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NEONATOLOGY

Recent Advances in NEONATOLOGY

Learn from the Legends



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CHAPTER 8

Volume-targeted Ventilation: One Size does not Fit All

Martin Keszler

INTRODUCTION

Mechanical ventilation is often lifesaving but is also associated with short- and long-term complications, such as hemodynamic impairment, pulmonary air leak, inadvertent overventilation with subsequent brain injury, and chronic lung disease. Our understanding of the pathophysiology of these adverse effects has improved considerably over the past few decades allowing us to reduce their severity but uptake of newer techniques of mechanical ventilation, such as volume-targeted ventilation remains uneven. Additionally, the more sophisticated modalities of ventilation require a good understanding of patient-ventilator interactions and careful implementation of support tailored to each individual patient and their underlying lung pathology.

MECHANICAL VENTILATION AND LUNG INJURY

The mechanisms of lung injury are multifactorial and usually triggered by some form of biophysical injury that triggers a cascade of events that includes an influx of activated neutrophils followed by the release of a variety of inflammatory mediators that initiate the process of lung injury and repair. Oxidative stress due to exposure to relative hyperoxia (compared to the intrauterine environment) even in room air contributes to the inflammatory response. Preterm infants are uniquely susceptible because of their immature lung structures and lack of antioxidant defenses. Moreover, prematurity is frequently associated with intrauterine exposure to infection which can initiate the inflammatory cascade even prior to birth and result in early progression to chronic lung disease. Because of the multifactorial etiology of bronchopulmonary dysplasia (BPD), no single intervention is likely to result in a dramatic reduction of its incidence; rather, a bundle of care designed to optimize all aspects of care is required.

THE GOLDEN FIRST HOUR

The immediate perinatal period, often referred to as the "golden first hour", is a time of greatest vulnerability for very preterm infants whose excessively compliant chest wall, lack of pulmonary surfactant, and insufficient muscle strength make it difficult to clear fluid from their lungs and establish and maintain functional residual capacity (FRC). Suboptimal respiratory support during this vulnerable period can easily launch the infant on a trajectory of progressive lung injury and chronic lung disease. Lung injury can occur quite rapidly during this period. Bjorklund et al. demonstrated that the beneficial effect of exogenous surfactant can be fully negated by as few as six excessively large manual inflations,[1] likely mediated by the outpouring of proteinaceous exudate as

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a result of excessive tissue stretch. Provision of positive end-expiratory pressure (PEEP) during positive pressure ventilation of preterm infants is essential to establish and maintain FRC. Using phase contrast radiography in premature rabbit pups, Siew et al. demonstrated that after 20 positive pressure inflations with 0 PEEP, there was virtually no FRC on exhalation and very poor aeration even at peak inflation. In contrast with 5 cmH_2O of PEEP, the lungs showed good, homogeneous inflation on inspiration and retained good FRC on exhalation.[2] Establishment of FRC using positive pressure ventilation with PEEP takes some time, and moving lung liquid through small airways results in much longer time constants than moving air, owing to the much greater viscosity of lung liquid; thus, a prolonged inflation ought to be more effective in moving liquid out of the airspaces and achieving uniform lung aeration. The practice of sustained inflation (SI) with pressure of 20–25 cmH_2O for 10–15 seconds became widespread in Europe and was supported by preclinical and smaller clinical trials,[3] but the large multinational Sustained Aeration of Infant Lungs (SAIL) trial performed in the most immature infants failed to demonstrate any benefit and was associated with increased early neonatal mortality.[4] A subsequent meta-analysis showed a strong trend toward higher mortality with SI;[5] therefore, this practice is no longer recommended. A randomized clinical trial comparing a static versus dynamic PEEP as a potentially better way to facilitate lung aeration in very preterm infants requiring positive pressure ventilation is underway and will hopefully answer the question regarding the optimal way to facilitate initial lung aeration. In spontaneously breathing preterm infants, provision of adequate continuous positive airway pressure is essential in allowing these infants with excessively compliant chest wall to achieve and maintain adequate FRC, because tidal breathing with lungs that are not uniformly aerated, whether spontaneous or generated by positive pressure, will result in regional lung injury, as will be discussed later in this chapter.

BAROTRAUMA OR VOLUTRAUMA?

