The use of positive-pressure ventilation (PPV) to treat respiratory failure exposes patients to several known risks. When invasive endotracheal intubation is required, PPV is uncomfortable and is associated with increased morbidity and mortality [1]. The depressive effect of PPV on the cardiovascular system is well known and is considered when applying ventilatory care [2]. Pulmonary air leaks are directly caused by the application of elevated positive pressure and are a known, direct risk of PPV [3]. Since the 1980s, ventilator-induced lung injury (VILI) caused by elevated airway pressures has been clearly characterized and is now well established as a significant risk of PPV.

An increased incidence of pulmonary air leaks in vulnerable patients receiving PPV is well documented [3] [4] [5]. These air leaks, also commonly known as barotrauma, may manifest as pneumothoraces, pneumomediastinum, subcutaneous emphysema, or interstitial air. The leaks may cause air pockets that frequently require treatment such as chest tube placement, careful ventilator setting adjustments, or even the use of high-frequency ventilation [6].

The incidence of air leaks in ventilated patients is significant (5%–15%), particularly when mechanical ventilation requires the use of peak airway pressures exceeding 50 cm H₂O [2]. In the National Institutes of Health ARDSnet trial, a large multicenter collaborative study of patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI), the incidence of barotrauma...
was 13% in the first four days of ventilation [8]. There was an association between barotrauma and increasing positive end-expiratory pressure (PEEP) settings (relative hazard = 1.67 per 5-cm H2O PEEP increment), independent of Acute Physiology and Chronic Health Evaluation (APACHE) score, age, or baseline plateau pressures. Thus, pulmonary air leaks have been considered the primary potential complication of ventilator care. Parenchymal lung injury or VILI does not necessarily occur when air leaks occur. Therefore, effects of PPV such as the increased risk of pneumonia with intubation, an adverse effect on the cardiovascular system, or pulmonary air leaks are considered ventilator-associated effects and not VILI.

Although the concept of VILI has become accepted, many aspects of the injury continue to be poorly understood. The initiating injurious insult, exposure to elevated ventilatory pressures (barotrauma), may be the sole cause of worsening lung injury; more commonly, a concurrent inflammatory process accelerates injury development. Despite the uncertainty of an actual mechanism, results from two clinical studies have confirmed the potential for VILI [8]. This article discusses several current concepts of this recently recognized risk of PPV.

The potentially deleterious effects of PPV were first considered in the 1960s. In one study, after only 2 hours, dogs ventilated at pressures of 26 to 32 cm H2O were found to develop significant lung damage [10]. In a clinical study of lung pathology in patients who had been treated with PPV, Nash [11] reported lung injury findings consistent with ARDS. Exposure to a high concentration of fractional inspired oxygen (F1O2) could not be excluded as a causal effect [11]. A report of sheep that were safely ventilated for 1 week at low F1O2 settings assured clinicians that chronic use of PPV could be safely applied if oxygen concentrations were carefully controlled [12].

Subsequently, victims of polio, cervical trauma, and neurologic disorders have been safely ventilated for months and even years without acute adverse effects of PPV [13]. In 1974, Webb and Tierney [14] first reported a direct, damaging effect on rat lungs by PPV of 45 cm H2O (Fig. 1 [Not Available]). Thereafter, the concept of parenchymal lung damage caused by PPV was further substantiated in studies conducted by Parker [15] and Dreyfuss [16] in the 1980s. Since 1980, the causative factors and features of VILI have been investigated more thoroughly.

**Mechanical stressors**

The initiating mechanical stressor is not simply a damaging, elevated pressure but rather is a complex interaction of injury-inducing factors. The means of applying the pressure may be important, and adjusting one setting often affects
several parameters. Fig. 2 is a construct for proposed stressors in the development of injury. Of greatest importance, the ventilator exerts the initial mechanical stressor to alveolar structural cells by applying positive airway pressure at a certain excessive magnitude (an injurious peak alveolar pressure). That pressure is approached during each breath through an adjustable inspiratory flow rate. The pressure exposure continues, either constantly (pressure controlled) or increasing to a peak (volume controlled), for a specific duration, or inspiratory time (Ti). During the expiratory period, an expiratory pressure can be continuously applied (PEEP). Expiration is terminated after a time (expiratory time) that sets a frequency, or respiratory rate.

