The purpose of mechanical ventilation is to rest the respiratory muscles while providing adequate gas exchange. Ventilatory support proved to be indispensable during the 1952 polio epidemic in Copenhagen, decreasing mortality among patients with paralytic polio from more than 80% to approximately 40%.\textsuperscript{1} Despite the clear benefits of this therapy, many patients eventually die after the initiation of mechanical ventilation, even though their arterial blood gases may have normalized.

This mortality has been ascribed to multiple factors, including complications of ventilation such as barotrauma (i.e., gross air leaks), oxygen toxicity, and hemodynamic compromise.\textsuperscript{2,3} During the polio epidemic, investigators noted that mechanical ventilation could cause structural damage to the lung.\textsuperscript{4} In 1967, the term “respirator lung” was coined to describe the diffuse alveolar infiltrates and hyaline membranes that were found on postmortem examination of patients who had undergone mechanical ventilation.\textsuperscript{5} More recently, there has been a renewed focus on the worsening injury that mechanical ventilation can cause in previously damaged lungs and the damage it can initiate in normal lungs. This damage is characterized pathologically by inflammatory-cell infiltrates, hyaline membranes, increased vascular permeability, and pulmonary edema. The constellation of pulmonary consequences of mechanical ventilation has been termed ventilator-induced lung injury.

The concept of ventilator-induced lung injury is not new. In 1744, John Fothergill discussed a case of a patient who was “dead in appearance” after exposure to coal fumes and who was successfully treated by mouth-to-mouth resuscitation.\textsuperscript{6} Fothergill noted that mouth-to-mouth resuscitation was preferable to using bellows because “the lungs of one man may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determin’d.” Fothergill clearly understood the concept that mechanical forces generated by bellows (i.e., a ventilator) could lead to injury.

However, it was not until early in this century that the clinical importance of ventilator-induced lung injury in adults was confirmed by a study showing that a ventilator strategy designed to minimize such injury decreased mortality among patients with the acute respiratory distress syndrome (ARDS).\textsuperscript{7} Given the clinical importance of ventilator-induced lung injury, this article will review mechanisms underlying the condition, its biologic and physiological consequences, and clinical strategies to prevent it and mitigate its effects.

**PATHOPHYSIOLOGICAL FEATURES**

**PRESSURES IN THE LUNG**

During a lifetime, a person will take approximately 500 million breaths. For each breath, the pressure necessary to inflate the lungs comprises the pressure to overcome airway resistance and iner-tance (a measure of the pressure gradient required...
to accelerate the gas) and the pressure to overcome the elastic properties of the lung. When airflow is zero (e.g., at end inspiration), the principal force maintaining inflation is the transpulmonary pressure (alveolar pressure minus pleural pressure) (Fig. 1). Thus, lung volume and transpulmonary pressure are inextricably linked.

Regional lung overdistention is a key factor in generating ventilator-induced lung injury. Since there is no well-accepted clinical method of

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**Figure 1. Intrathoracic Pressures and Lung Stretching.**

Panel A shows end inspiration in a patient with normal lung function who is breathing spontaneously (with an open glottis); the alveolar pressure (Palv) is 0, and the pleural pressure (Ppl) is negative (−8 cm of water), creating a transpulmonary pressure (Ptp) of +8 cm of water (Palv minus Ppl). Panel B shows the same lung while the patient undergoes general anesthesia and positive-pressure ventilation with the use of the same tidal volume as in Panel A. The lung would be similarly stretched, with an alveolar pressure of 9 cm of water and a pleural pressure of 1 cm of water for a transpulmonary pressure of +8 cm of water. Panel C shows end inspiration in a patient with severe obesity, massive ascites, or pleural effusions, who may have a very stiff chest wall. In such patients, much of the pressure that is applied by the ventilator will be used to distend the chest wall rather than the lung. As such, the plateau pressure may be high, but so will the pleural pressure, and hence there may not be an increase in transpulmonary pressure with accompanying lung overdistention. Panel D shows a musician playing a trumpet, which can result in airway pressures of as much as 150 cm of water. However, because of the positive pleural pressure developed by the respiratory muscles, the pressure across the lung will not exceed normal values. Panel E shows a patient with marked dyspnea who is undergoing a type of mechanical ventilation that requires the active contraction of the respiratory muscles to initiate the assisted breath (e.g., noninvasive ventilation or pressure-support ventilation). In such cases, there may be large negative swings in pleural pressure, leading to a very high transpulmonary pressure, even though the airway pressure is only 10 cm of water. (Additional details about the importance of transpulmonary pressure are discussed by Rahn et al.8)
measuring regional overdistention, limiting inflation pressure during mechanical ventilation is used as a surrogate strategy to limit overdistention. This is currently a reasonable therapeutic approach, but it is important to understand from a physiological standpoint the usefulness and limitations of the various pressures that are measured.

