Given that mechanical ventilation with a rate of 30 breaths/min will distend the lungs more than 40,000 times per day, it is surprising that mechanical ventilation is not more harmful. Nevertheless, the major association with the development of bronchopulmonary dysplasia (BPD) is the initiation and continued use of mechanical ventilation in infants with birth weights of <1250 g.1-3 The mechanisms resulting in lung injury with mechanical ventilation in the normal lung have been much better characterized in recent years, and strategies of ventilation to minimize injury are being evaluated.4-6 The lungs of the very preterm infant are uniquely susceptible to injury because they are structurally immature and are often surfactant-deficient, fluid-filled, and not supported by a stiff chest wall.7 Our goals are to identify the causes of ventilator-induced lung injury, apply the available information on minimizing lung injury to the preterm lung, and review the health consequences of lung injury in the preterm infant.

WHAT CAUSES LUNG INJURY?

Inadequate Alveolar Stability and Atelectasis

The term atelectrauma was coined to describe the observation that loss of alveolar recruitment is both a consequence and a cause of lung injury.8,9 Alveolar units are prone to collapse in patients with acute respiratory distress syndrome (ARDS) or respiratory distress syndrome (RDS) in which there is surfactant dysfunction. The breath-by-breath cycle of recruitment and subsequent “de-recruitment” of these units causes lung injury.10 This mechanism of injury explains the observation that recruitment of lung volumes to increase functional residual capacity (FRC) protects against ventilator-induced lung injury and also reduces the need for high levels of inspired oxygen.11-15

Meredith et al16 reported that ventilatory support with intermittent mandatory ventilation and a positive end-expiratory pressure (PEEP) of 4 cm H$_2$O contributed to the development of hyaline membrane disease (HMD) in premature baboons. In contrast, use of high-frequency ventilation (HFV) (small tidal volume ventilation) prevented the development of HMD, demonstrating that ventilator strategy can contribute to the progression of HMD. The protective ventilatory strategy used by Meredith et al16 also included an attempt to maximally recruit the lung by using a high mean airway pressure. Although this approach improved gas exchange, the animals developed clinical signs of cardiac compromise. The problems with cardiac output impairment were avoided if, after the lung was recruited, the mean airway pressure was gradually decreased. As a guide, Kinsella et al17 used the chest radiograph and oxygenation (PaO$_2$/partial pressure of oxygen in the alveoli [PAO$_2$]) to determine adequate but not excessive lung inflation.17

In another pivotal study, Froese et al15 showed that the ventilator pattern influenced the efficacy of exogenously delivered surfactant. Ventilator strategies associated with loss of FRC (lung de-recruitment) increased lung injury and decreased the efficacy of the surfactant therapy. High-frequency oscillation, with a high mean airway pressure, de-
increased lung injury and improved the efficacy of surfactant. During intermittent mandatory ventilation, use of inadequate end-expiratory pressure (EEP) to maintain an adequate FRC will also increase lung injury. Ventilation of surfactant-treated preterm lambs with no (zero) EEP resulted in deterioration in oxygenation, compliance, and surfactant function compared with lambs ventilated with PEEP of 4 or 7 cm H₂O. Several studies now show that optimizing lung recruitment with PEEP, surfactant, liquid ventilation, or oscillatory ventilation reduces lung inflammation, improves surfactant function, and decreases lung injury.

**Volutrauma**

A major cause of ventilator-induced lung injury is regional overdistension of alveoli and airways. Increased lung volume (stretch), and not pressure per se, promotes lung injury. In healthy adult and newborn animals, large tidal volume breaths cause damage to the pulmonary capillary endothelium, alveolar and airway epithelium, and the basement membranes. This mechanical damage causes fluid, protein, and blood to leak into the airways, alveoli, and the lung interstitium, interfering with lung mechanics, inhibiting surfactant function, and promoting lung inflammation.

In the preterm infant, numerous factors (eg, infection, antenatal exposure to inflammatory mediators, surfactant dysfunction, high chest wall compliance, antioxidant deficiency, infection, and malnutrition) increase the susceptibility to lung volutrauma and limit the ability to repair the damage. In addition, lung immaturity, alveolar atelectasis, and edema decrease the gas volume. In patients with RDS, the distribution of the underlying pathology is such that only a small portion of the lung may be recruited and available for ventilation. If only one third of the lung is being ventilated, then a tidal volume of 10 mL/kg delivered to the ventilated portion of the lung may be equivalent to 20 to 30 mL/kg and will result in volutrauma.

