limited to the delivery of a specified volume. Volume-targeted ventilation modes can be categorized as follows: patient trigger or time trigger, flow-limited, volume-cycled assist/control, or synchronized intermittent mandatory ventilation (SIMV) modes.

## Volume-controlled mode

In the volume-controlled mode, each machine breath is delivered with the same predetermined inspiratory flow–time profile. Because the area under a flow–time curve defines volume, the tidal volume ($V_T$) remains fixed and uninfluenced by the patient's effort. Volume-controlled ventilation (VCV) with constant (square wave) inspiratory flow is the most widely used breath delivery mode. Alternative flow–time profiles such as decelerating or sinusoidal inspiratory flow waveforms sometimes are used in the hope of reducing the risk of barotraumas. Pressure is the dependent variable in the modes of ventilation in which volume is the target. Because pressure will vary in

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doi:10.1016/j.ccc.2006.11.014 *criticalcare.theclinics.com*

volume-targeted modes of ventilation, careful monitoring and assessment of respiratory system compliance and resistance are necessary.

*Assist/control ventilation in volume-controlled mode*

Assist/control ventilation (ACV) is a mode in which patients are allowed to trigger the ventilator to receive an assisted breath from the device (Fig. 1). ACV is associated with the least amount of work of breathing and therefore is used widely during the acute phase of severe respiratory failure. A common problem associated with ACV is respiratory alkalosis in patients breathing at high respiratory rates and a significant decrease in venous return and cardiac output. Although all modes of MV can decrease venous return, mean airway pressures can be higher in ACV.

For early management of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), in ARDS network centers, volume-assist control was the most commonly selected mode of ventilation (56% overall), and volume-targeted ventilation was used in most patients (82%). SIMV or SIMV with pressure support (PS) was used more often in patients who had a $PaO_2/FiO_2$ (P/F) ratio of 201 to 300 than in patients who had ARDS. The use of pressure control was uncommon (10% overall), as was the use of permissive hypercapnia (6% of patients who had ARDS and 3% of patients who had a P/F ratio of 201 to 300) and the use of positive end expiratory pressure (PEEP) greater than 10 cm $H_2O$ [1].

*Synchronized intermittent mandatory ventilation*

During SIMV in volume-controlled mode, a specified number of volume-preset breaths are delivered every minute. In addition, the patient is free to breathe spontaneously between machine breaths from the reservoir or to take breaths augmented with PS. Unless the patient fails to breathe spontaneously, machine breaths are delivered only after the ventilator has recognized the patient's effort, such that ventilator and respiratory muscle activities are synchronized (Fig. 2). Because all intermittent MV (IMV) circuits now are synchronized, the terms IMV and SIMV are used interchangeably.

*Volume-targeted ventilation for neonates*

Unfortunately, traditional volume-controlled ventilation is not feasible in small newborns because of unpredictable loss of $V_T$ to gas compression in

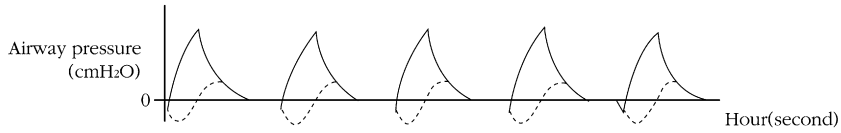


Fig. 1. Airway pressure curve of assist control ventilation (ACV). *Solid lines* represent mechanical breath cycle; *dotted line* represents spontaneous breaths.

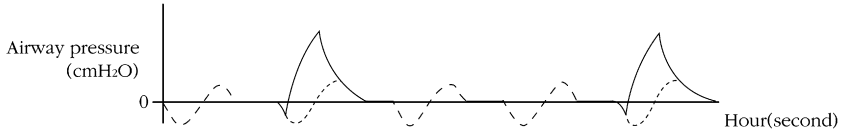


Fig. 2. Airway pressure curve of synchronized intermittent mandatory ventilation (SIMV). *Solid lines* represent mechanical breath cycle; *dotted line* represents spontaneous breaths.

the circuit, stretching of the tubing, and variable leakage around the uncuffed endotracheal tube (ETT). Therefore microprocessor-based modifications of pressure-limited, time-cycled ventilation were developed to try to combine the advantage of pressure-limited ventilation with the ability to deliver a more constant $V_T$. Three devices widely used in neonatal ventilation offer some form of volume-targeted ventilation, and each of the available modes has advantages and disadvantages. Clinical data validating the performance of these modes are limited. Pressure-regulated volume control (PRVC) is a pressure-limited time-cycled mode that adjusts inspiratory pressure to target a set tidal volume based on a compliance calculation from the pressure plateau of an initial volume-controlled breath. The breath-to-breath change in peak inspiratory pressure (PIP) is limited to 3 cm $H_2O$ to avoid overshoot.

The volume-assured PS mode is a hybrid mode that seeks to ensure that the desired $V_T$ is reached. Each breath starts as a pressure-limited breath, but if the set $V_T$ is not reached, the breath converts to a flow-cycled mode by prolonging the inspiratory time with a passive increase in PIP. This may result in a prolonged inspiratory time, leading to expiratory asynchrony. Targeting of tidal volume also is based on inspiratory tidal volume and is therefore susceptible to error in the presence of significant ETT leakage. The volume guarantee (VG) option regulates inspiratory pressure using exhaled $V_T$ measurement to minimize artifacts caused by ETT leakage. The operator chooses a target $V_T$ and selects a pressure limit up to which the ventilator operating pressure (the working pressure) may be adjusted [2,3].

## Setting the mechanical ventilator in volume-controlled mode

The mechanical output of a ventilator operating in the volume-controlled mode is defined uniquely by four settings: shape of the inspiratory flow profile, $V_T$, machine rate, and a time variable in the form of either the inspiratory-to-expiratory (I:E) ratio, or the inspiratory time (Ti) [4].

### *Inspiratory flow pattern*

In patients who had ALI, use of the ventilator mode with different inspiratory flow patterns and I:E ratios altered the nonlinear volume pressure behavior of the lung. This change was greatest with pressure control inverse

ratio ventilation (PCIRV) compared with VCV, and lowest with pressure control ventilation (PCV), despite minimal differences in gas exchange and hemodynamics [5].

In modern ventilators, the inspiratory flow waveforms can be altered. The constant square wave shape is probably the most widely used flow pattern, followed by linearly decelerating flow (DF). DF can reduce peak inspiratory pressure, resulting in a more even distribution of inspired air and better oxygenation than constant flow (CF). The DF pattern may enhance filling of the alveoli with the longest inspiratory time constant. Hence in patients with chronic obstructive pulmonary disease (COPD), combining increased flow rate with the DF pattern could be expected to lead to constant recruitment of the alveoli and reduced pulmonary hyperinflation, resulting in better oxygenation and a more even distribution of ventilation. Changing the ventilator in volume-controlled mode with a DF or CF profile, however, had no significant cardiorespiratory effect in intubated COPD patients mechanically ventilated for acute respiratory failure [6].

The patient's work of breathing (WOB) during assisted ventilation is reduced when inspiratory flow from the ventilator exceeds patient flow demand. Patients in acute respiratory failure often have unstable breathing patterns, and their requirement for flow may change from breath to breath. VCV traditionally incorporates a preset ventilator inspiratory flow that remains constant even under conditions of changing patient flow demand. In contrast, PCV incorporates a variable decelerating flow waveform with a high ventilator inspiratory flow as inspiration commences. In the setting of ALI and ARDS, PCV significantly reduced patient WOB relative to VCV. This decrease in patient WOB was attributed to the higher ventilatory peak inspiratory flow of PCV [7].

### *Tidal volume*

A recent study conducted by ARDSnet showed that reducing the tidal volume from 12 mL/kg to 6 mL/kg reduced mortality by over 20% [8]. The recent modest reduction in clinician-prescribed tidal volume may have resulted from heightened concerns regarding ventilator-associated lung injury.

In patients who have ARDS, MV with a low tidal volume results in decreased mortality, and therefore an increased use of MV with low tidal volume is expected. Even MV with a low tidal volume mode, however, induces proinflammatory and profibrinogenic responses with a nondependent predominance for interleukin-1β(IL-1β) and procollagen III (PC III) mRNA expression in supine, ventilated, previously normal rats. A possible explanation for increased mediator expression with low tidal volume is lung heterogeneity, which may cause alveolocapillar distension in the nondependent region and repetitive opening and closing of distal lung in the dependent lung region, rendering the lung more susceptible to ventilator-induced

lung injury (VILI). In addition, passive MV is not a physiologic condition, and it may induce a proinflammatory and profibrinogenic response [9].

*Respiration rate*

When $V_T$ and an end-expiratory volume have been decided, the mechanical backup rate should be selected considering the patient's actual rate demand, anticipated ventilatory requirement, and the impact of the rate setting on breath timing.

*Inspiratory-to-expiratory ratio*

The setting of timing variables, in conjunction with $V_T$ and PEEP, determines the volume range over which the lungs are cycled during ventilation. A long $T_I$, a high $T_I/T_{TOT}$, and a low mean inspiratory flow all promote ventilation with an inverse I:E ratio. Long pause times favor the recruitment of previously collapsed or flooded alveoli and offer a means of shortening expiration independent of rate and mean inspiratory flow. Although alveolar recruitment is a desired therapeutic endpoint in the treatment of patients who have ARDS, one should consider that keeping the lungs expanded at high volumes or pressures for some time may damage relatively normal units and may have adverse hemodynamic effects.

## Ventilator mode and ventilator-induced lung injury

MV, although life sustaining, can be harmful to the diseased lung, especially when high ventilatory volumes and pressures that cause lung overdistension are used. This observation led the author to think that ventilatory strategies designed to avoid exposure of the lung to high pressure or volume might improve outcome. Consequently, it was recommended that under conditions in which lung overdistension is likely to occur, tidal volume and airway pressure should be limited, accepting the attendant increase in arterial carbon dioxide levels. Theoretically, pressure-limited ventilation can be provided equally well by either pressure target modes that limit airway pressure to preset levels or by volume-cycled ventilation with tightly set pressure alarms and close monitoring of plateau pressure.

Many clinicians prefer PCV, because it is easy to control peak airway pressure and keep peak inspiratory pressure below critical limits, thus possibly reducing volutrauma. Davis and colleagues [10] have demonstrated an improvement in oxygenation and pulmonary mechanics in ARDS patients who were switched from VCV to PCV while $V_T$, inspiratory time and PEEP were held constant. The finding was thought to reflect an increase in mean airway pressure. The downside, however, is that the high peak inspiratory flow of PCV may aggravate lung injury because of greater shear forces than the lower peak inspiratory flow of VCV. Indeed, a rabbit model

revealed that the high peak inspiratory flow in PCV induced significantly more severe lung damage than low peak inspiratory flows in VCV [11].

Recognition that volume, rather than pressure, is the critical determinant of VILI has focused attention on the need to better control the delivered $V_T$. The author investigated the ventilator strategy that was most effective at reducing VILI. There are three basic mechanisms of VILI:

Volutrauma, expansion of alveoli because of high ventilation pressure
Atelectrauma, shear stress induced injury caused by unstable alveoli recruiting and derecruiting (R/D) with each breath
Biotrauma and inflammatory injury that occurs secondary to the tissue damage caused by both volutrauma and atlectotrauma [12]

## Ventilator mode and outcome

The increased incidence of extrapulmonary organ failure in patients of the VCV group was associated strongly with a higher mortality. The development of organ failure likely was not related to the ventilatory modes. There was no difference in outcome in patients with ARDS who were randomized to PCV or VCV [13].

## Volume-control ventilation type of noninvasive pressure ventilation

In clinical practice, pressure-type noninvasive pressure ventilation (NIPPV) generally is preferred over volume-type NIPPV in patients who have home MV, and pressure-type NIPPV has replaced volume NIPPV. Pressure and volume ventilation NIPPV were equivalent with respect to nocturnal and daytime physiology, and the resulting daytime function and health status in chronic respiratory failure caused by chest wall deformity [14]. Nocturnal volume- and pressure-limited NPPV had similar effects on gas exchange and sleep quality in patients who had hypercapnic chronic respiratory failure [15]. To date, no differences in the relative advantages or disadvantages of either type of NPPV have been demonstrated.

## Summary

Mechanical ventilation can be harmful to the diseased lung, especially when it involves high ventilatory volumes and pressures that cause lung overdistension. Ventilatory strategies designed to avoid exposing the lung to high pressure or volume might, therefore, improve outcome. The best approach to MV for patients who have ALI or ARDS has been controversial. The consensus conference recommendation is to limit tidal volume and end inspiratory airway pressure and to accept permissive hypercapnia. Theoretically, pressure-limited ventilation can be equally well-provided by pressure target modes that limit airway pressure to preset levels or by volume-cycled

ventilation with tightly set pressure alarms and close monitoring of plateau pressure. Physicians caring for patients early in the course of ALI/ARDS in ARDS network centers favored volume-targeted ventilation. Using phase variables, volume-targeted ventilation may be characterized as patient- or time-triggered, flow-limited, volume-cycled assist/control, or SIMV (IMV) modes. The method by which MV is provided to reduce the inspiratory plateau pressure, by decreasing either $V_T$ on VCV or inspiratory pressure on PCV, did not influence mortality independently. The mortality of ARDS was associated strongly with the development of multiple organ failure.

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Crit Care Clin 23 (2007) 169–181

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# Ventilatory Management in Patients with Chronic Airflow Obstruction

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Chronic airflow obstruction (CAO) includes chronic obstructive pulmonary disease (COPD), bronchiectasis, chronic asthma, pneumoconioses, sarcoidosis, and destroyed lung by pulmonary tuberculosis. Patients who have upper airway obstruction, however, would be excluded in this category. They should have an obstructive type of ventilatory abnormality on spirometry. This consists of a low percent predicted forced expiratory volume in 1 second ($FEV_1$) plus a low $FEV_1$/forced vital capacity (FVC) ratio on a well- performed test. In addition, this ventilatory limitation should persist despite maximal medical therapy given over a period of time.

These diseased patients show significant overlap with respect to increased airway resistance, pulmonary hyperinflation, and high physiological dead space ($V_D/V_T$), leading to increased work of breathing in spite of underlying disease difference. If ventilatory demand exceeds work output of the respiratory muscles, acute respiratory failure (ARF) follows. The overall mortality of these patients with ventilatory support in the ICU can be significant. Moreover, these patients use a substantial proportion of mechanical ventilation in the ICU.

The main goal of mechanical ventilation in this patient population is to improve pulmonary gas exchange and to rest compromised respiratory muscles sufficiently to recover from the fatigued state. Using current evidence, noninvasive positive-pressure ventilation is suitable for these patients, but invasive ventilation also is required frequently in patients who have more severe disease. The physician must be cautious to avoid complications related to mechanical ventilation during ventilatory support. One major cause of the morbidity and mortality arising during mechanical ventilation in these patients is excessive dynamic pulmonary hyperinflation (DH) with intrinsic positive end-expiratory pressure (intrinsic PEEP or auto-PEEP). The

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doi:10.1016/j.ccc.2006.12.008 *criticalcare.theclinics.com*

purpose of this article is to provide a pathophysiological approach for optimal ventilatory management in CAO patients.

## Features of chronic airflow obstruction relevant to mechanical ventilation

### *Increased work of breathing*

Mechanical breathing workload consists of mean inflation pressure and minute ventilation [1]. The mean inflation pressure is approximated by the sum of the flow-resistive and elastic pressure components. The total elastic pressure comprises the incremental pressure needed to inflate the respiratory system by the tidal volume and any residual elastic pressure remaining at end-exhalation that must be overcome before gas begins to flow into the lungs such as intrinsic positive-pressure ventilation (auto-PEEP). Mean inspiratory resistance and average inspiratory flow rate determine the flow-resistive pressure. Any conditions to narrow airway diameter (eg, asthma) and by the reduced elastic recoil support of the airways (eg, emphysema) can increase flow-resistive pressure requirements. CAO increases the work of breathing (WOB) by causing simultaneous increases in airway resistance, lung volume, and minute ventilation.

### *Dynamic pulmonary hyperinflation and auto-positive end-expiratory pressure*

DH occurs whenever insufficient exhalation time prevents the respiratory system from returning to its resting end-expiratory equilibrium position between adjacent tidal cycles. High resistance to expiratory flow, low elastic recoil, high ventilatory demands, and short expiratory time contribute to the development of DH. Auto-PEEP is defined as the positive difference between end-expiratory alveolar pressure and the end-expiratory airway pressure selected by the clinician [2]. When auto-PEEP exists, a positive-pressure difference drives flow throughout exhalation until the subsequent inspiratory cycle actively interrupts deflation. Auto-PEEP has been determined by measuring the fall in esophageal pressure that occurs before the onset of inspiratory flow (dynamic auto-PEEP) (Fig. 1) or by measuring the plateau proximal airway pressure during airway occlusion (static auto-PEEP). Static auto-PEEP has been measured accurately in spontaneously breathing patients by synchronous subtraction of the average expiratory rise in gastric pressure, which has been calculated from the three breaths just before an airway occlusion, from the airway pressure during airway occlusion [3]. Ventilator graphics are invaluable for detection and monitoring of auto-PEEP (Fig. 2), and these should be monitored routinely.

Contributions of expiratory and tonic inspiratory muscle activity to airway pressure can result in over- or underestimations of the level of auto-PEEP [4]. The magnitude of auto-PEEP does not correlate closely

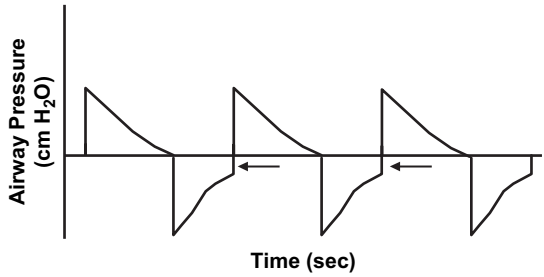


Fig. 1. Detection of Auto-PEEP (*arrow*) in pressure–time curve in patients who have pressure control ventilation.

with the degree of DH, which is a function of the product of auto-PEEP and respiratory system compliance [5,6]. Peak airway pressure, which is related predominantly to inspiratory flow, also does not reflect changes in lung volume [7]. Instead, end-expiratory lung volume, the total volume exhaled during a period of 20 to 40 seconds of apnea that interrupts mechanical ventilation, reflects hyperinflation [7].

DH occurs frequently during mechanical ventilation of patients who have CAO. During mechanical ventilation, DH increases lung volume and continues (for 6 to 12 breaths) until an equilibrium point is reached, at which point the increased lung volume results in a sufficient increase in elastic recoil pressure and reduction in small airway resistance to enable exhaled volume to equal inhaled volume [7]. The primary determinants of this equilibrium point are the severity of airflow obstruction, the inspired volume (tidal volume), and the expiratory time (a function of both the respiratory rate and the inspiratory flow rate). Therefore, DH, in part, is an adaptive process that serves to increase expiratory flow through the expiratory flow limitation by increasing airway patency and lung elastic recoil.

The beneficial effects of DH, however, are by far overwhelmed by the deleterious effects on the respiratory pump. In an experimental model,

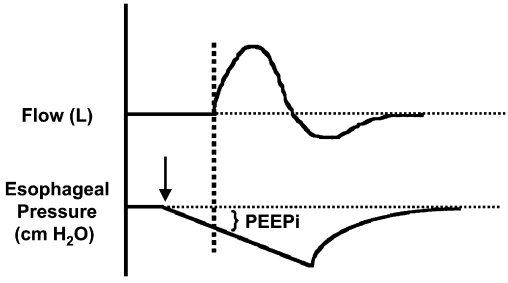


Fig. 2. Flow and esophageal pressure waveforms showing dynamic auto-positive end-expiratory pressure (PEEP). *Arrow* indicates the beginning of inspiratory effort. *Dotted line* shows the beginning of the inspiratory flow after overcoming the auto-PEEP.

DH impairs inspiratory muscle perfusion, while the flow to the transversus abdominis, an expiratory muscle, is increased during lung hyperinflation [8]. DH raises the mean intrathoracic pressure, increases the WOB [9], and reduces the pressure-generating capacity of the respiratory muscles [10]. DH may contribute importantly to acute breathlessness in patients who have CAO [11,12]. This increase in ventilatory workload in patients with DH is caused by:

The displacement of the respiratory system toward the upper, flat portion of the pressure–volume curve

The need to expand the chest wall and lung

The auto-PEEP effects

In addition, a high alveolar pressure may convert more of the lung into West zones 1 and 2, thereby increasing dead space and the minute ventilation requirement [13].

Raising mean right atrial pressure because of increased alveolar pressure tends to impede venous return. Therefore, initiation of mechanical ventilation in patients who have severe airflow obstruction may acutely reduce cardiac output and falsely elevate the measurements of end-expiratory pulmonary artery occlusion pressure [2]. Any unexplained hypotension developed during mechanical ventilation in a patient who has severe CAO first should be treated by disconnecting the patient from the mechanical ventilator, which will reduce DH and auto-PEEP (Fig. 3).

*Respiratory muscle dysfunction*

In addition to DH, malnutrition, high demands for oxygen, decreased cardiac output, blood gas abnormalities, electrolyte imbalance, and infections can aggravate this respiratory muscle dysfunction further. Hypercapnia reflects respiratory muscle dysfunction and is dependent on the severity of airflow limitation. In stable COPD patients who have severe airflow

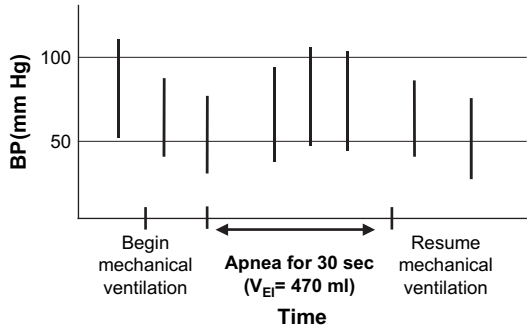


Fig. 3. A case showing the hemodynamic consequence in a patient with dynamic hyperinflation. The ventilator disconnection for 30 seconds recovered the dropped blood pressure caused by the application of positive-pressure ventilation. Measured $V_{EI}$ was 470 mL after 30 seconds of apnea in this patient with chronic obstructive pulmonary disease (COPD).

obstruction, shallow breathing and inspiratory muscle weakness are the main factors associated with hypercapnia [14].

*Panic cycle*

Patients who have severe airflow obstruction can enter a so-called panic cycle whenever increased minute ventilation or worsened respiratory impedance elicits forceful breathing [15]. Increasing breathing effort, in itself, increases oxygen consumption and minute ventilation in patients who have airflow obstruction. Increasing minute ventilation with airflow obstruction results in DH with auto-PEEP. Inappropriate ventilator settings (eg, inadequate flow rates, tidal volume, inspired oxygen percentage), machine malfunction, and patient-related acute problems (eg, pneumothorax, deterioration of blood gas tensions) are important causes of this panic reaction. Early intervention with verbal coaching, enhanced ventilatory support, reduction of anxiety, reduction of airway resistance, or the minute ventilation requirement often can terminate this self-reinforcing cycle and aid in the synchronization of the patient to mechanical support.

## Mechanical ventilatory support

Patients who have airflow obstruction requiring mechanical ventilation may require considerable inspiratory effort to trigger the ventilator. Factors responsible for increased effort are related to the patient and the ventilator, and may include:

- Narrow endotracheal tube diameter
- Increased airway resistance
- Decreased respiratory system compliance
- Auto-PEEP
- Insensitive triggering
- Decreased triggering threshold of the ventilator

When inspiratory efforts fail to trigger the ventilator (ie, missed effort), patient–ventilator dys-synchrony occurs. Missed efforts may occur more frequently at higher levels of mechanical ventilatory support [16].

*Positive-pressure ventilation with endotracheal intubation*

Respiratory arrest, mental deterioration, and progressive exhaustion of respiratory muscles are all indications for endotracheal intubation in these patients. The most experienced personnel available should perform rapid endotracheal intubation, because these patients have no reserve. Prolonged manipulation of the airway thus can produce serious morbidity including hypoxic brain damage. Manual ventilation with self-inflating resuscitators (eg, Ambu bag) should be performed cautiously and with a low respiratory

rate to avoid extreme DH. To rest the fatigued respiratory muscles in these patients, more than 24 hours of full ventilatory support may be needed, with sedation to suppress the patient's respiratory effort. Controlled modes should be used for as brief a time as possible to avoid disuse atrophy of respiratory muscles and unnecessary prolongation of the period of mechanical ventilation. Neuromuscular blockade should be avoided, because it is associated with significant side effects including pooling of airway secretions and prolonged muscle weakness [17].

Assist-controlled modes often are used after endotracheal intubation. Ventilation should be adjusted based on the degree of DH and not $PaCO_2$. If DH is excessive, the respiratory rate should be reduced to prolong expiratory time and to avoid further hyperinflation. Pressure-controlled ventilation with a prolonged I:E ratio is highly recommended and may aid in synchrony. Prolongation of the end-inspiratory time is not associated with improvement in gas exchange in patients who have airflow obstruction. Prolonged end-inspiratory times may exacerbate DH by decreasing the time available for expiration because of a reduction in elastic energy stored at the viscoelastic elements of the respiratory system, thus decreasing isovolume expiratory flow.

Low levels of PEEP in mechanically ventilated patients with CAO and DH may improve triggering and patient–ventilator synchrony by narrowing the difference between the alveolar pressure and mouth pressure at end-expiration (Fig. 4) [18,19]. PEEP application reduces the triggering work of breathing from level A to level B by off-setting the auto-PEEP in COPD patients with 2 cm $H_2O$ of triggering sensitivity.

This beneficial effect of PEEP is most evident in patients who have flow limitation during tidal expiration. Higher PEEP levels more than some critical point of auto-PEEP (usually 50–75% of static auto-PEEP), however,

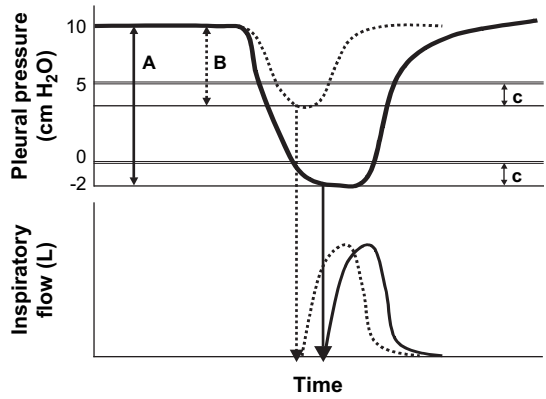


Fig. 4. Effect of applied PEEP on the triggering mechanical ventilation. 5 cm $H_2O$ of PEEP application reduces the triggering work of breathing from level A to level B by off-setting the auto-PEEP in this COPD patient with 2 cm $H_2O$ of triggering sensitivity (*arrow c*).

can increase lung volume and peak airway pressure in patients with CAO (Fig. 5). Moreover, because the degree of variability in auto-PEEP on a breath-to-breath basis can be high in asthmatic patients receiving mechanical ventilation, addition of applied PEEP without considering the breath-to-breath variability can lead to lung overdistention [20]. Therefore, PEEP should be used cautiously in asthmatic patients undergoing mechanical ventilation and titrated in real time.

Controlled hypoventilation appears to improve the clinical outcome of patients who have status asthmaticus [21]. When reduction of DH is an issue, and provided that there is no intracranial hypertension, and overt hemodynamic instability does not exist, acceptance of moderate acidemia (pH $>7.2$) is reasonable [22]. Profound hypoventilation may require deep sedation and neuromuscular blockade, both of which may increase the risk of myopathy [23]. Indicators to guide the degree of hypoventilation remain unclear. Thus, a balance must be achieved between reducing DH and hypoventilation, while minimizing the degree of sedation and neuromuscular blockade. Hypercapnia can be corrected once relief of airway obstruction improves conditions of ventilation–perfusion distribution. Correction of respiratory acidosis should be performed gradually and with caution. The goal is to return pH toward normal, not to return the $PaCO_2$ to normal.

As for a weaning method in these patients, both pressure-support ventilation (PSV) and a once-daily T-piece trial appear to be efficient. Weaning should be an active process aimed at trying to reduce the support level as soon as possible and repeatedly testing the ability of the patient to return to spontaneous breathing. CPAP helps severely ill COPD patients sustain

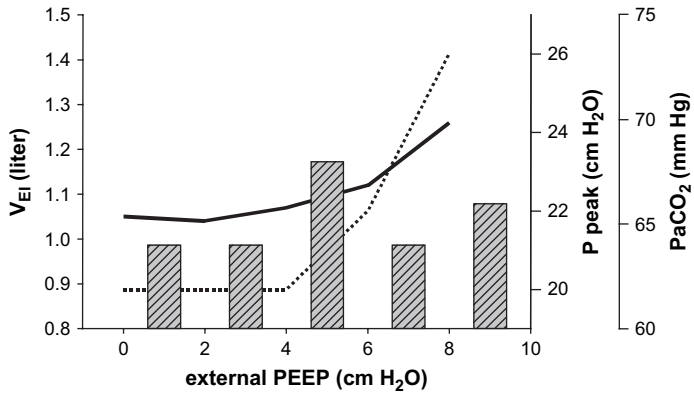


Fig. 5. A case of the effect of external PEEP application on volume of end-inspiration ($V_{EI}$) and peak airway pressure (Ppeak). $V_{EI}$ (*solid line in the figure*), the sum of trapped volume and tidal volume, and Ppeak (*interrupted line*) is increased in 71-year-old male asthma patient with 8 cm $H_2O$ of Auto-PEEP, when 6 cm $H_2O$ of external PEEP are applied to improve the triggering workload. Solid bar indicates the level of $PaCO_2$.

spontaneous breathing. Apparently it does so by promoting slower, deeper breathing, thus facilitating carbon dioxide elimination [24].

In summary, it is crucial to provide assisted controlled hypoventilation with longer expiratory times and titrated extrinsic PEEP to avoid dynamic hyperinflation and its attendant consequences. Avoiding overventilation is also crucial for better patient outcomes.

*Noninvasive positive-pressure ventilation*

With the recognition that noninvasive positive pressure ventilation (NPPV) has advantages, NPPV has become increasingly popular over the last decade in treating patients suffering from ARF [25]. NPPV has been accepted widely as the ventilatory mode of first choice in treating CAO patients with ARF [26,27]. NPPV has been shown to provide a significant reduction in endotracheal intubation and improved 2-month survival in COPD patients who have community-acquired pneumonia [28]. NPPV should be considered early in the course of respiratory failure and before severe acidosis ensues to reduce the likelihood of endotracheal intubation, treatment failure, and mortality [29]. Patients who have a pH less than 7.30 and more than 7.25 appear to receive the greatest benefit [30]. Patients who have normal mentation levels at the beginning of NPPV and improvements in pH, $PaCO_2$, and mentation level values after 1 to 4 hours of NPPV also are likely to benefit from NPPV [31,32]. The possibility of NPPV treatment failure could be evaluated by using a predictive risk charts [33]. The chance of COPD patients with ARF having a second episode of ARF after an initial (first 48 hours) successful response to NPPV is about 20% [34]. The decision to intubate should be based on the bedside assessment of the degree of respiratory distress instead of any absolute value of $PaCO_2$ or respiratory rate. NPPV could be used as a weaning facilitator in mechanically ventilated COPD patients by means of endotracheal intubation [35]. NPPV also could be applied to CAO patients who have declined intubation [36].

The role of NPPV in severe stable COPD patients, however, has not been established. NPPV has not been shown to benefit hospitalized patients with milder COPD exacerbations. A selected group of patients, however, might have clinical benefits from NPPV use during sleep at home. The longer-term effects of NPPV in hypercapnic COPD also have not been elucidative. Domiciliary NPPV for a highly selected group of COPD patients with recurrent admissions requiring NPPV may be effective in reducing hospital admissions and minimizing costs [37].

A sufficiently trained experienced team is needed for successful application of NPPV. Patient selection is also important; patients for NPPV should be able to protect their airway, be cooperative, and be otherwise medically stable. NPPV can be applied in skilled nursing facilities and community hospitals [38]. Conventional ventilators can be adapted for NPPV. Ventilators manufactured specifically for NPPV are as good as conventional ventilators

and may have some advantages with computer-controlled aspects of patient–ventilator interaction [16]. These machines may play a role in the use of this technology on the general ward. Interface intolerance is a significant barrier for successful NPPV. NPPV failure is largely caused by mask intolerance, which is reported at 18% [39]. Depending on the patient's tolerance and preference, nasal, facial, or helmet can be selected. PSV is the most common mode of ventilation for application of NPPV. PSV is more comfortable than assisted volume-cycled ventilation in NPPV use [40]. Applied pressure starts at low pressure (8 to 12 cm $H_2O$), and it is adjusted according to the patient's tolerance and tidal volume (at least 6 mL/kg). NPPV support duration can be reduced if improvement is noted.

### *Helium–oxygen mixture*

Helium–oxygen (heliox) mixtures improve ventilation by reducing density-dependent resistance. To be effective, heliox must be administered with a high percentage of helium, at least 60%. The density of heliox as a mixture of 80% helium and 20% oxygen is one fourth that of air. By reducing the WOB of patients with CAO, heliox can be applied as a temporizing measure until pharmacologic agents have improved airflow obstruction. Heliox has been reported to improve peak expiratory flow rates and reduce dyspnea and pulsus paradoxus in patients with asthma [41]. In mechanically ventilated COPD patients with auto-PEEP, the use of heliox markedly reduced trapped lung volume, intrinsic PEEP, and peak and mean airway pressures [42]. In addition, it can be used as symptomatic treatment of postextubation stridor [43]. It can be delivered to patients by means of a face mask or the mechanical ventilator.

## Pharmacological therapy

Mechanical ventilation is only a form of physiologic support, and it should be performed in conjunction with aggressive medical therapy for the primary disease. The mainstay of the pharmacological treatment in severe airflow obstruction includes high-dose inhaled $\beta_2$ adrenergic agonists, systemic corticosteroids, and supplemental oxygen. Inhaled beta-2 agonists can be delivered effectively to mechanically ventilated patients with the use of a spacer in the inspiratory limb of the breathing circuit [44,45]. The changes in resistance and static auto-PEEP after intravenous administration of salbutamol are too small to be of clinical significance [46], thus supporting an inhaled route.

The roles of theophylline and anticholinergic agents remain controversial for the routine treatment of acute exacerbation of asthma. Theophylline has been reported to improve diaphragmatic contractility and prevent diaphragmatic fatigue [47]. Corticosteroids can decrease inspiratory resistance and

auto-PEEP in mechanically ventilated patients with CAO and ARF [48]. The reports of acute myopathy related to use of corticosteroids in these patients are controversial [23,49]. Magnesium sulfate, halothane [50], and isoflurane [51] inhalation are not recommended as routine care in severe asthma. Zolpidem, the first imidazopyridine with a hypnotic action close to the benzodiazepines, seems to be appropriate for COPD patients who have sleep disturbance. Repeated 10 mg oral doses of zolpidem during 8 days did not impair nocturnal respiratory and sleep architecture parameters or diurnal pulmonary function tests, central control of breathing, and physical performances in patients who had stable COPD [52].

## Prognosis

Both hospital and postdischarge mortality of exacerbated COPD remain high, while quality of life appears to be poor. The in-hospital mortality rate for the COPD patients requiring admission to the ICU was 24.5% in a study [53]. The mortality rates at 6 months and 1, 3, and 5 years were 39.0%, 42.7%, 61.2%, and 75.9%, respectively, following admission to the ICU in the study [53]. The in-hospital mortality rate for the entire cohort was 28%, but fell to 12% for patients with a COPD exacerbation and without a comorbid illness in another study [54]. The actuarial survival rate for the 259 severe COPD patients with home ventilation, who were tracheostomized for at least 1 year, was 70% at 2 years, 44% at 5 years, and 20% at 10 years [55]. In-hospital mortality of severe asthma requiring mechanical ventilation has been reported as approximately 6% to 16.5% [56]. Posthospitalization mortality of life-threatening asthma was 10.1% after 1 year, and the deaths were observed mostly in patients over 40 year of age [56]. Survival was associated with premorbid level of activity, $FEV_1$, serum albumin level, and severity of dyspnea in the COPD patients who required mechanical ventilation [57]. Age, severity of respiratory and nonrespiratory organ system dysfunction, and hospital length of stay before ICU admission were associated with poor prognosis of these patients in another study [58]. The occurrence of extubation failure or the need for mechanical ventilation beyond 72 hours showed a worse prognosis in these patients [54]. The prognostic value of hypercapnia at admission is controversial. Hypercapnia at admission was reported as an independent predictor of better survival for the patients with tuberculous destroyed lung [59] who required mechanical ventilation.

## Summary

Mechanical ventilatory support allows patients who have CAO to gain time for pharmacologic treatment to work and to avoid and/or recover from respiratory muscle fatigue. The cornerstone to avoiding associated morbidity with mechanical ventilation in these patients is to prevent dynamic hyperinflation of the lung by limiting minute ventilation and

maximizing time for expiration and by inducing synchronization between the patient and mechanical ventilator. When mechanical ventilation is necessary, NPPV should be considered first, whenever possible, in these patients. Patients who have CAO requiring mechanical ventilatory support have an increased risk of death following such an event. Therefore, careful follow-up is needed after hospital discharge.

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Crit Care Clin 23 (2007) 183–199

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# Pressure Control Ventilation

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As mechanical ventilators become increasingly sophisticated, clinicians are faced with a variety of ventilatory modes that use volume, pressure, and time in combination to achieve the overall goal of assisted ventilation. Although much has been written about the advantages and disadvantages of these increasingly complex modalities, currently there is no convincing evidence of the superiority of one mode of ventilation over another. It is also important to bear in mind that individual patient characteristics must be considered when adopting a particular mode of ventilatory support. As emphasized in the 1993 American College of Chest Physicians Consensus Conference on Mechanical Ventilation, ''although the quantitative response of a given physiologic variable may be predictable, the qualitative response is highly variable and *patient specific*'' [1].

Partly because of the inherent difficulties in working with pressure ventilation, the Acute Respiratory Distress Syndrome (ARDS) Network chose to use a volume mode of support for their landmark low tidal volumetrial [2]. The preference for volume ventilation at ARDS Network centers was later demonstrated in a retrospective study of clinicians' early approach to mechanical ventilation in acute lung injury/ARDS. Pressure control was used in only 10% of the patient population before study entry. There was a modest tendency to use pressure control ventilation (PCV) in patients with more severe oxygenation defects ($PaO_2/FiO_2$, or $P/F < 200$) and a greater tolerance for higher airway pressures when using this mode. Volume control ventilation (VCV) in an assist-control or synchronized intermittent mandatory mode, however, was clearly a preferred method of support [3].

PCV may offer particular advantages in certain circumstances in which variable flow rates are preferred or when pressure and volume limitation is required. These desirable characteristics of PCV, however, can produce

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doi:10.1016/j.ccc.2006.12.005

unanticipated consequences when ventilatory strategies used in volume modes are similarly applied in pressure-regulated ventilation. The goal of the following sections is to provide clinicians with a fundamental understanding of the dependent and independent variables active in PCV and describe features of the mode that may contribute to improved gas exchange and patient-ventilator synchronization.