Alveolar pressure is relatively easy to estimate clinically as the airway pressure during a period of zero flow; in a patient undergoing mechanical ventilation who is not making spontaneous breathing efforts, the airway pressure that is measured during a period when airflow is stopped at end inspiration is called the plateau pressure. Unfortunately, pleural pressure — the other variable needed to calculate transpulmonary pressure — is more complicated. There is a gravitational gradient in pleural pressure, and it can be estimated in the broader clinical setting only by measurement of esophageal pressure.9 This measurement is somewhat cumbersome to perform and yields only approximate results. Therefore, the plateau pressure is the most common variable used in a clinical setting to indicate lung overdistention. However, there are nuances required in interpreting the plateau pressure. If the patient is not making respiratory efforts, the plateau pressure represents the pressure that is distending the lungs plus the chest wall. In a patient with a stiff chest wall (e.g., a patient with a pleural effusion or massive ascites), a large fraction of ventilator-delivered pressure is dissipated in inflating the chest wall rather than the lung. Thus, a high airway pressure — in this case, the plateau pressure — may not be indicative of excessive pulmonary stretching forces (i.e., elevated transpulmonary pressure) (Fig. 1C).

By analogy, when a musician plays the trumpet, airway pressure can reach 150 cm of water,10 but pneumothorax is uncommon, because pleural pressure is also elevated and there is no overdistention (Fig. 1D). In contrast, during noninvasive ventilation, if the patient is markedly distressed and generating very large negative pleural pressures, transpulmonary pressure (and hence lung stretching) may be extremely high, despite low airway pressures (Fig. 1E).

**PHYSICAL FORCES**

The following sections deal with major physical factors that are thought to be important in producing ventilator-induced lung injury. Other factors (e.g., respiratory acidosis, respiratory frequency, pulmonary vascular pressures, and body temperature) have been shown experimentally to be relevant to ventilator-induced lung injury, but these factors probably represent second-order effects and will not be addressed further in this review.

**Ventilation at High Lung Volumes**

Ventilator-induced lung injury can occur because of ventilation at high (absolute) lung volumes, leading to alveolar rupture, air leaks, and gross barotrauma (e.g., pneumothorax, pneumomediastinum, and subcutaneous emphysema) (Fig. 2). The term barotrauma can be misleading, because the critical variable leading to the air leaks is regional lung overdistention, not high airway pressure per se (Fig. 1D).

More subtle injury that is manifested as pulmonary edema can occur as a result of lung overdistention. In a classic experiment, Webb and Tierney14 ventilated rats with very high peak airway pressures (and therefore overdistention) and zero positive end-expiratory pressure (PEEP).
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**A Ventilation at low lung volume**

End expiration

End inspiration

Atelectrauma

Lung inhomogeneity

**B Ventilation at high lung volume**

Normal

Hyperinflation

Air leaks

Overdistention

**C Structural consequences**

- Epithelial–mesenchymal transformations
- Surfactant dysfunction
- Fibroproliferation
- Sloughing of bronchial epithelium
- Hyaline membranes
- Pulmonary edema
- Increased alveolar-capillary permeability

**Biologic alterations**

- Increased concentrations of:
  - Hydroxyproline
  - Transforming growth factor-β
  - Interleukin-8
- Release of mediators:
  - Tumor necrosis factor α (TNF-α)
  - β-catenin
  - Interleukin-6 (IL-6)
  - Interleukin-1β (IL-1β)
- Recruitment of:
  - Pulmonary alveolar macrophages (PAMs)
  - Neutrophils
- Activation of epithelium and endothelium