This concept has been tested in preterm animals; as few as 6 manual inflations of 35 to 40 mL/kg, given to preterm lambs before surfactant treatment and mechanical ventilation, injured the lungs and decreased the response to surfactant therapy. Similarly, preterm lambs ventilated with 20 mL/kg breaths for 30 minutes before surfactant treatment had more acute lung injury than lambs ventilated with 5 or 10 mL/kg tidal volume breaths. Surfactant treatment before the initiation of assisted ventilation decreased the degree of lung injury, presumably by promoting more uniform lung inflation.

**Oxygen Toxicity**

Although the term infant may tolerate hyperoxia better for extended periods, both preterm and term neonates treated with high levels of oxygen will develop chronic lung disease. Oxygen-induced lung injury is caused by the overproduction of superoxide, hydrogen peroxide, and perhydroxyl radicals. The premature neonate is particularly vulnerable to free radical–induced lung injury because antioxidant systems develop during the last trimester. Reactive oxygen metabolites can overwhelm the antioxidant system and oxidize enzymes, inhibit protein and DNA synthesis, decrease surfactant synthesis, and cause lipid peroxidation. Prolonged hyperoxia initiates a lung injury sequence that can lead to inflammation, diffuse alveolar damage, progressive pulmonary dysfunction, and death.

**Effects of the Combination of Atelectrauma and Volutrauma**

The combined processes of lung collapse (atelectrauma) and large tidal volume breathing (volutrauma) synergistically increase lung injury. The corollary is that lung recruitment reduces the injury caused by volutrauma. Compared with the use of zero EEP, the use of PEEP in conjunction with low tidal volume (9 mL/kg) to treat rats with acute lung injury improves survival. In addition, the use of PEEP reduces the elevation of serum cytokine levels associated with the use of large tidal volume (16 mL/kg) support.

The combination of high tidal volume and zero EEP not only caused severe lung injury but was also associated with marked increases in circulating tumor necrosis factor and macrophage inflammatory protein. Lambs randomized at birth to treatment with surfactant (an effective way to establish a more normal FRC) and then ventilated with 6, 12, or 20 mL/kg tidal volumes for 30 minutes had no indicators of lung injury. Similarly, the use of a lung recruitment strategy with HFV, liquid ventilation, or liquid ventilation is protective. Therefore, both end-expiratory and end-inspiratory lung volumes are important.

**Pulmonary and Systemic Inflammatory Responses to Acute Lung Injury**

From an anatomic and physiologic perspective, the lungs are uniquely poised to affect distal organs. Mechanical ventilation may affect distal organ function through effects on cardiac output, as well as the level of oxygenation and the distribution of blood to the various organ systems (eg, mesenteric, renal, and hepatic perfusion). The pulmonary vasculature not only receives the entire cardiac output but also harbors a large reservoir of marginated neutrophils (up to a third of all neutrophils outside the bone marrow). Thus, significant potential exists for the lungs to interact with, and contribute to, the circulating pool of inflammatory cells.

Mechanical ventilation affects the numbers of inflammatory cells and the expression of soluble mediators within the lungs. In saline-lavaged rabbits, manifestations of lung injury (ie, hyaline membranes, neutrophil infiltration, and impaired gas exchange), originally
attributed to barotrauma/volutrauma, were almost completely abrogated in granulocyte-depleted rabbits. Injurious mechanical ventilation of saline-lavaged rabbits increased lung neutrophil accumulation and chemiluminescence (an indicator of neutrophil priming), increased inflammatory mediators (platelet-activating factor and thromboxane B2) in bronchoalveolar lavage, and increased expression of tumor necrosis factor–α by alveolar macrophages. The combination of large tidal volumes and low end-expiratory lung volumes leads to a further synergistic increase in lung and serum cytokine concentrations. In preterm animal models of RDS, the initiation of respiratory support increases expression of lung inflammatory mediators, and continuous mechanical ventilation is associated with granulocyte recruitment and activation with cytokine expression.