Fig. 2. Schematic drawing of airway pressure waveform during pressure-controlled ventilation. Several aspects of PPV may contribute to VILI: the pressure magnitude or peak alveolar pressure, the inspiratory flow rate, inspiratory time, expiratory time, respiratory frequency, and PEEP.

Each of these factors plays a role in inducing lung injury. Derived from these factors are potentially important calculated indices of VILI risk such as mean airway pressure, pressure excursion (Peak–PEEP), and tidal volume (VT). Other factors may also influence the development of VILI such as acid–base status (hypercapnia, acidosis), positioning, and vascular status (related to fluid management).

The initial mechanical stressor causing injury is alveolar pressure that reaches a level of alveolar overdistension (Fig. 3). This alveolar pressure is attained by the pressure distribution from an airway pressure profile. Alveolar overdistension is caused by an excessive pressure difference across the lungs, so that excessive peak airway pressure itself is not necessarily damaging. If elevated airway pressure alone caused injury, a cough that generated 150 cm H₂O would surely injure the lungs. A damaging positive pressure is probably a pressure difference across the lungs (transpulmonary pressure) with intervening, vulnerable lung tissue between the two levels of pressure. For example, an opposing pressure to the elevated airway pressure reduces the pressure difference and has been shown to be protective.

Fig. 3. Pre- and post-injury pressure-volume curves. Alveolar pressures of 30 to 35 cm H₂O approach the elastic limits of the lungs. Overdistension-related injury becomes more likely when volume delivery causes excessive pressure exposure.

Studies employing chest wall or thoracic restriction have been found to reduce measures of overdistension injury [17] [18] [19]. Dreyfuss [17] applied thoracoabdominal strapping with rubber bands to rats ventilated at 45 cm H₂O. Lung edema was lower in the strapped rats than in the unstrapped rats. In another study, rabbits were fitted with full-body plaster casts to restrict thoracic expansion and ventilated at injurious pressure levels. A filtration coefficient (Kf), which is a measure of lung permeability that assesses microvascular damage, did not increase in these bound rabbits compared with rabbits with unrestricted chest walls [18]. In lambs catheterized to measure lymph flow (a measure of lung
leakage), Carlton [19] reported a reduction in lymph flow when the chest and abdomen were bound. The binding was adjusted to result in a peak pressure increase (34–54 cm H₂O) without a change in VT.

Chest wall restriction establishes an opposing thoracic force and, by extension, an opposing pleural pressure that reduces transpulmonary pressure. With this logic, an increase in abdominal pressure (another opposing force) would permit a greater plateau pressure exposure, because transpulmonary pressure may be lower with an elevation of abdominal pressure [20]. Open-chest lung studies or isolated, perfused lung studies develop lung injury at lower alveolar pressures, because pleural pressure is atmospheric or zero and is not allowed to rise because opposing pleural pressure cannot be generated. In such studies, lungs are injured at airway or alveolar pressures as low as 15 to 35 cm H₂O [15] [16] [21] [22] [23] [24] [25].

Basic physiologic studies of the pressure-volume relationships of normal lungs indicate that, in theory, pressures exceeding 30 to 35 cm H₂O may be injurious, because these pressures attempt to inflate the lungs above total lung capacity. Inflation above total or regional lung capacity would be expected to cause overdistension (Fig. 3). A specific pressure-time risk of VILI for humans is not known. Numerous animal studies have found that airway pressures exceeding 30 cm H₂O cause lung injury [26] [27] [28] [29] [30] [31]. To determine the features of VILI, investigators have applied elevated airway pressures in various manners to rat, rabbit, dog, sheep, and pig lungs for periods from 10 minutes to 72 hours. In large mammals, 2 to 24 hours of peak pressures greater than 35 cm H₂O have caused significant injury that may lead to death (Fig. 4).