**Physiological abnormalities**

- Increased physiological dead space
- Decreased compliance
- Decreased PaO₂
- Increased PaCO₂

**Systemic effects**

- Translocation of:
  - Lipopolysaccharides (LPS)
  - Bacteria
  - Various mediators

- Multiple mechanisms (e.g., increased apoptosis)
- Multiorgan dysfunction
- Death
poxemia developed in the animals, and post-mortem examination revealed perivascular and alveolar edema. Edema did not develop in animals that underwent ventilation with the same peak airway pressure but with the addition of a PEEP of 10 cm of water, showing an interaction between overdistention and low end-expiratory lung volume with respect to lung injury. The precise mechanisms underlying this interaction have not been completely elucidated.

Dreyfuss et al. found that pulmonary edema developed in animals undergoing ventilation with high tidal volumes, whereas such edema did not develop in animals undergoing ventilation with similar airway pressures but with straps around their abdomens and chests that reduced the tidal volumes. Thus, their experiments showed that volume (i.e., lung stretching), not airway pressure, was the most important factor in determining injury, a finding that led them to coin the term “volutrauma.”

Although ventilator-induced lung injury is a well-accepted term, it may be a misnomer. The key factor causing injury is lung overdistention, which may be caused by factors other than a ventilator. For example, Mascheroni et al. injected sodium salicylate into the cisterna magna of spontaneously breathing sheep, causing a marked increase in minute ventilation and alveolar overdistention with each breath. Hypoxemia developed in the animals, along with stiff lungs and severe morphologic pulmonary derangements consistent with lung injury observed during mechanical ventilation. Such effects did not develop in animals that were treated with sodium salicylate but underwent controlled ventilation without excessive lung stretching.

Ventilation at Low Lung Volumes

Ventilation that occurs at low (absolute) lung volumes can also cause injury through multiple mechanisms, including repetitive opening and closing of airways and lung units, effects on surfactant function, and regional hypoxia. This type of injury, which is characterized by epithelial sloughing, hyaline membranes, and pulmonary edema, has been termed “atelectrauma.” Atelectrauma is amplified in lungs in which there are marked homogeneities in ventilation. In a classic study, Mead et al. noted that the stretching forces in lung parenchyma at margins between aerated and atelectatic regions could be up to four to five times as high as those in other lung regions.

**Biologic Forces**

The physical forces described above may cause the release of various intracellular mediators either directly (by injuring various cells) or indirectly (by transducing these forces into activation of cell-signaling pathways in epithelial, endothelial, or inflammatory cells). Some mediators may directly injure the lung; others may set the stage for subsequent development of pulmonary fibrosis. Additional mediators may act as homing molecules recruiting cells (e.g., neutrophils) to the lung, and such cells can then release more injurious molecules (Fig. 2).

This process has been termed biotrauma. The translocation of mediators, bacteria, or lipopolysaccharide from the airspaces into the systemic circulation may occur in lungs that have increased alveolar–capillary permeability, which is inherent in the case of ARDS or which is induced by volutrauma or epithelial microtears. This translocation may lead to subsequent multi-organ dysfunction and death (Fig. 2).

**Clinical Management**

The recognition of the importance of ventilator-induced lung injury has led to a marked change in the philosophy underlying the provision of mechanical ventilation. Whereas previously the goals of mechanical ventilation were to maintain gas exchange while minimizing the work of breathing, an additional goal has been established: to provide gas exchange that sustains life while minimizing ventilator-induced lung injury.

In practice, this means that setting the ventilator often entails difficult tradeoffs. For example, is it better to use a smaller tidal volume and let the partial pressure of arterial carbon dioxide increase despite the associated risks (e.g., increased intracranial hypertension from respiratory acidosis) or use larger tidal volumes to normalize the PaCO₂ but increase the risk of lung injury? Whereas previously the answer might have been to increase the tidal volume, current philosophy has shifted to a stronger focus on pro-
tection of the lung with the use of smaller tidal volumes.