In addition to initiating an inflammatory cascade within the lungs, mechanical support can injure the alveolar-capillary barrier and allow the efflux of inflammatory mediators from the alveolar space into the general circulation. A systemic inflammatory response can also be promoted by translocation of bacteria and endotoxin from the air spaces into the circulation, somewhat analogous to the gut bacterial translocation hypothesis of multiple organ failure. In addition, mechanical ventilation strategy affects the function of both neutrophils within the lungs and circulating neutrophils.

The level of PEEP also influences cytokine expression when the inflammatory process initiated by lung injury leaks into the systemic circulation and causes injury to other organ systems. Findings in recent human studies in adults with respiratory failure support the observations made in animals and show that ventilatory strategy has an impact on pulmonary and systemic cytokines and that these changes are associated with multisystem organ failure.

**STRATEGIES TO PREVENT LUNG INJURIES**

**What Is the Definition of Optimal Lung Volume?**

In healthy neonates, lung volumes, both end-inspiratory and end-expiratory, change rapidly. At the end of a normal exhalation, the chest wall interacts with the lung to define FRC (lung volume at the end of expiration of a normal tidal volume breath). In neonates with lung disease or lung injury, FRC is decreased, and some of the lung, generally the dependent areas, is collapsed. A goal of respiratory support is to open these areas and to normalize FRC. Because lung injury creates an inhomogeneous pattern of inflation, the trick is to open the collapsed areas without overinflating the open areas of the lung. Thus, optimal lung inflation can best be described as the lung volume at which the recruitable lung is open but not overinflated. If this definition is met, intrapulmonary shunt is decreased, lung volume effects on cardiac output are minimized, and oxygen delivery is optimized.

Lung recruitment is possible because of the pressure-volume hysteresis of the lung. Once the lung is recruited, surfactant and alveolar interdependence act to keep it inflated. Thus, the pressure to open the lung is higher than the pressure needed to keep it open. Mean airway pressure or EEP can be decreased without a great loss of lung volume, so long as the pressure is not decreased below the closing pressure of the majority of the alveoli.

The delivery of tidal volume breaths on top of FRC creates changes in lung volume that are dependent on regional lung compliance. Again, the definition of optimal is the tidal volume that creates a homogeneous delivery of each breath to the open lung units without creating volutrauma. FRC and tidal volume both influence mean lung volume. In mathematical models of lung injury, the most important volume to optimize is FRC. An open lung allows more uniform distribution of each tidal volume breath and reduces the potential for volutrauma.

**How Might We Measure Optimal Lung Volume Clinically?**

The use of the chest radiograph to determine optimal lung volume can be misleading, and the correlation between measured lung volume and chest radiograph appearance has been questioned. The PaO2/PaO2 ratio can be used to estimate changes in lung inflation. An increase in lung volume from residual volume to total lung capacity is associated with a decrease in intrapulmonary shunt, an increase in alveolar surface area, and improvement in PaO2. However, cardiac output can be compromised as lung volume increases to total lung capacity. Therefore, the PaO2/PaO2 ratio can be high when oxygen delivery is low as a result of lung overinflation and compromised cardiac output. The PaO2/PaO2 ratio has been used in adult studies to adjust PEEP in conjunction with measurements of cardiac function. No similar measurements have been made in neonates.

Studies in animals demonstrate that respiratory inductive plethysmography can be used to estimate changes in mean lung volume caused by changes in mean airway pressure. In addition, these studies showed that the injured lungs of premature and term animals have pressure-volume hysteresis. When mean airway pressure was increased, lung volumes increased and the volume remained recruited as the mean airway pressure was decreased. The equipment to make these measurements and the efficacy of the volume recruitment maneuvers have not been evaluated in neonates.

At present, the best determinants of low lung volume are a chest radiograph showing atelectasis along with a PaO2/PaO2 ratio demonstrating poor oxygenation. When the chest radio-
What Can We Do Clinically to Prevent Atelectrauma?

Two studies suggest that lung recruitment is not simply a matter of answering the question, “Whom do we intubate?” The question really is “How do we safely establish and normalize FRC in neonates with immature and atelectatic prone lungs?” Three techniques can help promote better lung inflation. The oldest and most commonly used is continuous positive airway pressure (CPAP). Another comprehensively studied and effective tool is exogenous surfactant therapy. The use of a lung recruitment strategy with HFV is the most recently studied approach. Other strategies to improve lung recruitment include prone positioning, liquid ventilation, and sustained lung-inflation maneuvers.