Although neonatologists traditionally considered careful avoidance of high peak inflation pressure (PIP) as key to minimizing lung injury, preclinical studies and more recent clinical data clearly indicate that excessive volume, not high pressure by itself, is the key element in initiating lung injury. Hernandez et al. showed that young rabbits exposed to PIP as high as 45 cmH_2O did not show evidence of acute lung edema when their chest and abdomen were enclosed in a plaster cast that limited tidal volume delivery, while control animals whose lungs were free to expand showed massive acute pulmonary edema after a brief period of ventilation.[6] Dreyfuss and colleagues demonstrated that severe lung edema and protein leak occurred in small animals ventilated with large V_T, whether that volume was produced by positive or negative pressure, while control animals exposed to the same high PIP but with chest excursion constrained by a tight elastic bandage had much less acute lung injury.[7] Taken together, these studies indicate that the damaging effect of high PIP is mediated by excessive tissue stretch and that PIP that does not result in excessive tidal volume is not necessarily injurious. Hence, the term volutrauma is now increasingly adopted in describing biophysical injury due to mechanical ventilation.

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PRESSURE OR VOLUME: WHICH SHOULD BE THE PRIMARY CONTROL VARIABLE?

Attempts at using volume-controlled ventilation using the rather crude devices available in the early days of neonatology were disappointing. Pressure-controlled ventilation became the standard of care because it was easy to use even with a large leak around uncuffed endotracheal tubes and because of the conviction that controlling inflation pressure was key to success. This approach has persisted despite clear evidence regarding the key role of volutrauma in lung injury and the fact that volume-targeted ventilation became available in the 1990s. The basic functionality of a pressure-controlled ventilator is essentially the same as that of a T-piece resuscitator. The tidal volume that enters the patient's lungs is proportional to the pressure applied and the compliance of the lungs. The key drawback of pressure-controlled ventilation is that lung compliance often improves rapidly, leading to excessively large tidal volume that results in lung injury and to inadvertent overventilation that increases the risk of brain injury. For this reason, the impetus to change the paradigm to tidal volume as the primary control variable is intuitively obvious but has been slow to gain traction.[8]

VOLUME-CONTROLLED VERSUS VOLUME-TARGETED VENTILATION

Although the term volume-targeted ventilation is sometimes applied to all modalities that in some way prioritize tidal volume as the primary control variable, there are important differences between the traditional volume-controlled ventilation used in adult and pediatric intensive care units and volume-targeted ventilation used in neonatal ventilation. The limitation of traditional volume-controlled ventilation in small infants is that the volume of gas delivered into the ventilator circuit is not the same as the volume entering the patient's lungs because of loss of volume to compression within the circuit/humidifier and leak around uncuffed endotracheal tubes. Modern ventilators are now capable of delivering very small tidal volumes in volume-controlled mode and have a compliance compensation feature to correct for volume loss in the circuit, but this feature does not function adequately in small preterm infants, especially when there is an endotracheal tube leak. Also, the flow pattern of volume-controlled ventilation is different from pressure-controlled ventilation, with the full volume being delivered only at the end of inflation, rather than earlier in the ventilator cycle as is the case with pressure-controlled ventilation. The solution that takes the best of both approaches is volume-targeted ventilation, which is pressure-controlled ventilation with automatic adjustment of inflation pressure to maintain a user-set exhaled tidal volume. The original and best-studied iteration of volume-targeted ventilation is the volume guarantee (VG) mode on the Draeger ventilators. With VG, the exhaled tidal volume measured at the airway opening is compared to the target volume, and the inflation pressure for the next inflation is adjusted up or down as needed to maintain stable tidal volume in the face of changing lung compliance and variable patient's respiratory effort **(Flowchart 1)**. The magnitude of adjustment from one inflation to the next is limited to avoid overshoot, so it may take several cycles to return to target tidal volume if there is a large change in compliance. The inflation pressure increase is limited to a user-selected pressure limit. A secondary safety mechanism

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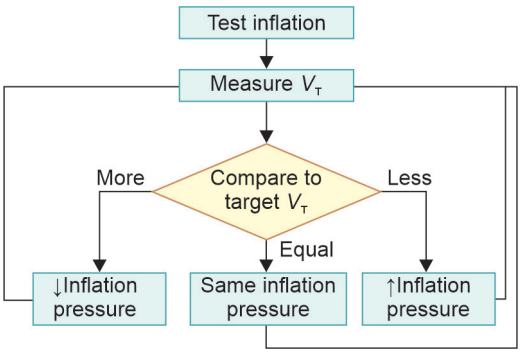
Flowchart 1: Basic algorithm of volume-targeted ventilation.