It is important to stress that any method of mechanical ventilation may contribute to secondary forms of injury in heterogeneous lung disease and that the injury incurred is currently beyond our capability of recognizing at the bedside. Developments in our understanding of pressure-volume curves and the recent demonstration of microscopic shear and stress injury in animal models of ventilator-induced lung injury call into question the whole concept of "safe" ranges of pressure and volume in mechanical ventilation [4–8]. As we explore the characteristics of flow and pressure generation in PCV, we draw attention to those aspects of pressure ventilation shown to be associated with adverse outcomes in experimental settings. In this way we hope to provide clinicians with a balanced framework in which to choose the most appropriate method of ventilatory support.

## Physiology of pressure control ventilation

PCV, unlike volume targeted modes, is pressure and time cycled and generates tidal volumes that vary with the impedance of the respiratory system. A working understanding of the factors that determine volume delivery is necessary for proper implementation of this mode of ventilation. During the inspiratory phase of PCV, gas flows briskly into the ventilator circuit to pressurize the system to a specified target. Once the target pressure has been reached, flow is adjusted to maintain a flat or "square wave" pressure profile over the remainder of the set inspiratory time [9,10]. This goal is achieved by sampling airway pressure approximately every 2 msec to provide critical feedback to flow controller mechanisms within the ventilator. By tracking the rate of change in pressure during inspiration, appropriate deceleration can occur as the pressure ceiling is approached. If the gradient between the circuit pressure and pressure target is large, flow is brisk. As the gradient between the recorded pressure and preset target narrows, flow decelerates to prevent overshoot. When impedance to flow is modest, the resulting flow curve demonstrates uni-exponential decay [11]. In situations of airflow obstruction, pressure targets are typically reached at lower flow rates, which contributes to a decelerating ramp profile (Figs. 1 and 2).

Flow into the ventilator circuit continues until conditions relating to pressure and time are met. Once the pressure within the alveolus rises to the level of the ventilator circuit, the gradient driving flow no longer exists and flow ceases. This process has important implications for tidal volume delivery in situations of altered compliance and resistance, as discussed later. In the PC mode of ventilation, the inspiratory time (I time) over which the pressure

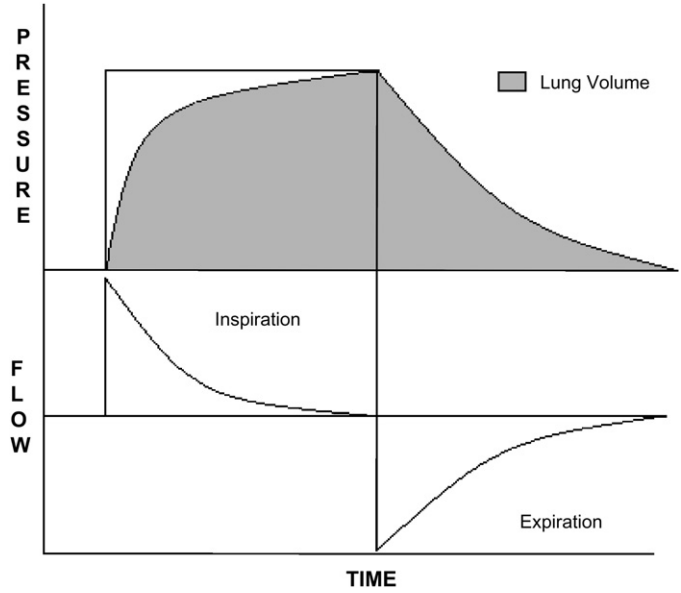


Fig. 1. Idealized pressure and flow time curve in PCV. A "square wave" pressure profile is achieved in inspiration by rapidly delivering flow into the ventilator circuit. Once the pressure target is met, flow rates decay in a uni-exponential manner, reaching a no-flow state at the termination of the inspiratory cycle. The bulk of the tidal volume is delivered early in inspiration when flow rates are maximum.

profile is maintained must be specified by the clinician. Shortening the inspiratory fraction of the duty cycle can lead to cessation of flow well before equilibration of circuit and alveolar pressures occurs. Extension of I time beyond the point of equilibration, on the other hand, increases mean airway pressure but generally does not lead to a further increase in tidal volume. Fortunately, the inspiratory time necessary to achieve pressure equalization can be established easily through various simple bedside maneuvers (see later discussion). Finally, to avoid potentially harmful pressure increases, flow ceases when circuit pressure exceeds the preset target by approximately 3 cm $H_2O$. This safeguard presumably decreases the risk of barotrauma during episodes of forced expiration, gas trapping, and vigorous coughing.

As a result of the high initial flow rates and large circuit-to-alveolus pressure gradient, a large percentage of the tidal volume is delivered early in the inspiratory cycle. During the ensuing pressure buildup, flow rapidly decelerates, which translates into a small volume of transported gas at the end of the inspiratory phase. Because of the disproportionate weighting of tidal volume delivery in early inspiration, the mean airway and alveolar pressures tend be higher in PCV compared with VCV when a constant flow rate (square wave) is used. The decelerating flow profiles characteristic of PCV, however, can be easily mimicked in volume modes of ventilation by adopting similar decelerating flow profiles. By using ramp waveforms and

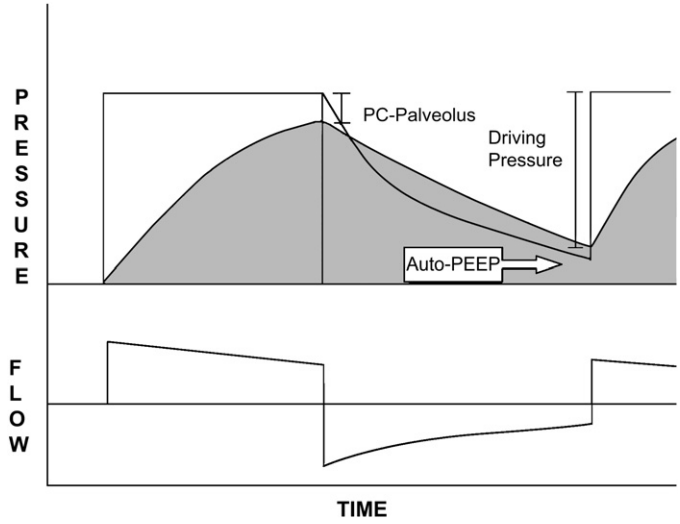


Fig. 2. Pressure and flow curves in obstructive disease states. The initial flow rates needed to reach the pressure target are reduced. Flow continues throughout the inspiratory cycle because of the slow equilibration of circuit and alveolar pressures. This process leads to ''squaring up'' of the flow profile. The slow delivery of gas and the decrease in pressure gradients driving flow lead to a reduction in tidal volume.

inspiratory holds in VCV, pressure and flow curves and parameters of gas exchange are similar in stable patients [12].

## Determinants of tidal volume and minute ventilation

The tidal volume output that results from a given applied pressure and inspiratory time is predominantly influenced by flow resistance and respiratory system compliance [13]. If resistance to flow is high, the flow component of impedance is dissipated slowly over resistive elements, which results in small driving pressures across the circuit. Under these circumstances, pressure targets are reached at lower initial flow rates and must be maintained for longer periods of time to ensure equilibration with alveolar lung units. Research has shown that the flow curves assume a shallower slope and that the decay profile becomes more linear as obstruction increases [14]. As the rate of flow decreases with increasing resistance, tidal volume may fall if no adjustment is made in inspiratory time.

Simple observations at the bedside can assist the clinician in determining whether I time is adequate to achieve equilibration of circuit and alveolar pressures under conditions of airflow resistance. If a steady state has not been achieved at the end of the inspiratory period, an inspiratory hold maneuver is associated with a fall in airway pressure below the pressure control target. In the absence of significant gas trapping, prolonging inspiratory time then leads to an increase in delivered tidal volume. If graphic displays

are available for review, flow-time curves demonstrate continuing gas delivery throughout the inspiratory cycle without a period of zero flow being evident on inspection. Modifying the duty cycle to the point at which inspiratory flow has ceased should produce the largest tidal volume for a given static compliance provided it does not lead to an increase in auto-positive end-expiratory pressure (PEEP) (Figs. 3 and 4).

Low tidal volumes that stem from alterations in respiratory system compliance on the other hand are influenced to a lesser extent by adjustments in inspiratory time. In the absence of airflow limitation, flow rates are brisk and lead to rapid equilibration of circuit and alveolar pressure (Fig. 5). The delivered tidal volume then depends primarily on the pressure applied over the duty cycle and the static compliance of the respiratory system as predicted by the following equation:

$$C_{ST} = V_T/[P_{Plat} - PEEP\ (\text{or auto} - PEEP)]$$

$$V_T = \Delta P \times C_{ST}$$

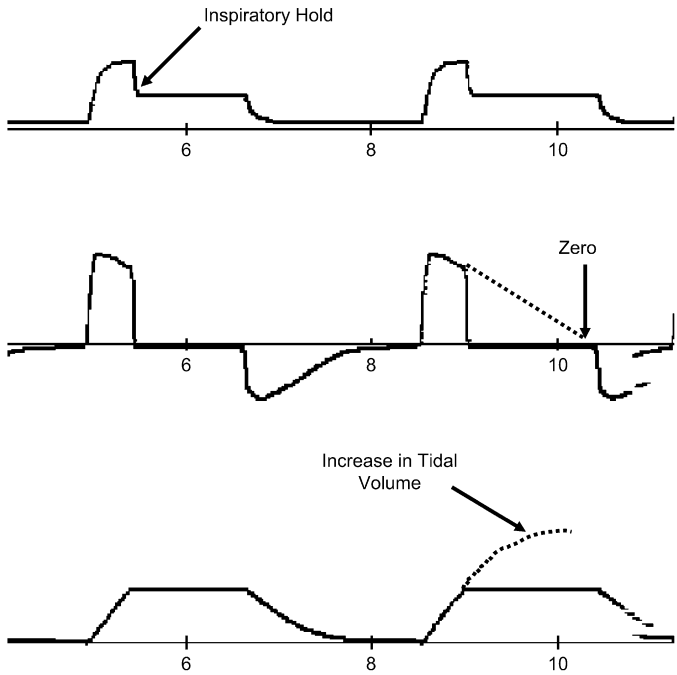


Fig. 3. PCV with short inspiratory times. The flow–time curve demonstrates abrupt cessation of flow well above the zero-flow point. Repetitive inspiratory hold maneuvers reveal large pressure drops that result from small delivered tidal volumes. In this instance, prolonging inspiratory time will lead to an increase in delivered tidal volume. (X-axis:Time.Y-axis:Top panel:Pressure; Middle panel:Flow;Bottom panel:Tidal Volume.)

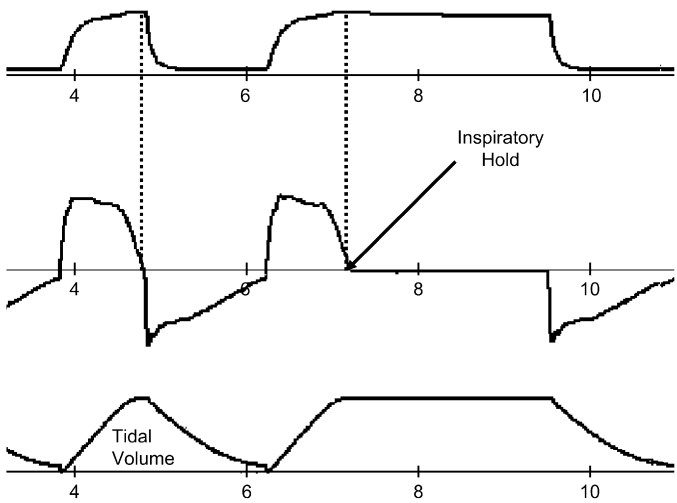


Fig. 4. In the initial breath, flow ceases at the end of the inspiratory cycle. During the subsequent breath, an inspiratory hold maneuver yields a stable pressure curve. These observations are consistent with pressure equilibration between the test lung and the ventilator circuit at the end of the regular inspiratory cycle. Prolonging inspiratory time in this circumstance would fail to increase tidal volume. (X-axis:Time.Y-axis:Top panel:Pressure;Middle panel:Flow;Bottom panel:Tidal Volume.)

in which $C_{ST}$ represents static compliance, $V_T$ represents tidal volume, $P_{plat}$ represents plateau pressure, and *PEEP* represents positive end-expiratory pressure. As the respiratory system compliance decreases, tidal volume falls and vice versa. It is particularly important to recognize the impact of changing compliance on delivered tidal volume during maneuvers such as proning or in circumstances of high intra-abdominal or intrathoracic (eg, pneumothorax) pressure. Cycling frequency also has been shown to influence tidal volume delivery. At high respiratory rates, the ability of ventilators to create rectilinear pressure profiles deteriorates. Recent evidence suggests that this is particularly true of certain models of mechanical ventilators used in the anesthesia theater [15]. As the ability to seek the pressure target declines, delivered tidal volume may be reduced. This feature of PCV, along with other determinants of tidal volume, makes it difficult to predict the impact of frequency changes on overall minute ventilation.

This seems particularly true in situations of airflow resistance. At high cycling frequencies, gas trapping can result from expiratory flow limitation. The resulting increase in mean alveolar pressure then limits flow into the system, which leads to a drop in delivered tidal volume. The relationship between mean airway pressure and mean alveolar pressure has been formalized in the following equation [16]:

$$\text{mean } P_{Alv} = \text{mean } P_{AW} + (V_E/60)(R_E - R_I)$$

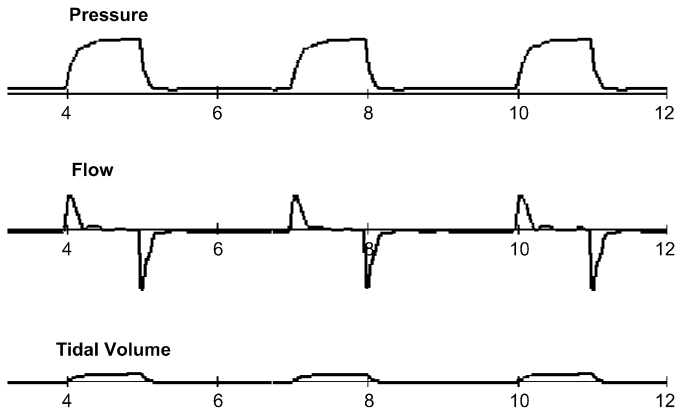


Fig. 5. A simulated PCV breath under conditions of decreased static compliance. Initial flow rates are high and quickly decelerate once the pressure target is achieved. Delivered tidal volumes are markedly reduced. (X-axis:Time.Y-axis:Top panel:Pressure;Middle panel:Flow; Bottom panel:Tidal Volume.)

in which $P_{Alv}$ represents the average alveolar pressure over a respiratory cycle, $P_{AW}$ represents the average circuit pressure over the respiratory cycle, $V_E$ represents minute ventilation, and $R_E$ and $R_I$ represent expiratory and inspiratory resistance, respectively. From inspection of the equation, it is apparent that in the setting of high minute ventilation and increasing airflow obstruction, dynamic recordings in the external circuit will underestimate alveolar pressures. At the bedside, unappreciated gas retention can result in falling tidal volume and minute ventilation with resultant hypercapnia. Increasing respiratory rate under these circumstances in an attempt to improve minute ventilation generally is met with further deterioration in gas exchange parameters (Fig. 6).

Mathematical modeling of PCV has led to a more thorough understanding of the determinants of minute ventilation under conditions of increased resistance [14,17]. As respiratory rates increase, minute ventilation rises to a point at which inspiratory and expiratory airflow limitation create a unique boundary that caps any further increase in minute ventilation. At extreme rates, gas delivery begins to fall as driving pressures are reduced by the development of auto-PEEP and limited available time for inspiration. In dealing with patients with obstructive lung disease, clinicians must be aware that the expected increase in minute ventilation that results from changing respiratory rates quickly reaches a theoretic maximum determined by the degree of airflow obstruction.

Increasing respiratory rates at the limits of minute ventilation also can lead to worsening gas exchange by altering dead space to tidal volume ratios ($V_D/V_T$). Once minute ventilation approaches the bounding limit, tidal volumes begin to fall. As a percentage of the breath, dead space ventilation

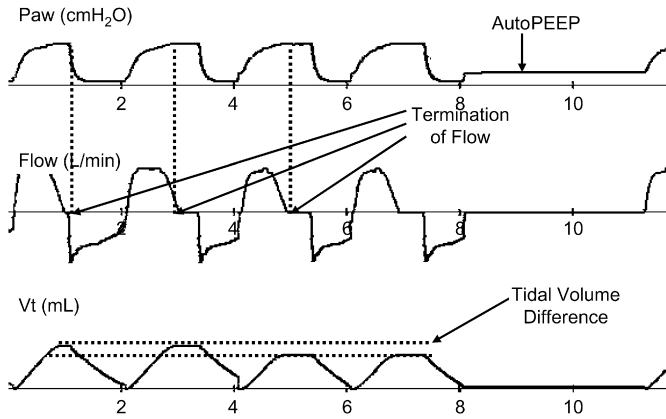


Fig. 6. The rapid development of auto-PEEP resulting from long inspiratory times and high respiratory rates leads to early cessation of flow and reduced tidal volumes. Auto-PEEP is demonstrated during expiratory hold maneuver. (X-axis:Time.Y-axis:Top panel:Pressure;Middle panel:Flow;Bottom panel:Tidal Volume.)

then increases, which leads to less effective $CO_2$ clearance. Animal models of PCV have demonstrated the development of progressive hypercapnia over relatively stable minute ventilation as cycling frequencies were increased [18]. Calculated dead space ratios revealed a strong tendency to change in the direction of the respiratory rate [18].

The response to changes in respiratory rate is different when impedance is dominated by the elastance of the respiratory system. In these circumstances, minute ventilation generally increases along with cycling frequency [11,17]. The slope of this relationship is determined by the individual static compliance. If the respiratory system is stiff, delivered tidal volumes are small and result in modest increases in minute ventilation. In the absence of significant gas trapping, the impact of cycling frequencies on dead space ratios in restrictive lung disease would be expected to be considerably less than seen in obstructed states.

## Theoretic advantages/disadvantages of pressure control ventilation

Interest in PCV and decelerating waveforms dates back several decades. Following the description of ARDS in the late 1960s, numerous animal studies were published that investigated the relative contribution of tidal volume, peak airway pressure, and end-expiratory pressure to ventilator-induced lung injury. These investigations, along with observational studies, suggested that high peak airway pressures were associated with macro- and microscopic barotraumas [8,19–21]. PCV, by virtue of its pressure ceiling, was seen as a possible means of avoiding transient high peak alveolar pressures in lung units close to central airways and possessing fast time constants. In conditions of heterogeneous lung pathology, significant

differences in regional pressure and volume may arise from local conditions that influence flow and compliance [6,7]. Pressure limits and decelerating flow profiles are thought to produce more uniform distribution of forces within the lung, possibly reducing the risk of volu- and barotrauma.

The decelerating waveform also may produce other advantages. Because the bulk of the tidal volume is delivered early in the respiratory cycle, the mean airway pressure over the duty cycle is increased [13]. Modell and Cheney [22] demonstrated that decelerating waveforms improve oxygenation in the setting of diffuse lung injury when compared with accelerating and square wave patterns of tidal volume delivery. Both of the latter profiles result in lower mean airway pressures and presumably produce less recruitment of poorly ventilated lung units. As might be expected from the effect on mean airway pressure, choice of flow pattern also can lead to improved lung mechanics. In a comparative trial of flow patterns in 14 patients with respiratory failure, Al-Saady and Bennett [23] demonstrated higher static and dynamic compliance along with improved measures of work of breathing when decelerating flow profiles were used. Changes in compliance that result from different flow profiles depend primarily on the percentage and threshold opening pressure of atelectatic lung units [4]. Any improvement in these measures likely will occur early in the course of lung injury and are affected by the nature of the insult [24]. A final mechanism by which flow profiles can influence the inflationary properties of the respiratory system involves changes in the "nonlinear" or viscoelastic behavior of the lung. Viscoelastance is responsible for the pressure drop that occurs between the time that flow ceases in the airways and a stable plateau pressure is achieved. The decay in pressure reflects time constant inequalities and tissue viscance and has been associated with the degree of lung injury. When various modes of ventilation were randomly applied in acutely ill patients, Edibam and colleagues [25] demonstrated that PCV was associated with the smallest viscoelastic pressure drop when compared with VC and pressure control inverse ratio ventilation modes. The clinical implications of these findings, however, remain unknown.

PCV also may significantly lower work of breathing in patients with variable or high drives to breathe [26,27]. In VCV, flow rates are fixed and generally determined by the respiratory therapist. If a patient's demand for flow exceeds the set rate, the patient may continue vigorously inspiring in response to internal cues. The sustained, high negative intrathoracic pressure contributes to additional work of breathing. Inappropriate flow rates are easily identified by examining pressure-time curves. If flow is inadequate, the inspiratory arm of the curve has a "scooped out" concave appearance (Fig. 7) [28]. Adjusting flow rates or changing to a pressure-regulated mode of ventilation often improves comfort and apparent respiratory effort. When flow rates are variable and determined by pressure targets, as in PCV, changing patient demand is met by similar directional changes in delivered flow. These changes avoid "flow starvation" commonly encountered in volume forms of ventilation (Fig. 8).

Specifying pressure and inspiratory time also may have implications for gas exchange and minute ventilation by additional mechanisms. Puddy and Younes [29] have demonstrated that respiratory frequency can be influenced by altering flow rates in normal individuals leading to ''flow related tachypnea'' [30]. By shortening inspiratory time through use of high flow rates, respiratory frequency increased in study subjects by approximately 60%. The response was thought to be mediated through the Hering-Breuer reflex that influences neural inspiratory and expiratory cycling. Decelerating patterns of flow, in contrast to square wave profiles, produce longer I times for a given tidal volume and may encroach on neural expiratory time, leading to changes in breathing frequency. This neuromechanical coupling may decrease the risk of flow-related hypocapnia that results from shortened inspiratory times.

Not all studies have shown benefits from pressure-regulated flow, however. Dembinski and colleagues [31] demonstrated that once PEEP was optimized, a square wave flow pattern produced a more favorable V/Q distribution than decelerating ramps in an animal model of acute lung injury. It seems that any improvement in gas exchange that arises from an increase in mean airway pressure (mAWP) depends on the amount of lung tissue available for recruitment. In the absence of recruitable, atelectatic lung units, increasing airway pressure leads to decreased cardiac output and, ultimately, worse gas exchange. A decelerating pattern also may conceivably lead to overinflation in regions of the lung with relatively normal

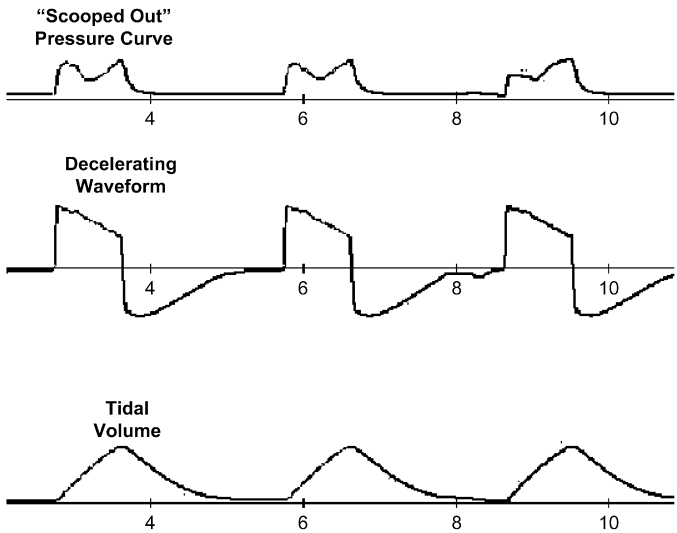


Fig. 7. Volume control breath with a decelerating ramp waveform. An exaggerated inspiratory effort is simulated midway through the inspiratory phase. The fixed flow pattern fails to meet the new flow demand, which leads to a ''scooped out'' appearance in the pressure time curve. (X-axis:Time.Y-axis:Top panel:Pressure;Middle panel:Flow;Bottom panel:Tidal Volume.)

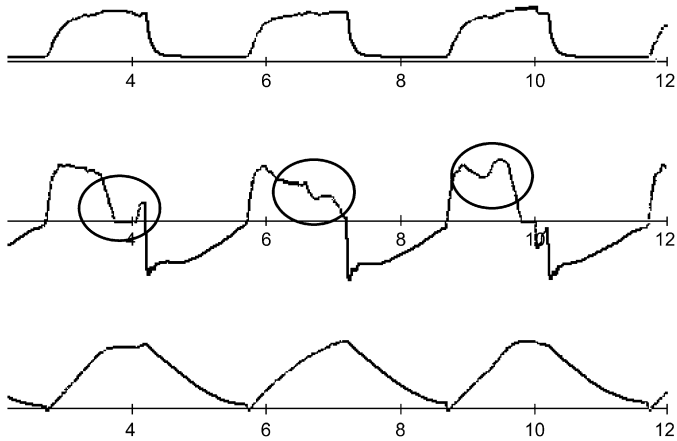


Fig. 8. Pressure control breath demonstrates variable flow. Initial breath: simulated early exhalation. Middle breath: simulated transient midcycle resistance. Final breath: simulated midcycle increased flow demand. (X-axis:Time.Y-axis:Top panel:Pressure;Middle panel:Flow;Bottom panel:Tidal Volume.)

mechanics. By comparing inspiratory and expiratory CT scanning in an ovine lung injury model, Roth and colleagues [32] noted a modest increase in high attenuation (ie, overinflated) lung regions. This small difference in density distribution was not reflected in either lung mechanics or gas exchange.

There are additional concerns regarding the use of PCV as a lung protective strategy. Early in the inspiratory cycle flow, rates are at their maximum and produce rapid changes in pressure within the conductance system, which can lead to high shearing forces in distal airways of the lung. In experimental models of ventilator-induced lung injury, high initial flow rates led to greater deterioration in gas exchange, higher dry-wet lung weights, and more severe histiologic evidence of barotrauma when compared with slower rates despite similar peak and plateau pressures [33,34]. Animal models of ventilator-induced lung injury also suggest that use of PCV with long inspiratory times leads to greater lung injury [35,36]. Several mechanisms have been postulated, including prolonged exposure to alveolar wall stress and greater opportunity for uniform equilibration of alveolar pressures with ventilator circuit pressures. It is clear that creating lower peak airway pressures through decelerating flow profiles does not provide protection from secondary forms of ventilator-associated lung injury, although this approach to ventilatory support is commonly undertaken in the belief that it occurs. Unfortunately, the relative contributions of shear and stress to secondary forms of injury cannot be judged at the bedside. Awareness of the potential contribution of these forces to ventilator-associated lung injury should temper clinicians' enthusiasm for PCV in situations of heterogeneous lung injury, however.

## Use of pressure control ventilation in various disease states

PCV has long been used in the setting of difficult-to-manage acute lung injury/ARDS. Clinicians have exploited the variable flow rates to improve patient work of breathing and limit high peak airway pressures. PCV also generally is associated with increased mean airway pressure, a ventilatory parameter found to correlate with oxygenation status. By delivering a larger proportion of the tidal volume early in the inspiratory phase, the lung is maintained at a higher volume, presumably recruiting alveolar lung units to participate in gas exchange.

Unfortunately, few human trials directly comparing conventional PCV with VCV in ARDS have been performed [37–41]. One of the better known studies was reported by Esteban and colleagues [42] writing for *The Spanish Lung Failure Collaborative Group*. Patients with the diagnosis of ARDS were randomly assigned to either VCV or PCV with adjustment in ventilator parameters to maintain plateau pressures $\leq$35 cm $H_2O$. Delivered tidal volumes, measures of gas exchange, and estimation of lung compliance were not significantly different over the course of the study. In-house mortality and multi-organ dysfunction occurred more frequently in the VCV arm of the trial but were attributed to differences in baseline characteristics and preceding organ failure. Multivariate analysis suggested that the mode of ventilation did not influence outcome.

With rare exceptions, PCV does not seem to offer any substantial advantage over volume control ventilation in terms of gas exchange or lung mechanics. This finding is particularly true when decelerating ramp waveforms and inspiratory hold maneuvers are used in VCV to mimic the flow profile achieved in PCV [12].

A modification of PCV termed ''pressure control inverse ratio ventilation'' proved to be a popular approach in the late 1980s and early 1990s to the management of patients who have ARDS and refractory gas exchange defects. It is occasionally still used. In this mode, inspiratory time is intentionally extended beyond an I:E ratio of 1:1. Prolonging inspiratory time and limiting expiratory time was thought to lead to two potential benefits: (1) higher mean airway pressure and (2) creation of intrinsic PEEP. Despite pressure control inverse ratio ventilation's theoretic advantages, multiple studies failed to demonstrate any significant improvement in oxygenation status when similar mean airway pressures were generated by matching extrinsic PEEP to the level of recorded intrinsic PEEP [43–45]. In studies that reported improved oxygenation with inverse ratio ventilation, an increase in mean airway pressure generally occurred and was not controlled for [46–49]. Cardiac indices and oxygen delivery often deteriorate at the higher mean airway pressures generated in pressure control inverse ratio ventilation [50,51]. Of note, $PaCO_2$ is either unaffected or modestly improved despite a reduction in minute ventilation. When calculated, the improvement in dead space ratios is small and of doubtful clinical

significance. After review of the available literature, Shanholtz and Brower [52] came to the conclusion that "IRV remains unproven in the management of ARDS."

The use of PCV in obstructive lung disease is even less clear. Few studies have been undertaken in this population, leaving clinicians appropriately skeptical of this mode of ventilation for patients with airway disease. The concern surrounding PCV relates to the impact that inspiratory resistance and auto-PEEP have on delivered tidal volume. Flow rates and circuit-to-alveolar pressure gradients may fall as inspiratory and expiratory resistance increases. Delivered tidal volume may become unpredictable and lead to unintended hypoventilation. In the setting of status asthmaticus, in which airflow obstruction can improve dramatically over the course of the illness, tidal volumes also may increase unexpectedly. Fortunately, modern ventilators track various parameters and allow early detection of changing lung mechanics. By establishing tight alarm thresholds, clinicians can respond quickly to falling or rising tidal volumes and minute ventilation.

The concern over possible hypoventilation and resultant hypercapnia in PCV may be overstated. Tolerance for respiratory acidosis is remarkable, with well-documented case reports describing patients with $PaCO_2$ levels exceeding 150 mm Hg [53,54]. Although systemic vasodilation is a known consequence of profound hypercapnia, hemodynamic parameters are generally well maintained in the absence of significant underlying heart disease or central sympatholysis.

In some ways, pressure control forms of ventilation may represent a safer alternative to VCV in severe airflow obstruction. Although the risk of hypoventilation may increase, the risk of overt barotrauma (eg, pneumothorax, pneumomediastinum) may be diminished. In VCV, as gas trapping develops, pressure can build rapidly beyond the alveolar lung unit's elastic limit. Plateau pressures have been used as a surrogate for alveolar volu- and barotrauma risk in volume modes of ventilation, but these measures do not predict the occurrence of barotrauma and directly measured gas volume at end inspiration. When trapped gas volume exceeds 20/mL/kg, the risk of barotrauma is significant [55,56].

Few centers in the United States use trapped gas volume to guide therapy in status asthmaticus. In the absence of regular monitoring of this parameter, PCV may provide a safer method of ventilating patients. As auto-PEEP increases, driving pressure falls, which results in a smaller delivered tidal volume. "Squaring up" of the flow profile as a result of airflow resistance also may serve to protect lung units with fast time constants from transient high pressures.

Despite these potential advantages, pressure-regulated modes of ventilation have been rarely studied in the management of status asthmaticus. Sarniak and colleagues [57] have reported the largest PCV experience in status asthmaticus to date. In their pediatric population, PCV seemed to be safe and associated with improved gas exchange. A review of ventilatory

parameters revealed average I times of 1 second, I:E ratios of 1:4, and peak inspiratory pressures of 36 to 40 cm $H_2O$. The duration of mechanical ventilation averaged 29 hours, with only one pneumothorax being recorded. Earlier studies of invasive and noninvasive pressure support ventilation also noted that pressure-regulated breaths can be used effectively in severe airflow obstruction [58–60]. Recent reviews of status asthmaticus suggest that the mode of ventilation is not terribly important as long as gas trapping is avoided. Some authors endorse PCV as a starting mode of mechanical ventilation in patients who have status asthmaticus [61–63].

In patients who have chronic obstructive pulmonary disease, decelerating waveforms are associated with improved dead space ventilation, lower $PaCO_2$, and less dyspnea when compared with either square or sine wave flow patterns. Work of breathing also may be reduced by decelerating flow profiles, particularly if the flow rate is variable and tied to airway pressure targets. Occasionally, clinicians may encounter patients with severe emphysema who possess little elastic recoil in the lung parenchyma. Pressure ventilation under these circumstances can lead to large tidal volumes and subsequent hyperinflation. A restrictive volume mode of ventilation may be preferable in these instances.

## Summary

Despite its popularity, PCV has not been proved superior to other modes of mechanical ventilation. Although it is associated with lower peak airway pressures, the impact on lung mechanics, gas exchange, and risk of macro- and microscopic barotrauma is variable.

The adjustable flow rates and pressure limitations may prove useful in certain populations. Patients with high drive to breathe may enjoy a decreased work of breathing with PCV compared with VCV. In patients who have obstructive lung disease, pressure limitation also may diminish the risk of barotrauma and increase the likelihood of unintentional hypoventilation. The role of PCV in other conditions, such as acute lung injury, remains to be defined. The potential for lung recruitment through increased mean airway pressure continues to make this an attractive mode in patients with large shunt fractions. Any potential benefit depends on the nature and timing of the lung injury, however, and may be offset by shear- and stress-related volu- and atelectrauma.

Implementation of PCV requires a practical understanding of the relationship between flow, time, and pressure. Unlike VCV, in which tidal volume is guaranteed, gas delivery in PCV varies in complex ways. The simplistic approach of ''turning up'' the ventilator may lead to unexpected clinical deterioration when using this mode. Careful, repeated observation, however, can make this a safe and effective method of ventilatory support.

## Acknowledgments

The authors would like to thank Per Thorburg, MD, for his constructive review of the manuscript.

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Crit Care Clin 23 (2007) 201–222

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# Noninvasive Ventilation

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Historically, all ventilation or control of the airway was done by negative-pressure ventilators. Negative-pressure ventilators supported ventilation by exposing the chest wall to increased atmospheric pressure during inspiration, with expiration occurring as the pressure around the chest was allowed to return to atmospheric levels. The iron lung was used widely in 1950s during the poliovirus epidemic. These bulky devices are no longer in use, however, because modern mechanisms provide ventilation with few complications. Today, positive pressure is used to support ventilation. These ventilators have computer devices incorporated within them and have become a favorite and standard within the ICU. In the last decade, noninvasive positive-pressure ventilation (NPPV), delivering mechanical-assisted breaths without placement of an artificial airway, has become an important mechanism ventilator support both inside and outside the ICU. Because of its versatile applications, NPPV is used for respiratory diseases, neuromuscular diseases, chronic obstructive pulmonary disease (COPD), diaphragmatic weakness, and heart failure.

## Types of noninvasive positive-pressure ventilation

NPPV, delivered nasally or by a facemask, continues to gain wider acceptance as improved masks and ventilator technology have developed. Face masks that cover the nose and mouth, nasal masks, nasal pillows that fit into the nostrils, and cushion devices that fit across the nostrils have been introduced. NPPV has two major modes of supplying support: bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP). These small portable devices allow mobility and transfer.

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0749-0704/07/$ - see front matter 
doi:10.1016/j.ccc.2006.11.015 *criticalcare.theclinics.com*

*Bilevel positive airway pressure*

BiPAP ventilators provide high-flow positive airway pressure that cycles between high-positive pressure and low-positive pressure. In the spontaneous mode, BiPAP response to the patient's own flow rate and cycles between high-pressure inspiration and low-pressure exhalation. BiPAP reliably senses the patient's breathing efforts and even air leaks that occur within the unit. When inspiration is detected the inspiratory pressure is known as inspiratory positive airway pressure (IPAP). During this cycle, higher pressures are delivered for a fixed time or until the gas flow rate falls below a threshold level, usually 25% of the expiratory volume. At this point in time, the expiratory positive airway pressure (EPAP) cycle begins delivering a lower positive pressure that splint and maintains a fixed alveolar pressure. In addition to support provided to each spontaneous effort, a backup set respiratory rate can be used. EPAP prevents airway and alveolar collapse, prevents atelectasis, and maintains functional residual capacity at increased levels. It maintains oxygenation, whereas IPAP augments tidal volume, increases airway pressure, and decreases fatigue. BiPAP is similar to pressure support ventilation. The terminology differs, however; for BiPAP, the expiratory pressure is equivalent to the sum of the positive end-expiratory pressure and the inspiratory pressure. Thus, a BiPAP setting of 12 cm of inspiratory pressure and 5 cm of water for expiratory pressures is equivalent to a standard ventilator setting of 7 cm of water for pressure support and 5 cm of water for positive end-expiratory pressure (PEEP). With BiPAP, supplemental oxygen is diluted by the high flow of air through the system. Thus, patients may require higher oxygen flows for BiPAP for nasal cannula. Devices using a common inspiratory and expiratory line can cause rebreathing of exhaled gases and persistent hypercapnia.

*Continuous positive airway pressure*

CPAP provides continuous positive pressure throughout the respiratory cycle, either by a portable compressor or from a flow generator, in conjunction with a high-pressure gas source. CPAP is only effective for spontaneous breathing. CPAP cannot provide ventilation for patients who have apnea. When used with a nasal mask, low pressures (5 cm $H_2O$) are effective in splinting the upper airway and preventing upper airway obstruction. During CPAP, airway pressure remains positive during the entire respiratory cycle. CPAP works by applying pressure though the airways at high enough levels to keep the upper airway patent, acting as a splint.

## Set up

NPPV works best in patients relaxed and prepared. The first few seconds should be used to fit the mask and familiarize the patient with equipment.

Patients may feel claustrophobic, especially when increasing respiratory drive and when difficult breathing is present. NPPV is tolerated best when pressures are increased gradually, as the work of breathing and respiratory drive eases.

## Neuromuscular weakness

Neuromuscular diseases, such as poliomyelitis, often were treated with the negative-pressure ventilators for respiratory failure management. Now, NPPV, particularly BiPAP and CPAP, are the first choice of ventilatory support for patients with upper airway dysfunction and chronic respiratory failure caused by neuromuscular diseases. NPPV ameliorates decline in lung function, improves gas exchange and cognitive function, and improves overall survival in patients who have neuromuscular disease [1–4]. For patients who have chronic progressive neuromuscular disease, noninvasive ventilation often is initiated at night for 6 to 8 hours once forced vital capacity is less than 50% of predicted. Duration is increased as respiratory muscle failure progressively worsens. Studies suggest NPPV in patients who have neuromuscular disease is cost-effective. Gruis and colleagues [5] demonstrated that NPPV slows the rate of lung function decline in patients who have acute amyotrophic lateral sclerosis if initiated at the time of diagnosis. This study also showed that the patient's quality of life scores improved by 30% with a cost savings of $50,000 per quality-of-life adjusted years.