Fig. 4. Dorsal and ventral views of porcine lungs ventilated for 6 hours at transpulmonary pressures of 35/3 cm H₂O. Although superficial atelectasis is apparent in this ex vivo preparation at a PEEP of 0 cm H₂O, hemorrhage is marked in the caudal and dorsal regions.

Injury vulnerability may be species specific to some degree. In a study of isolated, perfused dog lungs, Parker [15] reported an accelerated increase in Kf with airway pressures increasing above 30 cm H₂O (Fig. 5 [Not Available]). In smaller mammals, less pressure over a shorter time period causes injury.

Fig. 5. (Figure not Available) A curvilinear increase in Kf with increasing peak airway pressure. In this isolated, perfused lung-injury model, increasing lung injury corresponded with increased peak pressure exposure. This correspondence can be assessed by the filtration coefficient, which becomes curvilinear at pressures above 30 cm H₂O. From Parker JC, Townsley ML, Rippe B, et al. Increased microvascular permeability in dog lungs due to high peak airway pressures. J Appl Physiol 1984;57:1809–16.

Host-dependent factors such as lung prematurity or pre-existing injury may cause a predisposition to further injury development [33]. Vulnerable or previously injured lung tissue may be injured at moderate pressures between 25 and 30 cm H₂O.
In 1999, a Consensus Conference guideline recommended that plateau pressures be limited to less than 35 cm H$_2$O. A subsequent review recommended reducing the limit to less than 32 cm H$_2$O.

**Protective role of positive end-expiratory pressure**

Although exceeding the elastic limits of the lung is known to cause injury (high-stretch injury), another mechanism for VILI has been proposed. In lung tissue that has been previously damaged, lung collapse often occurs at end-expiration. If an adequate distending pressure (PEEP) is applied, this collapse (or derecruitment) may be avoided (Fig. 6). It has been suggested that persistent end-expiratory alveolar collapse and subsequent reopening during inspiration further induce lung injury (low-stretch injury). Maintaining end-expiratory lung volume above this derecruitment level by adequate PEEP, by extending the inspiratory:expiratory ratio (I:E), or by using a recruiting ventilatory strategy ($V_t$, frequency [$f$]) may prevent this source of VILI. Because PEEP is employed to elevate mean or end-expiratory lung volume, lung injury caused by repeated opening and closing might be avoided. Shearing forces at the junction between open and closed lung units are thought to be responsible for such injury.

The application of moderate levels of PEEP clearly provides protection against VILI. In rats ventilated at 45 cm H$_2$O, Webb and Tierney reported less hemorrhage and edema when PEEP of 10 cm H$_2$O was applied. Whereas increasing PEEP has been associated with increased pulmonary edema in clinical studies of acute respiratory failure, Dreyfuss reported a reduction in ventilator-associated pulmonary edema with an elevated PEEP setting (10 cm H$_2$O) in rats ventilated at 45 cm H$_2$O. Positive expiratory-end pressure applied in rabbits ventilated at 45 cm H$_2$O reduced injury as assessed by wet-weight:dry-weight ratio (WW/DW), compliance, and arterial oxygen tension (PaO$_2$) changes.