(V_T: tidal volume)

will terminate inflation if the inspiratory tidal volume exceeds the target by >30%, adjusted for endotracheal tube leak. If the infant consistently generates a tidal volume above the set target, PIP may progressively drop all the way to the level of PEEP, providing the infant with no cyclic positive pressure support (PS), a situation that should not be allowed to persist for long. Accurate tidal volume measurement is essential for volume-targeted ventilation and therefore should be measured at the airway opening. The flow sensor adds a small amount of instrumental dead space, but it allows for minimal trigger delay, high trigger sensitivity, and accurate tidal volume down to 2 mL. The most sophisticated specialty neonatal ventilators have accurate leak compensation algorithms that allow for accurate tidal volume delivery even with a moderately large leak around uncuffed endotracheal tubes.

PATIENT–VENTILATOR INTERACTIONS

Unlike older patients, neonates are allowed to breathe spontaneously during synchronized mechanical ventilation to take advantage of their own efforts and to reduce the adverse effects of analgosedation. While this practice is clearly beneficial, it does result in complex patient–ventilator interactions that must be clearly understood by bedside caregivers in order to optimize care. The tidal volume that enters the patient's lungs is a function of the transpulmonary pressure and lung compliance. With synchronized ventilation, the transpulmonary pressure is the sum of the positive pressure generated by the ventilator and the negative intrapleural pressure generated by the infant during spontaneous breathing; in other words, the ventilator pushes and the infant pulls gas into the lungs. In preterm infants, the infant's contribution is often highly variable and sometimes absent. The infant's respiratory effort is not measured or displayed on the ventilator screen, but it nonetheless importantly affects the delivered tidal volume whether pressure or volume is used as a primary control variable. The effect however is different, depending on the modality used. With pressure-controlled ventilation, the added effort of the baby increases the delivered tidal volume, sometimes dramatically. With volume-targeted ventilation, the increased effort of the infant results in a drop in the pressure generated by the ventilator, thus reducing the danger of excessive tidal volume delivery. Because of the variability of respiratory effort of the infant, the tidal volume fluctuates around the target value because the infant is constantly perturbing the equilibrium. If the infant is not breathing, the tidal volume will remain at the target with minimal variation.

VOLUME-TARGETED VENTILATION VERSUS NEURALLY ADJUSTED VENTILATORY ASSIST

As described above, volume-targeted ventilation is a negative feedback mechanism. If the infant generates a tidal volume above

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the set target value, the inflation pressure is reduced so as to maintain tidal volume near the target value. If the infant's effort wanes or ceases altogether, more pressure will be delivered to compensate. Greater stability of tidal volume with fewer episodes of hypocapnia was demonstrated already in the early days of volume-targeted ventilation.[9] Another modality that has gained some traction in the newborn intensive care units is neurally adjusted ventilatory assist (NAVA), a modality developed for adult ventilation but actively promoted for use in newborn infants. In contrast to volume-targeted ventilation, NAVA is a positive feedback system that generates inflation pressure in proportion to the patient's respiratory effort, as measured by an array of microelectrodes mounted on a special nasogastric feeding tube that senses the electrical activity of the diaphragm.[10] Having its origins in the adult world, this approach assumes mature respiratory control, and thus giving the patient full control over gas delivery throughout the respiratory cycle is seen as advantageous. However, when applied to extremely preterm infants with their periodic breathing and frequent apneas, interspersed with brief episodes of vigorous inspiratory activity when disturbed, it will amplify the respiratory instability and potentially lead to excessive tidal volume delivery and large fluctuations in minute ventilation. Only small studies with short-term outcomes have been carried out in newborn infants; therefore, we lack evidence of safety or efficacy in terms of important patient outcomes.[11]

