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SEMINAL STUDY

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Ventilator-induced lung injury: from the bench to the bedside

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Introduction

Once upon a time the existence of ventilator-induced lung injury (VILI) was debated. After all, most patients with lung dysfunction requiring mechanical ventilation had other potential causes of lung injury, and many patients appeared to tolerate mechanical ventilation for prolonged periods without any adverse sequelae. However, as a result of numerous studies over the past century, and especially during the past 20 years it is now generally accepted that mechanical ventilation per se can initiate as well as exacerbate lung injury and contribute to patient morbidity and mortality. This review examines the seminal bench and bedside studies that contributed to our current understanding of VILI, and that form the basis for current recommendations for mechanical ventilation of the critically ill. Figure 1 schematically depicts a timeline of bench to bedside research on VILI. Included in this review are many of the most frequently cited studies (with the number of citations, *N*, from the Institute for Science Information Citation Index as of August 2005 included in parentheses), as well as those studies which the authors feel have had a particularly significant impact on subsequent research and/or clinical practice.

Brief overview of the early years: air leaks, surfactant dysfunction, and "respirator lung"

As early as the 1700s investigators raised concerns that inflation of the lung with positive pressure ventilation could potentially damage the lungs and produce air leaks (for an excellent historical review see [1]). In 1887 Champneys [2] reported that lung rupture and cervical emphysema ensue if the lungs of dead infants are subjected to pressures of 20–80 mmHg. In 1939 Macklin [3] (Number of citations, *N*=467) published a frequently cited study demonstrating that excessive alveolar distension produces rupture at the junction of the alveolar wall and vascular sheath, allowing air to track along the bronchovascular sheath into the mediastinum and subcutaneous tissues or to rupture into the pleural or peritoneal spaces. Given that the development of air leaks appeared to be related to the use of high airway pressures, the term "barotrauma" was applied.

In addition to air leaks, laboratory investigations also demonstrated that mechanical ventilation can adversely affect lung compliance and surfactant function. Greenfield et al. [4] (*N*=115) showed that ventilation of dog lungs with large tidal volume (V_t; generated with a peak inspiratory pressure, PIP, of 36–32 cmH_2O) for 2 h produces surfactant dysfunction, and Faridy et al. [5] (*N*=178) observed in an ex vivo dog lung model that the addition of positive end expiratory pressure (PEEP) attenuates ventilation-induced increases in surface tension.

Early investigators also made a number of important observations. For example, in 1949 Fowler [6] (*N*=325)