CPAP. Specific decisions about respiratory care during the first day of life influence the outcome of a very low birth weight infant. Comparing nurseries that more commonly use assisted ventilation with nurseries that use CPAP in the initial treatment of very low birth weight infants, Van Marter et al showed that most of the increased risk of chronic lung disease was explained “simply by the initiation of mechanical ventilation.” Similar information has been reported from Europe, suggesting that practice differences influence outcome.

Techniques for applying CPAP are not equivalent. Neonates receiving “bubble” CPAP have chest wall vibrations similar to those associated with HFV. When compared with ventilator-derived CPAP, bubble CPAP reduced minute volume by 39% (P < .001) and respiratory rate by 7% (P < .004). Because blood gas variables were unchanged, the chest vibrations produced with bubble CPAP appear to contribute to gas exchange.

Intubation and assisted ventilation increase the risk of BPD, and the proactive use of CPAP ventilation may decrease the risk. However, the currently available evidence falls short of defining optimal practice on when to provide mechanical ventilation. A problem is the potential risks of waiting to intervene. If CPAP delays an inevitable intubation, are we delaying the “appropriate” use of surfactant as a lung injury prevention tool? Does the increased work of breathing associated with CPAP complicate feeding or reduce growth? Well-designed trials in which CPAP is compared with early intubation are needed. In addition, more information is needed on what constitutes optimal EEP and which device best recruits FRC and minimizes the work of breathing.

Surfactant. Surfactant is a lung recruitment tool that, when used early, decreases lung injury. Within minutes of surfactant administration, oxygenation improves in most infants. This response is associated with an increase in FRC, improved ventilation-perfusion matching, and a decrease in intrapulmonary shunt. Surfactant helps stabilize recruited lung volume and prevents atelectasis. Clinical trials show that surfactant reduces the occurrence of RDS, decreases pulmonary air leak, and appears to reduce the severity of chronic lung disease.

When given to animals before the initiation of ventilation, surfactant protects the lungs from ventilator-induced injury even when the ventilator strategy is inappropriate (large tidal volume breaths). Surfactant treatment decreases the amount of ventilatory support needed to maintain adequate gas exchange. Therefore, failure to decrease ventilatory support can lead to over-ventilation, hypocarbia, and hypoxemia and may increase the risk of developing chronic lung disease, intraventricular hemorrhage, and retinopathy of prematurity. In addition to improved early outcomes for infants treated with a strategy of prophylactic versus rescue surfactant, there may be long-term benefits. A follow-up study showed that a history of abnormal pulmonary findings was found in 22% of infants in an early surfactant treatment group compared with 39% in a late surfactant treatment group (P < .05). Further evaluations of the role of early surfactant administration, followed by extubation to CPAP, as a “prophylactic” approach to recruit lung volume and prevent injury are needed.

HFV. Effective HFV depends on optimizing lung volume and maintaining FRC. In animal models of HMD, the use of high-frequency oscillation at a mean airway pressure lower than those used with conventional ventilation resulted in progressive loss of lung volume and severe hypoxia. At autopsy, the lungs of animals that were maintained with low mean airway pressures were severely atelectatic and noncompliant. Maintaining optimal lung inflation by using higher mean airway pressures improves gas exchange, normalizes the pattern of lung inflation, and reduces lung injury.

The strategy of using a higher mean airway pressure has been called a high lung volume strategy, but the target is not high volume; rather, it is optimal mean lung volume. Meta-analysis of clinical trials that have evaluated the efficacy of HFV supports the concepts developed from animal studies in that a high lung volume strategy is required. In the 2 trials in which a high-volume strategy was not used, HFV (oscillatory) had no effect on the rate of chronic lung disease; however, periventricular leukomalacia was increased (summary relative risk = 1.64 [confidence limits 1.02, 2.64]). In the 4 trials in which a high-volume strategy was used, HFV (oscillatory) resulted in less “death or chronic lung disease at 28-30 days” (summary relative risk = 0.56).
[confidence limits 0.40, 0.77]), and there were no differences in the rates of intraventricular hemorrhage or periventricular leukomalacia.53a

**How Do We Avoid Volutrauma?**

The easy answer is to limit tidal volume without losing lung volume or promoting atelectasis. The best clinical evidence that limiting tidal volume improves outcome is from the ARDS net trial, which evaluated whether ventilation with lower tidal volumes (6 mL/kg vs 12 mL/kg) would improve the clinical outcomes in adult patients with severe respiratory distress.55 The trial was stopped after the enrollment of 861 patients because the mortality rate was lower in the group treated with lower tidal volumes (31.0% vs 39.8%, P = .007).