VENTILATION STRATEGIES

Various ventilation strategies have been used to minimize lung injury: low tidal volumes to limit overdistention, higher PEEPs to prevent injury from low lung volume (atelectrauma), and recruitment maneuvers (i.e., procedures that are used to reinflate collapsed lung units) that involve sustained application of an airway pressure of more than approximately 35 cm of water. The increase in pressure can inflate atelectatic lung regions and minimize ventilation heterogeneity. Studies addressing these interventions are summarized briefly below.

Low Tidal Volumes

Patients with ARDS often have relatively non-aerated dependent lung regions (i.e., regions that are lower from a gravitational perspective than other regions and hence are more likely to be collapsed) and relatively normally aerated nondependent lung regions. Because there is a smaller volume available for ventilation, this condition has led to the term “baby lung.” The implication is that a decreased tidal volume (i.e., one that might be normal for a baby) should be used to prevent overinflation of the relatively small, normally aerated regions. In a seminal study that built on previous studies, the ARDS Network investigators compared a control strategy that used a tidal volume of 12 ml per kilogram of predicted body weight with a low-tidal-volume strategy that used 6 ml per kilogram of predicted body weight. The low-tidal-volume strategy was associated with an absolute reduction of 9 percentage points in the rate of death (39.8% vs. 31.0%).

High PEEP and Recruitment Maneuvers

Pulmonary edema and end-expiratory alveolar collapse characterize several forms of respiratory failure. In these situations, a low PEEP may be insufficient to stabilize alveoli and keep them open, thereby increasing the likelihood of ventilator-induced lung injury from atelectrauma. Conversely, a higher PEEP has potentially adverse effects, including impairment of venous return and pulmonary overdistention. A recent meta-analysis of patient-level data in randomized trials addressed these tradeoffs in patients with ARDS and concluded that a higher PEEP was associated with an absolute reduction of 5 percentage points in the rate of death among patients who had worse oxygenation, defined as a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2:FIO2) of 200 mm Hg or less.

Given the importance of transpulmonary pressure in lung injury, an obvious approach would be to use transpulmonary pressure to set the PEEP, with the use of esophageal pressure as a surrogate for pleural pressure. However, the interpretation of absolute esophageal pressure is difficult because of cardiac artifacts, the uneven distribution of pleural pressure (i.e., no single value of pleural pressure describes the entire lung), and esophageal distortion and contraction (especially in supine patients). Nevertheless, this approach has been studied in patients with ARDS. In a pilot study, Talmor et al. set the PEEP to achieve an end-expiratory transpulmonary pressure of 0 to 10 cm of water, while limiting end-inspiratory transpulmonary pressure to 25 cm of water. They found improved oxygenation and a trend toward lower 28-day mortality. These data are promising, but a larger trial that shows improved clinically important outcomes would be needed before this approach could be recommended.

Recruitment maneuvers should theoretically reduce ventilator-induced lung injury. Although such maneuvers were used in some trials that were included in the meta-analysis described above and were implemented in a protective strategy that increased the number of lungs retrieved from heart-beating donors, the role of recruitment maneuvers in clinical practice remains uncertain because of questions about its effect on outcomes and concerns regarding complications (e.g., hemodynamic compromise or pneumothorax).

High-Frequency Oscillatory Ventilation

High-frequency oscillatory ventilation (HFOV) is a technique in which very small tidal volumes (sometimes less than the anatomic dead space) are applied at high frequencies (up to 15 per second). Theoretically, this technique should be ideal for minimizing ventilator-induced lung injury. In a meta-analysis of eight randomized, controlled trials involving a total of 419 adults with
ARDS, HFOV-treated patients had significantly lower mortality than did patients treated with conventional ventilation (risk ratio, 0.77; P=0.03), which suggested that HFOV might improve survival and is unlikely to cause harm. However, since two recent large multicenter trials involving patients with ARDS did not show improved outcomes with HFOV, this type of ventilation cannot be recommended as first-line therapy in such patients.

ADJUNCTIVE STRATEGIES

One goal of mechanical ventilation is to help meet the gas-exchange demands of the patient. Thus, one nonspecific approach that might limit ventilator-induced lung injury is to decrease a patient’s metabolic demands, thereby decreasing the required minute ventilation and decreasing breathing efforts. Other specific approaches are discussed below.