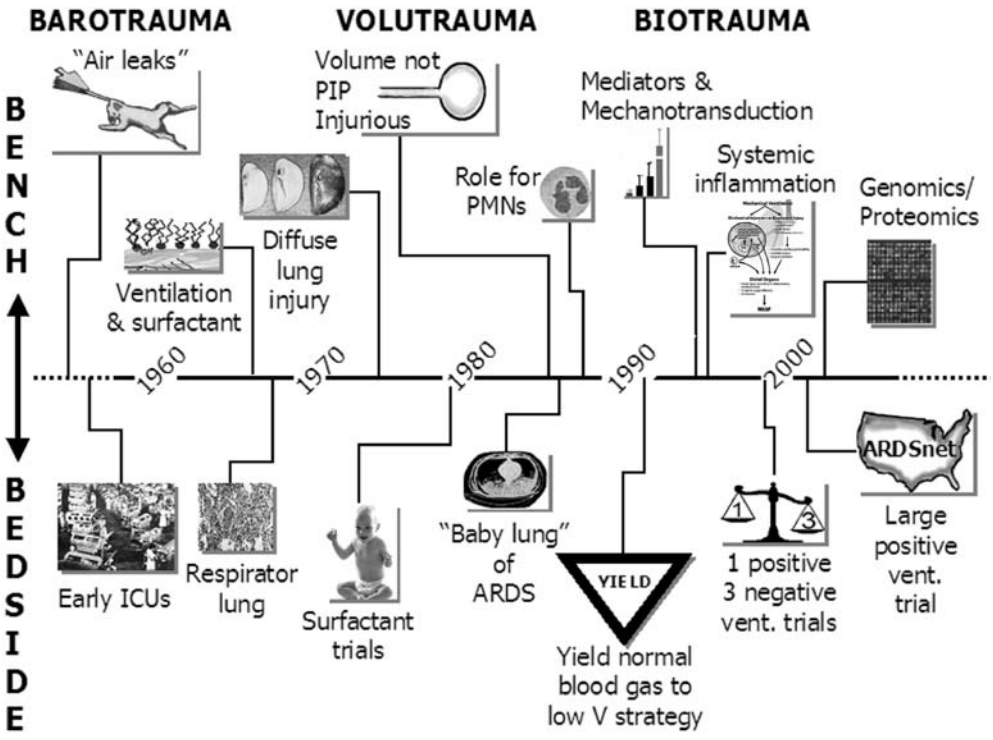

Fig. 1 Time line illustrating a number of the seminal basic science (*top*) and clinical (*bottom*) observations that have influenced our understanding of ventilator-induced lung injury and have changed ventilatory support of critically ill patients over the years

published a key observation that would be revisited in later studies of VILI: the fact that ventilation in lungs is not uniform, particularly in the presence of underlying lung disease. Mead et al. [7] (*N*=584) published an often cited paper examining the forces acting on alveoli within the lung. They illustrated that although uniform force proportional to the transalveolar pressure acts on adjacent alveoli in a uniformly expanded lung, the traction forces exerted by adjacent expanded alveoli on the walls of a collapsed alveolus can greatly exceed transpulmonary pressure (e.g., exceed 140 cmH_2O) due to interdependence.

On the clinical front the use of mechanical ventilation as a supportive therapy outside the operating theater became increasingly widespread in the aftermath of the polio epidemics of the 1950s, and the term "respirator lung" started being applied to autopsy findings of diffuse alveolar damage (dense pulmonary cellular infiltrates, pulmonary edema, and hyaline membranes) in critically ill patients who had required ventilation with high airway pressures prior to death. Indeed, when Ashbaugh et al. [8] (*N*=1193) submitted their landmark paper in 1967 on acute respiratory distress (ARDS) in adults, one reviewer purportedly dismissed this "new" syndrome as simply a manifestation of VILI [9].

Recognizing that it would be impossible in the clinical arena to dissect out the contribution of ventilator-induced injury from lung injury due to other causes, investigators turned to the bench.

Seminal bench studies on ventilator-induced injury

The initial challenge tackled by investigators was determining whether mechanical ventilation per se could produce diffuse lung injury (i.e., "respirator lung"), and if so, what ventilatory parameters (e.g., V_t, end-expiratory pressure) were responsible.

Can mechanical ventilation produce lung injury other than air leaks, and at what ventilatory settings?

A landmark paper examining this question was published by Webb and Tierney [10] (*N*=374) in 1974 entitled "Experimental pulmonary-edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure." Realizing that "some patients with ARDS may require pressures of 40–80 cmH_2O," Webb and Tierney set out to determine whether the "only complications of these pressures involve lung rupture with interstitial emphysema or pneumothorax." Their study design consisted of ventilating rats with normal lungs with PIP values of 14, 30, or 45 cmH_2O without PEEP, as well as with PIP of 30 or 45 cmH_2O and 10 cmH_2O of PEEP. In order to maintain similar $PaCO_2$ with the various ventilation strategies the dead space of the ventilatory circuit was altered.

This seminal study had several key findings. First, in keeping with prior studies, Webb and Tierney demonstrated that ventilation of normal lungs with low pressures

(PIP 14 cmH_2O) does not cause significant injury. Second, they dramatically showed that ventilation with high pressures (30 or 45 cmH_2O) produces perivascular edema, and that ventilation at high airway pressures (45 cmH_2O) without PEEP leads to severe lung injury (gross pulmonary edema, severe hypoxia) as well as death within 35 min. Third, they showed that PEEP confers protection from alveolar edema due to high inspiratory pressure ventilation.

Based on the results of this study, Webb and Tierney put forth a number of precepts that future research would validate: (a) that lungs from patients with ARDS have some "normal alveoli scattered among collapsed or fluid-filled alveoli, and that although the flooded alveoli "may be protected from over inflation... we are concerned that the normal alveoli may be over inflated and damaged," (b) that "tissue disruption secondary to a high inspiratory pressure is probably not the mechanism of the changes we observed," and (c) that surfactant dysfunction with certain ventilatory strategies likely contributed to the development of lung injury. Prophetically, they concluded with the comment that the results "have influenced our management of patients requiring ventilatory assistance. We avoid the use of high inspiratory pressure positive pressure breathing, especially if the end-expiratory volume is low, as for example in patients with ARDS..." and "in such situations we strive to avoid high inspiratory pressures, use a low frequency, and apply PEEP" (quite similar to current recommendations decades later).