Improved quality of life also was noted with the use noninvasive ventilation in patients with amyotrophic lateral sclerosis while on NPPV [6]. In their 5-year study, Cazzolli and Oppenheimer [6] reported improved quality of life and survival in patients who used noninvasive ventilation. Twenty-five patients used noninvasive ventilation, and 50 patients used intermittant positive pressure ventilation by means of tracheotomy. Patients using NPPV reported more independence and less need for help with self-care. Less mortality also was noted. In another study by Lyall and colleagues [7], improved quality of life and cognitive function in patients with amyotrophic lateral sclerosis who used noninvasive ventilation was observed. In this study, 14 patients who had advanced amyotrophic lateral sclerosis were compared with a similar control group with different neuromuscular diseases. Entry into the study required multiple quality-of-life questionnaires (eg, SF-36, Medical Outcome Test, Boston, Massachusetts) and the ALS functional reading score before and after 1 month of NPPV. Although functional ability decreased in all groups, greater vitality, energy, and mental health were noted in patients who used noninvasive ventilation.

Noninvasive ventilation prolongs life when used in palliative, end-of-life care. Hill and colleagues [8] showed that NPPV can prolong life by years, if not decades, in patients who have Duchenne's muscular dystrophy. In this report, noninvasive ventilation in terminal patients relieved disability and distressing symptoms of dyspnea, while prolonging life.

*Congestive heart failure*

Central and obstructive sleep apnea is very common in patients who have congestive heart failure (CHF). In randomized, controlled trials, NPPV has been shown to be an effective therapy for acute pulmonary edema, improving oxygenation and hypercapnia, while decreasing respiratory work and the rate of endotracheal intubations [9]. In a study of nasal BiPAP in patients who had CHF and severe respiratory distress, BiPAP was effective in reducing the rate of intubations by 9% [10]. In another controlled study, nasal BiPAP decreased arterial carbon dioxide and improved pH, respiratory rate, and dyspnea faster than nasal CPAP 10 cm of water pressure in patients who had acute pulmonary edema. The BiPAP group, however, experienced a rapid fall in blood pressure and a higher rate of myocardial infarction (71% versus 31%), causing concern regarding the use of this therapy for acute pulmonary edema.

In acute pulmonary edema caused by cardiac etiologies, NPPV provides partial ventilatory support, improves gas exchange, and relieves dyspnea. In addition, NPPV unloads inspiratory muscles and prevents respiratory muscle fatigue. Both CPAP and BiPAP decrease the work of breathing and prevent intubations in patients who have pulmonary edema [11–13]. In an early study of 100 patients randomly assigned to receive either oxygen or CPAP (including supplemental oxygen therapy), CPAP was initiated at 3 cm $H_2O$ with water pressure and titrated to 12 cm water pressure to achieve a $PaO_2$ of 80 mm Hg. All patients underwent pulmonary artery catheterization [14]. Patients who received CPAP plus conventional treatment showed a significant improvement in $PaO_2$, associated with a significant reduction in intrapulmonary shunting in alveolar–arterial oxygen tension difference. The CPAP group also had a higher cardiac stroke volume index in heart rate and blood pressure product as compared with the control group. The incidence of tracheal intubations was 16% in the CPAP group, compared with 36% in the control group. There were no observed differences in mortality at 1 year. The improvement in cardiovascular function during CPAP in patients who have CHF is associated with decreased left ventricular afterload [15,16]. Genovese and colleagues [17,18] showed an increase in stroke index from 40 plus or minus 5 to 51 plus or minus 8 $mL/m^2$ with CPAP of 5 cm water pressure. The authors noted the improvement in stroke index was caused by cardiac contractility, presumably because of increased sympathetic stimulation. Nocturnal NPPV in patients who have chronic congestive heart failure and sleep-related breathing disturbance reduces frequency of apneas and sympathetic nervous system activity, and improves oxygenation, symptoms of heart failure, and left ventricular ejection fraction [19–21].

Sleep disturbance is common in patients who have CHF. Nearly half of CHF patients with stable disease have an apnea–hypopnea index (AHI) greater than 26 episodes per hour [22,23]. Patients who have CHF commonly experience Cheyne-Stokes respirations, central apnea or mixed apnea

during sleep, and oxygen desaturations. Mortality is increased among CHF patients with Cheyne Stokes respirations [23–25]. CPAP is a safe and effective adjunctive therapy for CHF patients with sleep disturbances [21,26]. CPAP treatment of patients who have CHF in the absence of significant sleep-disordered breathing has not been established. In patients who have CHF, NPPV may improve oxygenation by recruiting atelectatic alveoli, redistributing lung water, and improving ventilation–perfusion matching [27]. It also can improve left ventricular function and cardiac outflow by reducing preload and afterload [9]. It increases lung volumes, stabilizing blood gases during periods of apnea or decreased ventilation. Apnea also leads to bursts of sympathetic outflow stimulation, which are detrimental to patients who have poor cardiac performance. Arias and colleagues [28] conducted a prospective randomized, placebo-controlled, double-blind crossover study of 27 newly diagnosed middle-aged patients with obstructive sleep apnea. Arias and colleagues [28] found that diastolic dysfunction abnormalities were related to repetitive obstructive apneic events during sleep, and these were common in patients who had obstructive sleep apnea. The exact mechanism of diastolic dysfunction, heart failure, and sleep apnea is unknown. Alternations in nocturnal blood pressure and sympathetic nervous system activity in the obstructive sleep apneic patients created ventricular pressure overload, however. The authors postulated that repetitive futile inspiratory efforts from hypopneas and apneas resulted in higher intrathoracic pressure and increased left ventricular afterload. How long does it take to improve cardiac performance? Cloward and colleagues [29] showed regression of ventricular hypertrophy after 6 months in patients using noninvasive ventilation effectively. During this study, cardiac echocardiograms and catecholamine levels were monitored, and patients improved mitral deceleration and relaxation.

*Chronic obstructive pulmonary disease*

Increasingly, the literature and several randomized controlled studies have shown that noninvasive ventilation decreases need for intubation in patients who have COPD [30–34]. In addition, noninvasive ventilation decreases mortality and medical ICU (MICU) stay when compared with conventional therapy [34]. Unless contraindicated, a trial of noninvasive ventilation in patients who have acute exacerbation of COPD may improve arterial blood gas levels and reduce intubation rates and prolonged hospitalization. There are no clinical predictors to identify which patients with respiratory failure would benefit from NPPV. In a study by Anton and colleagues [35], NPPV was successful for patients who had acute exacerbations of COPD. Patients demonstrating improvement in pH, a decrease in $PCO_2$, and a change in level in consciousness after 1 hour of use benefited from NPPV. The patients who did not improve these parameters after 1 hour experienced prolonged hospitalization and worsening respiratory failure leading to intubation [35]. Although patients exhibited different forced

expiratory volume in 1 second ($FEV_1$) and lung functions, lung function had no impact or response to therapy. The nature of respiratory obstruction also seems unimportant for selection of patients who respond to noninvasive ventilation. Response did not differ by patient's age, Acute Physiology and Chronic Health Evaluation (APACHE) score, or initial arterial blood gas. Noninvasive ventilation can be used as maintenance therapy in patients who have intrinsic lung disease and marked hypercapnia (eg, partial pressure of carbon dioxide greater than 60 mm Hg) [36].

Short use of NPPV for hours per day improves the respiratory pattern and blood gases in patients who have stable COPD and chronic hypercapnia [37]. Long-term use of nasal positive-pressure ventilation benefits hypercapnic patients who have COPD also. A randomized study found improvements in quality-of-life measures, sleep, $PaO_2$, and $PaCO_2$ after 3 months of positive-pressure ventilation [38]. Many patients who have severe COPD, however, do not tolerate long-term BiPAP. NPPV also may benefit patients who have intractable dyspnea. Lastly, noninvasive support ventilation can be introduced in stable patients who have known borderline decompensation. Acclimation to the device in this serious patient may result in future readiness and benefit.

NPPV is used commonly at night for managing chronic respiratory failure [39]. NPPV in respiratory failure improves arterial blood gases, lung volumes, and respiratory muscle strength and reduces hospitalizations [40,41].

## Facilitate weaning

NPPV also has been used when weaning patients from mechanical ventilators, especially when airway intubation and controlled mechanical ventilation for rapid hemodynamic stabilization are required. Udwadia and colleagues [42] have reported the utility of NPPV to facilitate weaning in 22 patients who had respiratory failure. In most patients, respiratory failure was caused by neuromuscular diseases, primary lung disease (COPD), or respiratory failure following cardiac surgery. Duration of mechanical ventilation was 31 days, (ranging from 2 to 219 days) [42]. NPPV was implemented when the following criteria were met: intact upper airway function, minimal secretions, low supplemental oxygen requirements, hemodynamic stability, and inability to maintain adequate spontaneous ventilation for 10 minutes. During the first day, noninvasive ventilation was continued for 20 hours and gradually was reduced to nocturnal ventilator support, depending on the patient's clinical state. In the series of 23 patients, 18 were transferred successfully to NPPV and were discharged (mean length of stay 11 days). Two patients who had pulmonary fibrosis were unable to tolerate NPPV because of dyspnea, and two patients required reintubation following extubation. One patient was unable to tolerate therapy secondary to pneumothorax, and the other patient's comorbidities included biventricular heart failure.

COPD patients who experienced postextubation hypercapnic respiratory failure were less likely to require reintubation compared with historical controls [43]. In this prospective observational study, the use of noninvasive ventilation in 50 patients who had severe COPD was evaluated. Patients who initially required airway intubation and conventional mechanical ventilation with severe hypercapnia (average $PaCO_2$ of 94 plus or minus 24 mmHg) were studied. A T-piece weaning trial was attempted 48 hours after intubation. Patients who failed attempted weaning were randomized into two groups: extubation plus application of noninvasive ventilation with face mask or weaning by pressure support. Although the sample size was small, at 60 days, 22 of 25 patients (88%) in the noninvasive ventilation group were weaned successfully compared with 17 of 25 (68%) in the invasive ventilatory group. The 60-day mortality was clinically and statistically different in the groups; 80% among those who received NPPV were still alive while only (28%) of those who received mechanical ventilation were. A similar study by Girault and colleagues [44] compared conventional weaning techniques (pressure support with the use of noninvasive ventilation after extubation) in 33 patients. Sixteen patients were weaned using conventional pressure support methods; 17 were extubated intermittently and placed on BiPAP or CPAP. The use of noninvasive ventilation allowed earlier extubation and decreased duration of daily ventilatory support without increasing the risk of weaning failure. In patients who had COPD, use of noninvasive ventilation improved gas exchange abnormalities and decreased the need for reintubation.

Nava and colleagues [45] compared weaning use of NPPV with continued noninvasive ventilation in 50 patients who were intubated and ventilated either from the onset or following the trial of noninvasive ventilation. After 48 hours, patients on noninvasive ventilation were subjected to a 2-hour T-piece trial. Failures were randomized to NPPV or continuous mechanical ventilation. Similar weaning studies were employed in the two groups. A clear advantage was seen for NPPV for weaning, duration of need for assisted ventilation, ICU stay, survival, and reduced incidence of ventilator-associated pneumonia.

Nava and colleagues [46] also looked at a decreased rate of extubation and decreased rate of reintubations with the use of NPPV in postextubation high-risk patients. In this study, 97 patients who were intubated for greater than 48 hours were considered high-risk as indicated by an elevated $PCO_2$, CHF, ineffective cough or excessive secretions, or one failure of wean trial along with increased airway obstruction. NPPV was used greater than 8 hours a day in the first 48 hours after extubation. NPPV lowered the reintubation rate by 4 out of 48 patients versus 12 out of 49 in controlled route. Reintubation was associated with a higher mortality, and noninvasive ventilation lowered this mortality by 10%.

Reintubation is common, reported as high as 10% to 24% in some studies [47]. Reports about the use of NPPV after extubation, however, have

been noted. A long-term study by Quinnell and colleagues [48] showed that NPPV can be used in patients even with prolonged mechanical ventilation. Assessment of readiness for weaning from mechanical ventilation is based upon pulse oximetry, nonrespiratory measures, and other clinical parameters. No one set of parameters can predict weaning success. In patients with a respiratory rate lower than 30 breaths per minute, heart rates less than 100, and saturation levels greater to or equal to 90%, weaning should be considered. NPPV for postoperative respiratory failure, acute pulmonary edema, or CHF can result in rapid respiratory improvement.

*Monitoring*

Monitoring patients on NPPV should include clinical assessment, combined with pulse oximetry and arterial blood gases. Monitoring may vary depending on the location in which the patient receives treatment. ICU or step-down unit patients are likely to be monitored according to routine unit standards. Clinical evaluation, including physiologic monitoring, is not a substitute for clinical assessment and patient observation. Clinical assessment should monitor measurement of chest wall, coordination of respiratory efforts, accessory muscle use, heart rate, respiratory rate, vital signs, and mental state. The physician and therapist should observe the effect of treatment on all parameters. Lack of improvement indicates that alveolar ventilation is not increasing, and intubation and airway protection should be considered. Factors such as deterioration in the patient's condition, failure to improve, arterial blood gas parameters, and development of new symptoms such as pneumothorax, sputum retention, and nasal bridge erosions should be considered. Alterations to noninvasive ventilation are made with intolerance to the BiPAP machine, deterioration of consciousness and mental status, and if the patient and family wishes to withdraw treatment if used as a comfort measure. The duration of the NPPV requirement is variable.

## Sleep apnea

Obstructive sleep apnea syndrome (OSA) is characterized commonly by instability of the upper airway during sleep, reduction or elimination of airflow, daytime hypersomnolence, oxygen desaturation, and sleep disruption. The prevalence of obstructive sleep apnea has been estimated to be 24% in men and 9% in women [49]. OSA is a risk factor for cardiovascular and cerebrovascular disorders, including hypertension, CHF, myocardial infarction, and stroke [50–52].

OSA also is associated with the impairment of cognitive function and alertness, and it could contribute to motor vehicle accidents and traffic fatalities [53]. Diagnosis and effective treatment of these patients have important individual and public health benefits [54]. Although CPAP has been used to

treat patients with OSA for several decades, the understanding regarding the mechanism of OSA continues to evolve. Positive pressure may provide a mechanical stent of the upper airway. This theory, first suggested by Sullivan and colleagues [55], followed and observed that at given esophageal pressure, inspiratory flow was greater during CPAP administration despite the presence of decreased genioglossal muscle activity compared with baseline [55]. Some investigators have suggested that increasing lung volumes during positive airway pressure administration mediates upper airway stabilizing treatment. This concept is based on data indicating that patients who have OSA have greater lung dependency in the pharyngeal cross-sectional area than individuals without sleep apnea [56]. In other words, pharyngeal cross-sectional area, measured during wakefulness by acoustic reflection, decreases more in patients who have sleep apnea than normal individuals. Two mechanical theories have been proposed to explain this modulation. One theory suggests that CPAP-associated augmentation of lung volume elicits a reflex, which increases upper airway dilator muscle tone. Another theory proposes that forces associated with increased lung volumes are transmitted to the upper airway by means of the trachea. The resulting stretch stiffens and stabilizes the upper airway. Regardless of the proposed mechanism through which changes in lung volume may modulate upper airway stability, evidence regarding the operational significance or the pathway is contradictory.

Optimizing patient acceptance and adherence to noninvasive ventilation treatment is challenging. Research teams have examined which patients who have OSA will adhere to CPAP and will reap physiological or quality-of-life benefits from treatment. All symptomatic patients with OSA, defined by an AHI greater than 5, should receive treatment [57]. The American Academy of Sleep Medicine Guidelines for CPAP recommend use in patients who have an AHI greater than 20 and for symptomatic patients who have an AHI or respiratory arousal index of greater than 10 [49].

OSA is a life-threatening condition; nasal continuous airway pressure is the treatment of choice. When used with the appropriate pressures, nasal CPAP eliminates episodes of apneas and hypopneas caused by upper airway obstruction. The patient therefore enjoys a more undisturbed state and in turn, less daytime hyper somnolence.

The optimal level of CPAP should be determined in a sleep laboratory. Usually patients attempt to sleep with the CPAP unit set low (a pressure 5 to 7 cm of water pressure) at home for few days to acclimate for the sleep laboratory. With a nose mask, the pressure sensation makes sleep a novel experience, and it is important to explain NPPV therapy in detail. Sufficient pressures may be used to prevent apnea in all sleep stages, preferably in supine and lateral positions. The minimal pressure that reduces apneic and hypopneic episodes to acceptable levels is appropriate. In addition, this pressure should be titrated to eliminate oxygen desaturations, snoring, and arousals. Because higher pressures can be uncomfortable for sleep, the

minimal pressure that reasonably eliminates most respiratory disturbances is recommended. In general, patients need higher pressures when supine and during rapid eye movement (REM) sleep. In addition, alcohol intake can depress the upper airway muscle tone. Therefore, a pressure that is adequate in a patient may not be therapeutic when the patient is intoxicated. Most patients need pressures between 7 and 15 cm of water pressure. Patients should use the same model machine at home as used in the laboratory for elimination of extraneous variables.

## Side effects

Side effects directly affecting the patient's adherence to treatment are known. Regardless of the nature of the relationship between side effects and adherence, minimization of any adverse impacts associated with NPPV is recommended. In general, these can be categorized as those related to nasopharyngeal symptoms, those related to interface or nasal route of delivery, and those related to the magnitude of pressure. The most prevalent nasopharyngeal symptoms include increased congestion or rhinorrhea, and these effects are related to inflammatory mediators and reduced humidity of inspired gas. Humidification of delivered gas may improve this symptom. Clinicians also may prescribe topical nasal steroids or ipratropium nasal spray to treat nasal complaints associated with noninvasive therapy. Adverse consequences of CPAP treatment also are related to poorly fitting mask, including skin breakdown and air leaks. Air leaks at the skin–mask interface or through the mouth when using nasal interface may preclude achievement of prescribed pressure and lead to inadequate treatment. Air leaks directed toward the eyes are associated with conjunctivitis. Local skin reactions to the interface are also very common. Additionally, air leaks may disrupt sleep. In general, interface-related problems can be resolved with careful and methodical assessment of all interface options. Finally, pressure applied to the upper airway and lungs can result in adverse consequences. Patients may report chest and ear discomfort, as well as exhalation discomfort associated high pressures. There are no known reports of barotraumas caused by NPPV. Regardless, clinicians should remain aware of the potential risk of noninvasive ventilation for the treatment of sleep apnea.

## Long-term benefits

In addition to eliminating snoring, apnea, and insomnolence, long-term CPAP has numerous other benefits. Mood, psychological function, and intellectual function improves [58]. Testosterone and somatomedin levels normalize. Sexual function has improved [55]. Right-sided heart failure, hypertension, and left ventricular dysfunction have improved in response to therapy with CPAP [27,59]. Long-term follow-up has demonstrated no

deleterious effects on lung function. Although CPAP greatly reduces severity of OSA, it does not lead to permanent cure. Sleep apnea, however, declines, and respiratory function improves over the first 3 to 12 months then stabilized [60]. Swelling, erythema, and edema caused by mechanical effects of snoring revolve during treatment, resulting in improved upper airway dimension. In addition to improving sleep architecture, CPAP is used to improve neurological function of the submental, postural, and upper airway muscles. Improvement in respiratory drive may occur. Finally, CPAP therapy may result in weight loss. Many patients find it easier to lose weight while undergoing CPAP because of less fatigue and increased activity during the day. In conclusion, NPPV is a safe treatment for sleep apnea and other sleep-related breathing disorders. Properly instituted CPAP is very effective in preventing significant complications, even in complex patients.

Treatment for OSA is cardiac protective. OSA is a major risk factor for cardiac arrhythmias, and cardiologists should consider the diagnosis and treatment of sleep disorders. There is also strong evidence that oxygen desaturation and OSA correlate with cardiac disturbance such as atrial fibrillation, bradyarrhythmias, and ventricular disturbances [26,61,62]. In a study that included 300 subjects referred to a sleep laboratory for snoring, OSA was diagnosed in 83% of subjects. There were more arrhythmias in the patients who had OSA than in those without sleep apnea (18% versus 11%); however, the difference was not significant. The patients who exhibited arrhythmias during sleep were older (58 versus 52 years of age) and had more profound oxygen desaturations (23% versus 15% of total sleep time spent with oxygenation less than 90%). Although no significant relationship was found between tachyarrhythmias and hypoxemia, patients who had bradyarrhythmias had significantly more hypoxemia compared with nonarrhythmic patients, with an apneic–hypopneic index of 54 versus 31 and an oxygen saturation nadir of 69% versus 77%. A study of a community-based general population using stricter definition of OSA found that people with sleep-disordered breathing have between two and four times the odds of having complex cardiac arrhythmias compared with those without sleep apnea [63]. The results showed that sleep-disordered breathing was associated with four times the odds of atrial fibrillation, three times the odds of nonsustained ventricular tachycardia, and twice the odds of complex ventricular ectopy after adjustment for age, sex, body mass index, and coronary heart disease [63].

Another published study found that obstructive sleep apneic patients had double the risk of stroke or death, even after adjustment for age, sex, race, smoking status, alcohol consumption, body mass index, diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension [64].

Although treatment of OSA with continuous positive airway pressure is established for the relief of sleep disturbances and improvement in quality of life, physicians also should recognize the value of CPAP for preventing cardiac arrhythmias. The mechanism of sleep disorder also affects cardiac

function. Long-term, these subjects may develop heart failure. Benefits of CPAP account not only for prevention of sleep-related heart arrhythmia, but also for correction of these disturbances.

## Heart failure

Heart failure is a major risk factor for sleep-related breathing disorders, which may affect cardiovascular function adversely [23]. Many trials have examined the effect of treating sleep apnea in patients who have heart failure, and considerable evidence supports the hypothesis that CPAP will improve outcomes [19,65–67]. Unfortunately, in the clinical management of heart failure, sleep-related breathing disorders remain underdiagnosed owing to unfamiliarity with sleep apnea on the part of primary care physicians, internists, and cardiologists.

The cardiovascular system goes through many changes during sleep [68]. Sleep proceeds through stages, which are monitored during polysomnography or sleep studies through electroencephalography, chin electromyography, and the tracking of eye movements. The nonrapid eye movement form of sleep called non-REM (NREM) consists of four stages. After stage 4, people cycle backward through other stages. Approximately 90 minutes after falling asleep, REM sleep begins. After the REM cycle, NREM sleep stages begin again. People have four to five REM cycles per night. Episodes of REM sleep increase in duration as the night progresses, with most REM sleep occurring in the last cycle before rising in the morning. REM sleep is characterized by dreaming and is noted to increase cerebral oxygen consumption and blood flow along with skeletal muscle atonia. In the cardiovascular system, the main difference between wakefulness, non-REM sleep, and REM sleep is the level of autonomic nervous system activity, which has a profound effect on cardiovascular function. In non-REM sleep, the activity of the sympathetic nervous system progressively and predictably decreases, while that of the parasympathetic nervous system increases. These changes are reflected in reductions in heart rate, cardiac output, and systemic blood pressure. In contrast, during REM sleep, sympathetic activity increases, as does blood pressure and the heart rate [69]. Because non-REM sleep accounts for 80% of total sleep time and REM sleep for about 20% of the total sleep time, most of the time spent in normal sleep is peaceful for the cardiac system.

Systolic heart failure is progressive, and there are several reasons why sleep-related breathing disorders, which are common in patients who have heart failure, can contribute to its progression. OSA and central sleep apnea and hypopnea have three major sequelae affecting the cardiovascular system. The first is arterial blood gas abnormalities, such as hypoxemia and hypercapnia, which are noted during this phase through sleep. Hypoxemia and hypercapnia result in increased sympathetic activity and pulmonary arterial vasoconstriction. Hypoxemia also may decrease myocardial oxygen

delivery. The second sequela is reoxygenation, which results in increased expression of redox-sensitive genes, encoding inflammatory mediators, such as endothelin. These adverse effects of altered blood chemistry may be more harmful in patients who have compromised coronary systems and contractility disorders. Additionally, arousals from sleep are associated with increased sympathetic nervous system activity and decreased parasympathetic activity [70].

The problem associated with OSA is the large negative swings in intrathoracic pressure that occur during apnea and the hypercapnic episodes of central sleep. They are reflected in variability in cardiac pressures, which increase transmural left ventricular pressure and wall tension. This increase in left ventricular afterload is deleterious in patients who have left ventricular systolic dysfunction. Additionally, increased negative pulmonary interstitial pressure promotes pulmonary edema. In patients who have heart failure and increased left ventricular end-diastolic pressure, transpulmonary capillary pressures are augmented by the increased capillary hydrostatic pressure.

The prevalence of sleep-related disorders has been studied in patients who have heart failure due to various causes [71]. At least 45% of patients with systolic heart failure have an AHI greater than 10 per hour, and at least 40% have an index greater than 15 per hour, which is considered a borderline between mild and moderate sleep apnea syndrome. A prospective study on this topic, which included polysomnography in 81 ambulatory men with stable, treated heart failure [70], revealed 41 patients (51%) with moderate-to-severe sleep apnea syndrome (defined as an AHI of 15 per hour or greater). Also in this group, there was an average respiratory disturbance index of 44 plus or minus 19 disturbances per hour sleep. Occurrence of central sleep apnea was related inversely to the ejection fraction but was not predicted by New York Heart Association heart failure classification. Approximately 40% of the patients had central sleep apnea, and 11% had OSA.

Sin and colleagues retrospectively studied polysomnographic findings from 450 men and women who had heart failure [72]. Of these, 61% had an AHI of at least 15 per hour, and prevalence of severe OSA was 32%. These prevalence rates were higher than those reported by Javaheri and colleagues.

Diastolic heart failure is also associated with sleep apnea [73,74]. In a small study by Chan and colleagues [73], 50% of patients with isolated diastolic heart failure had an AHI of at least 10 per hour. Large-scale studies, however, remain pending.

Treatment of sleep apnea in heart failure depends on whether the apnea is predominantly obstructive or central [67]. Treatment of OSA in patients who have heart failure is similar to treatment in people without heart failure. The two main differences are weight loss and nasal positive airway pressure device. Treatment of central sleep apnea in patients who have systolic heart failure, however, is somewhat different from that of obstructive sleep apneic patients. Cardiopulmonary function should be improved before polysomnography,

given limited resources and the cost of polysomnography. Solin and colleagues [59] showed that aggressive treatment of heart failure, according to evidence based guidelines, may improve or even eliminate periodic breathing. Several mechanisms may be involved, including decreased pulmonary capillary wedge pressure, normalization of $PaCO_2$, increasing stroke volume, improving arterial circulation time, and normalization of functional residual capacity. Controlled studies regarding the long-term effects of CPAP for patients who had heart failure and sleep apnea showed a reduction in the AHI and arousal index and an increase in left ventricular ejection fraction [59,72,75]. Naughton and colleagues [21] also reported CPAP decreases sympathetic activity, as noted by a reduction in the measured norepinephrine levels and urinary norepinephrine excretion. Both open and double-blinded studies have shown theophylline to effectively treat central sleep apnea in heart failure [76,77]. In a double-blind, randomized, placebo-controlled, crossover study, in which 15 patients who had stable systolic heart failure were treated, theophylline twice daily by mouth at therapeutic plasma concentrations on average of 11 μg/mL, decreased the AHI by about 50% and improved arterial oxygen–hemoglobin saturations. Theophylline significantly decreased central apneas but had no effect on OSA.

The mechanism of action of theophylline in improving central apnea remains unclear [76]. At therapeutic serum concentrations, theophylline increases ventilation. This is probably because of competitive inhibition of adenosine, which is a respiratory depressant. An increase in ventilation by theophylline could decrease the likelihood of occurrence of central apnea during sleep. Biatrial pacing is also an interesting phenomenon that has improved patients with systolic heart failure and minimum OSA [78,79].

## Limitations

Patients most likely to benefit from noninvasive ventilation are those with acute and chronic respiratory failure. NPPV, however, should not be used in patients who have hemodynamic instability, deteriorating mental status, increasing respiratory drive indicating respiratory failure, or increasing respiratory acidosis ($pH < 7.1$). When NPPV is applied, the patients must be monitored and attention given to their comfort, level of dyspnea, respiratory rate, and oxygen saturation. Patients must be watched for signs of ventilator asynchrony [80], nasal mask intolerance, serious air leaks, gastric distention, ocular drying, and facial skin breakdown, especially at the nasal bridge. Gastric distention is uncommon with pressure-support levels lower than 20 cm $H_2O$, but this has been described at other pressure support levels. Eye irritation and conjunctivitis have been reported in 16% of patients [81]. Skin–facial necrosis has been reported in 2% [32] to 18% [82] of patients. The development of intrinsic PEEP is worrisome when using NPPV. Typically, this is observed in patients who have higher respiratory rates at a higher trigger level. When a leak-tolerant noninvasive ventilation

system is used, application of an airtight interface is unnecessary. The device can be loosened for comfort. Mask selection for fit without excessive skin pressure is important and improves compliance, especially for long-term use of these devices. Home care companies that are reliable and knowledgeable may help patients with this problem. Office follow-up for use of NPPV machines and for mask–face interface is important to maintain stability and compliance long-term.

## End-of-life care

In the past 20 years, the use of noninvasive ventilation has emerged and gained widespread popularity for treating acute and chronic pulmonary problems. End-of-life care also has become more and more prominent in the last decade [83]. For the terminally ill patient, dyspnea is one of the most distressing and common symptoms. The most widely used treatment for this has been narcotics and anxiolytic medications. These medications are effective in relieving dyspnea, but they also have adverse effects. Noninvasive ventilation presents as an alternative measure to treat dyspnea; it can be used as both treatment and symptomatically. Dyspnea at the end of life is a very common and upsetting symptom for the patient and family. Very few data are available regarding the use of noninvasive ventilation. Hill [84] evaluated the efficacy of nocturnal noninvasive ventilation in symptom relief of patients with terminal illness. Devices were used for 1 week and routinely at night for sleep disorder breathing. These patients noted improvement in fatigue. The patients who had terminally ill cancer noticed improvement in fatigue and reported fewer headaches, less sleepiness, and improved energy.

## Postoperative patients

Benefits of NPPV include decreased use of sedatives and endotracheal tubes, fewer nosocomial pneumonias, and improved patient communication and neurofunctional status. Tobias [85], in examining the etiology of postoperative respiratory failure, documented direct effects from thoracic or upper abdominal surgeries and respiratory depression from anesthetic drugs. Patients' comorbidities and coexisting pulmonary disease were other reasons for postoperative respiratory failure. A decrease in compliance and ineffective cough led to increasing distress. Respiratory support to increase function residual capacity, improve ventilation perfusion mismatching, decrease resistance, and decrease atelectasis have been shown to be beneficial and prudent in postoperative respiratory patients.

## Mask interface

Widespread application of NPPV with continuous nasal airway pressure has been used in treatment of disorders. To optimize the fit and comfort, the

type of mask (nasal or full face mask) that is used depends on the patient's facial features. Masks are secured by an elastic head harness. A mask that fits properly is crucial in minimizing air leaks and maximizing noninvasive ventilation efficiency. Recommendations for evaluating different sizes and types of masks at the bedside are important to select the best fit for each patient. When the nasal mask is used, the chinstrap decreases air leakage from around the mouth. Larger leaks from around the mouth are irritating to the patient and trigger insensitivity and prolonged expiratory time, ultimately resulting in patient–ventilator dyssynchrony. Moreover, an ill-fitting mask may cause breakdown of facial skin and skin ulcers around the nasal bridge. In patients who require prolonged intermittent mechanical ventilation for ventilatory support, rotating the use of different types of mask may decrease these problems. In patients requiring long-term ventilatory support, such as those who have amyotrophic lateral sclerosis or congenital myopathies, custom-fitted masks that conform to the patient's facial features ensure proper fit and comfort.

## Physiologic effects of noninvasive ventilation

NPPV improves gas exchange of respiratory mechanics and relieves dyspnea in acute and chronic respiratory patients. These improvements in physiological parameters may be seen as early as 30 to 60 minutes after initiating use. Sustained daytime improvement in oxygenation and spontaneous alveolar ventilation may be documented after several weeks of NPPV used 4 to 8 hours per day. In acute respiratory failure, the mechanism of improving oxygenation is unclear but appears to be caused by increased functional residual capacity during CPAP just like PEEP improves the oxygenation during conventional mechanical ventilation. With the decreases in $PaCO_2$ using NPPV caused by increased alveolar ventilation, especially when enough inspiratory pressure is used, NPPV restores respiratory center sensitivity to carbon dioxide, providing overall readjustment and spontaneous ventilation to maintain eucapnia. Horner and Bradley [57] showed an increased ventilatory response to carbon dioxide in patients with COPD after 6 months with NPPV without any significant change in respiratory muscle strength. Another possible explanation for improved gas exchange is that noninvasive ventilation may be ventilation and perfusion mismatching because of collapse of the alveolar lung units. The pathophysiologic mechanism responsible for improved daytime gas exchange following long-term intermittent noninvasive ventilation remains undefined.

## Community-acquired pneumonia

Use of noninvasive ventilation in community-acquired pneumonia is becoming more common. One of the first randomized clinical studies evaluating application of NPPV was in patients who met American Thoracic

Society criteria for severe community-acquired pneumonia. Fifty-six patients were enrolled in this study. NPPV was well-tolerated, safe, and associated with a significant reduction in the respiratory rate and need for endotracheal tube intubation (21% versus 50%). Additionally, it decreased ICU stay by 4 days. Those with COPD had an improvement in 2-monthsurvival, 88% versus 37.5%. This multicenter prospective randomized trial to compare the efficiency of NPPV delivery by face mask with standard medical treatment with oxygen alone outlines significant benefits in early use of NPPV in patients who have severe community-acquired pneumonia. It also was found that the use of NPPV was safe and tolerated and did not compromise secretions or increase nursing care as previously thought. In an uncontrolled study Meduri [86] described 41 patients with severe community-acquired pneumonia, of whom 27 had COPD. With the use of noninvasive ventilation, more than 75% improved oxygenation, and 62% avoided intubation. Only three required intubation, and long-term outcomes were improved in the patients who used noninvasive ventilation at 3 months.

### Adverse events

Adverse effects of noninvasive ventilation include skin breakdown over the nasal bridge, gastric insufflation, and distention. Insufflation of mucus leading to tracheal plugs and/or airway cocoons and aspiration are additional risks. The patient's cooperation is important for the use of noninvasive ventilation.

### Summary

Many patients can avoid trauma or hazards of intubation and mechanical ventilation by using noninvasive ventilation. Recent studies show NPPV has improved treatment in selected patients with acute respiratory failure and lowered rates of endotracheal intubations and airway complications and improved survival.

NPPV can improve dyspnea, sleep, arterial oxygen content, $PaCO_2$, and quality of life in selected patients. NPPV appears to benefit patients who have acute pulmonary edema, CHF, and sleep-disordered breathing. Additionally, it facilitates in the weaning process. An expanded awareness of noninvasive devices and techniques will continue to improve as techniques and technology advance. Noninvasive techniques show great promise and likely will increase therapeutic options in the near future.

Use of NPPV has proliferated during the past decade. Noninvasive ventilation has undergone evolution over the past 10 years and has become important for managing acutely and chronically ill patients. Appropriate use can enhance patient comfort, improve patient outcomes, and increase the efficiency of health care. Over the next decade, continued advances in technology should make NPPV more attractive and acceptable to patients.

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Crit Care Clin 23 (2007) 223–240

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# Closed-Loop Ventilation: An Emerging Standard of Care?

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To the authors' best knowledge, the first report on closed-loop ventilation was published in 1957 [1]. In this 50 year-old paper, the authors described a servomechanism to automatically adjust the end tidal carbon dioxide ($CO_2$) partial pressure ($EtCO_2$) by regulating the negative pressure of an iron lung ventilator. They nicely reported how the system behaved in two poliomyelitis patients, one with high $EtCO_2$, and the other with low $EtCO_2$. Amazingly, the rational they used to design this closed-loop system is probably still valid:

> "It was known that the proper alveolar ventilation could not be assured by standardizing pressure settings on respirators because the physical characteristics of the lungs and thorax differ from patient to patient…As a result, patients in tank respirators are frequently overventilated for long periods of time, making it difficult to 'wean' them…Accordingly, it seemed worth while to develop a continuous and automatic control for mechanical respirators such as the 'iron lung' which would maintain the proper alveolar ventilation for each patient in the face of his particular variations of pulmonary distensibility, airway resistance, dead space or metabolic needs" [1].

As compared with the review published by Brunner [2] in 2001, the present one would like to summarize the recent publications on closed-loop ventilation and find some clues to help make care workers confident in using closed-loop ventilation. More specifically, this article discusses how the graphic user interface may help adopting closed-loop systems in the highly complex ICU environments.

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doi:10.1016/j.ccc.2006.12.011

## Closed-loop ventilation: actual status

*Changing reasons for using closed-loop ventilation*

Early closed-loop ventilation systems were developed to maintain blood gas values at normal levels and thus had clear physiologic goals. The rational was to reach homeostasis faster and with higher precision. There can be other reasons, however, to use closed loop ventilation: improving quality (consistency) and safety of care, and covering resource limitations.

## Physiological background

As mentioned by Saxton and Myers [1] in their seminal study, the possibility to automatically adjust the ventilatory support according to the patient's changes in respiratory mechanics and ventilatory demand is still valuable. A typical and modern example can be found in patients suffering from acute respiratory distress syndrome (ARDS) and receiving mechanical ventilation. In these patients, in order not to further damage the lungs, the actual recommendations are to provide protective ventilation by reducing tidal volume ($V_T$) and inspiratory pressure [3]. Having said that, though, it has been recognized that one $V_T$ may not fit all ARDS patients [4]. In addition, the disease is a dynamic process [5], and the patient may improve over time, which necessitates readjusting the $V_T$ [6]. In such conditions, a closed-loop system that is able to provide automatic readjustment of $V_T$ and/or respiratory rate would be desirable.

## Quality and safety

In the United States, the number of patients who die from medical error alone has been estimated to be between 44,000 and 98,000 patients every year [7], the equivalent to one airplane crash every day of the year. Medical errors are the fifth to eighth most common cause of death in the United States. This means that more people die from medical errors each year than from highway accidents, breast cancer, or AIDS [7]. As a consequence, improving safety and quality become a major concern in medicine especially in high technology and complex environments such as ICU.

For numerous reasons, errors and adverse events are more likely to occur in the ICU than in other settings of patient care. In the ICU, patients frequently have severe, multiple-system illness that presents with greater complexity and requires caregivers to do more testing and make more plans and decisions than are needed in other inpatient or outpatient settings [8]. The use of numerous medications increases the potential for errors with respect to drug dose, interval, and interactions. In general, the more problems encountered in a patient, and the more testing, monitoring, and treatment needed, the greater the risk of overlooking a critical physical finding,

an important laboratory test, or a radiograph abnormality, and the greater the risk of the patient suffering a complication related to treatment or procedure [8]. Several studies have been published to support this statement. For instance, in a direct observational study, Giraud and colleagues [9] found that 124 of 400 consecutive patients admitted to an ICU (31%) had 316 iatrogenic complications (2.5 complications per patient), many of which required life-sustaining treatment, additional medical or surgical therapy, additional testing, and/or increased monitoring. Rubins and Moskowitz [10] reviewed the medical records every 1 or 2 days of 295 consecutive patients admitted to a medical ICU and found that 42 (14%) had one or more complications of care during their treatment. Recent reviews [11,12] reported on the growing complexity in treating ICU patients over the last decades and the detrimental effects of treatments when applied improperly. Mechanical ventilation is indeed a typical example; the ventilator is doubtless a life-saving device but with major detrimental effects when improperly set [11–14] or overused [15]. Closed-loop ventilation has the potential to avoid improper setting of devices.