Another potential PEEP-protection mechanism is that elevated PEEP may allow a longer period of lung cell membrane stability before the next inspiratory mechanical stressor is delivered, because pressure stability is reached earlier in the expiratory period. This extended period of stability may be needed for cells to recover from the mechanical stressor of the inspiratory cycle (cell membrane resealing) if changing pressure is a component in VILI. Setting the level of PEEP to provide protection against VILI may be guided by constructing a respiratory pressure-volume curve, but the importance of setting PEEP above the lower inflection of a zero expiratory-end pressure (ZEEP) pressure-volume curve has been questioned.
Inspiratory flow

The inspiratory flow pattern or rate is another factor in the development of VILI. An increased inspiratory flow rate has been associated with greater measures of lung injury [22, 29]. In an isolated, perfused rabbit lung study, flow rates of 6 to 8 L/minute caused greater microvascular injury than flow rates of 1 to 2 L/minute [22]. There were, however, differences in ventilatory frequency between the two study groups (f = 10/minute in the low-flow group versus f = 25/minute in the high-flow group). In a 6-hour study of sheep ventilated at 50 cm H2O, reducing inspiratory flow rate to 15 L/minute maintained compliance and lowered intrapulmonary shunt (Qs/Qt) and reduced histologic injury scores compared with the high-flow group [29]. The high-flow group received pressure-controlled ventilation, and the low flow group received volume-controlled ventilation with a pressure limit of 50 cm H2O, but both groups were ventilated at a frequency of 5/minute. Increased flow rate was considered the injurious factor in each study.

Inspiratory time

At or above a certain threshold pressure, increasing Ti may be directly related to VILI development by increasing the time of overdistension. In a study specifically designed to investigate the role of Ti, Casetti [31] ventilated rats for 30 minutes at a peak pressure of 45 cm H2O with Ti of 0.5, 1, or 2 seconds. Increasing Ti caused greater injury as assessed by compliance, PaO2/FIO2 changes, WW/DW, and increased alveolar edema and hemorrhage. Casetti concluded that the practice of increasing Ti to enhance alveolar recruitment and improve oxygenation in patients with ARDS should be approached with caution. Another study found similar results in rabbits ventilated at 45 cm H2O for 2 hours: injury increased between Ti of 0.45 and 1 second, but a Ti of 2 seconds resulted in no greater injury than a Ti of 1 second [38].

Reduced injury development in the brief Ti periods may result from inadequate time for end inspiratory alveolar pressure to equilibrate with peak airway pressures. A comparison of Ti between 2 and 6 seconds in sheep ventilated for 6 hours at 50 cm H2O found no difference in VILI development between the two groups [29]. A Ti longer than 1.5 seconds may be less important than other causes of lung injury development. Of course, reducing Ti will decrease the period of overdistension if pressures are excessive, and a reduced Ti may avoid any period of overdistension altogether if a brief inspiratory time does not allow enough time for airway pressure to distribute to the alveoli. Directly affected by Ti, mean airway pressure may have a similar relationship with the development of VILI if the injurious pressure exceeds certain levels.

Frequency

The respiratory frequency or the number of insulting impacts per time period is thought to be associated with VILI. Hotchkiss [21] reported a role for frequency in an isolated, perfused model. Rabbit lungs were ventilated at 30 cm H2O and controlled for peak pulmonary artery pressure, vascular flow, mean airway pressure, and VT. Greater weight gain and a greater incidence of perivascular
hemorrhage were noted at a frequency of 20 breaths/minute than at 3 breaths/minute. Another study found no effect of frequency in rabbits ventilated at 9 versus 23 breaths/minute, although the higher-frequency group included animals with elevated PEEP [38]. In a sheep VILI study, no difference in injury level was detected in animals ventilated at peak pressure of 50 cm H$_2$O with a frequency of 5 breaths/minute compared with a frequency of 15 breaths/minute [29]. An adequately powered study will be required to discern whether a frequency threshold must be exceeded to induce injury or a continuum of increasing injury is associated with increasing frequency.