BENEFITS OF VOLUME-TARGETED VENTILATION

Real-time, breath-to-breath adjustment of inflation pressure has been shown to reduce tidal volume fluctuations and hypocapnia.[9] It is well known that completely monotonous tidal volume delivery leads to atelectasis over time, but this is not a problem with volume-targeted ventilation because in awake infants there is always some fluctuation of tidal volume because of the variable respiratory effort and the ability to generate a sigh breath. Avoidance of excessively large tidal volume and inadvertent hyperventilation leads to reduced risk of lung and brain injury. The ventilator does not wait for the next blood gas or for morning rounds to adjust settings. Weaning inflation pressure in real time leads to faster weaning from mechanical ventilation. Fewer blood gases are needed because of the stability of minute ventilation, and thus there is less blood loss and fewer painful procedures. There is no large, randomized trial to document the benefits of volume-targeted ventilation, but the most recent Cochrane systematic review with a meta-analysis of a series of smaller controlled trials totaling nearly a thousand infants has documented a significant reduction in the incidence of BPD, severe intracranial hemorrhage, periventricular leukomalacia, pneumothorax, and hypocapnia, as well as a reduction in the duration of ventilation **(Table 1)**.[12] Long-term follow-up studies are lacking, but the reduction in BPD and intracranial imaging abnormalities would be expected to improve neurodevelopmental outcomes.

IMPORTANCE OF THE OPEN LUNG STRATEGY

The benefits of avoiding excessive tidal volume cannot be fully realized unless we ensure that the tidal volume is evenly distributed into an adequately recruited "open" lung. Although surfactant deficiency-related respiratory distress syndrome is considered to be a homogeneous disease process and appears so on a plain chest radiograph,

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TABLE 1: Volume-targeted versus pressure-controlled ventilation.

	Relative risk or mean difference	*95% CI*	*NNTB (95% CI)*
Death or BPD @ 36 weeks PMA	0.75	0.53–1.07	NA
BPD @ 36 weeks PMA	0.73	0.59–0.89	8 (5–20)
Grade 3–4 IVH	0.53	0.37–0.77	11 (7–25)
PVL ± severe IVH	0.47	0.27–0.80	11 (7–33)
Pneumothorax	0.52	0.31–0.87	20 (11–100)
Hypocapnia	0.49	0.33–0.72	3 (2–5)
Days of mechanical ventilation	−1.35	−1.83 to −0.86	

(BPD: bronchopulmonary dysplasia; CI: confidence interval; IVH: intraventricular hemorrhage; NNTB: number needed to benefit; PMA: postmenstrual age; PVL: periventricular leukomalacia)
Source: Data from Klingenberg et al.[12]

there are important gravity-dependent differences in lung aeration that can be seen with imaging modalities that provide a cross-sectional view of the chest, such as magnetic resonance imaging or electrical impedance tomography. Tidal ventilation with incompletely aerated lungs leads to lung injury by several mechanisms, collectively referred to as atelectrauma. There is increased surfactant turnover in the atelectatic portion of the lungs, shear forces at the boundary between atelectatic and aerated lung, regions of the lung where there is repeated opening and collapse of the terminal air sacs, and perhaps most importantly, there is regional volutrauma. When lungs are incompletely aerated, the tidal volume delivered will preferentially enter the already aerated nondependent portion of the lungs, leading to overexpansion. This phenomenon is the manifestation of Laplace Law, which tells us that the pressure required to distend a balloon or an alveolus is directly proportional to 2× surface tension and inversely proportional to the radius. Thus, the already aerated portion of the lungs is more compliant relative to the high critical opening pressure of the collapsed air sacs in the dependent portion of the lungs and thus will receive the bulk of the delivered tidal volume. Tsuchida et al. demonstrated this phenomenon in an animal study, showing that when ventilating partially atelectatic lungs with high PIP and low PEEP, the most severe lung injury occurred in the nondependent portion of the lungs.[13] Thus, it is essential that atelectasis is corrected with some form of lung recruitment maneuver. With conventional ventilation, this can be achieved by stepwise increases in PEEP until oxygen requirement drops below 30%, indicating improved ventilation/perfusion matching.[14] High-frequency oscillatory ventilation is an effective way to achieve the "open lung" status, but it has been shown in preclinical studies that conventional ventilation using sufficiently high PEEP can be equally effective.[15,16]

CLINICAL GUIDELINES

Initiation of Ventilation

Because lung compliance changes most rapidly soon after initiation of mechanical ventilation, it is best to start VG as soon