In animal models of HMD and ARDS, limiting tidal volume by using HFV prevents the propagation of lung injury by supporting adequate gas exchange with small tidal volumes. Although results of animal studies are unequivocal and show that HFV and small tidal volume ventilation reduce injury, information on human neonates is less clear.56,59-62 Although some clinical trials show that HFV can reduce the occurrence of chronic lung disease, other studies have shown no effect. As discussed previously, use of a strategy that promotes lung recruitment is as important as limiting tidal volume.52a

**What Is the Correct Target PaCO₂?**

Defining the safe PaCO₂ level may be as important as defining the optimal tidal volume. Animal studies demonstrate that moderate hypercarbia protects the brain from hypoxic-ischemic injury and hypocarbia increases the injury.63 Animal studies also show that hypoventilation and the associated hypercapnic acidosis can protect the lung from acute injury.64 However, it is equally important to note that hypercarbia increases cerebral blood flow, decreases systemic pH, and, in animals, has been associated with an increase in retinopathy.65,66 Thus, a “normal” PaCO₂ value should remain the target until more data from human studies are available.

Carlo et al6 reported a randomized controlled trial to test whether minimal ventilation (defined by different PaCO₂ targets) in infants with birth weights between 501 and 1000 g would reduce the number of deaths or oxygen dependency at 36 weeks’ postmenstrual age. Infants were randomly assigned to minimal ventilation (PaCO₂ goal >52 mm Hg) or routine ventilation (PaCO₂ goal <48 mm Hg). After enrollment of 220 patients (1200 sample size estimate), the trial was halted because of unanticipated complications in a separate part of the study involving steroid treatment.6 Minimal ventilation did not decrease oxygen dependency or the number of deaths and had no effect on other major morbidities. However, ventilator support at 36 weeks was 1% in the minimal ventilation group versus 16% in the routine ventilation group (P < .005). The authors concluded that minimal ventilation strategies targeting tidal volumes and/or PaCO₂ levels warrant further study.6

**Preventing Oxygen-Induced Lung Injury**

The STOP ROP trial reported the use of supplemental oxygen in premature infants with confirmed pre-threshold retinopathy of prematurity and median pulse oximetry <94%.67 Neonates were randomly assigned to a conventional oxygen arm with pulse oximetry targeted at 89% to 94% saturation or to a supplemental arm with pulse oximetry targeted at 96% to 99% saturation. Treatment was continued for at least 2 weeks. Pneumonia, exacerbations of chronic lung disease, or both occurred in more infants in the supplemental arm (8.5% conventional vs 13.2% supplemental). Growth and developmental milestones did not differ.67 Milligan et al68 showed that neonates given enough supplemental oxygen to maintain a saturation of 88% to 98% for 8 weeks developed severe retinopathy 5 times more often than babies only given enough oxygen to maintain an oxygen saturation of 70% to 90%. The high saturation group also more often developed chronic lung disease. There was no difference in the incidence of cerebral palsy between the 2 groups. These outcomes indicate that the choice of pulse oximetry targets can influence the incidence of lung injury. The use of antioxidants to reduce lung injury has not shown benefit to date.69

**What Are the Effects of Mechanical Ventilation on Lung Growth and Development?**

**Animal Models of BPD**

In surfactant-deficient preterm animals injured with oxygen, the primary aberration is interrupted alveolarization.70 Baboons injured with intermittent mandatory ventilation and a fraction of inspired oxygen (FiO₂) of 1.0 for 7 days, followed by an FiO₂ of 0.8 for 14 days were compared with animals ventilated with appropriate oxygen support. At 33 weeks of age, animals ventilated with clinically appropriate levels of oxygen showed relatively normal well-alveolarized lungs, whereas the oxygen-injured animals had focally enlarged airspaces that were not classifiable as alveoli, alveolar ducts, or respiratory bronchioles. Hypoxic lung injury in premature animals resulted in a significant and permanent loss of alveoli.70 Additionally, this study suggested that appropriate use of oxygen and ventilatory support (even without exogenous surfactant treatment) in relatively mature preterm baboons does not cause significant perturbation in lung development. However, despite appropriate oxygenation and ventilator strategies...
to prevent volutrauma, very immature baboons (71% of gestation) develop pulmonary pathologic lesions similar to those that occur in extremely immature humans. The morphometric features include interrupted alveolar development, abnormal elastin distribution, minimal airway metaplasia, and abnormal pulmonary vascular development. The capillary hypoplasia present in the baboon model of chronic lung disease indicates an arrest in vasculogenesis. Acute lung injury during the canalicular phase of lung development may cause significant dysmorphic vascular changes and prevent normal alveolar development.