**Volutrauma**

Another interpretation of the cause and prevention of VILI emphasizes delivered VT rather than pressure exposure. Experiments have been specifically designed to determine the effect of VT as a causative factor. Dreyfuss [17] assessed water accumulation in the lung, microvascular permeability, and labeled albumin in rats ventilated with one of three strategies: (1) 45 cm H$_2$O, with a VT of 40 mL/kg; (2) 45 cm H$_2$O with a VT of 19 mL/kg, bound chest; or (3) a VT of 44 mL/kg delivered using an iron lung (negative-pressure ventilation). The two groups that received large VT had significantly greater injury than the chest-bound rats. Therefore, increased VT was associated with injury, because the chest-bound rats experiencing high pressure and low VT were not injured. Carlton et al [19] found that lymphatic drainage, a measure of vascular permeability, was increased after ventilation of lambs at a peak inspiratory pressure (PIP) of 61 cm H$_2$O and VT of 57 mL/kg. In lambs with chest and abdomen binding, no increase in drainage was seen after 4 to 6 hours of ventilation at PIP of 54 mL/kg and VT of 23 mL/kg. This study also concluded that peak pressure is not injurious; rather, the volume excursion experienced by the lungs caused injury.

The results of two clinical trials have emphasized the importance of reduced tidal ventilation [9,42]. In the ARDSnet trial of 861 patients, patients in the group receiving VT of 6 mL/kg experienced a 22% reduction in mortality compared with patients receiving VT of 12 mL/kg; in this study, the difference in VT was interpreted as causal [42]. Plateau pressure was greater in the high-VT group. Thus, pressure and volume excursions are linked: avoiding elevated plateau pressures and increasing PEEP settings decreases VT excursion. This relationship suggests a possible chicken-or-egg debate.

**Respiratory acidosis, positioning, vascular pressure management**

A recent provocative line of investigation in the prevention of VILI involves the management of acid–base status. Hypercapnia and acidosis have been studied for their possible protective roles in VILI. In an isolated, perfused rabbit lung study, Broccard [24] reported an independent role for respiratory acidosis in preventing VILI. Lungs insufflated with CO$_2$ to attain arterial carbon dioxide tension (PaCO$_2$) at 80 to 100 mm Hg exhibited less injury than eucapnic lungs. Sinclair et al [43] ventilated rabbits with either eucapnea or respiratory acidosis at excessive airway pressures and found greater injury in the eucapnic animals, as assessed by compliance and PaO$_2$ reduction, edema formation, and bronchoalveolar lavage (BAL) protein count [43]. Whether acidosis or hypercapnia
is protective or the roles are interactive has yet to be determined. Therefore, although hypercapnia (or acidosis) may be acceptable or permitted (permissive hypercapnia \[44\]), when guarding the lungs from excessive pressure or volume excursions, respiratory acidosis may actually be protective (prescriptive hypercapnia).

Body positioning has a potential influence on the development of VILI. A report from an investigation in dogs positioned either supine or prone found that prone positioning reduced and distributed VILI more widely than supine positioning \[32\]. Although the mechanism for this protective effect is unclear, the authors speculate that transpulmonary pressure distribution is more uniform in the prone position; this position then reduces the threat of opening/closing injury to the more vulnerable dorsal regions. Also, perfusion persists in the dorsal (nondependent) region in the prone position \[45\]. If perfusion is required for injury development, and ventilation is more uniform when prone, ventilation:perfusion (V/Q) mismatching is less likely in that position.

An effect of vascular pressures is probably important in the development of VILI. Because fluid administration and balance are important concerns in the critically ill patient, a role for vascular-flow pressures can be expected if lung tissue is rendered permeable by pressure-induced injury. Aggressive fluid administration might be expected to accelerate or exacerbate VILI. Broccard \[23\] examined this issue in a study of isolated, perfused rabbit lungs. Lungs ventilated at 30 cm H\(_2\)O and perfused at a rate of 900 mL/minute had greater weight gain, filtration coefficient changes, and reduction in compliance than lungs perfused at a rate of 300 mL/minute. Broccard concluded that lung perfusion contributes to VILI in this model.