However, the study by Webb and Tierney (and other animal studies to follow) had a number of significant limitations. As would subsequently become even more apparent, different species have different susceptibility to VILI (i.e., small species are generally more susceptible). Therefore it remained uncertain whether the bench findings were applicable to humans. Second, the period of ventilation in this study was only approx. 60 min (N.B. short periods of ventilation are a limitation of most bench studies). As such, it remained unclear whether the results were applicable to the lung injury found with longer periods of ventilation. Third, hemodynamic parameters were not measured or controlled between groups and lung volumes (e.g., V_t, end-inspiratory volume) were not measured. Thus it remained unclear whether other factors (e.g., hypotensive shock) may have contributed to the lung injury. Finally, the study did not dissect out the mechanisms responsible for high inspiratory pressure VILI.

What ventilatory parameters are injurious and how?

In a series of eloquently designed experiments Dreyfuss and colleagues [11, 12, 13] explored which of the many parameters of mechanical ventilation (e.g., V_t, PIP, end expiratory lung volume) is responsible for the development of pulmonary edema, and whether the physiological changes seen with injurious ventilation are associated with any ultrastructural changes (as assessed by electron microscopy). In their 1985 paper Dreyfuss et al. [11] demonstrated that high pressure (PIP 45 cmH_2O) ventilation of rat lungs in vivo increases extravascular water and lung albumin uptake rapidly (within 5 min of ventilation), and that with longer periods of ventilation (up to 20 min) a progressive increase in lung injury occurs (i.e., endothelial cell detachment and blebs progressing to diffuse injury including denudation of the epithelial basement membrane, interstitial and alveolar edema with hyaline membranes and cell debris) [11] (*N*=364). This study illustrated that injurious ventilation of normal lungs could not only produce ultrastructural cellular damage, but that this injury occurs within *minutes* of initiating an injurious ventilation strategy.

Dreyfuss et al. [12] (*N*=503) also explored whether it was the high airway pressure per se or the resulting lung volume that leads to VILI and pulmonary edema. In order to differentiate the effect of airway pressure from that of lung volume rats were subjected to one of the following five ventilatory strategies: (a) low PIP (7 cmH_2O) resulting in relatively low V_t (13 ml/kg); (b) high PIP (45 cmH_2O) resulting in high V_t (40 ml/kg); (c) high PIP (45 cmH_2O) and 10 cmH_2O PEEP (V_t 25 ml/kg); (d) high PIP (45 cmH_2O) but restricted V_t (19 ml/kg, produced by using a thoracoabdominal binder to limit chest wall excursion); and (e) negative inspiratory pressure (using a mini-iron lung) and high V_t (44 ml/kg). The key finding of this study was that high V_t ventilation, irrespective of airway pressure, produces severe lung injury characterized by pulmonary edema, increased alveolar-capillary permeability, and structural abnormalities. In contrast, ventilation with lower V_t, irrespective of airway pressure, does not produce ultrastructural changes or signs of alveolar edema or hemorrhage. In addition, PEEP once again was found to be "protective," as the presence of PEEP prevented pulmonary epithelial damage and alveolar edema and significantly reduced interstitial edema and endothelial cell changes. As a result of this study (and several confirmatory studies in other models, see [13]), researchers began to focus in on "volutrauma" (i.e., injury due to lung volume which is proportional to the transmural pressure gradient across the alveolus) rather than "barotrauma" (injury due to airway pressure) as the predominant injurious ventilatory parameter. These results agreed with Bouhuys' [14] observation in *Nature* in 1969 that musicians playing the trumpet repetitively develop pressures at the airway opening of approx. 150 cmH_2O without developing lung injury. Further laboratory studies showed that ventilation with either high V_t or high end-inspiratory lung volume is detrimental [13].

Meanwhile, other investigators such as West et al. [15] and Parker et al. [16, 17] focused on the injurious forces acting on the opposite side of the thin (<0.4 μm) alveolar

capillary interface, i.e., the endothelial surface. Using isolated perfused rabbit lungs, West et al. [15] (*N*=230) examined the role of three of the major forces acting on the pulmonary capillary wall (circumferential tension due to transmural pressure, surface tension of the alveolus, and longitudinal tension due to lung inflation) and demonstrated that at high lung volume or with high perfusion pressure, capillary stress failure greatly increases.