Prone Position
About 70% of patients with ARDS and hypoxemia have improved oxygenation when they are placed in a prone position. Possible mechanisms for this effect include increased end-expiratory lung volume, better ventilation–perfusion matching, less effect of the mass of the heart on the lower lobes, and improved regional ventilation. Most important, as has been shown in studies in animals, the prone position should minimize lung injury by increasing homogeneity of ventilation.

A recent meta-analysis of seven trials involving a total of 1724 patients showed that prone positioning lowered absolute mortality by approximately 10 percentage points in the subgroup of patients with ARDS and severe hypoxemia (PaO₂/FIO₂ ratio, <100 mm Hg). Patients who were treated with prone positioning had an increased number of potentially preventable complications, including pressure ulcers, endotracheal-tube obstruction, and chest-tube dislodgement. In a recently completed trial involving 456 patients with ARDS who had a PaO₂/FIO₂ ratio of less than 150 mm Hg while receiving an FIO₂ of 0.60 or more, the rate of death at 28 days was 32.8% among those who were treated in the supine position and 16.0% among those treated in the prone position.

Partial or Total Extracorporeal Support
One approach to preventing ventilator-induced lung injury is to avoid mechanical ventilation and instead use extracorporeal membrane oxygenation (ECMO). It is also possible to combine mechanical ventilation with partial extracorporeal support; with this approach, the intensity of ventilation that is needed to sustain life is decreased, and carbon dioxide is removed through an extracorporeal circuit. The advantages of this hybrid strategy are a decreased rate of complications, as compared with full ECMO, and a decreased rate of lung injury because tidal volumes can be reduced. Preliminary data have supported this approach, but further studies are required to show which mode of extracorporeal support to use, when to apply it, and which, if any, patients might benefit.

PHARMACOLOGIC INTERVENTIONS

Neuromuscular Blocking Agents
Because of extreme dyspnea, patients with ARDS often “fight the ventilator,” which may aggravate ventilator-induced lung injury. One therapeutic approach is to administer a neuromuscular blocking agent such as vecuronium, rocuronium, or cisatracurium. These drugs decrease the patient’s respiratory drive by blocking the transmission of impulses from the motor cortex to the spinal cord. However, they may also decrease the patient’s ability to protect themselves, so that spontaneous ventilation is necessary for their safety. Additionally, they may increase the risk of aspiration pneumonia. Because of this, these drugs are administered in the context of a protective lung strategy and with the goal of minimizing the injury caused by mechanical ventilation. The use of these drugs is recommended for patients with ARDS, particularly when the patient is unable to maintain adequate oxygenation and ventilation while receiving mechanical ventilation. However, their use should be carefully considered before they are implemented. PEEP denotes positive end-expiratory pressure, and P/F ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.
Heart-beating organ donor

- Tidal volume = 6–8 ml/kg PBW
- Plateau pressure ≤30 cm of water
- PEEP and inspired oxygen fraction table

Protective lung strategy

- Apnea tests using continuous positive airway pressure
- Closed airway suctioning
- Recruitment maneuvers after disconnecting

Caveat: If patient has acute brain injury, monitor for respiratory acidosis

- Tidal volume = 6–8 ml/kg PBW
- Plateau pressure ≤20 cm of water
- PEEP at 4–8 cm of water
- Recruitment maneuvers every 30 minutes for anesthetized patients

Protective ventilation strategy

Patient with ARDS

- Tidal volume = 6–8 ml/kg PBW
- Plateau pressure ≤30 cm of water
- PEEP and inspired oxygen fraction table

Protective lung strategy

- Apnea tests using continuous positive airway pressure
- Closed airway suctioning
- Recruitment maneuvers after disconnecting

If patient has stiff chest wall (e.g., with massive ascites or pleural effusion) consider

- Allowing plateau pressure >30
- Use of higher PEEP levels
- Measuring esophageal pressure to set pressures

Consider use of higher PEEP strategy

If P/F ≤200 mm Hg

Consider using prone position if staff are well trained in procedure

If P/F <150 mm Hg

Consider using neuromuscular blocking agent if early ARDS (approximately <48 hours)

If patient still is in distress or has extreme hypoxemia, consider rescue therapies