## Resources limitations

The situation is even more complex when cost-controlling policies and staff shortening become reality. The 2004 American Hospital Association Survey of Hospital Leaders reported a vacancy rate of 8.4% for nurses, with 40% of these hospitals reporting emergency department overcrowding as a consequence [16]. In addition, massive overtime by clinical staff is common. A study from Scott and colleagues [17] found that in 86% of the shifts, ICU nurses worked overtime, on average almost 1 hour longer. Nurse shortage, which was estimated to be 800,000 in 2020 [13], may impact the quality of mechanical ventilation [14]. Thorens and colleagues [14] found that when patient-to-nurse ratio increased, the duration of mechanical ventilation increased, which in turn may increase ICU costs. The mean incremental daily cost of mechanical ventilation has been reported to be $1520.00 per day based on a cohort of 253 diverse United States hospitals [18].

Finally people have a limited ability to incorporate data and information in decision making, and memory can simultaneously retain and optimally use only four to seven data constructs [19]. This limitation contrasts sharply with the clinical reality in which hundreds of variables are encountered by the clinician. The mismatch between human ability and the vast amount of data and information almost certainly contributes to unnecessary variation in clinical practice, clinical error, and poor compliance with guidelines [20].

In such complex environment, protocols, guidelines, expert reports, task forces, and other methods have been developed to help the clinician in the decision process [20], but with limited efficiency [21]. As an example, it

has been shown that in certain conditions, protocols may hasten the weaning from mechanical ventilation [22], while in other conditions, protocols were found to be of limited value [23–25]. Baseline awareness and expertise in weaning and the level of compliance to the protocols may explain such controversial results.

The drivers of quality and safety are clearly severity of disease, complexity of the clinician's work, the clinician's workload, and cost pressures. Automatic setting of ventilators (ie, closed-loop ventilation) holds the potential to positively influence some of those drivers, reduces complexity of device operation, and reduces the clinician's workload while maintaining an optimal care.

The following closed-loop systems are commercially available today: proportional assist ventilation (PAV), neurally adjusted ventilatory assistance (NAVA), the knowledge-based system (KBS), and adaptive support ventilation (ASV). The first three methods (PAV, NAVA, and KBS) are basically advanced versions of pressure support ventilation (PSV) and can thus be considered as modes of ventilation. In contrast, ASV covers the functions of numerous modes (PSV, but also pressure-controlled mode and synchronized intermittent minute ventilation) and thus could be termed as a nonmode.

## Proportional assist ventilation

PAV first was described in 1992 by Younes and colleagues [26,27]. PAV is a pressure-regulated mode of ventilation, in which inspiratory airway pressure ($P_{aw,insp}$) within each breath is titrated by the ventilator in proportion to the patient's inspiratory airflow, which is used as a surrogate of the patient's respiratory muscle effort. The proportionality between flow and $P_{aw,insp}$ is determined by a gain setting, which is adjusted by the clinician to determine the proportion of the total work of breathing that will be done by the ventilator and the patient. In PAV, the clinician sets a gain (percentage of proportionality) based on the patient's respiratory mechanics, resistance ($R_{rs}$) and compliance ($C_{rs}$) of the respiratory system. To use PAV correctly, Rrs and Crs should be evaluated continuously and the percentage of assistance adjusted accordingly. A recent summary [28] of clinical studies using PAV (and most often in comparison with PSV) failed to find any outcome benefits from PAV, although suggesting better patient tolerance and comfort through better patient–ventilator synchrony. A potential complication with PAV is instability, which can occur when the gain factor is above the optimal value according to $R_{rs}$ and $C_{rs}$ (or reversely when the gain factor is not changed as $R_{rs}$ or $C_{rs}$ decreases) and when there is a leak somewhere in the circuit (during noninvasive ventilation for instance). PAV recently has been updated (PAV+) by incorporating sophisticated multiple micro-occlusions at the airways opening to obtain a continuous estimation of $R_{rs}$ and $C_{rs}$ [29,30]. A preliminary clinical investigation [31] suggested better stability

with PAV+. Still, however, the gain factor needs to be correctly adjusted and the circuit should be leak-free.

### Neurally adjusted ventilatory assistance

The NAVA system just recently has been implemented in a commercially available ventilator. A specially designed (multiple electrodes) esophageal catheter needs to be inserted to collect the electromyographic activity of the diaphragm ($EMG_{dia}$), which in turn is amplified on a real-time basis to generate proportional $P_{aw,insp}$ [32]. Sophisticated algorithms to improve the signal-to-noise ratio on the $EMG_{dia}$ have been designed and implemented [33–35]. Preliminary studies in healthy subjects found the system able to match perfectly the patient's timing and generate $P_{aw,insp}$ in proportion to the patient's $EMG_{dia}$ [32]. The expected beneficial effect is a better patient–ventilator synchrony indeed. As for PAV, the gain factor between the $EMG_{dia}$ and $P_{aw,insp}$ generated by the ventilator should be adjusted depending on how much the patient needs to be supported. Very few clinical data are available so far with NAVA (especially in patients who have weak $EMG_{dia}$ signal). The need for inserting an esophageal catheter may be viewed as relatively invasive [36] and may limit its clinical application.

### Knowledge-based weaning system

The KBW is a system in which clinical data from the patient are interpreted in real time to adjust the level of PSV to maintain respiratory rate (RR), $V_T$, and $PetCO_2$ within a predefined range. This range of acceptable values was termed the comfort zone. The level of pressure support is adjusted automatically and eventually reduced to a minimal level at which a trial of spontaneous breathing is analyzed. When successful, a message on the graphic interface suggests possible successful separation from the ventilator. The principle initially was developed using a computer-controlled Hamilton ventilator [37,38] later boarded in a Dräger ventilator [39,40]. The switch, however, from controlled ventilation to the KBW and back to controlled ventilation requires manual intervention. Initial clinical studies found that by using the KBW as compared with manual adjustment of PSV, the time spent by the patient in the comfort zone was much higher [41]. A preliminary randomized controlled study comparing the KBW and PSV during a weaning process found that as compared with the physician, the KBW first was able to predict the patient's readiness to be weaned in 51% of cases, with a failure rate (as defined by reintubation) of 29% [39]. A recent multicenter randomized controlled study including 147 out of 1014 patients compared the KBW and standard weaning procedures [40]. Impressive results were obtained with a total duration of mechanical ventilation reduced by nearly 4 days (from 12 days in the controlled group to

7.5 days using the KBW). Limitations of the KBW have been observed with transient system interruption or voluntarily stop because of worsening of the clinical condition, which required assist-control ventilation, $CO_2$ sensor dysfunction requiring removal from the KBW, or manual adjustment of PSV deemed necessary by the physician.

Based on available evidence, the KBW might be efficient as a weaning tool in medical patients mechanically ventilated for more than 24 hours and not-so-easy to wean [40]. $EtCO_2$ is definitely a must for securing the system, but it may be a technical limitation when the signal is corrupted for any reason.

## Adaptive support ventilation

ASV was introduced in 1994 by Laubscher and colleagues [42,43]. It is based on an idea from a Japanese group [44,45] that proposed to select $V_T$ and respiratory rate based on minimal work of breathing, this idea being later patented [46]. ASV may be viewed of as an electronic ventilator protocol that incorporates the recent and sophisticated measurement tools and algorithms in an attempt to make ventilation safer, easier, and more consistent. ASV is designed to accommodate not only passively ventilated patients, but also patients who are breathing actively. ASV recognizes spontaneous respiratory activity and automatically switches the patient from mandatory pressure-controlled breaths to PSV breaths. As such, ASV combines different modes of ventilation into one nonmode. In contrast to conventional modes, the clinician does not set pressure levels, timing parameters, or $V_T$s. In ASV, the clinician sets the desired minute ventilation, and the algorithm determines the optimal respiratory rate–$V_T$ combination according to the patient's respiratory mechanics [2,47,48]. Any change in respiratory mechanics or patient effort will result in an updated optimal breathing pattern (rate–$V_T$ combination) and ASV will move the patient to the new target continuously. Sophisticated breath-to-breath safety rules maintain ventilation parameters within safety ranges (to minimize intrinsic positive end-expiratory pressure [PEEP], avoid hypoventilation, dead space ventilation, and baro-/volutrauma) if for any reason the patient fails to actively breathe, ASV automatically increases the number of mandatory pressure-controlled breaths needed to maintain the minute volume target. Intrinsic requirements for determination of the optimal breathing pattern are the breath-to-breath measurement of respiratory mechanics, including the expiratory time constant, based on the flow volume loop method [49]. Several studies have been published on ASV [28], the most recent studies will be described in this article only. The first, from Arnal and colleagues [50] was designed to confirm in a cohort of mechanically ventilated patients, the possibility that ASV was able to select automatically a different $V_T$–RR combination based on respiratory mechanics. Two hundred and forty three patients receiving 1327 days of invasive ventilation were prospectively included in the study. Breathing patterns were collected, and categorization

of the clinical conditions as normal lungs, acute lung injury (ALI)/ARDS, chronic obstructive pulmonary disease (COPD), chronic restrictive lung disease, and acute respiratory failure were done daily. The authors found that ASV gave higher $V_T$ and lower RR in COPD conditions as compared with ALI/ARDS conditions (Fig. 1), supporting the possibility with ASV to select specific breath pattern based on respiratory mechanics.

The second recent study is a European multicenter study designed to compare controlled modes (volume- and pressure-controlled) of ventilation set by experts in the field and ASV [51] in more than 80 patients passively mechanically ventilated for various respiratory disorders. The authors found that, overall, ASV was able to achieve the same $PaCO_2$ as the clinician but with lower minute ventilation. The breath pattern used was comparable to the one set by the clinicians yet with slightly higher $V_T$ and lower RR. This study suggests that a closed-loop system such as ASV is able to select a breath pattern similar to the one selected by the experts.

The respective role and place of each closed loop system (PAV, NAVA, KBS, ASV) needs to be investigated further. None of the studies available aimed to compare these different closed-loop systems, because all of them basically address different issues. PAV and NAVA are refinements of PSV to make it more synchrone to the patient's effort. The KBW reduces the complexity of adjusting the level of PSV and is a real advance in term of

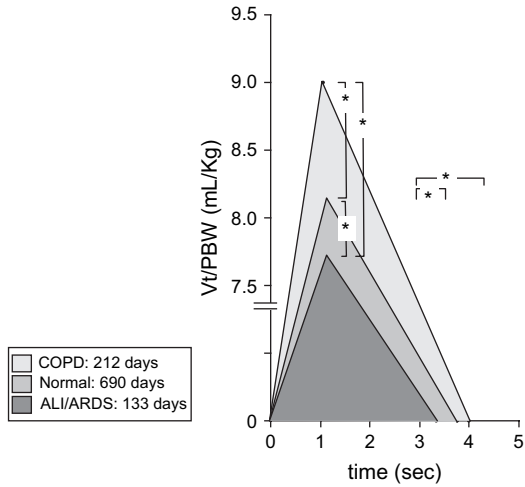


Fig. 1. The spirograms of COPD, ALI/ARDS, and normal patients during 1035 days of ventilation. Each spirogram was drawn using the median values of $V_T$ per predicted body weight *(summit of triangle)*, the median value of $T_I$ *(ascending part of triangle)*, and the median value of $T_E$ *(descending part of triangle)*. *: $P < .05$. (*Data from* Arnal JM, Nafati C, Wysocki M, et al. Utilization of adaptive support ventilation in a polyvalent intensive care unit. Intensive Care Med 2004;30:S84.)

weaning. ASV is the only approach that unifies all modes into one nonmode and has thus greatest potential to be clinically useful (Table 1).

## Closed-loop ventilation: gaining acceptance in the field

It is remarkable that PAV, which first was described in 1992 [26,27], and has been extensively investigated [28] and available in some commercial ventilators, is not used widely. The lack of automatic estimation of $C_{rs}$ and $R_{rs}$ (now possible with PAV+ [31]), and the intrinsic instability of the system may explain the reluctance of using PAV as a routine mode of ventilation, despite possible advantages in term of synchrony and patient's comfort [28,52,53].

ASV was described first in 1994 [42,43]. Several clinical studies have been published showing all the possibilities of using it [48,54–56]. Recent studies reported the use of ASV in clinical practice as a routine mode of ventilation [50], but again ASV likely is underused.

If there is a strong rational for developing closed-loop systems and if there is enough evidence on safety and effectiveness then the questions are: (1) What are the reasons for not changing practice and widely use closed-loop ventilation? (2) What are the barriers, which need to be overcome for making such a change possible?

The following section will explore three nonexclusive reasons that explain such resistance to change. Pathways to overcome such resistance are explored.

## Resistance to change—dealing with resistance to change

"If you want to make enemies, try to change something." Woodrow Wilson

Table 1
Main characteristics of proportional assist ventilation (PAV), neurally adjusted ventilatory assist (NAVA), knowledge based system (KBS), and adaptive support ventilation (ASV)

| | PAV | NAVA | KBS | ASV |
|---|---|---|---|---|
| Principle | Pinsp Proportional to $flow_{insp}$ | Pinsp proportional to $EMG_{dia}$ | Pinsp to maintain RR in comfort zone | Pinsp and RR to minimize the WOB |
| Breaths type | ≃PSV | ≃PSV | PSV | PSV, PCV, P-SIMV |
| Passive patients | NO | NO | NO | YES |
| Active patients | YES | YES | YES | YES |
| Automatic weaning | NO | NO | YES | YES |

*Abbreviations:* $EMG_{dia}$, diaphragmatic electromyographic activity; $Flow_{insp}$, inspiratory flow; PCV, pressure controlled ventilation; P-SIMV, pressure controlled intermittent mandatory ventilation; PSV, pressure support ventilation; RR, respiratory rate; WOB, work of breathing.

Several publications, mostly on how to manage organizational changes, are available [57] a few on how to manage changes in medical practices [58,59]. There are many differences between health care and other high-risk industries [60], and a patient obviously cannot be compared with a product. It also should be mentioned that the behavior of researchers, scientists, or medical doctors in a situation of change may be slightly different from a technician or an engineer working in a factory. There are indeed some similarities, and ICUs may be viewed as organizations and medical practices as processes, mechanical ventilation being one of them, producing cured patients. A recent publication [58] on implementing effective ventilatory practice at the bedside extensively reviewed the reasons for unchanged clinical practices despite clear evidence for change. Box 1 shows the nonspecific reasons to explain the resistance to change. In most cases, however, several reasons coexist with complex and nonlinear interaction, which can explain the high level of resistance [58] and low efficiency in corrective actions. As an example it has been shown that in 86% of the shifts, ICU nurses worked overtime, on average almost an hour [17]. It also has been shown that interns working in the ICU made substantially more serious medical errors when they worked frequent shifts of 24 hours or more than when they work shorter shifts [61]. In such cases, a combination of excessive workload and fears of making mistakes can explain relatively high level of resistance in changing the practices.

In addition to local conditions at the individual level, low tolerance or immunity to change may fit with the concept developed by Lewin (who was credited with the notion of resistance of change). From Lewin, it seems that at the individual level, the status quo represented equilibrium between the barriers to change and the forces favoring change. He believed that some difference in these forces—a weakening of the barriers (which seems easiest) or a strengthening of the driving forces—was required to produce the

**Box 1. Nonspecific reasons for resistance to change**

The purpose is not made clear.
The participants are not involved in the planning.
The appeal is based on personal reasons.
The habit patterns of the work group are ignored.
There is poor communication regarding a change.
There is fear of failure.
Excessive work pressure is involved.
The cost is too high, or the reward for making the change is seen as inadequate.
The present situation seems satisfactory.
There is a lack of respect and trust in the change initiator.

unfreezing that began a change. For the resulting change to become permanent after moving to a new level, refreezing is required to freeze at the higher level. Weakening the barriers (which also can be called certitudes) can be achieved by simple observation. Reporting the practices can be the prelude of questioning and eventually changing the practices. Several examples have been published with before-after study design: the authors reporting their practices before and after implementation of new guidelines or practices. It has been shown, for instance, that the rate of nosocomial infections has been reduced significantly by using noninvasive ventilation more frequently [62].

The question arises, how to make the change easier and users more likely to adopt new clinical practice? The review from Rubenfeld [58] detailed different approaches based on available publications. Passive education by distribution of guidelines or continuing medical education lectures or unsolicited written material seems to be the weakest approach to changing the practice. Economic incentives, audit and feedback, and local opinion leaders may have moderate or variable effects. Multifaceted interventions (combining two or more of feedback, reminders, education, and marketing) have been reported as the most efficient [63].

## Fluctuant standard of care—the closed-loop ventilation solution

A fluctuant standard sounds like an oxymoron, but that is basically the reality. In medicine as opposed to other fields, standards are changing very rapidly and with different time scales: over years depending on knowledge acquisition, over days for a given patient depending on the physiological conditions. Additional and external influences also may affect the standard of care such as financial resources, bed and manpower shortage, and technological innovations. Finally, ICU standards of care are changing very fast and basically faster than the individual capacity to change. That is particularly true in mechanical ventilation. In the 1980s the standard was to not delay endotracheal intubation in patients with acute respiratory failure. Today the standard is to start with an initial trial of noninvasive ventilation, especially in patients who have acute exacerbation of COPD [64–66]. By doing so, the outcome of COPD patients admitted to the ICU for acute exacerbation also has been improved [64,66]. Noninvasive ventilation, however, is a new practice, requiring special equipment, skills, and organizations that need significant resources. Finally, even by using incentive guidelines and protocols, time is required to change the practice with visible beneficial effects for the patient and the organization [67].

The ever fluctuant standards of care also can be exemplified by the body of evidence regarding ventilator-induced lung injury [68] and the need for optimizing the $V_T$ during mechanical ventilation. Twenty years ago the standard of care for the $V_T$ during mechanical ventilation was 10 to 12 mL/kg (even higher) and to normalize the $PaCO_2$ value. Solid evidence is now

available to support a protective ventilation by reducing $V_T$ in patients who have ARDS [3]. Based on the ARDS network study [69], a value of 6 mL/kg has been retained, which in turn has been debated highly [70]. Finally, recent surveys found $V_T$ values highly variable between patients, with a mean value $V_T$ close to 9 mL/kg [71]. Recent randomized controlled studies including large cohort of ARDS patients reported $V_T$ values higher than 6 mL/kg [72–74]. It is also noteworthy to mention that based on worldwide survey of ventilation practices [75], the $V_T$ in ARDS patients (8.5 mL/kg on day 3 of mechanical ventilation) was found to be comparable to that in patients who had COPD (8 mL/kg), pointing out the enormous resistance of clinicians to adapt a $V_T$ strategy according to the underlying disease [69]. Basically for a given patient, physiological conditions are changing over time (eg, as the patient is improving), and using one single $V_T$ all the time is certainly inappropriate. In a preliminary report [6], the changes over time in respiratory mechanics in a cohort of ARDS patients were reported in parallel with the change in the $V_T$ required to maintain a plateau pressure below a safe value. The authors found that in 60% of the patients, the $V_T$ on day 1 was below 8 mL/kg. To keep the same plateau pressure, a $V_T$ of 10 mL/kg was used in 80% of the patients as the lung condition improved on day 7.

For the daily practice and for nonexpert in mechanical ventilation, closed-loop ventilation may help to follow the fluctuant standard of care. As mentioned previously, a recent worldwide survey found that whatever the underlying pulmonary disease, the $V_T$s given to the patients were the same and above the value of 6 mL/kg in patients who had ARDS [75]. In contrast, recent publications found that by using a closed-loop system such as ASV, a specific breath pattern could be obtained according to the underlying pulmonary disease [50,76]. This finding supports the promise of closed-loop ventilation to significantly improve patient outcome by following the fluctuant standard of care.

## The black box effect—graphic user interface as a solution

A very frequent comment regarding closed-loop ventilation systems is the lack of visibility of what the ventilator is actually doing and how the internal decision process is conducted. This invisibility sometimes is called black box effect. As the confidence in a closed loop-system is low (at least at the beginning), the fear of making mistakes relatively high, and the risk important, the user wants to know all the details. At the same time, the level of knowledge required to understand the algorithm often is not reached. In short, the user wants to know but does not have the possibility to understand. Ideally, the level of confidence should be high enough to forget what is inside the box. Who cares about today's sophisticated closed-loop systems boarded in modern automobiles or commercial aircrafts? People trust the technology so much that they do not need full and detailed explanations. The question therefore is how to increase the level of trust and to forget the set of complex

equations within the box. Scientific evidence on safety/efficiency in large cohort of patients [50] certainly can help. Published data alone, however, are hardly sufficient for the reasons explained previously. So what can be done? A possible solution is: picture the situation. Using pertinent graphical representations will improve the user's awareness and provide pertinent information on the patient's position during ventilation. If available, such graphics displays may increase confidence in closed-loop ventilation. Numerous publications reported improved patient safety by using appropriate graphical user interfaces in complex environments such as anesthesiology or ICUs [77].

Traditional displays in mechanical ventilation give generally two to three traces over time (airway pressure, flow, and volume) plus some numerical values. Such displays were not designed fundamentally to help clinicians to detect critical events. Only very recently, some publications emphasized information that can be obtained from airway pressure and flow traces over time such as patient–ventilator synchrony [78,79]. To decipher information, the clinicians need to observe the traces, to detect how much the traces are abnormal, and mentally translate observation into a diagnostic before making a corrective action. Such design results in sequential, piecemeal data gathering, making it difficult and effortful to develop a coherent understanding of the situation [77]. Coherent understanding of a critical situation is a necessary precondition for high levels of performance, and the process of integrating information into a coherent picture is time consuming, increasing the likelihood of patient injury in case of a critical event. The consequence of the high cognitive demand of data integration is also the reduction of available cognitive resources for other tasks, potentially leading to other problems and a cascade of error. Based on preliminary publications [77], it seems that displaying information in a format that minimizes the cognitive resources to obtain a coherent picture may increase the safety of patients during mechanical ventilation and facilitate implementation of closed-loop ventilation.

Data displays of ventilators have grown over the years. Unfortunately, the clutter on the screens has grown with the screen size. No successful attempt was made to integrate data to form a comprehensive display, and information overload comes as no surprise. Integration of disjointed pieces of data into a comprehensive display seems mandatory and long overdue. Fig. 2 shows a recent attempt. Conventionally separate pieces of information and data, such as flow waveforms, lung mechanics, and patient triggering are combined into one moving lung picture. The traditional wave forms of pressure and volume are translated into the movement of the lung picture. The movements are synchronous to the filling and emptying process and proportional to the volume that enters the lung, calibrated to the size of the lung. Thus, immediately, and from afar, the clinician can verify that the patient receives adequate ventilation. Gross hypoventilation and excessive $V_T$s are immediately obvious. Data on lung mechanics also are

integrated into the lung picture on Fig. 2. The stiffness of the lungs is represented by the shape of the lung picture and resistance by the size of the airways. A good-looking lung is displayed if compliance and resistance are normal; an ugly lung is displayed as compliance and/or resistance worsen. The question of course is: what is good, and what is ugly? Cognitive research has shown that beauty is associated with a high degree of symmetry [77], while asymmetry is perceived as ugly. In the example of the lung display, this psychological effect is translated into a smooth and symmetrical lung picture for normal compliance, and progressively jagged and asymmetrical lung pictures as compliance gets worse. Finally, while the patient's respiratory efforts are shown conventionally as a separate trigger indicator, they are shown as diaphragmatic action in Fig. 2 and integrated into in the same picture as the lung. Thus, pertinent information, previously displayed separately, is combined into one animated lung picture.

There is another data display inconsistency on common ventilator displays: the artificial separation of control input and patient variables. It is commonly accepted to use the PEEP and the $FiO_2$ levels as a measure of the patient's severity, although none of the parameters $FiO_2$ and PEEP are measured in the patient. Both are set by the clinician, and yet they bear information on a patient's severity simply because they represent the therapeutic intervention, presumably based on the assessment of degree of sickness. A similar reasoning pertains to the level of inspiratory pressure support. Although in passive patients, the pressure reflects the need to

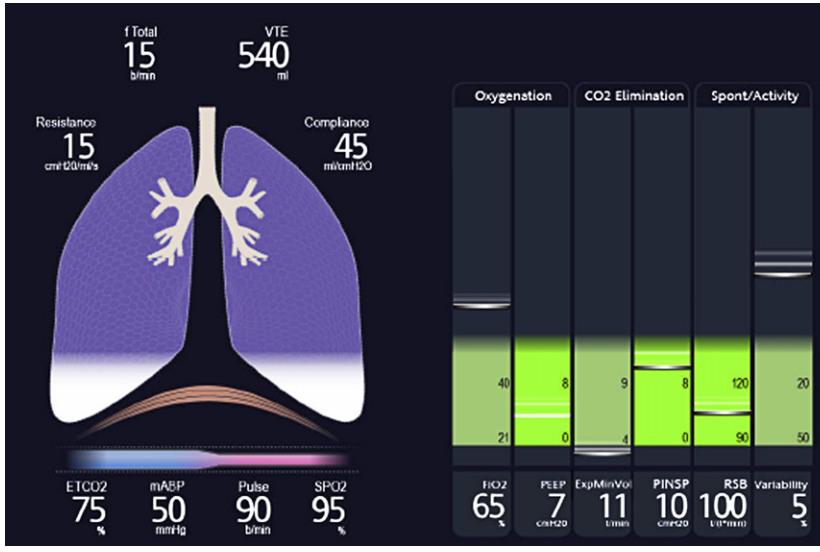


Fig. 2. Graphic user interface incorporating intelligent panels to display information in a simple integrative and dynamic format to reduce the user's cognitive resources to analyze the situation (see the text for explanation).

overcome respiratory impedance, in active patients the pressure is indicative of how much ventilatory support a patient needs. Thus inspiratory pressure, if set correctly, tells an observer if the patient needs a ventilator. Fig. 2 (right hand panel) shows an attempt to combine measured parameters with clinician-set parameters. Specifically, measured patient parameters like the RR/$V_T$ ratio and minute ventilation are plotted together with PEEP, inspiratory pressure, and $FiO_2$. A user-adjustable fuzzy reference line is provided on the graph to tell the clinician if a parameter is within normal limits, thus providing something like an artificial horizon. The idea is to clearly indicate whether the ventilator is needed. For example, if all parameters are inside the light blue field, the ventilator is no longer needed for a particular patient.

The effects of such intelligent graphical user interface as compared with conventional ones needs to be investigated further, but a very recent study [80] reported faster detection and treatment in obstructed endotracheal tubes and intrinsic PEEP problems with a graphical integrative display rather than conventional display. Clinician volunteers reported also significantly lower subjective workloads using the graphical integrative display.

## Summary

The rational for using closed-loop ventilation is becoming stronger. Studies are now available supporting the hypothesis that patient outcome is improved by using closed-loop ventilation. In the highly sophisticated ICU world driven by the triumvirate of cost-efficiency, quality, and safety, closed-loop ventilation will become unavoidable. The challenge is how to make that change effortless, friendly, and as fast as possible. Introducing novel graphical user interfaces and providing data displays that are pertinent, integrative, and dynamic will reduce cognitive resources of the clinician and have the potential to make ventilation safer. They may be the key for adopting closed-loop ventilation in everyday practice.

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Crit Care Clin 23 (2007) 241–250

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# The Open Lung Concept of Mechanical Ventilation: The Role of Recruitment and Stabilization

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Every year, worldwide millions of patients receive ventilator support in the ICU. Mechanical ventilation remains the most common intervention in the ICU and operating room to support patients in the acute and chronic phase of care. A key measure of patient outcome and the quality of care provided by the ICU is ventilator-free days.

The use of ventilatory management protocols for ventilation of acutely ill patients in the ICU has been evolving and improving continually. Strategies have changed from optimizing convenient physiology variables, such as oxygen and carbon dioxide levels, to protecting the lung from injury and decreasing the cytokine modulation of the lung [1]. It has become clear, however, that mechanical ventilation can attenuate lung damage and may even be the primary factor in lung injury. This has led to renewed interest in lung mechanics and ventilation. Much remains to be elucidated, however, and ongoing debate continues.

One of the most important and recent areas of research and clinical interest involves the strategy of lung recruitment. This strategy of lung recruitment or open lung concept (OLC) refers to the dynamic process of opening previously collapsed lung units by increasing transpulmonary pressure. The concept and

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doi:10.1016/j.ccc.2006.12.001 *criticalcare.theclinics.com*

its clinical use are not new. It first was proposed in the early 1990s [2]. Recent experimental evidence only reinforces that this strategy may play an important role in preventing ventilator-induced lung injury [3,4]. This article describes the pathophysiologic basis and clinical role for lung recruitment maneuvers. It reviews the literature and presents the authors' clinical experience of over 15 years in the collaboration between Erasmus MC and the University of Rochester. The authors are hopeful that these lung-protective strategies are presented in a useful format that may be useful to the practicing intensivist, thus bringing laboratory and clinical research to bedside practice.

## The physiology and pathophysiology of mechanical ventilation

### *Surfactant changes*

It is known that the decrease in lung distensibility is a disturbed surfactant system with elevated surface tension. This increase in surface tension leads to an increase in forces acting at the air–liquid interface, resulting finally in the end-expiratory collapse, atelectasis, an increase in the right-to-left shunt, and a decrease in $PaO_2$. This first was reported in the late 1950s, when Mead and Collier [5] reported that dogs that were ventilated displayed a progressive decrease in pulmonary compliance and that these changes were somehow related to the pulmonary surfactant system. Over many years, two primary mechanisms of surfactant failure related to mechanical ventilation have been described.

In the first mechanism, mechanical ventilation enhances surfactant release from the pneumocyte type II into the alveolus [6]. This material subsequently is lost into the small airways as a result of compression of the surfactant film. The changes in alveolar surfactant may affect the permeability of the alveolocapillary barrier to small solutes and proteins. The functional integrity of both the endothelium and epithelium is a prerequisite for maintaining a normal fluid balance at the alveolocapillary membrane; therefore, these changes may cause the increased pulmonary leak observed in respiratory failure and the formation of edema. Furthermore, surfactant composition and function can be impaired by inhibitory factors from protein-rich pulmonary edema fluid or by the degradation in the alveolar space, because of lipases and proteinases [7].

The second mechanism is based on the observation that the alveolar surfactant and the changes that are associated with mechanical ventilation may result in the conversion of surface-active, large surfactant aggregates into nonsurface-active aggregates [7,8]. Surfactant changes caused by mechanical ventilation are reversible as a result of a metabolically active process involving de novo production of surfactant. The barrier function of surfactant may collapse with barrier and mechanical ventilation, and there may be transmigration of bacteria [9–11]. One of the key studies to develop this concept of biotrauma was by Tremblay and colleagues [9]. Using isolated lungs,

they investigated the effect of different ventilatory strategies on lung inflammatory mediator expression and production of tumor necrosis factor-α (TNF α), interleukin-lβ (IL-1β), IL-6, IL-10, platelet activating factor (PAF), and interferon-gamma in the presence and absence of a pre-existing inflammatory stimulus.

The use of high-peak inspiratory lung volumes and the avoidance of positive end-expiratory pressure (PEEP) during mechanical ventilation have a synergetic effort on the release of proinflammatory mediators from the lung tissue into the airways. But using 10 cm $H_2O$ of PEEP at comparable peak inspiratory lung volumes or lowering peak inspiratory lung volume when ventilating with zero PEEP reduced these cytokine levels. Therefore, the lung is being identified as an important causative part of an inflammation-induced systemic disease state that can evolve to multiorgan failure (MOF) rather than merely a pulmonary disease process. Alveolar collapse with improper mechanical ventilation thus can lead to activation of a systemic inflammatory response (SIRS) both locally and systemically, which will play a role in modulating the individual patient's outcome [12].

## Modes of ventilation that will prevent ventilation-induced lung injury

Since its introduction in critical care medicine more that 45 years ago, artificial mechanical ventilation has been a standard lifesaving therapy. It was, however, a topic of much discussion and controversy, because artificial ventilation involves a disturbance of normal physiologic function of the lung. Broad-based investigation into the most basic aspect of mechanical ventilation tidal volume was published in the acute respiratory distress syndrome (ARDS) network trial by the National Institutes of Health (NIH) only 6 years ago [13]. The study illustrated how the standard physiologic tidal volume of 5 to 7 cc/kg had been adopted and the common practice of an unnatural tidal volume of over 10 cc/kg. The authors are hopeful that this natural tidal of 5 to 7 cc/kg has been accepted into practice and is common practice in all ICUs. This simple change in practice will contribute greatly to the outcome of ventilated patients.

## Pressure-controlled ventilation

Pressure-controlled ventilation has been a mainstay in the treatment of severe lung disease since described in the neonate by Colgan and colleagues [14] in 1960 at the University of Rochester.

The keystone to proper mechanical ventilation is a pressure-controlled platform. This mode of ventilation has many forms in modern ventilators and differs in name by manufacturer. It is paramount that the user be facile in the management of their ventilator fleet. Basic physiology serves as the rationale for the use of pressure-controlled ventilation [15,16]. Because it is established that artificial ventilation can both cause direct lung damage

and modulate cytokine release, it is imperative that one protects the lung from ventilator-induced injury. Atelectasis not only affects local gas exchange but also affects nonatelectatic areas [17]. The cycle of continuous expansion and collapse of alveoli during the respiratory cycle creates a biologic stress. This opening and closing affects structural changes by means of barotrauma and volutrauma, as well as surfactant function and cytokine release.

If one evaluates mechanical ventilation in light of the basic Law of Laplace (Fig. 1), one sees that using modes of ventilation that can control both expiratory and inspiratory pressure may be an optimal way to ventilate the lung. The rationale behind the high opening pressure to recruit the lung and the need for lower pressures to keep the alveoli open can be deduced from the pressure–volume curve of an individual alveolus. The Law of Laplace links the pressure applied by the ventilator to alveolar pressure (P), which relates surface tension (T) and radius (R):

$$P = 2\mathrm{TR}$$

In normal lung, alveolar surfactant plays a role in minimizing the surface forces of the air–liquid interface, thus guaranteeing alveolar stability at all alveolar sizes. In mechanically ventilated lungs, there may be varied levels of dysfunction of the surfactant system, because of either direct ventilator effects or the indirect effect of the systemic inflammatory response. The degree of this surfactant dysfunction will determine the amount of pressure needed to expand alveoli from closed to open.

Pressure-controlled ventilation allows the practitioner to control ventilatory pressure throughout the cycle, to generate the pressure necessary to

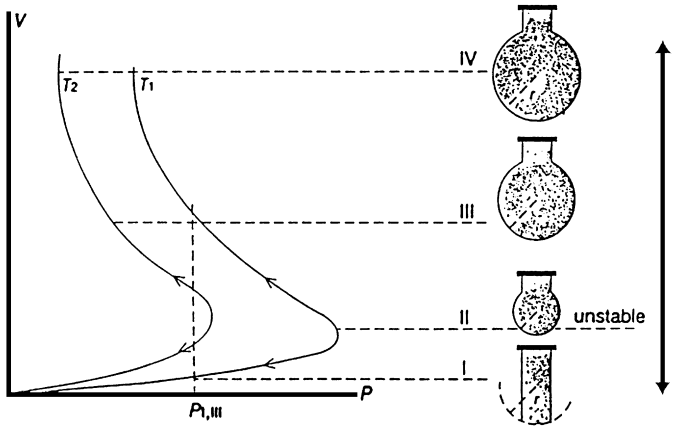


Fig. 1. Physiological behavior of the alveolus. The pressure–volume (P–V) relation on the X–Y axes. The right side shows the status of the broncho alveolar unit. Its radius (r) reflects the P–V relation (I-IV). Surface tension in pathological (T1) and normal conditions (T2) is shown. The *arrows* indicate the direction from closed (*bottom*) to open (*top*) states and vice versa.

expand alveoli. In true alveolar collapse, the pressure needed for alveolar recruitment may reach levels above 70 cm $H_2O$ [3,4,18,19].

Alveolar beds may be opened best using a classic wave pattern of pressure control, the decelerating wave pattern. This pattern is generated by pressure differences between the inspiratory pressure delivered by the ventilator and the pressure present inside the lung at the beginning of the inspiratory cycle, resulting in minimization of flow. As the intrathoracic pressure increases, the difference between the ventilator and the intrathoracic pressure diminishes, as does the resulting inspiratory flow. This decelerating flow pattern is in contrast to the constant flow pattern that is used in most forms of volume-controlled ventilation.

A very important concept of pressure-controlled ventilation is fresh gas distribution in the lung. The decelerating pattern opens alveoli better than does a constant flow pattern. The resistance of airways influences the absolute rate of the respiratory flow; therefore, if the resistance is high, the flow will be reduced, and if the resistance is low, the flow will increase.

When new alveoli are recruited during an inspiratory cycle, the volume necessary to fill these alveoli comes from the ventilator, which is the source of the higher pressure, not from the adjacent lung units, because there is always equal pressure in all areas of the lung. Any reduction in alveoli size immediately results in the flow of fresh gas from the highest pressure source, which is always the ventilator into the alveolar unit. Decelerating wave pattern pressure control ventilation also produces better pulmonary gas exchange through better gas distribution [15,20,21].

Volume control generates intrapulmonary redistribution of gas from other hyperdistended lung units, the so-called Pendelluft effect. Pressure control, in contrast, does not cause redistribution. Pressure-controlled modes always generate an efficient system in which only fresh gas is entering the recruited alveoli.

## The open lung concept

Gattinoni and colleagues [4,22] showed that patients with early ARDS had multiple areas of atelectasis, most commonly in the dependent lung regions, which resulted in a reduced volume of aerated lung. These studies revealed that the percentage of potentially recruitable lung varied widely among patients with acute lung injury and ARDS, from a negligible fraction to more than 50% of total lung weight. It is, therefore, recommended that routine CT scanning be performed in all patients who have acute lung injury, pulmonary contusion, chest trauma, and ARDS. This is very important, especially in managing complex patients who are failing therapy in the ICU.

The treatment for this alveolar collapse in clinical practice is lung recruitment, the OLC first coined by Lachmann [2] in 1992. The clinician should be aware that studies have shown that potentially recruitable lung is at a higher percentage in patients with markedly poorer gas exchange and respiratory

mechanics, a greater severity of lung injury [4]. An association between the percentage of potentially recruitable lung and the severity of lung injury, although unexpected, appears logical. In healthy lungs, the percentage of potentially recruitable lung is close to zero because of normally functioning surfactant, which maintains alveolar units in a noncollapsed state. When ARDS and other pulmonary pathologic states affect the lung, the extent of inflammatory pulmonary edema is linked to the likelihood of gravity-dependent alveolar collapse [23].

Thus, one must use the OLC to generate early lung recruitment and stabilization, which brings the mechanically ventilated patient to near normal physiology. The OLC of Lachmann slowly has found broad-based acceptance in the last few years [3,4,18,24]. The goal of OLC is simple: to have as little or no atelectasis in the mechanically ventilated lung and also to generate as close to optimal gas exchange for each specific patient.

Intrapulmonary shunt ideally should be less than 10%, corresponding to a $PaO_2$ of more than 450 mm Hg, when breathing 100% oxygen at sea level [25].

In the past few years, OLC has led to the development of various techniques to recruit and maintain a lung with minimal atelectasis [3,4,16,18,24]. The goal with all of these techniques is to minimize cyclic forces of alveolar collapse and reopening. Despite the increasing body of literature on recruitment, few studies have compared the various methods in terms of efficacy and adverse effects. A common adverse affect of sustained high pressure may be transient hypertension, but most recruitment techniques usually call for only a few recruitment breaths. The authors have described using only in the range of 10 breaths [16,24], which minimize this.