Multiple investigators also explored the relationship between PEEP and VILI (including what level of PEEP is associated with reduced alveolar edema, surfactant dysfunction, histological injury, and improved gas exchange). Studies showed that in experimental models in which excessive lung distension could occur with high PEEP (e.g., open chest models or ex vivo lungs), high PEEP worsened lung edema. However, with in vivo models in which lung volume was restricted by the chest wall, high PEEP resulted in cardiovascular compromise and was associated with either increased or decreased pulmonary edema. The particular level of PEEP that was injurious appeared to depend on a number of factors including the experimental model, animal species, and end-inspiratory lung volume (with similar PEEP leading to more adverse sequelae in ex vivo models, smaller species or with large lung volumes) [13].

Conversely, ventilation without PEEP did not appear to cause significant injury, provided low airway pressure/physiological V_t was used in normal lungs in vivo (i.e., with intact negative pleural pressure to maintain end-expiratory lung volume) for short periods of time. However, ventilation with low PEEP or no PEEP in ex vivo lungs, or lungs with surfactant dysfunction (such as occurs with high V_t ventilation) was associated with lung injury and dysfunction. For example, in an ex vivo rat lung model Muscedere et al. [18] (*N*=332) illustrated that ventilation using PEEP below the inflection point of the pressure-volume curve resulted in significant distal airway injury and reduced lung compliance as compared to the minimal injury found if PEEP greater than the inflection point was used. These studies led to a new concept in VILI—"atelectrauma" (injury from repetitive opening and collapse of distal lung units due to insufficient end-expiratory lung volume) [19] (*N*=46).

Factors that predispose to ventilator-induced lung injury

Multiple bench studies have also identified a number of factors (such as underlying lung disease, systemic inflammation, surfactant dysfunction, aspiration, pulmonary edema, extremes of age, heterogeneous lung ventilation) that increase the susceptibility of lungs to injury by mechanical ventilation. Often a synergistic interaction was found between mechanical ventilation and a preexisting lung abnormality. For example, in isolated perfused rabbit lungs Hernandez et al. [20] (*N*=63) demonstrated that, individually, oleic acid or ventilation with PIP of 25 cmH_2O has negligible effects on lung capillary filtration coefficients. However, when the insults are combined, severe lung injury (pulmonary edema, hyaline membranes, and extensive alveolar hemorrhage) ensue. Similarly, they found that age or surfactant inactivation predisposes to increased injury with subsequent mechanical ventilation [21, 22], and Dreyfuss et al. [23] (*N*=93) demonstrated a synergistic interaction between high volume ventilation (V_t 45 ml/kg) and pretreatment of rats with α-naphthylthiourea (a drug that increases alveolar capillary permeability and edema). Of the various factors studied particular attention was paid to surfactant dysfunction, given its prevalence in both neonatal respiratory distress and in adult lung disorders such as aspiration and lung sepsis (for review see [24]).

Several explanations have been put forth as to why such preexisting lung abnormalities increase the susceptibility to mechanical VILI. First, for structural disruption to occur the magnitude of force applied must exceed the resilience of the underlying lung parenchyma. Thus it follows that factors that either increase the forces applied to regions of the lung (e.g., surfactant dysfunction, heterogeneous ventilation due to atelectasis and flooded alveoli, repetitive opening and collapse of alveoli) or weaken lung tissue (such as age, inflammation) predispose to injury. In addition, factors that prime the inflammatory response or inhibit tissue healing also increase the lung's susceptibility to VILI [25], as does genetic predisposition. It is thought that the interaction of mechanical ventilation with other coexisting lung abnormalities is one explanation as to why identical ventilation settings produce VILI in some individuals but not all.

Is the mechanism of ventilator-induced injury due solely to physical disruption due to excessive force?

Most of the investigations cited above suggest physical disruption of the lung (e.g., capillary stress failure by alveolar overdistension) as one mechanism whereby mechanical ventilation produces lung injury. However, evidence of a potentially important role for ventilator-induced molecular and cell-mediated events in the pathogenesis of ventilator-induced injury soon began to emerge.