Studies of preinjured lungs

Studies of VILI have clearly delineated a damaging effect of alveolar overdistension on normal lungs. The effect of elevated pressures on previously injured lungs has not been extensively investigated and is of greater clinical importance. Along the margin of healthy versus injured lung, the potential for opening/closing injury may be greater. In a study of rats ventilated at increasingly high volumes, the effect of previous exposure to alpha-naphththiourea produced an additive effect on edema accumulation. At a VT of 45 mL/kg the effects were interactive \[46\]. Corbridge \[47\] studied dogs that had been previously injured by hydrochloric acid causing a pulmonary edema. A high-VT – low-PEEP strategy resulted in a significantly greater WW/DW than a low-VT – high-PEEP strategy. The investigators concluded that PEEP protects against surfactant depletion and provides protection against the transfer of fluids from vessels to alveoli.

Indicators of injury

Because the signs or symptoms of VILI cannot be distinguished from other sources of a developing lung injury, the development of VILI is insidious. Thus, worsening lung injury is tracked by clinical and laboratory signs used in monitoring of the ICU patient: decreasing oxygenation or a reduced PaO\(_2\)/FiO\(_2\), decreasing compliance, or worsening radiographic patterns. A useful, distinct pattern or course of VILI development has not been determined. A consistent
observation has been made that has possible clinical utility. In rabbits ventilated at 45 cm H₂O to cause VILI, VT increased during the initial period of VILI development [38]. This observation is consistent with reports in two previous studies from Kolobow’s group [26] [28]. In sheep ventilated for 48 hours at 50 cm H₂O, VT started at 500% of baseline and subsequently increased to 600% to 700% of baseline from 2 to 6 hours after the study began. There is no clear explanation for this increase under static ventilatory conditions. Increasing VT would be expected with improving compliance, but the lungs were initially normal, and compliance eventually decreased throughout the study. During VILI development, lung recruitment may initially occur as a functional lung remodeling occurs in response to high airway pressure ventilation.

Another observation made during the course of injury is a consistent transformation in the inspiratory pressure waveform that suggests a conversion from a homogenous to heterogeneous lung. In a study of neural network analysis of inspiratory pressure waveforms, Rasanen et al [48] discovered that a waveform transformation occurred as VILI developed. A subsequent study reported changes from an exponential wash-in function, representing filling of a homogeneous lung, to a biphasic waveform in rabbits that developed VILI [38]. The change may represent normal lungs converting to injured, heterogeneous lungs.

**Biotrauma**

A recent comprehensive review of VILI defined injury components as either barotrauma (caused by mechanical forces) or biotrauma (caused by cellular or molecular changes) [49]. This article has, thus far, discussed issues related to barotrauma. Biotrauma can be further defined as cellular and mediator-related lung injury inflammation. Biotrauma is the process by which PPV-related stresses either induce or enhance an immunologic, inflammatory response.

The pulmonary inflammatory response to PPV is multifaceted. Alveolar epithelial cells and alveolar macrophages (AMs) are involved in this process. Alveolar macrophages recruit and activate polymorphonuclear neutrophils (PMNs) to the alveolar space from the bloodstream. Both PMNs and AMs synthesize and secrete cytokines. Cytokines are a large group of molecules involved in signaling between cells during immune responses. The different cytokines fall into a number of categories. Several proinflammatory cytokines have been detected during VILI and are probably involved in a coordinated response: interleukin (IL)-1β, IL-8, IL-6, macrophage inflammatory protein-2 (MIP-2), and tumor necrosis factor (TNF)-α. Tumor necrosis factor is the prototype of a family of molecules that are involved with immune system regulation and inflammation. Enzyme-Linked ImmunoSorbent Assay (ELISA) is the method performed to detect cytokines.

Proinflammatory cytokines are potential candidates for initiating or increasing VILI and possibly initiating systemic effects. The basic mechanisms that account for the biotrauma of VILI are relatively unknown, however. In vitro and in vivo studies have suggested that cellular stretching is important to the development of VILI through biotrauma [50]. Matthay [51] hypothesizes that the lung epithelium is an important mediator of VILI. Furthermore, another review suggests that the lung may serve as the body’s overall regulator of the inflammatory response; that is, the lungs may monitor inflammatory mediators and activate cells as they pass into and through the lungs [52]. Constraining or modulating the inflammatory...
response may be necessary to limit mechanical injury.