The choice of recruitment maneuver may depend on the individual patient and the baseline ventilatory mode; a spontaneously breathing patient may not tolerate a sustained high-pressure inflation, and a transient increase in PEEP and peak pressure may be more appropriate in these patients. There is some evidence that the type of lung injury (pulmonary versus extrapulmonary) may affect tolerance to and efficacy of various recruitment modalities [26].

The frequency with which recruitment maneuvers must be applied is also unknown. The authors' ICU uses a recruitment maneuver when the patient arrives to the unit and after any secretion management. Thus, this protocol must be multidisciplinary with buy-in from physicians, nurses, and respiratory therapy specialists. The authors have developed a simple way to understand the concept. Fig. 2 shows the predetermined sequence of therapeutic phases, each with its treatment objective. As shown in this figure, the goal of the initial increase in inspiratory pressure is to recruit collapsed alveoli and to determine the critical opening pressure. Then, the minimum pressure that prevents the lung from collapsing is determined. Finally, after an active reopening maneuver, sufficient pressure is implemented to keep the lung open.

After opening the lung and finding the lowest pressure to keep it open, the resulting pressure amplitude is minimized and the same time pulmonary gases improve after a successful alveolar recruitment. Should a renewed

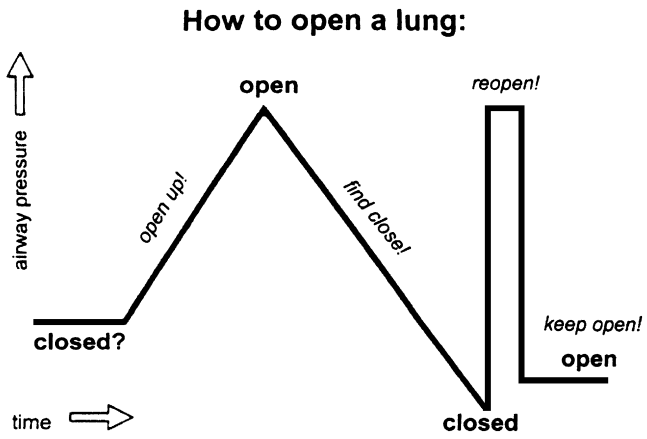


Fig. 2. Representation of the opening procedure for collapsed lungs. Note: the imperatives (!) mark the treatment goal of each specific intervention. The **bold** words mark the achieved state of the lung. At the beginning, the precise amount of collapsed lung tissue is not known.

collapse of alveoli occur, often caused by intrapulmonary suctioning or disconnection, a fall in $PaO_2$ indicates that a reopening maneuver has to performed in the same way as previously described. This is a highly important point, in that secretion management must be balanced with alveolar recruitment.

Another important variable in the management of these patients is when, in the process of the development of ARDS, the patient is received into care. There are reports of higher response rates noted in patients early in the course of their disease (eg, $<72$ hours) rather than later [27]. This probably relates to the change in disease from an exudative to a fibroproliferative process. Therefore, the authors believe that early application of OLC may not only improve ventilatory mechanics but also affect outcome secondary to cytokine modulation, bacterial translocation, and other factors [28,29]. OLC may be applied in at-risk patients during surgery [30,31]. It may be an ideal technique in multitrauma patients with pulmonary injury as described by Schreiter and colleagues [32] and others [33,34] who showed that a recruitment maneuver applied at an early state of severe lung injury can dramatically improve oxygenation recruit lung tissue and maintain the newly recruited lung tissue. The authors, therefore, would include mandatory recruitment procedures as a part of the treatment of suspected lung contusion patients, thus obtaining and maintaining oxygenation values above acute lung injury values, while minimizing further injury by applying low tidal volume ventilation at minimal mean airway pressures. Guidelines are available elsewhere [24].

Recruitment success and maintaining the OLC throughout the ventilatory status should be evaluated through ventilator graphics, CT scanning and blood gas analysis. The management of patients with OLC is fluid, and patients are evaluated and treated throughout their stay in the ICU.

General guidelines are simple to install in any ICU. The peak inspiratory pressure (PIP) is adjusted to the lowest pressure, which keeps the lung open. This lowest pressure is realized when the tidal volume remains stable, and the arterial blood gases are constant. The ideal pressure is generally 15 to 30 cm $H_2O$ to prevent alveolar collapse. The level of PEEP should be titrated through the use of best PEEP protocols to guide its use in conjunction with recruitment protocols [35]. The advent of ventilator graphics has made it much easier for respiratory care therapists to titrate to best PEEP to individual patient needs; this process is one of continuous re-evaluation. Fig. 3 illustrates the pressure volume curve for the calculation of the inflection point.

## Conclusion

The literature regarding the use of recruitment maneuvers is growing. The pathophysiological rationale of cytokine modulation and compelling laboratory and clinical trials support an open lung strategy in all mechanically ventilated patients in the ICU and operating theater. Through real-time titration, the additional benefit of reduced ventilator-induced lung injury can be accrued. It is essential to avoid doing harm by close monitoring and ensuring that the overriding ventilatory strategy is one of pressure limitation. Many questions remain, but the authors hope that the great interest in the OLC over the last 5 years will generate an interest in the development of clinical trials that will answer many of these questions in

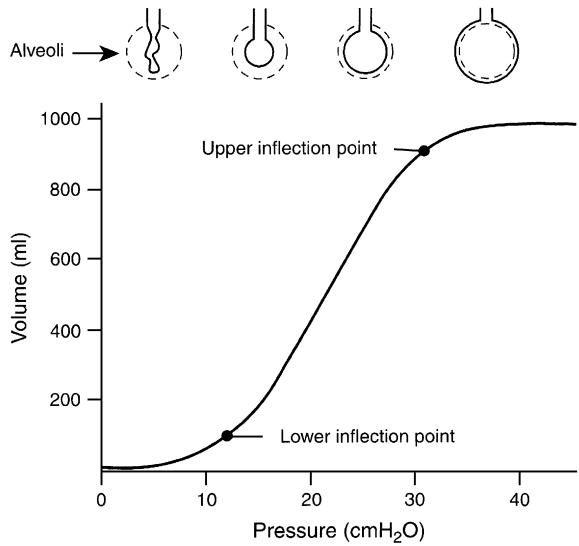


Fig. 3. Best positive end-expiratory pressure calculation of inflection point.

diverse patient populations, and also stimulate readers to develop a lung recruitment protocol in their facilities.

## Summary

The basic treatment principals therefore are:

Open up the whole lung with the required inspiratory pressures.
Keep the lung open with PEEP levels above the closing pressures.
Maintain optimal gas exchange at the smallest possible pressure amplitudes to optimize carbon dioxide removal.

With the strict application of these principals, a prophylactic treatment is available that is aimed at preventing ventilator-associated lung injury and pulmonary complication without compromising optimal ventilation.

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Crit Care Clin 23 (2007) 251–261

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# "The Use of Positive End-Expiratory Pressure in Mechanical Ventilation"

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In patients receiving mechanical ventilation, the term positive end-expiratory pressure (PEEP) refers to the pressure in the airway at the end of passive expiration. In patients who have hypoxemic respiratory failure, one of the methods widely used to improve oxygenation is through the use of PEEP, in an attempt to recruit and stabilize lung units. Improvement of oxygenation in patients with acute respiratory failure using PEEP was described 40 years ago [1]. At the end of the 1970s, it was thought that PEEP not only improved hypoxemia, but also reduced the incidence of acute respiratory distress syndrome (ARDS) when used prophylactically [2,3]. Since then, a considerable amount of research has allowed clinicians to use this therapeutic modality in various ways. There has been significant controversy, however, as to the optimal use of PEEP in critically ill patients receiving mechanical ventilation. This article reviews historical data and modern adaptations of PEEP while attempting to reconcile the controversy over its use.

## History

Positive pressure ventilation has been used for centuries. Paracelsus introduced a mechanical device to support respiration in resuscitation efforts [4]. By inserting the nozzle of a bellows into the nostrils of apneic patients, he

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doi:10.1016/j.ccc.2006.12.012

attempted to inflate their lungs. Two centuries later, this method was refined by John Hunter, who used a double-chambered bellows of his own design to ventilate experimental animals [4,5]. His device induced both positive pressure ventilation and negative pressure exhalation. Continuous positive pressure breathing first was seen as part of the treatment of pulmonary edema and severe pneumonia before World War II [6]. In 1948, Cournand and colleagues [7] found that the use of PEEP with mechanical ventilation was associated with a decrease in cardiac output as compared with ambient end-expiratory pressure. The use of mechanical ventilation in conjunction with PEEP first was accomplished with the Engström mechanical ventilator, introduced in Sweden in mid-1950s [8]. By 1959, Frumin [9] correlated the use of PEEP in a cohort of anesthetized patients, with an increase in lung volumes and arterial oxygenation.

It was not until the1960s, with the contribution of Ashbaugh and colleagues [1] when PEEP formally was introduced into clinical practice. These investigators coined the term adult respiratory distress syndrome (ARDS) in mechanically ventilated patients with hypoxemic respiratory failure, and they proved that the addition of PEEP was capable to reversing life-threatening hypoxemia. The publication of their work became a major advance in respiratory intensive care medicine [10]. Further investigations done in the1970s, showed that the improvement in arterial oxygenation with PEEP could be co-related to an increase in functional residual capacity (FRC) [11]. In the process of figuring out how high to go on the PEEP, it was found that compliance would increase only with lower levels of PEEP [12].

In the 1970s, a type of assisted mechanical ventilatory support, described as pressure painting, characterized by the use of low tidal volumes with a relatively high PEEP and high respiratory frequencies, helped elucidate same of the advantages of PEEP [10]. Falke and colleagues [6] showed that patients who had ARDS had marked decreased lung compliance and lung volumes and that mechanical ventilation with high tidal volumes plus PEEP may lead to overdistention of the lungs.

The introduction of pulmonary imaging with CT and seminal studies by Gattinioni and Presenti [13] in 1987 with the so-called baby lung concept gave a better understanding of the pathophysiology of ARDS and the rationale for the use of PEEP in this clinical scenario.

## What is positive end-expiratory pressure?

Clinicians are concerned about maintaining the adequacy of two important lung volumes:

1. The tidal volume of each breath and the resting lung volume in between breaths
2. The pressure generated during active inspiration either by the ventilator or the patient will determine the tidal volume (mediated, of course,

through compliance). The resting lung volume is determined by the resting transpulmonary pressure [14].

In normal people (with normal lung compliance), the vectorial difference between airway and intrapleural pressures (ΔP) determines the resting lung volume, known more precisely as the functional residual capacity (FRC). The resting lung volume (FRC) therefore is determined by the ΔP and compliance. Because ΔP is positive and present at end-expiration, this article is concerned with PEEP. It should also be clear that PEEP directly determines FRC. This kind of PEEP is also known as extrinsic PEEP.

## Extrinsic positive end-expiratory pressure

Inflating a balloon is difficult at first, and then it suddenly gets easier once some volume is inside. As full inflation is reached, it again may become difficult as the limits of the balloon's compliance are reached. If one lets go, the balloon recoils (elastance) and collapses. Alveoli, in many ways, are similar. If they start fully collapsed, they are difficult to inflate at first. Once there is some volume, it becomes easier; this point of change in compliance is referred to as critical opening pressure (COP) [8].

Unlike balloons, normal alveoli do not lose all of their volume immediately when pressure is released but may maintain some volume (thanks in large measure to surfactant) until distending pressure is critically low and then collapses. The point at which this occurs is the critical closing pressure (CCP). If one could maintain end-expiratory pressure (ie, PEEP) above CCP, then alveoli would not collapse. Their volume would be enhanced, and, in the aggregate, lung volume (FRC) would be enhanced. If low lung compliance results in high CCP, then PEEP must be increased above the CCP to prevent alveolar collapse or partially reverse the collapse in parts of the lung. This is known as lung recruitment. The capacity for prevention or recruitment varies from patient to patient [15]. This is precisely the rationale for PEEP in the management of acute low-compliance lung disease (ie, ARDS). Examples of lung disorders with lung compliance include:

Interstitial lung disease
Idiopathic pulmonary fibrosis
Hypersensitivity pneumonitis
Bronchiolitis obliterans organizing pneumonia
Sarcoidosis
Pulmonary edema

In ARDS, the upper lobes will stay either partially or totally supplied with air. The lung volume is increased or normal. This would suggest that the lung does not collapse on its own weight. On the other hand, low lung volumes are found on the lower lobes, because the heart and abdomen compress the lungs.

This his will provide loss of aeration [16]. This is the reason why patients in the prone position will improve their lung oxygenation, at least temporally [17].

## Intrinsic positive end-expiratory pressure

Most patients who are on assisted mechanical ventilation have their own inspiratory effort triggering the ventilator [18]. A threshold for airway pressure is set to trigger the ventilator. To reach this starting point, the patient must initiate an inspiratory effort. The breaths that do not reach this starting point on the ventilator have greater tidal volumes and shorter expiratory times than do breaths that trigger the ventilator.

Each time a person takes a breath, the airway pressure remains positive during the expiration. An elastic—recoil pressure builds up within the thorax; this is known as intrinsic PEEP or auto-PEEP [19]. In conditions where there is expiratory flow limitation secondary to airway narrowing (ie, chronic obstructive pulmonary disease (COPD), air trapping develops [20]. This impairment in expiration will increase the possibility of hyperinflation, increasing the risk of hypoxemia and barotrauma [21].

In mechanical ventilation modes where high respiratory rates are used, the interval between end expirations is shorter. Using higher tidal volumes, the amount of air inspired exceeds the expiratory capability of the patient, causing more air trapping [22]. Intubation has a major role in air trapping. If the size of the endotracheal tube is incorrect, causing narrowing of the airway, or the tube is kinked, plugged with secretions, or the patient is fighting the ventilator, causing desynchronization, a higher intrinsic PEEP is found. This also is called increased expiratory resistance. Although this phenomenon has been described mainly in patients who have COPD, it also has been seen in other forms of acute respiratory failure [23].

Amazingly, the impact of intrinsic PEEP can be diminished in mechanically ventilated patients when extrinsic PEEP is used [24,25]. Bronchodilators in combination with extrinsic PEEP and optimizing the ventilator settings (eg, tidal volume, rate) decrease the amount of auto-PEEP [26].

## Physiological positive end-expiratory pressure

The benefits of using a small amount PEEP (3 to 5 cm $H_2O$), almost considered physiologic, have been applied to patients who have obstructive airway disease and hyperinflation in an attempt to decrease incomplete exhalation [21].

## Indications for the use of positive end-expiratory pressure

Despite decades of clinical debate, PEEP is indicated for patients who have acute lung injury and ARDS. The use of PEEP will improve pulmonary shunting, helping the respiratory muscles to decrease the work of

breathing [21]. The addition of PEEP also helps to decrease the amount of infiltrated–atelectatic tissues [18]. PEEP also is used to overcome intrinsic PEEP in patients who have COPD, bronchomalacia, or who have other causes of expiratory flow limitation with hyperinflation [25,26].

Other indications include cardiogenic pulmonary edema, when there is diastolic or systolic dysfunction and there is an elevation of the pulmonary capillary pressure, as it will prevent the accumulation of fluid in the alveolar space. The addition of PEEP may also be useful in patients with diffuse pneumonia, requiring mechanical ventilation. In this clinical scenario, there is less likelihood of overdistention, and the distribution of lung recruitment is more balanced (Box 1) [27].

### Effects of positive end-expiratory pressure on surface tension

The pulmonary surfactant is a complex of highly active phospholipids, neutral lipids, and four specific surfactant proteins (A, B, C and D) that

**Box 1. Summary of the effects of positive end-expiratory pressure**

Stabilizes and recruits lung units
Increases functional residual capacity
Raises lung compliance
Increases dead space by overdistending normally compliant alveoli
Preserves and recruits lung units
Reduces shunt fraction by maintaining volume for gas exchange in perfused lung units in between breaths
Improves arterial oxygenation ($PaO_2$)
Reduce risk of $O_2$ toxicity by lowering $FiO_2$ requirements
Increases intrathoracic pressure, which can impede venous return into the chest or specifically restrict cardiac filling
Decreases cardiac output
- Hypotension and organ hypoperfusion may occur, especially in the presence of hypovolemia.

Decreases left ventricular afterload
Decreases ventricular compliance
Increases intraluminal central venous pressure (CVP)
Increases intracranial pressure
PEEP may contribute to barotrauma, because it represents the baseline (end-expiration) for all pressure changes, because it may cause overdistention of compliant lung regions, and because of the nature of the acute lung diseases in which PEEP is most frequently useful

synthesized in alveolar type II pneumocytes and secreted into the alveolar space [28,29]. Surfactant lies as a monolayer at the air–liquid interface. This reduces the lung surface tension and prevents alveolar collapse [28].

Ashbaugh and colleagues [1] were the first to demonstrate that surfactant abnormalities had a major role in the pathophysiology of ARDS. Mechanisms of surfactant dysfunction in ARDS included: altered surfactant composition, metabolism, and inactivation [30]. Pulmonary surfactant dysfunction is characterized by alveolar instability, floating, and collapse [28,31]. Even if hyperinflation can stimulate the surfactant production, repetitive cycles of "recruitment/derecruitment" will induce surfactant depletion [31]. When lung regions collapse at the end-expiration, the surfactant moves away from the alveolar surface to the bronchioles, and can no longer be reused at the next inflation. This progressive surfactant depletion can be limited by PEEP, and this will prevent lung collapse [32]. Current therapies with exogenous surfactant are used to restore the normal composition of the surfactant system and to overcome ongoing inactivation of endogenous surfactant [33].

Animal models have proved that therapy with continuous dosing of exogenous surfactant and PEEP will increase the oxygenation in patients who have endotoxin-induced lung injury [30]. The addition of surfactant only has been proven beneficial in animal models and in neonatal respiratory distress [30].

## Positive end-expiratory pressure contraindications

As noted previously, the use of PEEP increases intrathoracic pressure, which can decrease venous return into the chest or specifically restrict cardiac filling, both of which may result in reduced cardiac output and hypotension. These hemodynamic changes are worse in hypovolemic patients [34].

When PEEP is added to patients with intracranial abnormalities (ie, intracranial hypertension), it may decrease cerebral perfusion by decreasing mean arterial pressure [35]. Some authors have expressed concerns over harmful reactions in ventilating areas with compensatory hypoxic vasoconstriction causing overdistention in normal aerated areas in patients who had focal pneumonias treated with PEEP [25].

Patients with pulmonary embolism have a decreased venous return to the chest and PEEP may elevate alveolar pressure and compress adjacent nonobstructed blood vessels in the lung, worsening ventilation–perfusion mismatch [36]. Other contraindications for the use of PEEP include the presence of a pneumothorax (without a pleural catheter), bronchopleural fistulas, and recent pulmonary resection surgery.

## Initiation and titration of positive end-expiratory pressure

For most clinicians, an initial setting of PEEP at 5 cm $H_2O$ is acceptable, titrating up or down by 2 or 3 cm $H_2O$. It is recommended that after each

adjustment of PEEP a complete assessment of pulmonary function, pressure–volume relationships, oxygenation, and hemodynamics—is performed [14]. The goal of titration for ideal PEEP will be defined as the level of PEEP that allows the lowest $FiO_2$ while maintaining adequate oxygenation and avoiding adverse effects [8].

## Monitoring positive end-expiratory pressure

This includes monitoring pulmonary function with assessment of gas exchange either by pulse oximetry or arterial blood gases, overseeing plateau pressures and inspiratory:expiratory (I:E) ratios, and looking for changes on lung pressure–volume relationships (Fig. 1).

To monitor the hemodynamic effects of PEEP, it is useful to asses for changes in heart rate, blood pressure, and other parameters of organ perfusion such as urine output. If it is also feasible, monitor changes in cardiac output and $S\hat{V}O_2$. It is important to remember that PEEP alters the interpretation of CVP and pulmonary artery occlusion pressure ($\overline{PAOP}$). By increasing intrathoracic pressure, PEEP increases CVP and $\overline{PAOP}$, even though the preload is decreased [37].

Clinicians should be aware that barotrauma is a potential hazard, and they should look for any manifestation of this undesirable effect. They

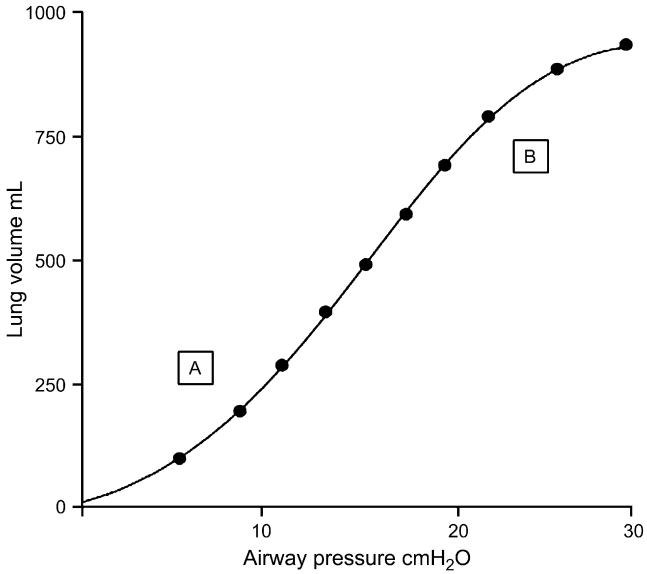


Fig. 1. Pressure and volume points are plotted as a curve. Critical opening pressure (*Point A*) and critical closing pressure (*Point B*) are shown. Airway pressures above critical closing pressure are at higher risk for barotrauma, and pressures below critical opening pressure are associated with low compliance, alveolar collapse, and atelectasis.

should check for pneumothorax, subcutaneous emphysema, pneumomediastinum, interstitial emphysema, pneumoperitoneum, pneumopericardium, gas cysts, and systemic gas embolism [8].

Newer-generation ventilators can provide automated assessment of intrinsic PEEP, which is another variable that should be monitored. It also can be manually determined by placing patients on assist-controlled mode, occluding airway at end-expiration, and observing passive increases in airway pressure. Assessing intrinsic PEEP is also mandatory because of the potential adverse effects. These include increased work of breathing, risk of barotrauma, miscalculation of compliance, and hemodynamic alterations. Some clinical techniques are recommended to minimize intrinsic PEEP (Box 2) [38].

## Outpatient use of positive end-expiratory pressure

In patients who have expiratory flow limitation with hyperinflation (eg, COPD, bronchomalacia), long-term oxygen therapy and the application of PEEP can be useful [39]. The use of home mechanical ventilation has a positive impact in patients who are using it. Furthermore, the use of noninvasive ventilator techniques has proved a significant improvement in oxygenation therapy [40].

## The positive end-expiratory pressure controversy

The question of whether the use of PEEP actually will reduce mortality rates or number of ventilator use days remains an issue after 40 years of debate. The use of low tidal volumes (which is one of the two important lung

**Box 2. Strategies used commonly to minimize intrinsic-positive end-expiratory pressure**

- Aggressive bronchodilation
- Secretion removal
- Increasing size of endotracheal tube
- Adequate pain and fever control

(Secretion removal, Increasing size of endotracheal tube, Adequate pain and fever control) } Decrease airflow obstruction

- Avoid alkalosis
- Modify ventilator settings to minimize I:E ratio
- Minimize inspiratory time and increase expiratory time and inspiratory flow rate
- Reduce tidal volume and respiratory rate
- Reasonable application of extrinsic PEEP will counter intrinsic PEEP and decrease the work of breathing

volumes that should be balanced in mechanical ventilation) rather than traditional tidal volumes has been proved to decrease the mortality rate and decrease the ventilator use days in patients who have acute lung injury and ARDS [41]. PEEP in and of itself, however, never has been proven to do so. Moreover, the use of higher PEEP levels has not been demonstrated to decrease mortality rates and may even have a harmful effect in patients with a low percentage of potentially recruitable lungs [36]. Recruitment and overdistention are increased when PEEP is increased in some patients. Gattinioni and colleagues [42] showed that many patients who have ARDS will not have too much lung recruitment after the PEEP is increased. Interestingly, it has been shown that the percentage of potentially recruitable lung is an important predictor of mortality [38].

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Crit Care Clin 23 (2007) 263–274

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# Weaning from Mechanical Ventilation

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Mechanical ventilation (MV) is a life-supporting modality that is used in a significant proportion of patients in ICUs. Most such patients are extubated quite readily. As many as 20% of mechanically ventilated patients, however, will fail their first attempt at weaning, and more than 40% of the total duration of MV is spent in the weaning process [1,2]. Prolonged MV is associated with a host of complications (eg, infection, gastrointestinal [GI] bleeding, and deep venous thrombosis). On the other hand, premature extubation followed by reintubation is associated with increased morbidity and mortality [3]. Choosing the right time for a successful discontinuation of MV, in the light of available physiologic and laboratory factors, remains a challenge. This article reviews the causes of weaning failure and an approach to liberating patients from MV.

## Pathophysiology of respiratory failure during weaning and extubation failure

Weaning from MV depends on the strength of respiratory muscles, the load applied to those muscles, and the respiratory drive to breathe. Respiratory failure may occur because of any of these. For example, muscular dystrophy (weakness of respiratory muscles), acute bronchospasm (increased respiratory load), or narcotic overdose (reduced central drive) all may lead to respiratory failure. In general, the etiology of unsuccessful weaning is the imbalance between the respiratory muscle pump and the respiratory muscle load. This could happen secondary to inadequate resolution of the initial problem that rendered the patient on MV, a rise of a new problem, a ventilator-associated complication, or a combination of these factors. It

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0749-0704/07/$ - see front matter 
doi:10.1016/j.ccc.2006.12.002 *criticalcare.theclinics.com*

is imperative to correct the key elements listed in Box 1 to optimize the chance of successful weaning.

The relationship between respiratory load and muscle strength may be viewed as a balance. If the load is too heavy, or muscle strength is too weak, muscular contraction cannot be maintained, and muscles acutely fail. This is termed fatigue. The predominate feature of the pathophysiology of weaning failure is high levels of load relative to the strength of the respiratory muscles. As compared with those who succeed with a weaning trial, for those who fail, load increases. Almost always, the drive to breathe is high in such cases.

Many investigators have combined the failure to liberate from MV and extubation failure into one entity. In contrast, recent work indicates that these are distinct processes with discrete pathophysiological causes and outcomes [3].

An extubation failure may occur secondary to upper airway obstruction or respiratory secretions that could not be managed by the patient. These factors do not manifest themselves until the removal of the translaryngeal tube. Significant trauma to the airway from translaryngeal intubation is more common in females and increases with increased duration of intubation.

Another potential reason for extubation failure is the loss of positive pressure in the thorax after extubation in pressure support ventilation (PSV)-weaned patients. The transition from intrathoracic positive-pressure ventilation to negative-pressure ventilation occurs after the removal of the endotracheal tube. This may cause left heart failure, because the positive-pressure ventilation acts to reduce afterload on the left ventricle. This phenomenon is not seen by using a T-piece trial for weaning.

It is important to remember that the extubation failure that requires reintubation is associated with an increase in the duration of MV, ICU and hospital length of stay [4]. There is also a significant increase in hospital

**Box 1. Key elements to optimize weaning**

Determine cause of ventilatory dependency
Rectify correctible problems
- Pulmonary gas exchange
- Fluid balance
- Mental status
- Acid-base status
- Electrolyte disturbance

Consider psychological factors
Optimize posture
Provide ambulation

mortality, especially in the case of delayed reintubation. This is why there has been so much effort directed at improving the prediction of extubation outcome to prevention extubation failure.

## Timing for the initiation of weaning

Recognizing and treating the processes that caused the patient to go on the ventilator is the first goal in liberating him or her from MV. The complete resolution of the inciting event that led to respiratory failure does not need to be accomplished to start the process of weaning. Partial resolution of the cause of respiratory failure may be enough to be able to discontinue MV.

There are many reasons to attempt to get patients off MV as soon as possible. Common side effects of MV are hemodynamic disturbances, need for sedation, tracheal damage, ventilator-associated pneumonia (VAP), increased incidence of GI stress ulcers/bleeding, skin breakdown and decubiti, muscle wasting and weakness, and barotrauma. It is imperative to attempt to decrease the occurrence of these iatrogenic problems (eg, reducing plateau airway pressure, reducing tidal volumes, and semirecumbent position 30 to 45 degrees upright) and reduce the time of exposure by reducing the length of MV. Not only have studies shown that about 40% of the time during MV is devoted to weaning, but they also have shown that the most common approach to weaning is a progressive reduction of ventilatory support [5,6]. Others have noted that most patients do not need progressive withdrawal of MV [7]. Evidenced-based practice now supports early attempts at weaning in a protocol-driven fashion [2,8–10]. Successful extubation in the shortest possible time is associated with improved patient outcomes and minimized cost associated with MV.

About 70% to 80% of patients who require MV for respiratory failure will be extubated after a trial of spontaneous breathing trial once the precipitating process has been corrected. About 20% to 30% of patients who require intubation, however, do not tolerate initial attempts to breathe without the help of the ventilator [11,12]. This is especially true in the patients who required MV for more than 24 hours. As stated, failure to wean is caused by the imbalance between the capacity of the respiratory system and the load placed on the system.

The following problems found in mechanically ventilated patients will affect either the capacity of or the demand on the respiratory system. These include: hemodynamic instability, acid–base disorders, electrolyte disturbances, volume overload, altered mental status, and decreased respiratory muscle function. To improve chances of weaning, all should be addressed and corrected. Box 1 lists the key elements to optimize outcomes in patients weaning from MV. In regards to hemodynamic stability, the patient should have no evidence of myocardial ischemia, new arrhythmia causing

significant decrease in cardiac function, or have need for vasopressors. As far as the acid–base status is concerned, a normal serum pH (7.35 to 7.45) is desired but not essential. Treating acidosis is important, because acidosis increases the minute ventilation required to normalize pH. Of special note, in chronic hypercapnic patients, correcting PCO2 by the ventilator during MV will promote bicarbonaturia through renal compensation to normalize the pH. This likely will produce acute respiratory acidosis at the time of spontaneous breathing trials and lead to failure.

Electrolyte disturbances during weaning have been studied extensively. It has been shown that hypophosphatemia, hypocalcemia, hypomagnesemia, and hypokalemia reduce muscle contractility and affect weaning [13]. These disturbances must be corrected before weaning attempts.

Volume overload frequently occurs during treatment of the systemic inflammatory response syndrome precipitated by severe infection, pancreatitis, major surgery, or other issues. This extra volume will lead to decreased functional residual capacity of the lungs and alveolar collapse. This is associated with ventilation/perfusion mismatch, which requires an increase in the positive end-expiratory pressure (PEEP) to keep the alveoli opened and maintain good oxygenation. The mobilization of such fluid usually happens upon resolving the systemic inflation, and may be augmented at that time by diuretics.

Neurological deficit secondary to brain injury may impose quite a challenge as to the optimal time for weaning and/or extubation. Many clinicians believe that extubation of brain-injured patients who lack a gag reflex, are comatose, or have significant respiratory secretions should be delayed. In a recent study by Coplin and colleagues [14], it was shown that the delay in extubation of brain-injured patients capable of spontaneous breathing secondary to the reasons mentioned carried an increased risk of pneumonia and longer hospital and ICU stays.

In general, altered mental status in the ICU is multifactorial. Causes include pain, anxiety, delirium, and toxic/metabolic processes. All of these should be addressed and/or treated, before the initiation of weaning. It has been shown that oversedation with long-acting sedatives prolongs the days of MV, ICU stay, and subsequently hospital stays [9]. Many institutions have implemented protocols and guidelines to help in the administration of sedatives in the mechanically ventilated patient. Some of these guidelines use a scoring system, daily interruption of sedation, and automatic reduction of dosing [15].

Fatigue of patients undergoing weaning from MV is a major factor in failure to wean. Several studies showed by electromyogram (EMG) diagnosis that diaphragmatic fatigue occurs in the first day in all patients on MV, and those who recovered were extubated successfully [16,17]. The patients who continued to exhibit fatigue needed reintubation. It is not known how much diaphragmatic strength is needed to sustain spontaneous breathing, or how long the resting period should be to recover from diaphragmatic

fatigue. It is possible that 1 day of rest, fully supported by MV, may be enough for diaphragmatic recovery [18].

Adequacy of sleep and sleep deprivation should be considered when agitation and lethargy are hindering the weaning. It is unrealistic, however, to delay weaning until the patient has achieved a normal sleeping pattern. In addition, one should not ignore the psychological factors in achieving successful weaning. If the patient is alert he/she should be informed about the weaning trial with explanation and assurance that may decrease the level of stress. Daily orientation to the day, time, and surroundings, and environmental stimulation by using televisions, books, and radio are widely used now in many ICUs in the country.

Malnutrition causes reduction of muscle mass, endurance, and muscle strength. It also causes decreased immunity, predisposing the patient to further infections. Nutrition repletion in critically ill patients showed improved respiratory forces and facilitated weaning [3,13].

## Weaning criteria and physiologic indices: key elements for successful weaning

The difficulty in integrating all the physiological parameters involved in weaning from MV has fueled a range of research to find the weaning parameters to determine readiness to wean. Conventional criteria for readiness to wean are relatively easy to use, but their sensitivity and specificity are relatively poor. These criteria include tidal volume (VT), minute ventilation (MV), vital capacity (VC), maximum voluntary ventilation (MVV), respiratory frequency, maximal inspiratory pressure as well as integrative indexes.

VC is the greatest volume of gas that a patient is able to exhale in taking a maximum inspiration from residual volume. VT is that volume of gas moved during a normal respiratory cycle. The threshold values for these two parameters predictive of weaning remain controversial but are in the order of 5 to 8 mL/kg for VT and 10 to 15 mL/kg for VC. Measurement of VC is relatively difficult, because it depends on considerable cooperation of the patient. Given the large variability in VC, it is not surprising that some studies have shown that VC often failed to predict weaning outcome with a high degree of accuracy [19,20]. Using a VT cutoff of 4 mL/kg, the positive predictive value was 0.67, and negative predictive value was 0.85 [8].

Maximum voluntary ventilation (MVV) is the volume of air that can be exhaled with maximum effort over 1 minute. Normal values for MVV range from 50 to 200 L/min. In a resting, healthy adult, MV is about 6 L/min. The relationship between resting MV and MVV indicates the proportion of the patient's ventilatory capacity required to maintain a certain level of PaCO2 and also indicates the reserve available for further respiratory demands. The combination of a MV of less than 10 L/min and the ability to double this value during an MVV maneuver was associated with the ability to wean successfully [21]. Both of these tests, however, are associated with

significant false-positive and -negative rates. Furthermore, the MVV can be difficult to obtain in critically ill patients, as they may be unable to cooperate.

Measuring muscle strength is one simple assessment of respiratory muscle function. Respiratory muscle function can be measured at the patient's bedside by recording the maximal inspiratory pressure (MIP) by means of an aneroid manometer. Maximum static inspiratory pressures for healthy young men and women are approximately -120 cm $H_2O$ and -90 cm $H_2O$, respectively. Maximal inspiratory efforts may be performed easily in uncooperative intubated patients by using a one-way valve connected to the manometer, which allows the patient to exhale freely but forces the patient to inhale against the manometer. An MIP less than -30 cm $H_2O$ is associated with successful extubation, but an MIP greater than -20 cm $H_2O$ is associated with the inability to maintain spontaneous breathing. Studies have shown these values to have a better negative than positive predictive value [22,23].

Several more recent predictive criteria of weaning outcome have been described (Box 2). These include measurement of transdiaphragmatic pressure, airway occlusion pressure, gastric intraluminal pH (pHi), and several integrative indices. These techniques, however, all share in common the

**Box 2. List of commonly used weaning parameters**

Simple ventilatory parameters [3,22]
- Vital Capacity (VC)
- Minute ventilation

Oxygenation parameter
- PaO2/$F_{IO_2}$

Respiratory muscle strength parameters [22]
- Maximum inspiratory pressure (MIP)
- Maximum expiratory pressure (MEP)

Central respiratory drive parameter [24]
- Airway pressure developed 100 ms after the beginning of inspiration against an occluded airway (P0.1)

Respiratory muscle reserve parameters [20]
- Maximal voluntary ventilation/minute ventilation (MVV/MV)
- Mean transdiaphragmatic pressure per breath/maximal transdiaphragmatic pressure (Pdi/Pdimax)

Pattern of spontaneous breathing parameter [22]
- Respiratory rate/tidal volume (f/Vt) rapid shallow breathing

Integrated multiple variables index [22]
- P0.1 X f/Vt
- Compliance, rate, oxygenation, and pressure

requirement for specialized equipment, difficulty of measurement, or complicated equations, which make bedside utility poor [3].

One exception is the rapid shallow breathing index described by Yang and Tobin [22]. They found that MV is well-maintained in patients who fail a weaning trial, but its components VT and respiratory frequency are combined in a manner that results in inefficient gas exchange. In general, patients who fail weaning trials drop their tidal volumes and increase their respiratory rates. Tobin and Yang have shown that the rapid shallow breathing index as reflected by frequency (breaths/minute)/VT (liters) is an accurate predictor of weaning outcome. Using a threshold of less than 105, the frequency (f)/VT ratio had a positive predictive value of 0.78 and a negative predictive value of 0.95.

The advantages of the f/VT ratio as a weaning predictor are that it is easy to measure and not dependent on patient cooperation and effort. The f/VT ratio was evaluated while patients were breathing spontaneously through an endotracheal tube. A bedside spirometer was used to measure VT. The predictive value of this index may be lower if measured while patients are on the ventilator with either continuous positive airway pressure (CPAP) or pressure support.

It is important to understand that no index has proven to be ideal and highly predictive of weaning. In patients mechanically ventilated for less than 72 hours, it is likely that conventional weaning parameters and bedside assessment by an expert physician have predictive value that would equal the measurement of the work of breathing. In complex long-term ventilated patients, however, work of breathing may be more predictive of successful weaning outcome (ie, successful spontaneous breathing for at least 24 hours post extubation).

## Weaning modes of mechanical ventilations there a preferred technique?

Weaning from MV has been described as either a gradual decrease of ventilator support to allow liberation from the ventilator or determining when the patients will have the ability to be separated from the ventilator safely. Multiple different techniques have been proposed to facilitate the transition to spontaneous ventilation. The studies that have addressed this issue, however, have conflicting results. These studies focused on the impact of the weaning mode on the work of breathing, rather than the relevant outcome of a timely and successful weaning.

There is a significant heterogeneity in the population on MV. The weaning of a short-term ventilated patient who is in the ICU for a drug overdose differs markedly from weaning a long-term ventilated patient with COPD, pneumonia, or ARDS. Many of these studies focused on short-term ventilated patients less than 72 hours. Nevertheless, the commonly used techniques of weaning are T-piece, synchronized intermittent mandatory ventilation (SIMV), or PSV. The important question is: In

difficult-to-wean patients, which of these three techniques will lead to the highest proportion of successfully weaned patients and the shortest weaning time?

Unfortunately, the optimal mode of MV used during weaning remains controversial. It generally is accepted that SIMV weaning prolongs the duration of MV. Daily T-piece trials consistently have been superior to the SIMV mode in weaning, and at least equivalent to PSV weaning. More than once daily T-piece trials have not been shown to be superior to daily trials [25].

PSV provides a progressive unloading of inspiratory muscles compared with SIMV. The results of trials with PSV, however, have been variable. What appears to be consistent is that a protocol-directed weaning strategy leads not only to a significant reduction in the duration of MV, but also to a significant decrease in the number of complications and costs [2,8–10]. Several of the PSV weaning trials have been protocol-driven, and questions remain as to whether SIMV could do better in weaning if used in a different way (eg, volume-controlled mandatory breaths interspersed with spontaneous pressure-supported breaths reduced in a protocol driven fashion).