**Ventilator Strategy and the Development of Chronic Lung Disease in Animal Models of HMD**

Studies in lambs that were delivered prematurely, treated with surfactant, and mechanically ventilated with supplemental oxygen to maintain normal blood gases for 3 weeks show that ventilator strategy alters histopathologic outcome. The 2 strategies that were compared were slow, deep ventilations (20 breaths/min with a tidal volume of 15 mL/kg) and rapid, shallow ventilation (60 breaths/min with a tidal volume of 6 mL/kg). Both groups of long-term ventilated preterm lambs had nonuniform inflation patterns, impaired alveolar formation, abnormal abundance of elastin, increased muscularization of terminal bronchioles, inflammation, and edema. Low-rate, large-volume ventilation was associated with increased elastin and decreased secondary saccular crest formation, but low-volume, high-rate ventilation was associated with increased atelectasis. Thus, BPD was not prevented by surfactant replacement at birth when the lungs were ventilated with either of these approaches.

In a study of very immature (67% of gestation) baboons, HFV was compared with low tidal volume positive-pressure ventilation. After administration of prenatal steroids, baboons delivered by cesarean section were treated with exogenous surfactant and began receiving the assigned mode of ventilation by 5 minutes of age. Animals treated with high-frequency oscillation had consistently lower P/F ratios and higher PaO2/PAO2 ratios for the first 10 days of life and at 1 to 2 months of age had significantly better lung inflation patterns. Both groups had the alveolar hypoplasia, variable saccular wall fibrosis, and minimal airway disease described in immature humans with BPD. Although in these experimental models the choice of ventilation style can improve inflation patterns, the altered alveolar development was not prevented.

**What Is the New BPD?**

With the survival of increasingly immature neonates, the number of neonates at risk for developing lung injury and chronic lung disease has increased, and the histopathologic characteristics of BPD have changed. In the 1960s and 1970s, BPD developed in the more mature infants who were treated with high levels of supplemental oxygen and positive pressure ventilation. In the 1980s, the development of better modes of support resulted in improved outcomes for more premature infants and increased survival in more immature infants. In the late 1980s and early 1990s, the development of surfactant and the more proactive use of prenatal steroids led to the survival of extremely premature infants.

The consistent pathologic finding in infants who undergo very premature delivery and who are receiving mechanical support is a decrease in alveolarization. As compared with infants with “old” BPD, human infants with “new” BPD and the long-term animal models of chronic lung disease do not have the prominent airway changes of squamous metaplasia and peribronchial fibrosis, severe alveolar septal fibrosis, or hypertensive vascular changes. However, airflow muscle thickening and derangements in elastic fiber architecture persist as abnormalities in new BPD. The morphometric features consistently found in the new BPD include alveolar hypoplasia, variable saccular wall fibrosis, and minimal airway disease. The new histopathology of BPD indicates interference with normal lung anatomic development, which may prevent subsequent lung growth and development.

**SUMMARY**

The process of supporting gas exchange in the very low birth weight infant may have lifelong consequences. Our choices begin in the delivery room where we must support a safe transition from fetal to neonatal life. How we support gas exchange and normalize lung inflation from the first breath is important. CPAP, surfactant, and HFV all may be useful in establishing and maintaining normal FRC. The establishment of normal FRC reduces the risk of acute lung injury caused by atelectasis. As lung volume is recruited and maintained, it is important to avoid high end-inspiratory lung volumes to reduce volutrauma and the development of hypocapnia. Reducing oxygen exposure to that needed to support normal oxygen delivery can also reduce lung injury. If these strategic principles are followed, we can reduce the pulmonary and systemic inflammatory changes associated with ventilator-induced lung injury and hopefully promote better long-term health.

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