A reasonable approach to understanding available data on the role of cytokines in VILI development is an application of a corollary of Koch’s postulates [53]. Three types of experimental evidence must be present to accept a role for cytokines:

1. When VILI prevails, cytokines are present.
2. When a purified cytokine is administered to a test subject, VILI ensues.
3. When steps are taken to nullify the cytokine signal, VILI is alleviated or attenuated.

Ventilator-induced lung injury and cytokine release

In an isolated, perfused (blood-free), and ventilated mouse lung (with no possible influence of extrapulmonary organs), hyperventilation has been shown to induce the synthesis and release of cytokines [54]. During low-VT ventilation, only trace amounts of TNF-α and IL-6 were found in the perfusate. During hyperventilation, these indicators were markedly increased. On light microscopy, no gross physical damage was noted from hyperventilation. The authors assert that mechanisms other than tissue destruction must account for the release of these mediators. Therefore, mediator release must have been caused by hyperventilation (stretching or overdistension) of the lung. In an in vitro study of cellular deformation, stretching triggered inflammatory signaling. Vlahakis [55] concluded that alveolar epithelial cells may be active participants in the alveolitis associated with VILI.

In studies using a rat lung model, an association was found between injurious ventilatory strategy and proinflammatory cytokine release. In an ex vivo rat lung model, a significant relationship was found between respiratory system pressure-time characteristics, lung injury score, and elevated proinflammatory cytokine (IL-6 and MIP-2) levels [56]. In another isolated, rat lung model, a low-VT-low-PEEP ventilation strategy yielded the lowest levels of cytokines (TNF-α, MIP-2, IL-1β, IFN-γ, IL-6, IL-10), whereas a high-VT-ZEEP strategy produced the highest levels of cytokines [57].

In a recent clinical study, PMNs were activated by mechanical ventilation [58]. Subsequent release of elastase (a proteolytic enzyme) was found to correlate with the degree of systemic inflammatory response and multiple-organ failure. Bronchoalveolar lavage fluid obtained from patients ventilated with a conventional ventilatory strategy revealed greater amounts of activated neutrophils and elastase than BAL from patients ventilated with a protective ventilatory strategy. High plasma concentrations of IL-6 correlated with an increased release of neutrophil elastase. Therefore, the activation of neutrophils and release of elastase may be important mechanisms of VILI.

In another recent clinical study [59], 37 patients were studied in one of two experimental groups: controlled ventilation or lung-protective strategy. Patients in the controlled-ventilation group had an increase in BAL concentrations of IL-1β, IL-6, and IL-1 and plasma increases of TNF-α and IL-6 over 36 hours. The authors conclude that mechanical ventilation can induce a cytokine response that may be attenuated by a strategy to minimize overdistension and recruitment/derecruitment of the lung.
Although the studies cited thus far have found a correlation between injurious ventilation and proinflammatory cytokine release, two studies [60] [61] do not corroborate their results. In a rat study, VT ventilation of 42 versus 7 mL/kg was compared for effect on cytokine release [62]. High VT did not cause a significant release of proinflammatory cytokines (TNF-α, IL-1β, MIP-2) into the airspace. In a clinical study [63], 39 patients were randomly assigned to receive mechanical ventilation with either high or moderate VTs. There were no differences between groups in terms of plasma levels of all cytokines; all levels remained low in all settings. Initiation of mechanical ventilation for 1 hour in patients without previous lung injury caused no consistent changes in plasma levels of studied mediators.