Noninvasive positive pressure ventilation (NPPV) also has been used as a method to support ventilation following early extubation [3,26]. A clinical study showed that this technique ,compared with standard oxygen therapy, averted respiratory failure after extubation and decreased ICU mortality among patients at increased risk. The benefits in mortality, however, were seen only in the hypercapnic patients. The length of ICU and hospital stays, and mortality at 3 months were similar in the two approaches [26].

With recent advances in technology, new features on ventilators like automatic tube compensation (ATC) have been developed. Several new trials have been performed to evaluate the prediction of weaning outcome using this new feature [27,28]. ATC compensates for the pressure drop across the endotracheal or tracheostomy tube by delivering exactly the amount of pressure necessary to overcome the resistive load imposed by the tube for the flow measured at the time (variable pressure support). ATC has been shown to decrease the work of breathing necessary to overcome endotracheal tube resistance more effectively than PSV or CPAP. It is possible, however, that ATC could allow more marginal patients to tolerate a breathing trial, who then would develop ventilatory failure after extubation. No comprehensive trial has been done to compare ATC with T-piece in terms of successful weaning outcome.

Lastly, another new technique holds some promise in the field of weaning from mechanical ventilation. Proportional-assist ventilation (PAV) is a form of synchronized partial ventilatory support in which the ventilator generates pressure in proportion to the patient's instantaneous effort. This proportionality applies from breath-to-breath as well as continuously throughout each inspiration. In fact, patient effort is amplified as if the

patient has acquired additional inspiratory muscles that remain under the control of the patient's own respiratory control system. Unlike other modes of partial support, there is no target flow, tidal volume, ventilation, or airway pressure. The objective of PAV is to allow the patient to comfortably attain whatever ventilation and breathing pattern his or her control system sees fit. The responsibility for determining the level and pattern of breathing is shifted from the caregiver to the patient.

To accomplish the objectives of PAV, the machine provides pressure assistance in proportion to an ongoing inspiratory flow (flow assist [FA]) and volume (volume assist [VA]). For FA and VA to result in airway pressure being proportional to instantaneous effort, both FA and VA need to be used simultaneously. FA (expressed in cm $H_2O$/L/s) must be less than the patient's resistance (Rrs). VA (expressed in cm $H_2O$/L) must be less than patient's elastance (Ers), and finally the fractions (ie, FA/Rrs and VA/Ers) ideally should be similar [1].

## Protocolized weaning from mechanical ventilation—the role of nonphysician health care professionals

Several studies have evaluated weaning parameters to identify patients who are ready for extubation and how to apply those parameters in a guideline or protocol for the weaning to be successful in the shortest possible time [2,8–10]. Fig. 1 is an example of such a guideline. The initial step in any protocol-driven ventilator weaning is daily screening for readiness to wean using several weaning parameters. To do so, every appropriate patient in the ICU also should undergo a daily interruption of sedation to be in optimal neurological condition for the screening [9,15].

Most of these guidelines start by identifying potential candidates for the daily screening. Candidates for such a protocol are patients who have adequate oxygenation (PaO2 $>60$ mm Hg with $F_{IO_2} \leq 0.5$ and PEEP $\leq 8$ cm $H_2O$). The screening for readiness may include calculation of the rapid shallow breathing index (RSBI), which is the frequency to tidal volume ratio (f/Vt) measured after 1 minute of spontaneous breathing. In general, patients who fail weaning trials drop their VTs and increase their respiratory rate. Yang and Tobin [21] have shown that the RSBI is an accurate predictor of weaning outcome. Using a threshold of less than 105, the f/VT ratio had a positive predictive value of 0.78 and a negative predictive value of 0.95. After manifesting adequate coughing during suctioning to ensure intact airway reflexes, those patients passing the rapid shallow breathing trial will be subject to spontaneous breathing trials using PS, CPAP, or T-piece for up to 120 minutes.

The spontaneous breathing trial (SBT) is terminated if the patient successfully tolerates SBT from 30 minutes to 2 hours or starts showing signs and symptoms of failing (respiratory rate $>35$ for $>5$ minutes, SaO2 $<90\%$ for $>30$ seconds, 20% increase or decrease in heart rate for

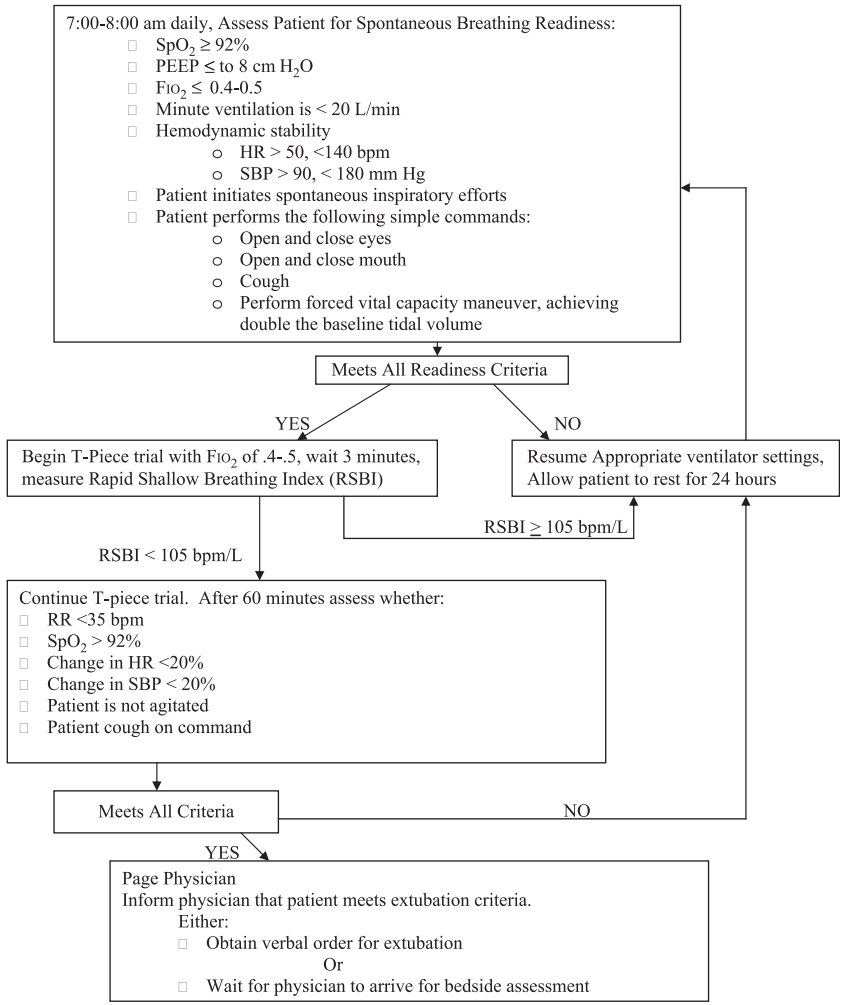


Fig. 1. Example of mechanical ventilation weaning protocol flow diagram.

> 5 minutes, systolic blood pressure SBP > 180 or SBP < 90 for 1 minute with repeated measurements, agitation, anxiety, or diaphoresis as a change from the baseline).

In general, these protocols are driven by the unit respiratory care practitioners and/or nurses. Several recent studies have shown that protocol-driven weaning by nurses or respiratory therapists is superior to independent physician-directed weaning regardless of what weaning mode is employed [8,10]. This is likely because providers are distracted easily by more acute patients, and stable weaning patients may not undergo their daily trial of spontaneous breathing unless it is under protocol direction.

The next improvement of protocolized weaning may be computer-driven. Closed-loop knowledge-based algorithms have been introduced into ventilators to act as a computer-driven weaning protocol. The computerized protocol used in a recent trial included an automatic gradual reduction in pressure support, automatic performance of SBTs, and the generation of an incentive message when an SBT was passed successfully [2]. This computer-driven system reduced MV duration from 12 to 7.5 days ($P = .003$) and ICU length of stay 15.5 to 12 days ($P = .02$) and caused no adverse effects when compared with physician-controlled weaning. This approach will need to be compared with protocolized weaning rather than standard of care before universal adoption of computer-driven weaning.

## Summary

MV is a life-sustaining therapy fraught with side effects. The successful removal of MV at any time is associated with a higher survival rate. Therefore, removing the patient from the ventilator as soon as possible is in the patient's best interest. The best approach to weaning patients from MV involves a team approach of all caregivers (physician, nurses, respiratory therapist, physical therapist, and nutritionists). The team uses a weaning protocol that gives the nurses and/or the respiratory therapist the authority to start a daily screening of ventilated patients. If patients meet certain criteria, a trial of spontaneous breathing (positive pressure flow mode or T-piece) is undertaken. If patients pass the trial, they are extubated. Patients who do not pass the SBT will be reassessed to identify and treat any reversible factors and undergo daily SBTs if they continue to meet the criteria.

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Crit Care Clin 23 (2007) 275–290

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# Special Cases: Mechanical Ventilation of Neurosurgical Patients

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Mechanical ventilation first was developed at the turn of the 20th century. It was not until the 1950s, however, that it became an important part of clinical practice, a necessity driven by the poliomyelitis epidemic in Europe [1]. Since then, mechanical ventilation as a technology has advanced greatly and is now employed across several specialties, with applications tailored to the needs of different disease states. A large multinational study demonstrated that approximately 20% of all patients who require mechanical ventilation do so as a result of neurological dysfunction [2]. Neurocritical care is a comparatively new subspecialty that has emerged to manage the specific needs of this patient subpopulation, of which appropriate mechanical ventilation is an important aspect. Neurosurgical patients, particularly victims of traumatic brain injury (TBI), comprise a significant portion of admissions to such units and require unique consideration. The types of ventilation and indications for their use, as well as appropriate monitoring, are imperative to the successful management of these patients. Various aspects of the strategies of mechanical ventilation applied to neurosurgical patients remain controversial.

## Summary of relevant physiology and pathophysiology

In understanding the aims and indications for endotracheal intubation and mechanical ventilation, it is necessary to comprehend the underlying

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0749-0704/07/$ - see front matter 
doi:10.1016/j.ccc.2006.12.003 *criticalcare.theclinics.com*

physiology and pathophysiology that necessitate their use. The adequate provision of oxygen to tissue relies upon a patent airway, effective movement of gas into and out of the lungs, efficient gas exchange in alveoli, and sufficient vascular collection and delivery. All of these things directly or indirectly depend upon an intact neurological system.

First, in the conscious patient, the patency of the upper airway is maintained by appropriate and persistent tone in the upper airway dilator muscles and multiple reflexes. Neurological dysfunction, including loss of consciousness, can lead to a loss of these reflexes and put the airway at risk. Indeed, obstruction caused by the flaccid tongue falling back against the posterior pharynx is the predominant reason for airway closure in the unconscious patient [3]. In addition, aspiration can result from loss of such reflexes and the development of pulmonary complications including pneumonitis, pneumonia, or adult respiratory distress syndrome (ARDS) [4,5]. Aspiration has been shown to increase in direct association with decreased consciousness as measured by the Glasgow coma scale (GCS) [6] and is a frequent problem in neurologically ill patients [4,5,7].

In addition to having a patent upper airway with minimal resistance, the patient must have the ability to generate the appropriate pressures within the lung to permit inspiration and expiration. Controlled, rhythmical muscular contraction is required in association with effective compliance of the lung tissue. Neural ventilatory control or drive originates in the dorsal and ventral respiratory neurons of the medulla oblongata [5,8]. These groups of neurons generate an intrinsic respiratory rhythm that is actuated by means of the phrenic and intercostal nerves. Modification of this rhythm can be achieved by means of higher centers, including the cortex and pons, and afferent input directly from lung stretch receptors (Hering–Breuer reflex) and peripheral chemoreceptors [8]. Insult to the central nervous system (CNS) can result in aberrations in this system to cause either an increase or decrease in respiratory drive and consequential hypo- or hyperventilation.

Even with adequate neural stimuli from the respiratory centers, these impulses must be detected appropriately at the neuromuscular junction and result in sufficient muscular contraction. This muscular effort must be able to overcome both elastic (compliance) and nonelastic (primarily airway resistance) forces to allow an increase in lung volume and create negative pressure [8]. In the neurosurgical patient, dysfunction of compliance may occur secondary to aspiration pneumonia/pneumonitis, neurogenic edema, or even gross chest pathology such as pneumothorax or flail chest in the multitrauma patient [5]. Any increase in compliance will increase the work of ventilation and can lead to rapid ventilatory failure through muscle fatigue. It is also important to consider that patients may have preexisting chest pathology that may compound any acute neurologically derived respiratory presentations.

The pathology of respiratory dysfunction in the neurosurgical patient is challenging. Neurologically mediated dysfunction of respiration may be only part of the problem with secondary pulmonary complications,

coexisting trauma and pre-existing cardio–respiratory pathology contributing to performance. In addition, iatrogenic influences such as anesthetic agents or certain analgesics may have both peripheral and central effects on respiratory function.

## Indications for endotracheal intubation and mechanical ventilation

The placement of an endotracheal tube (ETT) is indicated when airway patency is compromised and when airway protection is needed (ie, from aspiration). Thus an ETT may be necessary even in situations where ventilation is adequate. Patients who have decreased consciousness, bulbar dysfunction, or mechanical obstruction may require intubation [5]. Patients who have a GCS less than 10 also should be considered to have their airway at risk [6].

In the neurosurgical patient, mechanical obstruction secondary to head and neck injuries or even profound neck edema may be a particular problem [5]. In addition, a special consideration with regard to ETT placement in neurosurgery is the issue of intubating patients who present with potential cervical spine pathology. Patients who have spinal cord lesions warrant early attention, as concomitant gastrointestinal ileus puts them at a much greater risk of aspiration [9], and high cord lesions (C5 and above) necessitate immediate ventilatory support [10]. An obvious concern is that hyperextension during placement of the tube may result in the extension of cord pathology. Despite this, it has been demonstrated by several groups that no development of new, or worsening of pre-existing, neurological deficit occurs when ETT placement is performed by experienced physicians in the hospital, including the emergency department [11–14]. Fiberoptic guidance and nasotracheal intubation are alternative approaches that may pose less risk to spinal cord [5]. Emergency tracheotomy may be required in cases of severe head and neck injury when ET intubation is not possible. The timing of tracheotomy is otherwise controversial, but there is accumulating evidence that in neurological patients, early tracheotomy is advantageous in terms of overall duration of mechanical ventilation, ventilation weaning, and acquired infection [15–19].

Protection of the airway and maintenance of adequate ventilation initially can be achieved using simple and noninvasive techniques such the jaw thrust maneuver accompanied by a bag and mask to deliver the desired oxygen concentration. Various other airways can be employed such as oral and nasal airway, or, less commonly, the laryngeal mask airway [5]. These techniques are beneficial for short periods and particularly for use by staff unskilled at performing endotracheal intubation. Placement of an ETT, however, is the optimal approach to protecting the airway and allowing appropriate delivery of oxygen to the patient.

Mechanical ventilation is required when the respiratory system fails to provide sufficient oxygen to meet tissue demands. The reasons why this

might occur are diverse and normally multifactorial. However, they essentially can be categorized into four groups (1) a loss of neuronal control or respiratory drive, (2) altered lung compliance, (3) impaired gaseous exchange, and (4) ventilatory failure secondary to muscle fatigue or dysfunction of the neuromuscular junction.

Within neurosurgery, the issue of respiratory drive is of great importance. The aim of mechanical ventilation is to compensate for dysfunction and correct any resultant hypoxemia and respiratory acidosis, in addition to preventing any secondary damage that may result from these abnormalities. The decision to initiate mechanical ventilation often is based on acute clinical observations before time to gather information from more sophisticated laboratory tests is available. This is particularly true in the neurosurgical setting, when pathologies involve acute presentations such as trauma and resultant intracranial bleeding or upper spinal pathology. Otherwise, the laboratory parameters for initiation of mechanical ventilation are not well-defined. The development of respiratory failure should be regarded as an indication for the consideration of mechanical ventilation. Type I respiratory failure and type II respiratory failure are defined as a failure of oxygenation ($PaO_2$ $<60$ mm Hg with low of normal carbon dioxide [$CO_2$]) and a failure of ventilation ($PaCO_2 > 50$ mm Hg), respectively. Clinical warning signs including respiratory rate less than 6 or greater than 30, use of accessory muscles, paradoxical breathing, and apneas should be monitored and used in conjunction with other suggestive laboratory parameters (vital capacity, negative inspiratory force, forced expiratory volume in 1 second [$FEV_1$], minute ventilation) to time initiation of mechanical ventilation appropriately [5,20,21].

Another indication for mechanical ventilation may be the therapeutic application of forced hyperventilation. This is a controversial topic that will be discussed later.

## Neurosurgical effects on ventilation and appropriate ventilatory modes

The numerous modes of mechanical ventilation can be initially daunting because of the abundance of acronyms used. Upon reverting back to the basic physiology, however, modes vary across just a few basic parameters, namely volume, pressure, timing, and the way in which delivery is triggered. A brief summary of the various conventional modes is shown in Table 1. These are reviewed in more detail elsewhere [20,22]. With regard to the neurosurgical patient, the mode chosen is tailored to the needs of the patient and depend very much on the nature and location of the neuropathology.

### *Brainstem and cortical pathology*

Pathology that directly affects the dorsolateral aspect of the medulla will prevent the normal functioning of the dorsal respiratory neurons and likely decrease or remove respiratory drive with resultant hypoventilation or

Table 1
Summary of common modes of mechanical ventilation

| Parameter-controlled | Mode of ventilation | Description |
|---|---|---|
| Volume-controlled | • Controlled mechanical ventilation (CMV) | Breaths all triggered by ventilator; predefined rate and volume set |
| | • Assist-controlled ventilation (ACV) | Breath triggered by patient's effort, if no patient breath per unit time, ventilator triggered; predefined tidal volume set |
| | • Synchronized intermittent mandatory ventilation (SIMV) | Spontaneous breathing permitted with no ventilator assist; mandatory, timed breaths delivered in synchrony with patient's breaths when possible; predefined tidal volume set. |
| Pressure-controlled | • Pressure-controlled ventilation (PCV) | Timer-triggered, timer-cycled, and pressure-limited |
| | • Pressure support ventilation (PSV) | Triggered by patients inspiration only; assist with pressure limitation provided. |
| | • Continuous positive airway pressure (CPAP) | All breaths patient triggered; provides gas at a constant predefined pressure |
| Volume- and pressure-controlled | • Pressure support (PS)/ SIMV | Combination of PS and SIMV; ensures spontaneous breaths permitted in SIMV receive pressure assist |

apnea [23,24]. If conscious, voluntary cortical control may compensate to allow respiration to persist; however, when voluntary control is lost during sleep, apnea may occur. Loss of respiratory drive is approached best with controlled forms of ventilation where the ventilator assumes control of initiating breaths [5].

Higher localized brainstem lesions in the pons may have an impact on the rate or pattern of breathing. For example, lesions of the pontomesencephalic junction can induce increased respiratory drive with hyperventilation, resulting in hypercapnia, acidosis, and possibly muscle fatigue [25]. Midcaudal pontine lesions can cause apneusis or Cheyne-Stokes breathing [26]. For these lesions, controlled modes of ventilation are required, usually with sedation to suppress any intrinsic neural control. More widespread pathology, such as large intracranial bleeds, gross cerebral edema or raised intracranial pressure (ICP) (discussed later), also may result in brainstem compression and suppression of respiratory drive and altered higher cortical influences.

The use of controlled forms of ventilation are initially useful but can be problematic later in recovery when spontaneous breathing recurs in a progressive fashion [22]. Assisted modes are more appropriate at this time, and careful monitoring should be in effect to aid decisions about the timing of conversion between ventilatory modes.

### *Spinal cord injury*

In patients with spinal cord injury (SCI), the necessity for mechanical ventilation will depend upon the level and extent of the lesion. Approximately

55% of SCI lesions occur in the cervical region [10]. Lesions at C5 and above clearly will require immediate and likely long-term ventilation because of complete paralysis of the phrenic and intercostal nerves [8,10]. Lesions at C6 and below still may necessitate mechanical ventilation because of varying degrees of paralysis and extension of the lesion through edema and bleeding up to C5 and above. The course of ventilatory failure in these patients has certain unique features. The initial insult to cervical cord results in an acute and severe respiratory decrease with vital capacity dropping to 30% or less [27]. In lower lesions, various delayed declines in function have been reported, possibly because of fatigue, ineffective clearance of secretions, pneumonia, or atelectasis [28]. Reports of delayed and sudden apnea also have been published in patients with lower c-spine lesions who demonstrated no initial severe compromise in respiratory function [29]. Such patients tend to undergo respiratory arrest often after seemingly normal function, commonly 1 to 2 weeks after injury. Instability and lesion expansion have been suggested as explanations, although radiological evidence is unable to support this [29]. Others argue that active degeneration triggered at a cellular level is likely responsible [29,30]. Risk factors and warning signs for this delayed apnea have been identified as diffuse and extensive cord lesions, transient respiratory distress, and bradycardia. It is more likely to occur in sleep, further suggesting a neurologically based etiology [29].

After several weeks following injury, it often is found that respiratory function improves in c-spine transected patients. This is because of the spasticity that arises in the intercostal muscles. The airway is contracted tonically, and the chest remains expanded during inspiration as opposed to collapsing as it does in the acute, flaccid stage of paralysis [31]. Thus, requirements of the ventilator in patients who have SCI evolve with changing levels of intrinsic muscular contraction and varying transmission of centrally controlled respiratory drive. There is therefore no set ventilation formula, but rather a determination of how much respiratory drive is present, the pressure and volume needed to maintain adequate blood gas levels, and the level of muscular fatigue affecting the respiratory system. Thus, both assisted and controlled methods may be appropriate.

A further consideration when initiating ventilation in SCI patients and patients with neurological trauma is the use of certain neuromuscular blocking agents, particularly suxamethonium. In these patients, suxamethonium can result in hypersensitivity and exaggerated potassium release, putting the patient at risk of hyperkalemic arrest [32,33]. This can be a long-term phenomenon, with reactions being reported several months after injury and as long as 7 years after injury [34]. Nondepolarizing agents are more appropriate for induction before ventilation.

Although most patients will require acute ventilation, possibly before arrival at the emergency department, early elective ventilation always is preferred to emergency initiation of ventilation; monitoring and preparation are key.

## Raised intracranial pressure and positive end-expiratory pressure

Raised intracranial pressure (RICP) is an extremely common problem in neurosurgical units, with most traumatic brain injury patients requiring neurosurgical services having some degree of RICP [35]. The basic principle of intracranial pressure was described by Kellie [36] and Munroe [37] almost 200 hundred years ago in Scotland. The skull can be viewed as a closed box with uncompressible contents, with the intracranial compartment existing in a nonlinear pressure–volume curve [38]. Essentially, the intracranial volume is constant, and so the addition or removal of any matter will result in pressure changes. Thus, a continuous outflow of venous blood is required to make room for the continuous inflow of arterial blood [39]. Raised intracranial pressure can cause secondary ischemic damage when persistently above normal range, and this remains the most frequent cause of death and disability after severe TBI [40–42].

In the context of ventilation, raised ICP generates several concerns. First, the preparation for intubation, like in spinal cord injury, is problematic. The act of intubation itself can stimulate an increase in ICP [5]. In addition, certain depolarizing agents such as suxamethonium have been suggested to worsen ICP [43]. Several other studies refute this [44,45]. It has been suggested that if it is necessary to use this drug, it should be administered in conjunction with a nondepolarizing agent [46]. Alternative drugs such as propofol (Diprivan) or lidocaine (Xylocaine) may be more appropriate and may prevent the rise in ICP during intubation.

The influence of mechanical ventilation on the vascular system, particularly the cerebral vasculature, has been and remains a controversial issue. At the center of this lies positive end-expiratory pressure (PEEP). PEEP was introduced conceptually in the late 1960s [1]. At the end of expiration, the pressure within alveoli is approaching atmospheric levels, the elastic recoil of the chest having propelled the inspired gas out. At this point in the ventilation cycle, the volume of gas in the alveoli is at its lowest. The aim of introducing a positive pressure at the end of expiration increases the end-expiratory volume (or functional residual capacity), preventing alveolar collapse, and helps to recruit alveolar units. PEEP has also been demonstrated to decrease the incidence of ventilator-induced lung injury (VILI) and prevents the use of high inspired oxygen levels [47,48]. There is some evidence, however, to suggest that the use of PEEP will cause an increase in raised intracranial pressure and a decrease in cerebral perfusion pressure (CPP) [49–52]. The physiological hypothesis behind this is that increases in PEEP will alter intrathoracic pressures to impede venous return. A decreased venous return from the head, according to the Munro-Kellie principal, will result in an increase in intracranial pressure [53]. The evidence to support this, however, is somewhat conflicting. One group showed that administration of PEEP of 4 to 8 cm $H_2O$ resulted in an increase of ICP of 10 mm Hg, which resulted in approximately half of the patients having

a decrease in CPP [49]. Other groups more recently have demonstrated no change in ICP with even higher levels of PEEP applied [54,55]. The variation in results may be because of the patients included. There appears to be some association between the effect of PEEP on ICP and lung compliance [47,50,51,56,57]. It is logical that lungs which are not compliant will fail to transmit the pressure derived from the change in PEEP. This in turn will prevent any impedance of venous return and subsequent increases in ICP. Based on this, some have suggested that PEEP is safe to use as long as the pressure used does not exceed that of the ICP [55,58]. In addition, a recent study demonstrated that patients with low lung compliance tolerated PEEP values up to 12 cm $H_2O$ with no effect of cerebral of systemic hemodynamics [57]. Patients who were susceptible to hemodynamic effects, including raised mean arterial pressure, were those with normal lung compliance. These same authors suggest that lung compliance may be important to identify patients at risk of deleterious ICP changes [57].

Upon reviewing the literature to date, it seems logical that the use of PEEP at low to moderate levels will be unlikely to cause significant increases in ICP in most cases. The potential benefits of its use likely outweigh the risk. An individual approach to each patient with careful and appropriate monitoring is paramount to effective use of PEEP.

## Hyperventilation as a therapy

Therapeutic hyperventilation has been used in patients who have raised ICP for several decades but has fallen out of favor in recent years. It is a treatment that has been researched and extensively used within the context of TBI.

Hyperventilation results in an increase in blood $CO_2$ levels. Indeed, the drop in blood $CO_2$ tension is what many use to define hyperventilation [59]. $CO_2$ is a potent vasoconstrictor that acts to decrease cerebral blood flow by around 1 to 2 mL per minute per 1 mm Hg drop of $PaCO_2$ [60,61]. The drop in blood flow creates space within the intracranial compartment and thus decreases ICP. The physiology of hyperventilation is complex, as it has multiple CNS and systemic effects. In neurosurgical terms, the major concern with the use of hyperventilation is that cerebral blood flow will fall to ischemia-inducing levels. Although the potentially detrimental physiological changes are understood well, the evidence to show how this impacts on clinical outcome is scarce. Only one prospective randomized controlled trial has been performed in TBI patients comparing those treated with hyperventilation with those who were not [62]. They showed that neurological outcome was worse in the hyperventilation group, although this study's methodology has been subject to some criticism [59]. Despite this, based on this one trial, hyperventilation is not recommended for use in patients who have TBI within the first 24 hours because of the potentially hazardous drop in cerebral perfusion pressure [63]. Interestingly, is

has been shown that unintentional hyperventilation may occur frequently before the patient's arrival in the hospital before appropriate ventilation volumes and rates can be determined [64,65]. In protracted and refractory cases or raised ICP or during acute deteriorations in neurological function, hyperventilation still is considered acceptable when used with caution [59]. It should not be used as a sole treatment or for prolonged periods, and typically $PaCO_2$ should be maintained between 30 and 35 mm Hg [61].

## Monitoring

Clearly patients with acute neurosurgical presentations requiring mechanical ventilation will undergo a barrage of constant monitoring, much of which will provide contributory information about what is happening in the CNS. Appropriate monitoring is essential, because clinical status can often change rapidly and unpredictably in neurosurgical patients. In addition, it allows the clinical status to be tracked longitudinally, thus allowing the evaluation of recovery and prognosis. Monitoring may include basic clinical observations, vitals signs, intensive hemodynamic monitoring, including fluid balance, arterial blood gases, continuous oxygen saturation, transcranial Doppler, end-tidal $CO_2$, and ICP monitoring. This article discusses just two aspects of monitoring in the neurosurgical patient—one established ($CO_2$ monitoring) and one novel (brain tissue oxygen monitoring).

First, in light of what was discussed previously with regard to the interplay between hyperventilation, ICP and PEEP, $CO_2$ monitoring and management are important parameters when dealing with the mechanically ventilated neurosurgical patient. In addition to basic clinical signs, $CO_2$ can be measured in numerous different ways. The most accurate way of determining $CO_2$ is by direct measurement in arterial blood using serial blood gas measurements. This has to be done at routine intervals, however, and does not provide the luxury of continuous monitoring. Continuous transcutaneous blood gas monitoring has been developed in attempts to overcome this, although readings with these devices are less accurate, and their practicality and use in adults have been questioned [66–68].

Capnography is also a less accurate determination of $CO_2$, but it is less invasive and permits continuous measurement. Capnography measures $CO_2$ as a time–concentration curve [69]. It measures end tidal $CO_2$, which is representative of the alveolar concentration. Thus, capnography provides information about gas exchange, pulmonary perfusion, alveolar function, and respiratory patterns. It is a useful way of detecting episodic changes in $CO_2$, but it provides no information regarding overall improvements or deteriorations in the patient. Some argue that it is an effective way of detecting and drawing attention to respiratory compromise, whereas others question its accuracy at $PaCO_2$ extremes and its usefulness as a sole parameter upon which to base management decisions [69,70].

Rate and tidal volume can be manipulated to compensate for hyper/hypocapnia. It is important to remember that changes in acid–base balance may be related to an underlying metabolic disturbance with compensatory respiratory changes. Thus, careful examination is required before initiating any ventilatory changes.

The aim of both mechanical ventilation and ICP reduction is to preserve blood flow and, more importantly, oxygen delivery to brain tissue. All of this is in an attempt to permit normal tissue metabolism (for which the brain relies upon continuous oxygen to complete successfully) [71]. Historically, preservation of tissue integrity has been achieved by monitoring and adjusting a multitude of vascular and respiratory parameters. Measuring ICP and CPP invasively are the current standards for monitoring in TBI patients [72]. This, in combination with arterial oxygen concentrations, indicates the amount of oxygen delivered to brain. In recent years, however, the concept of simply measuring the presence of oxygen directly within the brain tissue is coming to light in the form of brain tissue oxygen monitoring. There is an abundance of evidence showing that outcome following episodic hypoxia is worsened [73–75]. By monitoring brain oxygen directly, it can be assumed that a more rapid detection of hypoxia and correction of this may improve outcome. Indeed, brain tissue oxygen monitoring recently was associated with a reduced mortality rate when used to guide treatment in patients who had severe TBI [72]. Brain tissue oxygen monitoring is likely to become an increasing feature in the neurological ICU and, in conjunction with ICP measurements, this will guide the strategy of mechanical ventilation used.

## Ventilation-induced lung injury

In recent years, lung injury has become a major focus in the approach to mechanically ventilating patients. There is now clear experimental evidence that use of mechanical ventilation can induce damage by means of numerous mechanisms, including overdistension, oxygen toxicity, and atelectrauma (opening and closing injury) [76–78]. Many of the ventilation strategies used to reduce the risk of VILI cannot be applied readily to neurosurgical patients. For example, use of higher levels of PEEP and lower tidal volumes may benefit a patient with normal intracranial functioning but potentially could be detrimental in a patient who has raised ICP. To make matters worse, it appears that neurosurgical patients, specifically those with a TBI, have a high incidence of pulmonary complications. Of TBI patients admitted to trauma centers, up to 50% were found to have lung injury or acute respiratory distress syndrome (ARDS) [79–81]. ARDS has been associated with a decreased neurological outcome and increased mortality in such patients [80].

The use of PEEP has been shown to attenuate some of the effects of ARDS, mainly by reopening alveoli and preventing them from collapse

[77,82,83]. It also allows lower inspired oxygen concentrations to be used [84]. These trials, however, primarily excluded neurosurgical patients because the issues regarding raised intracranial pressure. As there is no conclusive evidence that PEEP has significant ICP effects, and it is presumed safe at moderate levels, it should be considered beneficial in patients who have ARDS, particularly because lung compliance likely is decreased in such patients.

The issue of hyperventilation is also pertinent when considering potential VILI. The evidence regarding both harm and benefit caused by therapeutic hyperventilation, however, is insufficient to draw definitive conclusions about its use [85]. The difficulty of maintaining $CO_2$ with enough volume to provide adequate $O_2$ and not result in overdistension injury will require careful monitoring and detection of respiratory function, blood gases, and determination of ICP and CPP.

Oxygen-associated damage is a further complication that should be avoided. Increasing the fraction of inspired oxygen has been shown to have no benefit in brain oxygen delivery [76,86]. Thus normal oxygen saturations should be attained without using excessive inspired $O_2$ fractions. Using this strategy, $O_2$ is maintained, and oxidative lung damage is minimized.

The clear benefits of mechanical ventilation must be balanced with the risk of VILI as best as is possible in this difficult patient subgroup.

## Extubation and weaning of mechanical ventilation

The removal of ventilatory support requires frequent patient assessment and careful consideration before being implemented. It is a careful balance between the benefits offered by continued support and the risks associated, including ventilatory-induced lung damage and muscular atrophy. The difficulty in re-establishing an airway if necessary should also play a role in the decision-making process.

In assessing readiness for ventilation withdrawal, the McMaster University Evidence-Based Medicine Group reviewed current literature and published eight parameters that were useful in predicting outcome from ventilation discontinuation [87,88]. This included assessments on the ventilator (minute volume, maximum inspiratory pressure, airway occlusion pressure 0.1 second after the onset of inspiratory effort and an index involving compliance, respiratory rate, oxygenation, and pressure) and assessments off ventilation (respiratory rate, tidal volume and a ratio of these parameters.). This group also suggests that the most valuable assessment is a well-controlled spontaneous breathing trial (SBT). When an SBT is part of a formal protocol, it has been demonstrated to reduce the number of weaning days and total ICU stay [89,90].

Patients with neurological injury who undergo weaning typically have recovery of ventilatory drive first [5]. This allows ventilation to be changed

from controlled to assisted modes. The choice of assisted mode varies, but generally a pressure-support mode with or without permittance of spontaneous breathing (SIMV) is reasonable [5]. This allows a period of gradual recovery of respiratory muscle function.

Several predefined weaning protocols have been tried within the medical and surgical ICU settings. There is substantially less evidence supporting the use of these or any other protocol specifically in neurosurgical patients. One recent study investigated the use of a medical ICU protocol in neurosurgical patients and found considerable limitations with its use [91]. Neurosurgical patients as a subpopulation have been demonstrated to have more difficulty in this period, with higher rates of reintubation being required [91–93].

Extubation is indicated when spontaneous ventilation is sufficient to maintain blood gases and patients have the independent ability to protect their airway. Intensive monitoring in this phase is essential.

## Summary

Ventilatory management is a diverse subject involving the complex interplay of physiology and technology. The nature of neurosurgical patients makes them a unique subpopulation that demands careful consideration with respect to multiple aspects of ventilatory support. In addition, mechanical ventilation can be used as a therapy, as opposed to being simply supportive in this setting. The evidence looking specifically at neurosurgical patients is limited. The growing emergence of specialist neurological ICUs, however, offers growing opportunity to investigate optimal management of this challenging group of patients.

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Crit Care Clin 23 (2007) 291–298

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# Mechanical Ventilation for Cardiac Support

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Postoperative lung injury is a commonly identified complication of cardiac surgery. Because of advancements in anesthetic, operative and cardiopulmonary bypass (CPB) techniques, the incidence this complication has decreased. Cardiac surgery is known to induce variable degrees of a systemic inflammatory response, resulting in a wide spectrum of disturbances, ranging from subclinical dysfunction to acute respiratory distress syndrome. The cause of this dysfunction is complex but revolves around CPB-induced increase in pulmonary endothelial permeability [1]. Lung injury has been associated with increases in alveolar–arterial oxygen differences, shunt fractions, microvascular lung permeability, and pulmonary vascular resistance (PVR). This often results in a reduction in functional residual capacity and vital capacity. Atelectasis and pleural effusions are the most common abnormalities after cardiac surgery, seen in over 60% of patients. Hypoxic episodes and pneumonia are frequent, occurring in 3% to 10% of patients [2–4].

## Lung-protective strategies

Numerous intraoperative lung protective strategies over the years have been proposed to attenuate the inflammatory response associated with postoperative lung injury.

### *Postbypass hemofiltration*

Continuous hemofiltration after bypass has been studied in the past. This filtration system theoretically removes inflammatory cytokines generated by the body in response to extracorporeal circulation and reverses

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doi:10.1016/j.ccc.2006.12.004 *criticalcare.theclinics.com*

hemodilution. Some improvements in lung function have been noted postoperatively [5]. Modified ultrafiltration (MUF), along with conventional ultrafiltration, has been used to improve the efficacy of the ultrafiltration technique. MUF produces an immediate improvement in lung gas exchange capacity. These improvements, however, have been demonstrated inconsistently, and have not resulted in decreased duration of intubation or hospital stay [6].

*Intraoperative lung perfusion*

Lung ischemia–reperfusion injury is a well-known entity. CPB imposes a low- or no-flow state within the pulmonary arteries, making lung perfusion in these cases purely reliant on bronchial circulation. It has been demonstrated that the lung may act to scavenge the numerous inflammatory mediators released as a part of the inflammatory response from the heart after CBP [7]. Recently, a pilot study evaluated the effect of isolated lung perfusion during CPB (ie, short-term hypothermic pulmonary artery perfusion with cold oxygenated blood with post-CPB ultrafiltration) [8]. These preliminary data found that pulmonary perfusion improved oxygenation and had a beneficial effect on the inflammatory response and capillary leakage in the lungs. This promising study hopefully will promote more extensive research in the subject.

*Open lung ventilation*

During CPB, it is a common practice to stop ventilation, allowing surgeons better anatomical exposure. This has been known to accentuate postoperative lung dysfunction by promoting atelectasis, increasing lung edema, and decreasing compliance [9]. New insights into the development of postoperative atelectasis have emerged recently, and ventilation according to the open lung concept (OLC) as gained much attention [10,11]. The OLC of ventilation aims at avoiding atelectasis by implementing maneuvers to keep alveoli open. This commonly is achieved by short periods of high inspiratory pressures to open collapsed alveoli and subsequent high levels of positive end-expiratory pressure (PEEP) to keep them open [12]. Miranda and colleagues [10] hypothesized application of open lung strategies, early or late, attenuated the reduction in functional residual capacity after extubation, compared with conventional ventilation modes. Application of OLC immediately after intubation resulted in significantly lower reduction of functional residual capacity after cardiac surgery when compared with conventional mechanical ventilation. In their study, there was a considerable decrease in hypoxic episodes in both OLC groups, early and late (ie, on arrival to ICU), compared with those receiving conventional ventilation. The incidence of pneumothoraces was similar in the all groups, and the use of high levels of PEEP in the OLC groups did not affect cardiac output or right ventricular ejection fraction.