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as practical after intubation. The most important decision is the choice of an appropriate target tidal volume, based on the infant's size, pulmonary diagnosis, and postnatal age.[17] The tiniest infants require a slightly larger tidal volume/kg because of the disproportionally larger effect of the added instrumental dead space of the flow sensor.[18] Infants with conditions that lead to increased alveolar dead space (wasted ventilation), such as meconium aspiration syndrome or BPD, also need a larger tidal volume.[19,20] VG can be combined with any of the basic synchronized modes, but assist/control or PS ventilation is preferred to synchronized intermittent mandatory ventilation (SIMV).[21] When SIMV is combined with PS, it must be recognized that only the SIMV inflations are subject to volume-targeting, and as the SIMV rate is lowered, the infant is gradually transitioning back to pressure-controlled ventilation (i.e., PS). Improved lung compliance and patient respiratory effort can lead to a situation where the SIMV PIP drops below the PIP of the PS breaths, which can be problematic.

Initially, PIP limit should be set at about 5 cmH_2O above the level estimated to be sufficient to achieve a normal V_T. If the child previously received positive pressure ventilation with a T-piece resuscitator or was on pressure-controlled ventilation, that PIP can be a useful guide. If the target tidal volume cannot be reached with this setting, the pressure limit can be cautiously increased until the desired tidal volume is generated. If more than the expected level of PIP is needed, make sure that the endotracheal tube is not kinked or misplaced, e.g., into the mainstem bronchus or obstructed on the carina. The pressure limit is then set about 20% above the current working pressure to allow sufficient room for adjustment both up and down and still provide important feedback if the set tidal volume cannot be reached with the current PIP. It is important to evaluate the infant's response to the initial settings and adjustments are made if needed even before a blood gas is obtained **(Table 2)**. The suggested tidal volume settings are only a starting point based on population averages and individual patient requirements may vary. Observation of the respiratory effort and rate along with assessment of the ventilator graphics will confirm if the selected tidal volume is appropriate for the patient.

Subsequent Adjustments

Once ventilator settings are confirmed with a satisfactory blood gas and clinical assessment, relatively few adjustments are needed because the VG mode will reduce respiratory support automatically and in real time. When used with assist/control as recommended, there is no need to adjust the ventilator rate, making frequent monitoring of blood gases unnecessary. With improved lung compliance and improved respiratory effort, the PIP will come down, and the PIP limit should be brought down to maintain the appropriate relationship with the measured PIP. Maintaining the pressure limit only a few cmH_2O above the actual PIP that is needed to achieve the target tidal volume serves as an early warning system that will alert the clinician that something has changed. When the tidal volume is no longer reached within the set limit, the clinician should look for the reason for this change, e.g., atelectasis, pneumothorax, endotracheal tube malposition, or abdominal distention.

If oxygenation is a problem, especially with rising oxygen requirement, the response should be to increase the mean airway pressure, primarily by increasing PEEP. However, if the PIP is very low, a larger

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TABLE 2: Suggested initial settings of tidal volume. Evaluate the patient's response and adjust as indicated.

Condition	*Initial V_T (mL/kg)*	*Rationale*	*Reference*
Healthy infant, normal lungs	4–4.5	Baseline	Dawson and Davies[22]
Preterm RDS 800–2,500 g	4.5–5	Low alveolar dead space	Dawson and Davies[22]
Preterm RDS <700 g	5.5–6	Dead space of the flow sensor	Nassabeh-Montazami et al.[18]
Preterm evolving BPD, 3-week old	5.5–6.5	Increased physiologic dead space	Keszler et al.[23]
Term MAS with classic CXR	5.5–6	Increased alveolar dead space	Sharma et al.[19]
Term MAS with whiteout CXR	4.5–5	Surfactant inactivation Alveolar dead space is not a problem	Keszler[24]
Term CDH	4–4.5	Normal CO_2 production requires normal alveolar minute ventilation	Sharma et al.[25]
Established severe BPD	7–12	Very high physiologic dead space; low respiratory rate needs larger V_T	Abman et al.[20]