Patient with normal lungs in ICU

- Anesthetized patient undergoing major abdominal surgery, at high risk for complications

Protective ventilation strategy

- Tidal volume = 6–8 ml/kg PBW
- Plateau pressure ≤20 cm of water
- PEEP at 4–8 cm of water
- Recruitment maneuvers every 30 minutes for anesthetized patients

Patient with ARDS

- If P/F <150 mm Hg
  - Consider using prone position if staff are well trained in procedure
  - Consider using neuromuscular blocking agent if early ARDS (approximately <48 hours)
  - If patient still is in distress or has extreme hypoxemia, consider rescue therapies

If patient still is in distress or has extreme hypoxemia, consider rescue therapies
blocking agent to ensure patient–ventilator synchrony and facilitate limitations on tidal volume and pressure. In a recent multicenter, placebo-controlled, randomized trial involving 340 patients with ARDS and a Pao2/Fio2 ratio of less than 150 mm Hg, Papazian et al.54 found that the adjusted 90-day mortality was lower among those who received a neuromuscular blocking agent for 48 hours than among those who received placebo, without any increase in residual muscle weakness. The precise mechanism for the decreased mortality is unclear,50 but a previous study showed reduced serum cytokine levels among patients receiving a neuromuscular blocking agent.52 In the study by Papazian et al., the divergence in mortality between groups occurred relatively late (approximately 16 days after the initiation of treatment), which could be explained by a decreased rate of multiorgan failure due to biotrauma.27

Antiinflammatory Agents and Stem Cells
Pharmacologic interventions that are aimed at minimizing biotrauma have not been reported in humans, but antiinflammatory strategies53 and the use of mesenchymal stem cells54 have been investigated in studies in animals. The key advantage of such therapies in the prevention of the consequences of ventilator-induced lung injury, as compared with their use in other inflammatory conditions (e.g., sepsis), is that the therapy could be delivered before the inciting agent is initiated (i.e., immediately before mechanical ventilation). These treatments remain experimental and of unproven benefit.

Areas of Uncertainty and Recommendations
Although the trials described above help clinicians make difficult tradeoffs, they often do not address the complexity of many clinical situations. In these cases, it is advisable for clinicians to integrate underlying physiological principles with trial data. For example, in the ARDS Network study, investigators used ventilation with a tidal volume of 6 ml per kilogram of predicted body weight and limited the plateau pressure to 30 cm of water.7 However, since regional overdistention occurs in some patients despite these settings, the use of a reduced tidal volume (or reduced PEEP) may be warranted.55

Conversely, the plateau-pressure limit of 30 cm of water may be too low in some patients. If a patient has a markedly stiff chest wall (e.g., because of massive ascites), the lungs may not be overdistended at 30 cm of water or even at higher plateau pressures (Fig. 1C). In this situation, in a patient with hypoxemia, higher plateau pressures may be appropriate, even though the ARDS Network study did not recommend such adjustments. Another possibility is to consider measuring esophageal pressure to help set the ventilatory strategy.

When clinicians use assisted modes of ventilatory support (i.e., mechanical ventilation that requires active contraction of respiratory muscles) or noninvasive ventilation, it is important for them to be aware that large tidal volumes may be delivered despite relatively low airway pressures.

From a theoretical perspective, all patients receiving ventilator support should benefit from strategies that minimize ventilator-induced lung injury. However, it is important to bear in mind the effects of any strategy to reduce lung injury on other important physiological or clinical phenomena (e.g., the effect of a lung-protective strategy on hemodynamics). Figure 3 summarizes clinical scenarios in which lung-protective ventilation has been shown to have substantial or possible benefit. Of particular interest is whether patients with relatively normal lungs should undergo ventilation with low tidal volumes. Uninjured (normal) lungs tolerate relatively large tidal volumes delivered at relatively low pressures as long as the stress and strains applied are below an injurious threshold.50 The specific thresholds are uncertain, but a recent meta-analysis showed that ventilation with smaller tidal volumes in patients without ARDS may be associated with improved outcomes.57 Although these data suggest that lung-protective ventilation strategies should be adopted widely, the ideal ventilation strategy remains to be determined, and more definitive studies are necessary before the use of such strategies becomes standard practice.

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