## Pharmacologic strategies

Anti-inflammatory agents have been studied as possible agents for lung protection, on the assumption that inflammation holds a pivotal role in lung injury. The use of corticosteroids in cardiac surgical patients remains controversial and unconvincing. Kilger and colleagues' [13] study shows some promise with regards to the administration of hydrocortisone in coronary artery bypass graft (CABG) patients with high risk of severe systemic inflammatory response syndrome (SIRS) postoperatively. Patients randomized to receive hydrocortisone had decreased ICU and hospital stays. Further studies are necessary to detect any differences in mortality. Aprotinin is a nonspecific serine protease inhibitor. Its use, particularly in reoperations, has been shown to reduce excessive blood loss during cardiac surgery. Aprotinin may reduce pulmonary injury following cardio–pulmonary bypass. Experimentally, it was found to decrease cytokine-induced bronchial inflammation, attenuating lung reperfusion injury after bypass in one study [14].

## Cardiovascular effects of mechanical ventilation

The cardiovascular effects of mechanical ventilation are well-known and described in those with normal lungs and heart. A patient's ability to tolerate mechanical ventilation depends on numerous variables including myocardial function, intravascular volume status, intrathoracic pressure, lung inflation, and intrinsic autonomic tone. Postoperative cardiac surgical patients bring unique challenges and numerous questions with respect to mechanical ventilation and weaning. General anesthesia is a well-known cause of atelectasis [15]. With the systemic inflammatory response-associated sternotomy, hypothermia, extracorporeal circulation, and reperfusion, some degree of pulmonary dysfunction is inevitable. In cardiac surgical patients, this usually is coupled with intrinsic pump dysfunction and valvular abnormalities. The advantage of mechanical ventilation is by decreasing the work of breathing, in the setting adequate cardiac output, will result in increased oxygen delivery.

During positive-pressure ventilation, lung inflation can result in changes in right ventricular preload and afterload. Because of increases in intrathoracic pressure, the gradient between the right atrium and venous system is reduced, resulting in the reduction of preload, and hence, right ventricular cardiac output. Depending on the extent of change of lung volume, pulmonary vascular resistance may change. With a reduction in end-expiratory lung volume, alveolar collapse stimulates hypoxic pulmonary vasoconstriction (HPV), shunting blood flow to areas with better ventilation [16]. When alveolar collapse is prevented with recruitment maneuvers and the addition of PEEP, PVR was reduced, and HPV was prevented [17]. Miranda and colleagues [18] studied the effect of lung open procedures on

right ventricular afterload after cardiac surgery. Patients were randomized to receive either a lung-opening maneuver with greater amounts of PEEP with low tidal volume ventilation (4 to 6 mL/kg) or conventional ventilation with PEEP (5 cm $H_2O$ with 6 to 8 mL/kg tidal volumes) after surgery. Cardiovascular measurement, including right ventricular ejection fraction and PVR, was recorded. Greater amounts of PEEP were applied after recruitment maneuvers to re-expand atelectatic lung units. No significant increases in right ventricular afterload were noted.

Left ventricular afterload is the maximal left ventricular (LV) wall tension in systole or in easier terms, the pressure against which the left ventricle ejects. In those with normal LV function, during positive pressure ventilation, increases intrathoracic pressure decrease cardiac output because of a reduction in LV preload. When cardiac function is impaired, cardiac output may increase because of a concurrent reduction in afterload [19]. The influence of PEEP on the left ventricle is complex. It is known that PEEP improves arterial oxygenation and decreases intrapulmonary shunting. PEEP increases the pressure around the thorax. The pressure differential between the left ventricle and systemic circulation rises. This, at a constant arterial pressure, decreases the force necessary to eject blood from the left ventricle [20]. This effect is more predominant in those sensitive to changes in afterload, such as those with congestive heart failure.

The contrary may be seen during weaning from mechanical ventilation. As patients begin to breath spontaneously, the negative intrathoracic pressure produced results in increased left ventricle afterload. The augmentation of LV ejection is lost. In response to increasing metabolic demands, cardiac output increases. Myocardial oxygen demand may increase with a lowering of mixed venous oxygenation [21]. This, in susceptible individuals, may result in myocardial ischemia and failure to wean from the ventilator.

## Fast-track cardiac anesthesia

Because of advancements in perioperative anesthesia management with improved intraoperative myocardial protection and bypass techniques, the fast tracking of cardiac surgical patients has become the norm in most cardiac surgical institutions. Fast-track cardiac anesthesia and surgery entails the early extubation of patients (within 6 hours of arrival in the ICU), with the concomitant reduction in length of stay and cost. It also includes the use of newer short-acting induction agents, lowdose opioid techniques, and the timely use of antifibrinolytics drugs and antiarrhythmics to prevent postoperative coagulopathy and arrhythmias.

Numerous studies have found that early extubation is safe in this patient population [22,23]. It was concluded, after much research, there was no evidence of increased mortality or morbidity with fast track cardiac anesthesia (FTCA) when compared with the traditional high-dose opioid technique. In

addition, FTCA has been show to reduce length of stay and ICU costs [24]. The question arose whether every coronary artery bypass requires a stay in a conventional ICU. Can low-risk CABG and valve patients safely recuperate in a step-down or intermediate care environment? Recently, the concept of short-stay intensive care treatment has come into play. Ghislaine and colleagues [25] conducted a randomized clinical equivalence trial to evaluate the safety and cost effectiveness of short-stay intensive care treatment (8 hours of intensive care treatment) verses conventional overnight treatment for low-risk coronary artery bypass patients. Readmission rates, total hospital stay, and postoperative morbidity were similar in both groups. The total hospital costs for short-stay treatment group were significantly lower compared with control groups. This and other studies have demonstrated that the transfer of appropriate patients to high-dependency areas from intensive care following cardiac surgery is a safe option, allowing allotment of intensive care beds to more than one patient per day and cutting costs by reducing nursing-to-patient ratios [26].

### *Off-pump coronary artery bypass graft verses conventional coronary artery bypass graft*

Is there a difference with respect to outcomes in the fast tracking of off-pump coronary artery bypass procedures verses conventional coronary artery bypass? Cheng and colleagues [27] studied this aspect and concluded that off-pump coronary artery bypass (OPCAB) did not significantly reduce mortality and other postoperative events like stroke, myocardial infarction, or renal dysfunction. But the procedure did reduce the rate of atrial fibrillation, transfusion, inotrope requirements, plus ICU and hospital stays. Further long-term outcome studies are required to confirm the economic benefits of OPCAB procedures.

Prolonged ventilation has been associated with a very high hospital mortality and expense. To optimize nursing care and timely bed allotment, identifying the predictors of prolonged ventilation is crucial. In 1999, Wong and colleagues [28] studied the risk factors for delayed extubation (ie, $>10$ hours) and prolonged stay in the fast-track anesthesia patient population. In it, they found that increased age, female gender, and multiple postoperative factors such the use of intra-aortic balloon pump, inotropes, excessive bleeding, and atrial arrhythmia were risk factors for delayed extubation. In their review, perioperative variables such as recent myocardial infarction, intra-aortic balloon pump use, inotropes, renal insufficiency, and atrial arrhythmias were more predictive of prolonged ICU stay ($>48$ hours).

In terms of morbidity and resource use, the practice of fast-track cardiac anesthesia and surgery has led to a decrease in consumption of resources and no significant morbidity differences within a year after initial hospitalization [29]. Risk factors associated with increased mortality rates included female gender, emergency surgery, and poor left ventricular function [30].

Early extubation practices resulting from judicious use of sedatives and narcotics in fast-track anesthesia have led to concerns of increased risk of intraoperative awareness and inadequate postextubation analgesia. Cardiac surgery is known to have a higher incidence of awareness when compared with other surgical procedures. But because fast-track cardiac anesthesia consists of a balanced anesthetic technique including induction agents, volatile gases, and low-dose opioids, some studies have reported the incidence of awareness to be as low as 0.3% [31]. A commonly employed analgesic regime consists of the combination of carefully titrated narcotics (either patient-controlled analgesia or nurse-administered) and nonsteroidal anti-inflammatory drugs [32]. Other analgesic adjuvant include parasternal block and local anesthetic infiltration of the sternotomy wound. Although not shown to reduce time to extubation, local infiltration has resulted in reduced opioid requirements and side effects like respiratory depression and sedation, making this technique a successful adjuvant [33].

Regional anesthesia (ie, intrathecal narcotics like morphine and thoracic epidural analgesia) is an attractive alternative. Although inconsistently, low-dose intrathecal morphine has, in some studies, been show to facilitate early tracheal extubation and reduce postoperative analgesic requirement [34–36]. Regional anesthesia in this setting has well-known advantages, including a reduction in mechanical ventilation costs. This must be weighed against the risks of subarachnoid and epidural hematomas, which in the anticoagulated cardiac surgical patient may be as high as 0.35% [37]. Thoracic epidural anesthesia has been used in the setting of OPCAP surgery with some degrees of success. It has been shown to provide better postoperative pain relief than with patient-controlled analgesia [38]. The advantages of thoracic epidural analgesia including excellent analgesia, attenuation of the surgical stress response, and beneficial hemodynamics (ie, reduction in heart rate) with overall reduction in myocardial oxygen consumption [39]. As with any regional anesthesia technique, there is a risk of epidural hematoma and the potential of lost operating room time due to inadvertently obtaining a bloody tap.

The postoperative care of the cardiac surgical population is unique and ever challenging. Understanding of cardiac physiology and pathophysiology is essential to providing optimal care for these patients. With advancements in anesthetic and surgical techniques, fast tracking has become an exciting aspect of postoperative management. There is a growing body of evidence suggesting the need for intraoperative lung-protective strategies. Further research in these areas, will lead to safer, more effective management of this patient population.

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Crit Care Clin 23 (2007) 299–315

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# Mechanical Ventilation Strategies in Massive Chest Trauma

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In the realm of trauma and critical care, intensivists are challenged in the management of patients demonstrating respiratory and hemodynamic instability after sustaining massive chest trauma. A fundamental goal of critical care management is to avoid hypoxia and hypoventilation, the two main causes of mortality in the acute period following trauma. For most chest trauma patients, endotracheal intubation and chest tube insertion are the mainstays of treatment; however, a subset of these life-threatening injuries will require a more specialized approach.

A good trauma history and physical examination are essential. Elucidating the mechanism of injury, combined with assessment of the respiratory and hemodynamic status of the patient, can lead to prompt and appropriate intervention. Hemodynamic instability or a high output of bloody chest tube drainage may require other surgical intervention, such as a thoracotomy for pericardial tamponade or uncontrolled hemorrhage. In some cases, a laparotomy is required (eg, diaphragmatic rupture) [1].

In a recent multicenter review, Karmy-Jones and colleagues [2] noted a 40% incidence of emergent thoracotomy for penetrating injury, versus 17% incidence of emergent thoracotomy for blunt chest injury. Their reported 31% incidence of patients requiring pulmonary parenchymal procedure at thoracotomy was higher than the 20% rate generally reported in the literature [3–6]. On the other hand, the mortality following blunt trauma (68%) was significantly greater than that following penetrating injury (19%). The difference in mechanism-based mortality is primarily because of more severe systemic injuries commonly seen with blunt trauma as opposed to penetrating trauma [2].

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0749-0704/07/$ - see front matter 
doi:10.1016/j.ccc.2006.12.007 *criticalcare.theclinics.com*

## Pathophysiology of lung injury caused by trauma

The patient's mechanism of injury is important, because penetrating and blunt injuries have different clinical courses and sequelae. Blunt injuries are common and are primarily managed nonoperatively, whereas penetrating injuries tend to require operative intervention.

The pathophysiology behind the injury seen with massive chest trauma (blunt or penetrating) is a two-hit process: (1) direct parenchymal damage, and (2) alveolocapillary changes caused by systemic inflammation. Lung injury begins with the direct transmission of energy or lacerative traumatic injury resulting in pulmonary contusion, hemorrhage, and rupture.

In many cases, deterioration of lung function is caused by the systemic inflammatory effects of injury. Eventually, acute lung injury (ALI) and adult respiratory distress syndrome (ARDS) can ensue. Following trauma, pulmonary dysfunction is associated with increased vascular permeability in remote organs [7]. Consequently, extravascular fluid sequestration leads to third-spacing and contributes to hemodynamic instability. Excessive bronchial secretions can lead to lobar collapse, hypoxemia, decreased compliance, and postobstructive airway infection. Half of these patients will develop pneumonia [8]. All of these pathophysiologic events result in ventilation/perfusion mismatch, which compromises oxygen absorption in the lungs and subsequent oxygen delivery to vital organs.

## Supportive management

The mainstay of most clinical management in chest trauma is supportive care to control and contain the primary lung injury. The goal is to minimize the development of systemic inflammatory response syndrome (SIRS) and subsequent ALI/ARDS. Bilkovski and colleagues [9] suggested that early goal-directed therapy, such as avoidance of profound shock or, conversely, avoidance of excessive fluid overload, should take place by means of a continuous process of hemodynamic monitoring for adequate circulatory resuscitation. This can be achieved by a judicious balance of crystalloids and—once the initial resuscitation is completed—oncotic support, diuretics and inotropes.

## Thoracotomy for severe blunt chest injury

One indication of a need for operative intervention is an uncontrolled hemorrhage or air leak following chest trauma. In an unstable patient with the triad of hypothermia, acidosis, and coagulopathy, however, a damage control thoracotomy (DCT) may be the only option [10–13]. Massive hemoptysis caused by bronchial vessel rupture/laceration, severe pulmonary contusion, tracheobronchial injury, massive air leak (MAL), and bronchopleural fistula (BPF) must be corrected. Temporary measures to control

and contain bleeding either by bronchoscopic endobronchial balloon tamponade followed with bronchial artery embolization [14] or by operative stapler tractotomy can be life-saving [2]. As soon as the patient is hemodynamically stabilized, a CT scan of the chest is of paramount importance as an adjunct to diagnosis and to provide guidance for further management.

## Role of nonthoracic injuries

Long bone fractures complicate pulmonary management in that they prevent the mobilization of a patient that is required for good pulmonary toilet. Some literature suggests that early temporary stabilization of a fracture (eg, external fixation or damage-control orthopedics) will allow improved pulmonary toileting while deferring final fixation to when the patient is recovered. After temporary immobilization of long bone fractures, definitive fracture fixation that is delayed 2 to 3 days after injury has been shown to reduce the incidence of post-traumatic ARDS [15,16].

Combined severe abdominal and thoracic trauma represents a major risk factor for early-onset pneumonia [17]. Mechanical ventilation administered during the first days after trauma seems to reduce the risk of early-onset pneumonia. Mechanical ventilatory support lasting more than 5 days, however, is associated with an increased risk of late-onset pneumonia [17]. Rigorous pulmonary toileting, including endotracheal suctioning and bronchoscopy as necessary, is required to reduce the incidence of late-onset pneumonia. Because it is difficult to distinguish between lung injury and lung infection, either clinically or by imaging, bronchioalveolar lavage (BAL) sampling can help to limit the use of antibiotics and tailor the spectrum of antibiotics [18].

In any patient with an anticipated ventilatory duration over 2 weeks, consideration of performing a tracheostomy should be done early as an adjunct to pulmonary toilet [19]. Additional adjuncts to pulmonary toileting include the management and provision of adequate sedation and analgesia, which should include a scheduled reduction of sedation to allow patient cooperation with pulmonary toilet efforts. Epidural anesthesia/analgesia for regional block has been shown to have a significant impact on improving pulmonary mechanics and modifying the immune response in patients with severe chest injury [20].

## Independent lung ventilation

Independent lung ventilation (ILV) is a method of mechanical ventilation in which the right lung and left lung are managed independently, either by anatomical or physiological separation. ILV can either be one-lung ILV (OL-ILV) or two-lung ILV (TL-ILV). Of note, the usage of ILV is

only possible because of the development of the double-lumen endotracheal tube DL-ETT.

## Evolution of the double-lumen endotracheal tube

The DL-ETT first was introduced in 1949. The first tube was introduced by Carlen, which was a DL tube made up of firm red rubber, with a carinal hook to secure the tube, two separate cuffs (tracheal and bronchial), and a side hole between the cuffs. One lumen ends distally and the other lumen opens on the side hole. The Robertshaw tube is a modification of Carlen's tube with basically the same framework but without the carinal hook. The design has both left- and right-sided variants, where the bronchial cuff of the right-sided tube is slotted for right upper lobe ventilation (Box 1).

Currently, DL-ETT is made of polyvinyl chloride. It is softer, more flexible, and less irritating, thus reducing iatrogenic trauma to the tracheobronchial area. The tubes have larger internal-to-external diameter ratio, allowing more space for diagnostic and therapeutic intervention. The tube is transparent, allowing bronchoscopic visualization of the blue endobronchial cuff for adequate inflation and evaluation of the tracheobronchial mucosa. The cuffs are a high-volume low-pressure design, reducing the incidence of injury [24].

The concept of ILV first arose in 1931 when it was used for the practice of anesthesia during thoracic surgery. Subsequent to this, its usage spread in 1976 within an intensive care setting [30,31] and was specifically mentioned in 1981 for chest trauma [32].

The first noted use of ILV in chest trauma was in a 53 year old female who developed a unilateral "white lung" three weeks after injury. This was eventually diagnosed as an intra-parenchymal pulmonary hematoma. ILV was used with high-frequency positive-pressure ventilation within the diseased lung [32]. Although this was the first reported usage of ILV in a trauma patient, it was not used in the acute stage of injury (Table 1) [27,32–48].

The indications for ILV use in critical care for acute respiratory failure are defined poorly as compared with its use in thoracic anesthesia [49]. There is some evidence that ILV is an excellent option as a rescue ventilator strategy in critical care when conventional techniques fail, specifically in the case of a unilateral chest injury. One established criterion for ILV use in asymmetric lung injury is the demonstration of the effects of paradoxical PEEP: (1) hyperinflation of the normal lung, (2) a fall in $PaO_2$, and (3) an increase in shunting due to redistribution of blood flow [50,51].

## One-lung–independent lung ventilation

OL-ILV is a technique in which the patient undergoes ventilation of one lung while the other main or subsegmental bronchus is blocked

**Box 1. Double-lumen endotracheal tube insertion technique and maintenance**

*Choose which mainstem bronchus to cannulate*

*Select the size of the DL-ETT appropriate for the patient.*
*For adults of varying weight, Fr# 37, 39 and 41 are recommended [21].*

*Route of insertion*
Transoral
Transtracheal [22]

*Method of guided insertion [23]*
Laryngoscopic
Retrograde wire
Flexible bronchoscopy

*Confirm proper positioning [24,25]*
Auscultation
Radiography
Flexible bronchoscopy

*Check air leak around bronchial cuff to ensure functional separation [26].*
Water bubble technique
Balloon technique

*Dual monitoring to detect tube displacement [27–29]*
Noninvasive
- End tidal capnography
- Peak and plateau pressure
- Continuous spirometry

Invasive
- Flexible bronchoscopy

*Prevention of displacement*
Sedation and neuromuscular paralysis
Wiring the tube to upper teeth
Suspending the ventilator tubing close to DL-ETT

mechanically for the purpose of controlling and containing the spread of harmful fluid or secretions. In trauma, one indication is to prevent the spread of blood to normal lung parenchyma and allow for adequate alveolar capillary gas exchange.

There are several techniques available to achieve this goal, ranging from a simple mainstem bronchus intubation to the use of a DL-ETT or placement

Table 1
List of reported use of independent lung ventilation in trauma

| Year | Author | Diagnosis and comment | N |
|---|---|---|---|
| 1981 | Miranda, et al [32] | Lung parenchymal hematoma—white lung 3 weeks after injury | 1 |
| 1982 | Dodds and Hillman [33] | Massive air leak | 1 |
| 1984 | Barzilay, et al [34] | Chest injury with flail chest | 2 |
| 1985 | Hurst, et al [35] | Severe unilateral pulmonary injury | 8 |
| 1987 | Crimi, et al [36] | Acute lung injury, three cases with bronchopleural fistula (BPF) and three cases without BPF | 6 |
| 1989 | Frame, et al [37] | Pulmonary contusion in a 6-year-old child | 1 |
| 1989 | Wendt, et al [38] | Unilateral chest trauma with BPF | 1 |
| 1991 | Jooss, et al [39] | Traumatic bronchial rupture | 1 |
| 1991 | Watts, et al [40] | Chest blast wound—shotgun | 1 |
| 1992 | Miller, et al [41] | Pulmonary contusion with massive hemoptysis | 1 |
| 1997 | Johannigman, et al [42] | Pulmonary contusion treated using independent lung ventilation (ILV) with nitric oxide | 1 |
| 1997 | Diaz-Reganon Valverde, et al [43] | 26/45 acute respiratory distress syndrome (ARDS) caused by trauma, a controlled prospective study | 26 |
| 1998 | Ip-Yam, et al [44] | Unilateral ARDS caused by trauma in a 22 year-old patient treated with ILV-high frequency jet ventilation | 1 |
| 1999 | Pizov, et al [45] | Blast lung injury resulting from explosions on two civilian busses | 15 |
| 1999 | Wichert, et al [46] | Tracheal rupture near carina following blunt chest trauma | 3 |
| 2001 | Cinnella, et al [27] | Unilateral thoracic trauma—prospective study | 12 |
| 2004 | Moerer, et al [47] | Blunt chest trauma—total rupture of right mainstem bronchus | 1 |
| 2005 | Katsaragakis, et al [48] | Massive chest trauma with contusion, flail chest and pneumo–hemothorax and massive air leak | 2 |

of a bronchial blocker with a single-lumen ETT (SL-ETT). All of these techniques can be performed blind but are preferably guided by a bronchoscope.

## Two-lung–independent lung ventilation

TL-ILV is a mechanical ventilation strategy where independent ventilator circuits are used for each lung, working either synchronously or asynchronously. The purpose is to administer different modes of ventilation and/or different parameter settings to each lung.

In synchronous TL-ILV, the respiratory rate is kept the same between the two lungs but the cycle can be in phase or out of phase. Inspiratory flow rate, tidal volume (TV), and PEEP are set independently. This can be achieved by using either one ventilator system with a Y piece to accommodate separate PEEP valves, or two ventilators that are synchronized by using an external cable.

Asynchronous ILV must use two separate ventilators to be able to administer not only different ventilator settings but also administer different modes.

### Anatomical separation

Anatomical separation is useful in chest trauma in cases of one-sided endobronchial bleeding with hemoptysis. OL-ILV can be achieved using an SL-ETT with endobronchial blocker or by use of selective DL-ETTs. OL-ILV provides limited respiratory support and is a short-term measure pending definitive management to control the bleeding site. Direct vision using flexible bronchoscopy will help to localize the bleeding site to guide the process of blockade and to suction the airways of blood and secretions. This will prevent the flooding of the remaining functioning alveoli with blood and thereby prevent further compromise of gas exchange. At present, however, there is no established consensus as to when to institute OL-ILV, whether before, during, or after damage control surgery. Regardless, the ultimate goal is to stabilize the airway status of the patient. Remember advanced cardiac life support… airway, breathing, circulation!

When site of bleeding is unknown, DL-ETT should be used instead of bronchial blockers. DL-ETT intubation may be difficult in the setting of massive bleeding, but it will permit bronchial toilet and limited bronchoscopic therapy [24]. After the bleeding is isolated and contained, any necessary definitive treatment should be sought expeditiously [49].

### Physiological separation

Physiological separation is the process of ventilating each lung as an independent physiologic unit. In this case, the two lungs are managed using different ventilator modes and strategies (and potentially two different ventilators).

In complex thoracic injuries, there are situations in which there is an asymmetric or disproportionate degree of injury to the two lungs resulting in an asymmetric and disproportionate alteration in lung mechanics. Physiological separation with DL-ETT and TL-ILV can be implemented in asymmetric:

1. Pulmonary contusion
2. MAL or BPF
3. Bronchial injury

The clinical experience with the use of TL-ILV in bilateral lung injury is very limited.

### Patient management under two-lung independent lung ventilation

Once the DL-ETT is in place and the patient has a secure airway, a plan for the ongoing management of the patient should follow. Initial vent settings should correspond to equivalent ARDSNet protocols, obviously adjusted for lung size; a 55%/45% ratio for right/left volumes should be used. These

protocols are the result of data that showed that high levels of TV and/or airway pressure ($P_{aw}$) can harm the diseased lung parenchyma. Ventilation-induced lung injury (VILI) is a known complication of high TV and $P_{aw}$ [52–54]. TL-ILV can selectively lower the TV and provide higher PEEP in the diseased lung to prevent further VILI. Maintaining the plateau pressure ($P_{plat}$) not greater than 30 cm $H_2O$ to the diseased lung is suggested to prevent VILI [54]. Selectively titrating the TV and PEEP to the diseased lung by maintaining the $P_{plat}$ less than 26 cm $H_2O$ was shown to improve gas exchange and lung mechanics without affecting the hemodynamic status [27,48].

During ILV, monitoring of each circuit's airway pressures and compliance allows for adjustment of ventilator settings and avoidance of barotrauma to the less-diseased lung, as compared with conventional ventilation. PEEP is applied in amounts inversely proportional to lung compliance in an attempt to equalize the functional residual capacity of each lung. End tidal CO2 (Et-$CO_2$) is used as a measure of gas exchange, while $P_{plat}$ and static compliance ($C_{st}$) are used as a measure of lung function. Equalization of TV use and Et-$CO_2$ level on both DL and NL was the criterion for switching from TL-ILV to SL-ETT conventional mechanical ventilation [27,55].

## Pulmonary contusion

In most cases of minor pulmonary contusion, supplemental oxygenation by mask will be sufficient to prevent hypoxemia. Few adjuncts outside of endotracheal intubation are available to the trauma patient with pulmonary contusion. Although the use of biphasic positive airway pressure (BiPAP) has been described for managing hypoxemia in a patient with respiratory compromise, its usage is generally unwise in chest trauma patients. BiPAP predisposes to gastric distention and possible aspiration, especially in a population that may have depressed mental status at baseline because of injury or narcotic use. In these cases, prophylactic intubation should be instituted early on, before significant development of hypoxemia.

An extreme form of pulmonary contusion is seen secondary to blast injury, wherein the pulmonary contusion is diffuse and ill-defined. Several studies have used an extracorporeal shock wave lithotripter (ESWL) to induce a blast effect in a rat model. Results showed that the shock waves caused both intra-alveolar and intrabronchial hemorrhages, with an immediate threefold increase in lung weight [56,57].

These hemorrhages can complicate the mechanical ventilation of a noncompliant lung (either because of contusion or ARDS). Mechanical ventilation with higher mean airway pressure is therapeutic to counteract the low lung compliance seen in such cases. Strategies to achieve higher mean airway pressure include the use of positive end-expiratory pressure (PEEP), inspiratory/expiratory (I/E) ratio reversal, or use of a pressure control mode.

When the conventional methods of mechanical ventilation that have been described fail in a setting of an asymmetrical or a disproportionate degree of

lung injury, intensivists may wind up resorting to more unconventional methods like ILV to maintain oxygenation.

In an asymmetric pulmonary contusion, lung compliance is lower in the affected side compared with the less or noninjured side. Patients with lung contusions thus may experience hypoxemia because of impaired gas exchange. A common tendency is to use higher PEEP and/or TV to recruit the diseased alveoli. This will lead to hyperinflation of the normal lung. In such cases, the use of SL-ETT with conventional mechanical ventilation will divert most of the TV to the more compliant lung, leading to barotrauma. Distention of normal alveoli causes a shift of blood flow to the nonventilated lung (nonrecruitable air spaces filled with blood or exudate, which will increase the intrapulmonary shunt fraction further.

The use of TL-ILV is beneficial in this subset of patients with asymmetric or one-sided lung contusion to allow different ventilator modes and settings. Initial volumes of 4 to 5 mL/kg per lung can be used, and this can then be adjusted according to target plateau pressures [27]. Furthermore, selective PEEP to improve recruitment in the diseased lung without overinflating the normal lung can be applied. Preferential PEEP can be adjusted to gas exchange parameters or mean airway pressures. A selective lung opening procedure [58] also can be applied, as an aide to the re-expansion of collapsed alveoli on the diseased side of the lung. ILV can be discontinued safely when the TVs and compliance of the lungs differ by less than 100 mL and 20% [27]. Other modes using TL-ILV selectively that have demonstrated success are synchronized pressure-controlled inverse-ratio ventilation (PC-IRV) [40] and high-frequency oscillatory ventilation (HFOV) [44].

## Bronchopleural fistulas and massive air leaks

Large air-space leakages can occur in both blunt and penetrating chest trauma. Large volume losses tend to be related to a bronchopleural fistula (BPF). In blunt chest trauma, a massive air leak (MAL) can be from many disparate sources in an extensively damaged lung. In BPF, the air leak is typically through a single discrete pathway after a penetrating lung injury, following lung surgery, or following lung infection [59]. Ventilator management of BPF is often not applicable to management of MAL [60].

The treatment of BPF includes various surgical and medical procedures to reduce or seal the leak: manipulation of chest tube suction, HFOV [61], ILV, and bronchoscopic application of different glues, coils, and sealants [38,62–66]. Treatment options should be individualized depending on the site, size of BPF, and the severity of patient's comorbid conditions.

When conventional ventilation fails, ILV can administer mechanical ventilation selectively in the fistulous side by giving the lowest possible (TV), respiratory rate (RR), PEEP, and inspiratory time [24,60,67]. Conversely, HFOV is another technique that can be used to reduce the TV

exchange [64]. Both strategies can minimize the air leak to hasten the healing of MAL and BPF.

## Tracheo–bronchial injury

Tracheo–bronchial injury following blunt chest trauma is rare but potentially life-threatening. Trauma intensivists should have a high index of suspicion for this diagnosis, because there are no direct signs, and CT scan may fail to provide the diagnosis. Indirect signs of tracheo–bronchial injury include pneumothorax, pneumomediastinum, subcutaneous emphysema, or a nonexpanding lung after chest tube drainage of a pneumothorax. The fastest and most reliable diagnostic modality is the use of flexible bronchoscopy. After emergent surgical repair, TL-ILV is an option to protect the bronchial anastomosis during the early postoperative period [47].

## Acute bilateral lung injury

Acute bilateral lung injury remains a controversial indication for the use of ILV. Before the era of ILV, HFOV using an SL-ETT was used in trauma-induced ARDS [8]. No specific modality of ventilatory support has been shown definitively to change the prognosis of ARDS. PEEP does not influence the course of the syndrome, nor does it prevent ARDS [68].

The idea behind using TL-ILV in bilateral lung injury is still the existence of asymmetry in the degree of contusion. Successful use has been reported in ARDS [43]. ILV can be combined with lateral decubitus positioning with the diseased lung on the dependent side. Application of selective PEEP to the more diseased lung/dependent side will recruit alveoli in the better-perfused, less-ventilated dependent side while diverting perfusion from the better ventilated nondependent side. Although some data show an improvement in gas exchange with use of ILV in bilateral lung injury, this remains a controversial strategy [43,69,70].

## Less conventional strategies

There are times when the patient's disease process progresses beyond the capabilities of standard supportive care. This leaves the intensivist with other less well-described techniques to provide oxygenation. Some more extreme methods that have been described include: inhaled nitric oxide, prone positioning (PP), partial-lung liquid ventilation, and extracorporeal membrane oxygenation (ECMO).

Several published reports of these options showed promising results, while others were inconclusive. In the chest trauma literature, studies of this sort have been done mostly to treat trauma-induced ARDS. There

are very limited data on the use of these techniques in the acute stage of pulmonary contusion-induced acute pulmonary failure (APF).

*Nitric oxide*

Nitric oxide, in combination with TL- ILV, was reported to be a complementary management strategy for unilateral pulmonary contusion [42]. Both therapies are intended to minimize volutrauma to the normal lung. Given as a gas, NO induces pulmonary vasodilatation in areas of normal alveoli, thus preferentially altering the ventilation–perfusion ratio. An acute lung contusion causes a ventilation–perfusion mismatch by obstructing gas exchange, similar to a primary intrapulmonary shunt. In a study by Johannigman and colleagues [42], the greatest improvement in pulmonary function was seen when NO was delivered to either the normal lung or to both lungs. This suggests that NO treatment using an SL-ETT with conventional mechanical ventilation may be a viable alternative to DL-ETT/TL-ILV for treating asymmetric lung contusion. Theoretically, the use of NO also may be beneficial for patients who have a bilateral lung injury consisting of multiple patchy contusions and acute respiratory failure.

*Prone positioning*

From a clinical point of view, PP is a promising treatment for ALI/ARDS, even though its use is not yet a standard clinical practice. The idea of using PP in trauma patients was patterned from Bryan and colleagues' [71] classic study using PP as a factor affecting regional distribution of ventilation and perfusion in the lung. In ALI/ARDS patients, PP leads to a reversal of the typical alveolar inflation and ventilation distribution, because of the reversal of hydrostatic pressure overlying lung parenchyma, the reversal of heart weight, and the changes in chest wall shape and mechanical properties.

Relatively little data are available addressing the modifications in regional lung perfusion. The possible mechanisms involved in oxygenation improvement during PP in ALI/ARDS patients are: increased lung volumes, redistribution of lung perfusion, and recruitment of dorsal spaces with more homogeneous ventilation and perfusion distribution [72]. In two small studies, Stocker and colleagues [73] and Fridrich and colleagues [74] investigated the effect of PP on trauma patients with sepsis and trauma-induced ARDS with good results. Repeated PP recruits collapsed lung tissue and improves gas exchange [75] with improved patient outcome [76]. Despite the general concern for safety, Michaels and colleagues [77] safely and effectively used PP in patients who had ARDS, including many with medical issues generally considered to be contraindications. PP was used in all patients, including those who had recent tracheostomies, open abdomen following damage control laparotomies, thoracotomies, extremity internal and external

fixators, and central nervous system injuries, and during usage of large-bore continuous vascular access catheters (eg, ECMO or continuous veno-venoushemofiltration), vasopressor therapy, and facial fractures.

### *Partial liquid ventilation*

Partial liquid ventilation (PLV) first was reported in 1966 when Clark and Gollan [78] published its use in an animal study. Subsequent animal studies and a small number of human studies later reported overall improvement in lung compliance and gas exchange [79,80]. While receiving ECMO therapy in 10 adult patients with ARDS (1 trauma-induced), Hirschl and colleagues [81] reported that additional PLV treatment over ECMO showed better improvement in lung compliance and physiologic shunt.

These trials were performed using a perfluorocarbon solution to ventilate and oxygenate the lung. Perfluorocarbon is a highly dense insoluble liquid that allows free diffusion of $O_2$ and $CO_2$ in the alveolo–capillary interface when it is instilled into the airspaces of the lung. It also has surfactant properties and thus is capable of increasing alveolar surface tension. Because surfactant is deficient in ALI/ARDS patients, perfluorocarbon acts as liquid PEEP, recruiting collapsed alveoli and thereby improving oxygenation.

Anti-inflammatory properties also are attributed to perfluorocarbon. Smith and colleagues [82], in an in-vitro study, exposed alveolar macrophages to the solution, resulting in a decreased production of hydrogen peroxide and superoxide anions when compared with a control without perfluorocarbon. Other studies claim that perfluorocarbon has a local anti-inflammatory property in the alveolo–capillary interface, but the human ARDS study looking at its local anti-inflammatory effect was called into question as needing a better study protocol [83]. Despite all the theoretical beneficial properties of perfluorocarbon, trials in people who have respiratory failure have failed to show significant clinical improvement, especially in trauma patients.

### *Extracorporeal membrane oxygenation*

The use of ECMO in trauma-induced APF first was reported by Hill and colleagues [84] in 1972. Subsequent to this, many controlled studies were performed that used ECMO for APF in mixed populations of trauma and nontrauma patients. Subsequent published reports have failed to demonstrate its benefit, with mortality rates between 50% and 90% [85–91].

When the lungs fail to act as a ventilation/oxygenation unit, and all known therapeutic options fail, ECMO can serve as a temporary lung replacement. ECMO functions to oxygenate the blood and remove carbon dioxide outside the body. In practical terms, it serves as an adjunctive treatment while allowing mechanical ventilation under minimal settings. Using very small amounts of volume, pressure, rate, and FIO2 prevents lung

atelectasis, volutrauma, barotrauma, and oxygen toxicity. It is suggested that ECMO be used early on for a better response, at least within 5 days after starting mechanical ventilation [92,93].

ECMO can be compared with the process of hemodialysis. It uses a catheter (veno–venous or veno–arterial) connected to a machine. It is therefore not without complications. The use of heparin in the process may potentiate further bleeding in an already bleeding or coagulopathic chest trauma patient. ECMO is labor-intensive and requires a highly experienced critical care team.

In the same vein, ECMO, like hemodialysis, is a life support extender allowing intensivists to buy time for the lung to recuperate if at all possible. If the final outcome is end-stage lung disease, ECMO may serve as a bridge to lung transplant. At present, ECMO remains an invasive and expensive adjunct of unproven efficacy for the treatment of APF due to pulmonary contusion. At this point, because of its cost and complications, ECMO is reserved for those patients who have an isolated lung injury, with no other complicating factors preventing its use (eg, intracranial hemorrhage).

## Summary

Patients who have severe chest trauma can present significant challenges to the intensivist. In most patients, the mainstay of care is primarily supportive. There is a subset of difficult multisystem-injured patients, however, that can tax an intensivist's ability to balance contradictory concerns such as the titration of a mean airway pressure in a patient who has a large volume air leak.

Tools such as those outlined in this article should be a part of the intensivist's armamentarium in dealing with these complex issues. The employment of these tools can be done most effectively with an understanding of the capabilities and drawbacks of all the techniques outlined here. The creative use of these tools demonstrates the potential elegance of the practice of the art of critical care, ultimately suiting the needs of the injured patient.

## Acknowledgment

We would like to thank Alison M. Panzer, University of Rochester, School of Medicine and Dentistry and Margaret Chretien, Miner Library, University of Rochester Medical Center, Strong Memorial Hospital for their assistance in the making of this article.

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# Discontinuation of Mechanical Ventilation at End-of-Life: The Ethical and Legal Boundaries of Physician Conduct in Termination of Life Support

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"The task of medicine is to cure sometimes, to relieve often, and to comfort always."

16th-century French surgeon Ambroise Pare

The ICU is the point in health care where most end-of-life decisions are made. It generally is believed that most patients who die in modern ICUs do so following limitation of life support and allowing the underlying disease process to take its course. Reviews based on survey data suggest that approximately 25% of ICU deaths follow a failed attempt at cardiopulmonary resuscitation, whereas approximately 75% of ICU deaths occur after a deliberate decision to withhold or withdraw some form of life-supporting therapy [1,2].

By its nature and purpose, the ICU represents both a dense concentration of life support technology and an ethical battlefield where patient and family

The information presented herein represents generic medical and legal theory and analysis. It should not be construed to represent either medical or legal advice. By its nature the topic presented is controversial; every effort is made to present an unbiased neutral viewpoint. Dr. Szalados reports no conflicts of interest. The views and viewpoints expressed are those of the author and may not represent those of any of the entities with whom the author is affiliated.