**Anticytokine therapy**

Based on previous studies, TNF-α has been shown to initiate an inflammatory cascade in the lung [64]. To blunt or block an inflammatory response, Imai et al [65] pretreated rabbits with an intratracheal instillation of an anti-TNF-α antibody. Rabbits were ventilated for 4 hours to cause VILI. Compared with control rabbits, the rabbits receiving anti-TNF-α antibody displayed improved oxygenation and respiratory compliance, reduced infiltration of leukocytes, and decreased pathologic changes. In the treatment group, the antibody effectively suppressed TNF-α.

As an anti-inflammatory agent, an IL-10 activator was used in a rabbit model of pancreatitis. Injection of IL-10 activator resulted in a significant reduction in the blood levels of TNF-α and IL-8 (proinflammatory cytokines) from 3 to 6 hours. The activator also reduced the amount of ascitic fluid, significantly inhibited the neutrophil infiltration and margination, and reduced the degree of edema and vascular thrombosis in the lung interstitial tissue [64].

Several animal and clinical studies have been conducted to investigate the corollaries to Koch's postulates proposed earlier.

The first postulate (“When VILI prevails, cytokines are present”) is supported by evidence that stretching the lungs causes cytokine release. Animal and clinical studies have detected cytokine release governed by the ventilatory strategy employed. Two studies contradict these findings, however.

The second postulate (“When a purified cytokine is administered to a test subject, VILI ensues”) has not been investigated, to the authors’ knowledge.

Two studies present preliminary data supporting the third postulate (“When steps are taken to nullify the cytokine signal, then VILI is alleviated”).

**Association with multiple-organ dysfunction**

Several experimental studies have supported the concept that VILI precipitates the onset of multiple-organ dysfunction (MOD) by transmigration of bacteria from the lung or by decompartmentalization of locally produced cytokines [65]. In a dog study of *Escherichia coli* instillation that caused pneumonia, Nahum [66] reported an increased rate of bacterial translocation into the peripheral bloodstream with a high-VT–low-PEEP ventilator strategy. Several studies report
shifts in cytokines from vascular to alveolar compartments and vice versa [67]. Ventilator-associated systemic inflammation may play a key role in the development of MOD [68]. Pulmonary translocation of lung-derived endotoxin has been found to depend on the ventilatory strategy employed [69]. In rats injured by hydrochloric acid instillation, a high-VT-ZEEP strategy markedly increased levels of MIP-2 and TNF-α detected in the circulation [70]. In a VILI study of rats ventilated at peak pressures of 45 cm H₂O, TNF-α was found to shift from alveolar to vascular compartments (and vice versa), and high levels of PEEP prevented decompartmentalization of TNF-α. In a recent review of the topic, Dreyfuss and Saumon [65] conclude that systemic cytokine release and MOD might result from bacterial translocation from the lungs during VILI.

**Summary**

Ventilator-induced lung injury has been established as a significant risk to patients receiving PPV. Animal studies have provided definitive experimental data that support the existence of VILI. Clinical studies have implied the role of VILI in ARDS and ALI patients. In patients who have ARDS or ALI, however, VILI cannot be distinguished from exacerbation of the primary condition. Animal and clinical studies that clearly show elevated levels of cytokines when PPV is applied beyond certain limits support the concept that an inflammatory process is activated by PPV. Whether the induction of inflammatory mediators contributes to the mortality or morbidity of the ventilated patient has not been established. A potential role for anti-inflammatory therapeutic agents is promising.

Therefore, the following considerations can guide the clinical care of ventilator patients:

- Alveolar pressure exposure (plateau pressure) should be limited to less than 32 cm H₂O.
- Positive end-expiratory pressure should be applied to avoid end-expiratory collapse and reopening.
- Tidal volume should be set at approximately 6 mL/kg or further guided by plateau pressure limitation.
- Although studies suggest that reducing Ti, flow, and f may be important in avoiding VILI, there are no current guidelines.
- The results of preliminary studies investigating the preventative potential of respiratory acidosis, prone positioning, or careful vascular pressure management seem promising.
- Inflammatory response in VILI has been established, but a role for intervention, such as general or specific suppression of the response, has not been established.

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Abstract