(BPD: bronchopulmonary dysplasia; CDH: congenital diaphragmatic hernia; Classic CXR: classic chest radiograph showing air-trapping and heterogeneous lung aeration; MAS: meconium aspiration syndrome; RDS: respiratory distress syndrome; V_T: tidal volume)

tidal volume target may help to recruit lung volume by providing higher inflation pressure. Endotracheal tube malposition and pneumothorax should be ruled out if the change is abrupt. If the partial pressure of carbon dioxide (PCO_2) is high, the clinician should verify that the prescribed tidal volume is actually being delivered and the patient is receiving an appropriate respiratory rate (i.e., breathing above the set ventilator rate). Evidence of partial airway obstruction, air trapping, or abdominal distention should be ruled out. Tidal volume needs to increase over time, so an increase in tidal volume may be appropriate; do not forget to adjust tidal volume for weight gain! Low PCO_2 may be a manifestation of compensation for a metabolic acidosis or autocycling due to water in the circuit. If those causes are ruled out, a small decrease in tidal volume may be appropriate, but always interpret the PCO_2 in the context of pH (see also the subsequent paragraph).

Weaning Support with Volume Guarantee

Volume guarantee is a self-weaning mode. The tidal volume required by the infant does not come down as lung disease improves. Instead, the pressure needed to generate that tidal volume comes down and this occurs automatically with VG. Inappropriate lowering of tidal volume target is likely to lead to excessive work of breathing and may set the infant up for extubation failure. It is important to ensure that the pH is low enough (<7.35) to ensure adequate respiratory drive. Frequent blood gases are not needed. When the PIP is sufficiently low without excessive work of breathing and a reasonably low fraction of inspired oxygen (FiO_2), the baby can be extubated.

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Barriers to Adoption of Volume Guarantee

Volume-targeted ventilation presents some unique challenges compared to simple pressure-controlled ventilation because the patient–ventilator interactions are more complex. As previously mentioned, ventilator settings should not be based solely on blood gas measurement. Normal blood gas is not a guarantee of optimal support. Tachypnea and retractions indicate inadequate support and a need for a larger tidal volume. The need for a larger tidal volume is confirmed by observation of a relatively low PIP and measured V_T that exceeds the target tidal volume in an infant who is tachypneic and retracting, indicating increased work of breathing. If, on the other hand, the baby is comfortable with low oxygen requirement without increased work of breathing, extubation to noninvasive support may be the correct step. Metabolic acidosis makes management of VG more challenging because clinicians often forget that pH, not PCO_2, is the primary stimulus acting on the respiratory control center. Anyone who doubts this fact should recall the child with diabetic ketoacidosis and Kussmaul breathing. Unfortunately, clinicians sometimes look at PCO_2 values in isolation. A common error is to wean the target tidal volume in response to a slightly low PCO_2 despite a pH that is well below 7.35. When the set tidal volume remains below the baby's need and she is able to generate spontaneously a tidal volume that exceeds the set target, the ventilator algorithm will progressively drop the PIP, sometimes all the way to the level of PEEP, resulting in increased work of breathing and possible fluctuations in PCO_2. Another challenge is the progressively larger leak around uncuffed endotracheal tubes as the trachea and larynx dilate as a result of prolonged mechanical ventilation. Ventilators that do not measure exhaled tidal volume at the airway opening and/or do not have sophisticated tidal volume compensation algorithms are not able to safely deliver volume-targeted ventilation if the leak exceeds about 40%. In contrast, the modern Draeger ventilators (VN 500, 600, and 800) are able to accurately deliver the desired tidal volume with leaks as large as 80%. Therefore, it is imperative to know your device's capabilities. The final barrier to successful implementation of volume-targeted ventilation is lack of understanding of the paradigm shift that is involved in changing the primary control variable from pressure to volume and failure to appreciate that one size does not fit all.[17,26]

CONCLUSION

Prevention of lung injury must be a multifaceted undertaking that begins with the initial stabilization and goes beyond respiratory support. Volume-targeted ventilation is a key piece of this effort but must be coupled with the optimal lung volume strategy in order to fully realize its potential. The importance of individualized patient care and appreciation of the maxim that "one size does not fit all" cannot be overemphasized. Clinical assessment at the bedside that includes observation of the patient–ventilator interactions and ventilator graphics is essential in optimizing outcomes. Ventilator strategies and settings must be based on an understanding of the underlying pathophysiology and should be reevaluated periodically as the disease process evolves. No ventilator is inherently lung-protective; it is the operator's skill and knowledge that make it so.

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