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doi:10.1016/j.ccc.2006.12.006 *criticalcare.theclinics.com*

wishes are reconciled daily with medical judgments regarding prognosis and outcome, and the potential utility and futility of ongoing intensive care. ICU physicians are the gatekeepers of medical technologies that can save or prolong lives, but they also remain cognizant and vigilant of the common fallacy that "disease, aging, and death are unnatural acts, and all things are remediable" [3]. To the expert and the layman alike, the trappings of technology lie in in their ubiquity and mystery. In fact, "no social, human, or spiritual fact is as important as [technology] in the modern world; and yet no subject is so little understood" [4,5]. Moreover technology, a rational and efficient means of accomplishing a routine task, also inevitably displaces core human values and compassion from those enterprises to which it is applied [6]. People transfer a sense of the sacred to new technology in the hope that some magic in the technology will intervene and stop death. In today's highly technological society, so well-exemplified by the ICU, it is all too easy to forget that death is a natural end to all life, and technology is only a tool to be used judiciously, cautiously, and with an understanding of its inherent limitations.

The application of ethics to the management of medical technology has become increasingly important since the 1950s when rapid and progressive advances in medical science developed life support tools with an inherent potential to extend life beyond a point that some patients would wish to live. As a result of technology, the distinction between prolonging life and prolonging the dying process has become increasingly relevant. On the one hand are those who would "not gently go into that good night" [7], whereas there are also those for whom "the thought of an ignoble end, steeped in decay, is abhorrent. A quiet, proud death, bodily integrity intact, is a matter of extreme consequence" [8]. An important personal task of every physician is to determine the preferences of his or her patients, a determination best made during close personal communications before a health crisis supervenes. Perhaps the most important societal task of medicine is to better define the limits of medical care and support that most difficult of roles—where the fight for a cure turns to caring and compassion.

End-of-life care in the ICU generally encompasses both the withholding and withdrawal of life support and the administration of palliative care. Palliative care refers to the prevention or treatment of pain, anxiety, and physical symptoms in terminally ill patients. The withholding and withdrawal of life support each represents specific limitations of life-sustaining medical interventions and refers to either the noninitiation of specific medical technologies or the withdrawal of specific technologies, respectively. Note that, although the phrase is common in the medical vernacular; care is never withheld or withdrawn. Care and caring continue and perhaps even increase during palliation as the focus of medicine changes. Patients and their families all require reassurance that a limitation of life-sustaining treatment does not necessarily equate with acceptance of inevitable death, complacent surrender, or abandonment.

There is little practical distinction in the specific technology or life support modality that is limited or removed with respect to the subsequent medical, ethical, or legal analysis. Although it could be argued that limitation or removal of mechanical ventilation causes a more imminent demise than does limitation or removal of artificial nutrition, hydration, medications, or dialysis, the limitation of cardiopulmonary resuscitation and other critical interventions also can have as imminent a ramification. Thus, although relatively little of end-of-life care debates have centered specifically on mechanical ventilation, the distinctions between mechanical ventilation and other forms of life support technology are probably artificial and irrelevant.

Thus, the pivotal ethical issues one must address in the ICU at the point of life support discontinuation are:

- The distinction between allowing patients to die in accordance with their wishes and causing them to die
- The fine line between respecting a patient's wish to die with dignity and control and the risk of subsequent allegations of euthanasia or physician-assisted suicide
- The adjunctive use of medications that simultaneously provide comfort but also may hasten death

The inquiry is an essential one, because patients require reassurance that their wishes will be respected and not be subject to arbitrary dictates of individual providers. Clinicians deserve a clarification of currently permissible practices so that they can conform their behavior to the law, and legislators need to understand the potential bedside discord that can result from discrepancies between laws and ethical principles.

## Review of ethical principles

Medical ethics is focused on the application of the pivotal ethical principles of autonomy, beneficence, and nonmaleficence (or nonmaleficence). Autonomy speaks to the right of an individual to make decisions regarding his or her own personal self-determination. Autonomy represents the recognition of one's own sovereignty over one's own body. In medical care, autonomy is balanced against paternalism. Paternalism refers to a desire to make decisions and act on the behalf of others, in their presumed best interest, based upon a sense of superiority of understanding, knowledge, experience, or training. Paternalism is manifested either by active decision-making, or alternatively, by the conscious or subconscious withholding or diluting of key information. Until the time that patient autonomy gained widespread acceptance, it was customary for physicians to decide on the behalf of their patients. Beneficence refers to the fiduciary duty of physicians and health care providers to act in the best interest of their patients. Nonmaleficence expresses the guiding principle of medical care, ''primum non

nocere'' which translates from Latin as ''above else, do no harm.'' Harm itself can be defined variably as the intentional or careless infliction of physical, psychological, or emotional distress through acts of commission or acts of omission.

Respect for the notion of individual autonomy is held as paramount ideal in American society. Indeed, as early as 1891, the US Supreme Court clearly articulated that ''no right is held more sacred, or is more carefully guarded, by the common law, than the right of every individual to the possession and control of his own person, free from all restraint or interference of others, unless by clear and unquestionable authority of law'' [9]. The right of a person to control his or her own body has since been considered a basic societal concept, well-recognized in the common law. Judge Cardozo succinctly captured the essence of this theory as follows: ''Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages'' [10].

The ethical and legal justification of limitation and withdrawal of life support rests on the importance of patient consent, which itself is rooted in the concept of autonomy. The doctrine of informed consent is a primary means developed in the law to protect this personal interest in the integrity of one's body. ''Under this doctrine, no medical procedure may be performed without a patient's consent, obtained after explanation of the nature of the treatment, substantial risks, and alternative therapies'' [11]. Refusal to consent is a logical corollary to informed consent. It is the voluntary choice of a competent and well-informed patient that should determine whether life-sustaining therapy will be undertaken, continued, or removed. That same principle of informed consent is the basis for other decisions about any other medical treatment. Health care institutions and professionals must work to enhance patients' abilities to make decisions on their own behalf and to promote understanding of the available treatment options. Asking a patient to sign a form is not enough; there must be comprehensive explanations in layman's terms until there is full comprehension. There are three basic prerequisites for informed consent:

- The patient must have the capacity to reason and make judgments
- The decision must be made voluntarily and without coercion
- The patient must have a clear understanding of the risks and benefits of the proposed treatment alternatives or nontreatment, along with a full understanding of the nature of the disease and the prognosis [12]

Capacity refers to the ability to make decisions within a specific circumstance; patients under the influence of medications, cognitive dysfunction, injuries, or metabolic derangements that impair judgment are said to lack capacity. Informed consent and any advance directives for refusal or limitation of medical care (ie, do not resuscitate [DNR] forms) resemble legal contracts and must be obtained without fraud, duress, or coercion, after full

reasonable disclosure, from patients who have both competence and capacity.

Health care professionals serve patients best by maintaining a presumption in favor of sustaining life, while recognizing that competent patients are entitled to choose to forego any treatments, including those that sustain life [13]. The Council on Ethical and Judicial Affairs of the American Medical Association in its statement issued March 15, 1986, noted that "even if death is not imminent but a patient's coma is beyond doubt irreversible and there are adequate safeguards to confirm the accuracy of the diagnosis and with the concurrence of those who have responsibility for the care of the patient it is not unethical to discontinue all means of life-prolonging medical treatment. Life-prolonging medical treatment includes medication and artificially or technologically supplied respiration, nutrition or hydration."

Decisions about health matters and advance directives belong within the realm of medicine, not law. It is primarily because physicians so often have failed to address end-of-life matters and communicate the realities of disease and the limits of technology to patients and their families that the legislature and the courts have become the arena in which end-of-life are discussed and debated publicly.

## Advance directives

Advance directives are based in the ethical principle of autonomy. Advance directives generally take the form of documents such as living wills or personally signed do-not-attempt-resuscitation (DNAR) or DNR orders. Living wills may or may not within themselves also provide for the appointment of a proxy or executor. Advance care planning generally is perceived as an opportunity for patients to direct their care at a future time when illness otherwise would prevent them from speaking on their own behalf. The logical theory on which the notion of advance directives are based is summarized by the following syllogism: If patients could commit to and communicate explicitly, in advance of disability, the specifics of the health care they would want to receive in the future, then they could override the individual ethical and legal qualms of providers who could rest secure in the moral certainty that the patient's care was appropriate and legally protected.

All advance directives, however, are inherently ambiguous, because they cannot foresee the eventualities and the options. They additionally are limited by communication and comprehension. Even the most diligent attempts to pursue the content of written advance directives to the letter is frequently not medically practicable. The key phrases in almost every advance directive, "If I am ever hopelessly ill … unable to recognize and relate to loved ones …and my doctors say that I will not recover, then I would or I would not want" inevitably encompasses a huge range of available objective data, provider skills, and available technologies, and involves substantial individual subjective judgments and value analyses. Mortality prediction models

provide very precise and highly accurate estimates of patient mortality when applied to populations; however in the case of individual patients even the best model remains very limited. There nonetheless remain two key, but rarely considered considerations to which ICU patients and families have poor insight. First, even tight and logically derived confidence intervals centered around overall prognosis is of relatively little usefulness in individual patient care; and second, survival to ICU discharge is only a small factor in the complex process of hospital survival and ultimately, to functional recovery and eventual future quality of life.

On the other hand, if the patient, in an advance directive were to state that "I don't want a ventilator (and/or other aggressive life support measures) forever, but I would be willing to accept one for a few days to see if my medical condition improves," then the patient would implicitly abdicate autonomy in favor of medical paternalism, exactly the type of explicit and disproportionate the reliance on values and judgments of individual physicians that advance directives were intended to replace.

Nonetheless, the distinction is likely moot. Because the individual physician judgment and the collective cultural values of the specific care team often will drive the actions that are taken, with or without advance directives. Patients and families will decide on the basis of what is said, by whom, what is offered, and on the basis of what they understand and believe. Therefore, it may be argued that paternalism, although indirect, is alive and well in modern medical decision-making.

In fact, the more complete and complex an advance directive document is, the greater the scrutiny it attracts, because it is more likely to represent involvement of a careful and attentive lawyer. This type of intervention and supervision generally is regarded with suspicion. Hospitals are risk-averse institutions, and physicians are risk-averse professionals. Complex documents frequently fail to direct medical care, because they are patently ambiguous, and the underlying complexity easily forms the basis for a potential future lawsuit to challenge the medical decisions.

## Modern legal theory as it relates to the limitation and withdrawal of life support

Beneficence refers to the duty to do what is medically right or good for the patient; whereas nonmaleficence refers to the duty to do no harm. Medically right and legally right (especially with respect to end-of-life issues), however, have not always been as philosophically aligned as they are today. In fact, there remains significant controversy, which is likely to continue into the future.

United States federal and state courts reached broad consensus on matters of end-of-life medical care with the seminal cases of Karen Ann Quinlan in 1976 and Nancy Cruzan in 1990. Nonetheless, the current state of ethical

unrest [14] is well-exemplified in the recent case of Theresa Marie (Terri) Schiavo [15]. In the case of Schiavo, the public-at-large expressed concerns about:

- The lack of factual and medical clarity—family members took divergent positions, and commentators questioned the medical diagnosis
- Withdrawal of hydration and nutrition—food and water were thought to have special moral significance
- The level of decision making—politicians clashed on whether intimate decisions should be made by the family or the government
- The implications for the elderly and disabled, particularly the poor—concerns that the vulnerable would be abandoned and denied life-sustaining treatment [16].

Given the resurgence of these moral controversies, which previously had appeared to have been well-settled, it is essential that each practitioner consider his or her individual practice setting and base his or her decisions on applicable standards of care.

The legal dilemma of whether a physician can be held liable for withdrawing life support is not a simple matter of omission versus commission. A physician who removes a ventilator without the patient's authorization simply because the physician wishes to save electricity is homicide, and the act of ventilator withdrawal is the legal or proximate cause of death. Euthanasia is defined as "the act or practice of painlessly putting to death persons suffering from incurable and distressing disease as an act of mercy" [17], and, because it represents the intentional taking of the life of one human being by another, is homicide under the laws of every state. It is not a sufficient defense to a charge of homicide that the killing was undertaken with a benign motive.

States vary in the wording and scope of their respective homicide laws. Notwithstanding applicable defenses, however, the minimal requirement for criminal liability is the performance by a person of conduct that includes a voluntary act or the failure to perform an act that he or is physically capable of performing [18]. Thus, the legal definition of homicide requires an element of intent, where the actor's conscious objective is to cause death, or an objective to either knowingly or recklessly engage in such action. The termination of life-sustaining treatment could be done with the intent to kill, but there is no evidence to suggest or support that physicians directly and intentionally act with the intent of causing death. The competent patient's prerogative for self-determination at the end of his or her life represents the determinative factor and forms the basis for the intent of subsequent medical decisions and actions.

On the other hand, a person may be guilty of criminal negligence when he or she fails to perceive a substantial and unjustifiable risk, a risk that a reasonable person would perceive, and that failure to perceive risk constitutes a gross deviation from the standard of due care [19]. Criminally negligent

homicide is a lesser offense that involves a failure to perceive the risk in a situation where there is a legal duty of awareness; it is a criminal offense applicable to conduct that is obviously socially undesirable and is premised on preservation of the interests and claims of other persons in society [20]. For example, criminally negligent homicide has been applied to child welfare cases where a parent failed to summon help and subsequently refused medical care for a child in a dehydrated and malnourished condition, and the child subsequently died [21].

There may be a cognizable distinction between inaction in the face of a legal duty to act and an action or inaction based in a personal duty to another. Courts have held that a husband was not subject to criminal liability for his failure to summon medical aid for his competent adult wife where she had made a rational decision to refuse medical assistance on the basis of her religious beliefs [22]. The critical ethical and legal distinction might be seen as one of inaction versus active intervention. Courts, however, have rejected such a distinction, and instead recognized the patient's prerogative to forgo medical intervention (either by requesting the withholding or withdrawing of life-sustaining therapy) based in notions of individual self-determination, autonomy, and bodily integrity. Similarly, a differentiation between the noninitiation of and the withdrawal of life support would be meaningless and might even create a disincentive to attempt a trial of life support. Thus, the courts generally recognize a patient's "authority to forgo therapy even when such steps lead to death" [23].

In the case of Perlmutter, the Florida courts determined that a patient who suffered from terminal Amyotropic Lateral Sclerosis, would die were it not for a respirator. Here, the court determined that disconnecting a ventilator, instead of "causing … unnatural death by means of a death-producing agent in fact will merely result in his death, if at all, from natural causes… Mr. Perlmutter … really wants to live, but do so, God and Mother Nature willing, under his own power" [24]. The intent of the patient is limited to the removal of the feeding tube or ventilator, not necessarily to die, even though it is clear death will surely follow. Therefore, it appears that the courts generally agree that ending medical treatment does not itself cause death.

The word futility comes from a Greek term meaning useless or a goal that is incapable of being achieved. The most limited form of futility is physiologic futility, which is present when a certain treatment, such as a vasoactive medication, cannot achieve a desired physiologic effect, such as raising or lowering the blood pressure. By virtue of their training and experience, physicians are expected to be especially knowledgeable about what constitutes physiologic futility. The concept of futility, however, has been criticized given the absence of an accepted consensus definition, the absence of applicable clinical research data to define a percentage threshold, the variable application of this arbitrary standard, and the setting of goals of care by assertion rather than discussion [25]. Thus, the key problem associated with futility is that it represents a fluid concept defined situationally; it is

an individual or institutional perception rather than a defined and generally accepted standard. Interventions perceived as futile in one institution by some providers at a certain point in time may not be perceived as such elsewhere by others at a different time. Medical futility frames limitation of life support as an issue of prognosis. When the likelihood of functional recovery after a proposed course of therapy is less than a set percentage, usually 1%, physicians may assert the prerogative to withdraw therapy without the consent of the patient or surrogate decision maker. They are not obligated to provide care they consider physiologically futile even if a patient or family insists [26]. The history of legal cases involving futility has been that courts have almost uniformly ordered treatment when asked to resolve disputes between families favoring treatment and physicians who oppose it [27].

## Limitation and withdrawal of life support: advance directives and suicide

In fact, it is a generally well-accepted principle under modern medical and legal doctrine that a physician who limits or removes life support in response to a dying patient's directive is fulfilling an ethical duty to respect that patient's autonomy. In such as case, the underlying disease process, not the limitation of life support, is considered the proximate cause of death [28]. Thus, limitation of life support, based on a valid directive is legally protected, even though the technology is otherwise essential to life, and its removal clearly results in the patient's death.

Four compelling state interests appear to have been commonly identified by courts and commentators in such decisions:

- The preservation of life
- The prevention of suicide
- The protection of innocent third parties
- The maintenance of the ethical integrity of the medical profession [29]

When a patient declines life-sustaining medical treatment, the courts balance the patient's common-law and constitutional rights against these four important state interests.

In the years following the widespread availability of mechanical ventilation, the withdrawal of ventilation as an end-of-life care measure was highly controversial. In the case of Karen Ann Quinlan, who had been in a persistent vegetative state for 9 months, parents asked that her ventilatory support be withdrawn. The parents were supported in their request by the primary care physician (PCP) but were opposed by the hospital and professional medical societies including the American Medical Association (AMA). Nonetheless, since the Quinlan case was decided in 1976, courts have uniformly upheld the prerogative of a competent person who is facing a potentially fatal disease to decide whether to initiate or maintain life-sustaining medical intervention.

That personal prerogative is has based in a respect for individual freedom and autonomy, and the common law notion of informed consent and its

corollary, informed refusal. In dictum for its 1991 decision in Cruzan [30], the US Supreme Court strongly suggested that the concept of liberty guaranteed in the 14th Amendment to the US Constitution may encompass the right to refuse unwanted medical intervention.[1] Nonetheless, the due process clause has been specially interpreted by the Court to protect those fundamental rights and liberties that are, objectively, "deeply rooted in this Nation's history and tradition" [31]. The court also recognizes that "appropriate limits on substantive due process come not from drawing arbitrary lines but rather from careful respect for the teachings of history [and] solid recognition of the basic values that underlie our society" [32].

When the limitation or withdrawal of life support or the administration of potentially lethal medications occurs in the context of assisting a suicide, the ethical and legal stance is significantly less supportive. The pivotal issue here and once again, is that of intent. At one extreme are those cases where the suicide involves a hastening of death in the context of progressively debilitating or soon-to-be terminal illness, simply to allow the patient a measure of control over his or her death. At the other extreme is a patient with a nonlethal medical condition who simply desires to die. The first case might be colored as an extension of the doctrines relating to the limitation of life-sustaining therapy and thereby fall within the realm of quasi-ethical behavior. The doctrine of double effect holds that it is morally acceptable to cause an otherwise unacceptable result if that result is the unintended consequence of a legitimate act. The classic example of the application of the principle of double effect in the right-to-die context is the administration by a physician of a pain-killing medication to a terminally ill patient suffering from intractable pain, which, though not intended to be lethal, in fact turns out to be lethal. In such a case, the physician's intent is said to be the relief of the patient's suffering, which is a morally and legally acceptable practice. On the other hand, the second case falls clearly outside the bounds of ethical conduct and also has the elements of a criminal act, perhaps because medicine provides some options for treatment and even cure of depressive disorders. In general, however, there is no persuasive evidence that physicians administer analgesia or sedation to terminal patients with the intent to end their lives. A tenable distinction between high-dose analgesia and/or sedation and euthanasia is a fine line that separates the calculated risk of providing comfort at the end of life from conduct that otherwise would be uniformly recognized to be lethal. Comfort measures are accepted widely as medically ethical, whereas high-dose narcotics are more likely to be questioned. Although there is a logistical slippery slope that connects the two types of cases

[1] In 1997 Chief Justice Rehnquist acknowledged that his opinion in *Cruzan* opinion had "strongly suggested" the existence of this federal constitutional right. In the *Cruzan* decision per se, Justice O'Connor's concurring opinion declared that a forced medical intervention offends a person's constitutional "freedom to determine the course of her own treatment" (*Cruzan,* 288–9).

and there is no bright-line test distinguishing right from wrong, the closer one comes to assisting a suicide in the absence of a terminal condition, the stronger the case must be to survive scrutiny. For society, the potential inherent dangers are:

- That safeguards might be ignored
- That safeguards may erode, either in practice or through judicial decision, and people will demand assisted suicide for trivial reasons
- That life gradually will become devalued
- That gradually physician-assisted suicide will be converted from something that is practiced by a few under rare and specific circumstances into something that becomes commonplace and trivial [33]

Likewise, too fine a distinction between withholding life support and terminating it would be medically, ethically, and legally problematic. Decisions to withhold life support most often are based in refusal to consent or advance directive documents. Rationing of scare ICU resources might also, although less often, fall into this category [34]. Although it might seem to be a potentially easier, more passive, and a more psychologically rationizeable decision to forgo or withhold life support by not initiating it, such a legal distinction could be an affront to good medical decision-making. If such a distinction were to assume a position of paramount importance, then providers would be discouraged from a reasonable trial of aggressive therapy. Also, patients come to the ICU as they are, from other centers, through other providers, or through the clinical rotations of the ICU team.

Today, committing suicide is typically not a crime in all States, although aiding and abetting or soliciting suicide both represent acts that are generally criminalized in state statutes [35]. If the withdrawal of life support occurs against a patient's explicit wishes, however, or in the setting of a realistic potential for recovery, then disconnection would be a criminal homicide. On the other hand, if the intent of the patient was simply to die, then the disconnection of the ventilator could be seen either as euthanasia or assisted suicide, and both acts are generally characterized as felonies under United States laws.

The US Supreme Court's decisions in Washington v Glucksberg and Vacco v Quill addressed the issue of whether there was a constitutionally protected right to die as a result of physician-assisted suicide and failed to find such a right. The Washington State courts initially held Washington's state statute unconstitutional, because it was felt to place an undue burden on terminally ill mentally competent adults who wished to commit physician-assisted suicide [36]. The US Supreme Court reversed holding that "an examination of the nation's history, legal traditions, and practices revealed that the asserted right to assistance in committing suicide was not a fundamental liberty interest protected by the due process clause; the … right to assistance in committing suicide was not consistent with the Supreme Court's … line of cases" [37]. Therefore, "suicide requires a specific intent to die which courts have found absent in persons who have refused

extraordinary methods of medical care'' [38]. Even the opinion of New Jersey Supreme Court in Quinlan distinguished informed refusal of unwanted medical intervention in the setting of futility from suicide when it commented that ''[w]e would see… a real distinction between the self-infliction of deadly harm [suicide] and a self-determination against artificial life support… in the face of irreversible, painful, and certain imminent death.''

The natural death and living will statutes enacted in the period between 1976 and 1997 concurred and uniformly provided that medical limitation or withdrawal of life support pursuant to a terminally ill patient's instructions was not to be equated with suicide or assisted suicide. In such circumstances, the prevailing legal structure appears to regard the patient as acquiescing to a natural dying process, or as letting nature take its course, rather than as a desire to end one's life prematurely. More recently, the Second Circuit Court of Appeals contended in Quill v Vacco that withdrawal of life support at the request of a competent patient is ''nothing more nor less than assisted suicide'' [39]. In Vacco, the court has recognized implicitly a distinction between letting a patient die and making a patient die. Thus, for a dying patient in whom prolongation of life support is likely to be meaningless or futile, the withdrawal of life support allows nature to again take its course by allowing circumstances to be restored to a point similar to those prevailing before the artificial intervention.

The AMA emphasizes a ''fundamental difference between refusing life-sustaining treatment and demanding a life-ending treatment'' and notes that ''physicians have an obligation to relieve pain and suffering … of dying patients in their care. This includes providing effective palliative treatment, even though it may foreseeably hasten death'' [40].

Many state statutes make legal exceptions for the medically supervised administration of comfort-promoting medications in end-of-life care situations. For example, the Indiana State Code specifically notes that the section pertaining to assisted suicide does not apply to ''a licensed health care provider who administers, prescribes, or dispenses medications or procedures to relieve a person's pain or discomfort, even if the medication or procedure may hasten or increase the risk of death, unless such medications or procedures are intended to cause death.'' In 1994, Oregon became the first state to legalize assisted suicide following voter approval of a ballot measure that resulted in the Oregon Death with Dignity Act (ODWDA) [41]. The ruling survived a 1997 court challenge and also a US Attorney General challenge brought under the Controlled Substances Act [42].

## Limitation and withdrawal of life support: substituted judgments

The term health care proxy refers a person appointed by a patient specifically for the purpose of making health care decisions on his or her behalf. An alternate form of proxy is the durable power of attorney for healthcare,

which is recognized in some jurisdictions as a proxy substitute who assigns authority to perform specified health care functions and decisions on behalf of the signer. The power is durable, because, unlike the usual power of attorney, it continues to be in effect even if the signer becomes incompetent.

In Cruzan, the US Supreme Court concluded that "a state may apply a clear and convincing evidence standard in proceedings where a guardian seeks to discontinue nutrition and hydration of a person diagnosed to be in a persistent vegetative state" [43]. Many states have adopted the clear and convincing standard, although the standard may be mitigated by the application of various balancing tests. Balancing tests weigh competing priorities and interests to determine the proper legal and ethical choice.

In the case of Cruzan, the Missouri Supreme Court determined that Nancy Cruzan's parents did not have the authority to have life-sustaining nutrition and hydration removed since the was a lack of clear and convincing evidence of Nancy's desire to have life-sustaining treatment withdrawn under such circumstances. The US Supreme Court agreed. Although the principle of informed consent and informed refusal articulated in Quinlan and other cases is well-established, states may individually legislate processes and rules regarding the selection of surrogate decision-makers and the limits of what surrogates can decide.

With respect to the scope of surrogate decision-making, all states seem to agree that such decisions should be guided by the wishes of the patient. The legal guidelines are less clear for circumstances in which incompetent patients lack surrogates. For example, in Illinois, for a person who lacks decisional capacity and suffers from a terminal condition, permanent unconsciousness, or irreversible condition, the Illinois Health Care Surrogate Act authorizes a surrogate decision maker to decide whether to forgo life-sustaining treatment on that person's behalf [44]. The Illinois statutory criteria appear to be especially comprehensive and compelling:

> A surrogate decision maker shall make decisions for the adult patient conforming as closely as possible to what the patient would have done or intended under the circumstances, taking into account evidence that includes, but is not limited to, the patient's personal, philosophical, religious and moral beliefs, and ethical values relative to the purpose of life, sickness, medical procedures, suffering, and death. Where possible, the surrogate shall determine how the patient would have weighed the burdens and benefits of initiating or continuing life-sustaining treatment against the burdens and benefits of that treatment. In the event an unrevoked advance directive, such as a living will, a declaration for mental health treatment, or a power of attorney for health care, is no longer valid due to a technical deficiency or is not applicable to the patient's condition, that document may be used as evidence of a patient's wishes. The absence of a living will, declaration for mental health treatment, or power of attorney for health care shall not give rise to any presumption as to the patient's preferences regarding the initiation or continuation of life-sustaining

> procedures. If the adult patient's wishes are unknown and remain unknown after reasonable efforts to discern them or if the patient is a minor, the decision shall be made on the basis of the patient's best interests as determined by the surrogate decision maker. In determining the patient's best interests, the surrogate shall weigh the burdens on and benefits to the patient of initiating or continuing life-sustaining treatment against the burdens and benefits of that treatment and shall take into account any other information, including the views of family and friends, that the surrogate decision maker believes the patient would have considered if able to act for herself or himself.
>
> 755 ILCS 40/20 (2006)

In Connecticut, a statute similar to that of Illinois, the Removal of Life Support Systems Act exculpates physicians from liability…

> for damages in any civil action or subject to prosecution in any criminal proceeding for such withholding or removal, provided (1) the decision to withhold or remove such life support system is based on the best medical judgment of the attending physician in accordance with the usual and customary standards of medical practice; (2) the attending physician deems the patient to be in a terminal condition or, in consultation with a physician qualified to make a neurological diagnosis who has examined the patient, deems the patient to be permanently unconscious; and (3) the attending physician has considered the patient's wishes concerning the withholding or withdrawal of life support systems. In the determination of the wishes of the patient, the attending physician shall consider the wishes as expressed by a document …. if any such document is presented to, or in the possession of, the attending physician at the time the decision to withhold or terminate a life support system is made. If the wishes of the patient have not been expressed in a living will, the attending physician shall determine the wishes of the patient by consulting any statement made by the patient directly to the attending physician and, if available, the patient's health care agent, the patient's next of kin, the patient's legal guardian or conservator, if any, any person designated by the patient … and any other person to whom the patient has communicated his wishes, if the attending physician has knowledge of such person. All persons acting on behalf of the patient shall act in good faith. If the attending physician does not deem the incapacitated patient to be in a terminal condition or permanently unconscious, beneficial medical treatment including nutrition and hydration must be provided.
>
> Conn. Gen. Stat. § 19a-571

In summary, limitation and withdrawal of life support appear to have the widespread acceptance and support of the medical, legal, and ethical communities. It could be a reasonable conclusion that patients who suffer from a permanent or progressively incapacitating medical condition, an imminently terminal diagnosis, or an acute massively debilitating condition with little hope of functional recovery are probably protected under existing philosophy and law. In the case of most of the decisions that take place in ICUs, the patients' wishes, the prognosis and available therapeutic options,

and the families' understanding are aligned and therefore allow for a simplified approach to end-of-life care.

There remain instances, however, where the diagnosis and the patient's wishes are not congruent with the mainstream of medical and legal ethics; in such circumstances providers may not be protected under existing laws or standards of care. Physicians are well-advised to approach end-of-life care issues conservatively, albeit compassionately, unless they are prepared to challenge the status quo. What should always remain, unambiguously entrenched in the medical ethic, is that the duty of the physician runs first and foremost to his or her patient.

## A proposed algorithm for the management of terminal weaning: general considerations

The management of the care of patients at the end of life may be divided arbitrarily into two phases: (1) first, the process of shared decision-making that leads from the pursuit of cure or recovery to the prioritization of comfort and (2) the actions required once this shift in treatment goal has been determined and the resulting focus on humanistic and technical issues that ensure that the needs of the patient and family are met [45].

Intensivists generally appreciate that difficult end-of-life decisions should be based on team discussions, reducing subjective elements to a minimum and providing input from all members of the ICU team. Each member of the team will see the patient's dilemma from a slightly different viewpoint, and the combined opinions of all members can facilitate a sound decision-making process [46]. The multidisciplinary team model of critical care is a strategy to increase patient safety and improve the quality of care. Nonetheless, the final stages of end-of-life care decision making almost invariably will fall under the responsibility of either the patient's private physician or the ICU attending physician. It is the responsibility of physicians as health care team leaders to ensure that the ICU environment is characterized by open communications, caring, and support. In situations where some members of the team have conflicts of belief, internal emotional conflicts, or conflicts of interest that preclude open and objective communication and decision-making, they may request that they be excused and transfer their patient care responsibilities to a colleague. Patients and families sense uncertainty and ambiguity and react with suspicion and confusion. Suspicion and confusion subsequently fuel challenges and potentially litigation.

The ethics committee sometimes can render additional insight to the ICU care team. All hospitals have ethics committees that provide ethics consultations. In general, the recommendations of ethics consultations are not binding, but they nonetheless can be useful to document ongoing dialog and the ethical considerations. Ethics consultations may useful in resolving conflicts regarding nonbeneficial or unwanted treatments in the ICU [47].

There remains, however, wide variability in ethics consultants' recommendations and a lack of objective guidelines [48], which may significantly undermine the utility of ethics service consultations [49].

Many hospitalized patients die with untreated but potentially treatable pain, even in ICUs [50]. The initiation of palliative care reverses the clinical priorities from the treatment of diseases and emphasizes symptom management. The recently accepted concept of pain as the fifth vital sign is one way of emphasizing the importance of treating pain assessment as a core element of patient care. The use of pain scales such as the visual analog scale provides for semiobjective quantification of the patient's experience. Pain assessment in dying patients often relies primarily on evaluation of level of consciousness and awareness, breathing pattern, and hemodynamics. When pro re nata orders are written for analgesics and sedatives, the indication for administration should be stated clearly to minimize the likelihood of misinterpretation or abuse. For example, where a clinician titrates morphine in increments to a documented clinical effect, any reasonable reviewer should conclude that the intent was to make the patient comfortable and not to directly cause the patient's death. On the other hand, where a large dose of morphine is administered acutely to a patient who is not otherwise tolerant, it may be seen as an intentional overdose calculated to cause the death of the patient.

Grenvik [51] was the first to describe a systematic approach to ventilator withdrawal at the end of life and advocated a gradual reduction in the ventilator settings over several hours. Although there remains some element of controversy [52], it is generally well-settled that noninvasive mechanical ventilation has no role in end-of-life care and serves to promote confusion among care providers and usually violates the intent of the end-of-life directive. Parenthetically, noninvasive ventilation does have a potentially important, but time-limited, role in the specific circumstance where a patient chooses not to accept intubation but would be amenable to a trial of BiPap or other similar modality of noninvasive ventilation [53,54].

There remain two commonly employed strategies for withdrawal of ventilator therapy: immediate ventilator removal (either T-piece or extubation) or terminal weaning. In all circumstances, the patient's comfort and the family's perceptions should be considered in making the appropriate choice. Additionally, the patient's family must be informed so as to conform expectations to perceptions.

Immediate extubation represents the most direct approach that also implicitly reflects unified strength of conviction and also a strict adherence to the explicit intent of the new goals of care. The process of terminal extubation also has the advantages of being morally transparent; the intentions of the care team are clear, and the process cannot be confused with a therapeutic weaning. The endotracheal tube (ETT) is removed following appropriate suctioning of the airway. Humidified room air may be administered only if it is important to prevent the airway mucosa from drying to the point of discomfort. The concept of anticipatory dosing of anxiolytics and analgesic is a vitally important

consideration when an immediate extubation occurs; it is insufficient to attempt reactive dosing in the situation of acute distress. Breathing patterns can be misleading indicators of discomfort in terminally-ill patients; irregular breathing patterns are a natural part of dying and may not be uncomfortable for the patient (the use of the term agonal respirations in discussions with the family is strongly discouraged). Similarly, gasping is a medullary reflex and may occur in the absence of consciousness [55]. In the instance where airway obstruction supervenes, a nasal airway is minimally invasive and can provide important psychological comfort to the family. On the other hand, ventilator removal and replacement of positive-pressure ventilation with spontaneous ventilation by means of a T-piece may be reasonable in those instances where the patient has been dependant on high levels of support. Here, the removal of positive pressure and $F_IO_2$ likely will precipitate a rapid hypoxemia without intermittent airway obstruction.

Terminal weaning, the other alternative, is rapid weaning performed without attention to the usual indicia of weanability over a period of as little as 30 to 60 minutes. The advantages of terminal weaning are that the administration of sedatives and analgesics can be titrated to individual needs before the removal of the ETT, and therefore patients may be less likely to develop air hunger, pain, and anxiety.

## A proposed algorithm for the management of terminal weaning: practical considerations

During the determination of directives and delineation of end-of-life care, clinicians should:

- Familiarize themselves with state laws, institutional polices, and medical staff by bylaws regarding end-of-life care.
- Determine if advance directives are available, review them and document findings, and place copies of the original document in the medical record. Where advance directives are obtained in-house after admission, the attending physician should participate in the discussions personally. Although house staff and physician extenders may obtain necessary signatures, the attending physician must remember that the final responsibility for the communication of prognosis, explanation of issues of consent and refusal to consent, and the delineation of an end-of-life care plan rest (medically, ethically, and legally) with him or her alone.
- Determine if a health care proxy (or a durable power of attorney for health care, or other similar document depending on state laws) is available. Review the document and refer to that document in the chart. Place a copy of the original health care proxy document in the medical record.
- Where applicable, ascertain that the patient is not clinically depressed or suicidal. Ensure that a limitation of life support is medically reasonable under the circumstances. In the instance that an existing ICU patient

who may be delirious or confused is limiting his or her life support, carefully perform and document a mental status examination. Postoperative cognitive dysfunction represents a long-lasting but subtle cognitive deficit following anesthesia or sedation in susceptible patients. They may not understand the ramifications of the informed consent. Consider obtaining the documented opinion of a second physician. Consider the opinion of a psychiatrist if competency might be raised as an issue later.

- Communicate frequently, at least daily, with the patient, or his or her appropriate representative. Communication should be unhurried but professional. Remember that disclosure of protected health information is restricted under Health Insurance Portability and Accountability Act, state statutes, and hospital policies. Document these communications to the best extent possible in the medical record.
- Involve the patient's PCP in the ICU plan of care, ifappropriate and if possible. Explore any insights that the PCP may have regarding the diagnosis, the patient's wishes, existing off-site documentation, and any pertinent psychosocial issues. Make sure that the PCP is fully aware of the ICU team's diagnosis, prognosis, and plan before he/she approaches the patient or family. Likewise, involve consultants who have a relationship with the patient, where applicable.
- The ICU physician must regularly meet with the patient's care team. Explore individual perspectives, biases, or preferences. It is vitally important that the ICU care team present genuinely unified and consistent information and opinions to the patient and family. Where discontinuation of life support is contemplated and some team members dissent, dissenters should be convinced and not overridden, if at all possible.
- In potentially difficult situations, consider proactively obtaining the advice of in-house legal counsel, medical administration, or the ethics committee.
- Adhere to all applicable standards of medical care and adhere to all medical documentation requirements.

Prior to discontinuation of life support or ventilator withdrawal, physicians should:

- Review and ascertain all pertinent documentation. Notify all the PCP, pertinent services, and consultants as appropriate.
- Discuss the patient's and family's wishes for rituals (pastoral support, prayer services), visitation (children, pets, friends). Make sure that access is accorded to all necessary parties regardless of the time of day or general visitation policies. Provide for seating, special access needs, and refreshments.
- Disengage all monitors and alarms in the patient's room.
- Remove physical restraints, medical paraphernalia (sequential compression device, cooling blankets). Determine if removal of a nasogastric tube is appropriate (may be necessary to prevent vomiting). Determine if discontinuation of nutrition is compatible with the patient's or family's wishes. Discontinue laboratory work and radiology studies.

- Discontinue paralytics, vasoactive medications, total parenteral nutrition, aggressive hydration, noncomfort medications (antibiotics, deep vein thrombosis prophylaxis, glucose control).
- Maintain secure intravenous access for administration of palliative care medications. Determine if discontinuation of hydration is compatible with the patient's or family's wishes.
- Establish and document objectively adequate symptom control prior to extubation.
- Keep a reasonable rescue dose of sedative at hand in the case of acute symptomatic distress. Ensure that the nursing care plan clearly documents the need for sedation and the patient's responses. At least until the situation and the patient's condition is stabilized with respect to symptom control, nursing assignments should be such to allow immediate availability and close personal support. Likewise, the attending physician should be present until at least the point after which the ventilatory support has been removed and the patient is comfortable.

The following steps should be followed for ventilator withdrawal:

- Optimize sedation and pain control as the situation warrants and per the specific needs of the patient and family. Educate the family about the ventilator withdrawal process, the use of anxiety and pain control, and explore their expectations. Determine specifics ahead of time (use of a nasal airway, humidified air administration, transfer plans from the ICU).
- Whenever possible, extubate the patient without the family immediately present. Suction the airway, deflate the ETT cuff and remove the ETT, silence alarms, turn off and remove the ventilator. Nursing and respiratory therapy staff should be present.
- Allow for family privacy but be available. Have tissues, moist towels, lip balm, wash cloths, and medications available. The family should be encouraged to hold the patient's hand, hug the patient, and communicate.
- Address concerns and perceptions immediately. Be prepared to spend additional time with the family. After death, encourage the family to spend as much time at the bedside as they may need; provide acute grief support. It is completely acceptable for physicians and their staff to share in the emotions of the family.
- Consider attending the funeral and/or allowing members of the ICU care team who have had developed a close relationship with the patient or family to attend the funeral. Consider a sympathy card.
- Debrief the entire ICU care team afterwards.

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