In 1983 Hamilton et al. [26] (*N*=263) published a study showing a benefit of high-frequency oscillation (i.e., using 15 Hz, V_t 1.5 ml/kg; mean airway pressure 15 cmH_2O) compared to "conventional" ventilation (using PIP 25 cmH_2O; PEEP 6 cmH_2O) in surfactant depleted rabbits. In this study the authors found significantly better lung function with fewer signs of histological lung injury in the high-frequency oscillation study group than in the conventional ventilation group. On further analysis, however, the investigators noted the presence of granu-

locyte infiltration in the alveoli and interstitium of the rabbits in the conventional ventilation group. To determine whether the granulocytes had a significant role in producing ventilation related lung injury Kawano et al. [27] (*N*=126) repeated the study using both neutrophil-depleted rabbits and neutrophil-depleted rabbits in which the granulocytes were reintroduced. They found that in contrast to rabbits with neutrophils, the neutrophil-depleted rabbits did not develop significant lung injury (changes in oxygenation, vascular permeability, hyaline membranes or granulocyte infiltration) with conventional ventilation. However, when neutrophils were reinfused into the neutrophil depleted rabbits, lung dysfunction ensued. Thus lung injury due to surfactant dysfunction/VILI in this model was not due simply to structural disruption but was mediated in large part by granulocytes.

Other investigators have observed that ventilation of lungs can increase levels of inflammatory mediators within the lungs, and that treatment with blockers of inflammatory mediators can reduce ventilator associated lung injury. For example, Tremblay et al. [28] (*N*=364) found increased bronchoalveolar lavage levels of several inflammatory mediators—including tumor necrosis factor (TNF) α, interleukin (IL) 6, and IL10—in ex vivo rat lungs subjected to injurious ventilation strategies. The same investigators in another report [29] (*N*=75) coined the term "biotrauma" to encompass this new field of investigation of molecular and cell mediated mechanisms of VILI. Supportive of this hypothesis, investigators such as Narimanbekov and Rozycki [30] (*N*=52) demonstrated that use of cytokine modulators can reduced lung dysfunction following mechanical ventilation. Administration of an IL-1 receptor antagonist prior to initiation of the injurious ventilation strategy in surfactant depleted rabbits reduced the severity of lung injury (bronchoalveolar lavage levels of polymorphonuclear cells, elastase, and albumin) produced by hyperoxia and 8 h of ventilation with 24 cmH_2O PIP. Of note, in this study the use of IL-1 receptor antagonist (RA) did not significantly improve either lung compliance or oxygenation. Other investigators, however, have demonstrated reduced ventilator associated lung injury as well as reduced ventilator-associated systemic abnormalities (such as increased gut permeability) using mediators such as anti-TNF or transgenic mice strains (for a concise summary of these studies see [31]).

Numerous subsequent studies have revealed species and model-specific differences with regards to levels of multiple mediators (including cytokines, receptors, ion channels, proteases, and extracellular components such as collagen/laminin) as well as a role for various cell types in addition to neutrophils in mediating the ventilator associated inflammatory response (e.g., type II pneumocytes, macrophages). Studies have also suggested that mechanotransduction (the conversion of externally applied forces on cells into activation of various cell signaling pathways and alterations in gene expression or cell structure) plays a role in VILI, and multiple stretch-activated signal transduction pathways (e.g., mitogen-activated protein kinases, stretch-sensitive ion channels, integrin receptors) have been identified. In a seminal study using an isolated perfused rat lung model Parker et al. [16] (*N*=51) abrogated the increase in microvascular permeability due to high PIP ventilation (20 and 30 cmH_2O) with gadolinium (an inhibitor of endothelial stretch-activated cation channels). In a subsequent study Parker et al. [17] demonstrated in the same model that inhibition of phosphotyrosine kinase increases the susceptibility of the lungs to high PIP injury; in contrast, inhibition of tyrosine kinase attenuates lung injury. The results of these studies lent further support to the contention that ventilation-induced changes in microvascular permeability is actively modulated by a molecular response to ventilation rather than simply a result of passive structural failure of the alveolar capillary membrane.

Not surprisingly, significant debate has ensued and continues as to the relative contribution of physical disruption vs. biotrauma in the pathogenesis of ventilator-induced injury [32, 33].

Is ventilator-induced injury limited to the lung?

Early investigators appreciated that in addition to lung injury, mechanical ventilation can also have adverse systemic sequelae including death from tension pneumothorax, or hypotension and impaired renal function secondary to high PEEP. In recent years experimental evidence has emerged that mechanical ventilation may also produce numerous other systemic sequelae. For example, Kolobow et al. [34] (*N*=378) compared the effect in sheep of ventilation with prolonged high V_t (50–70 ml/kg, PIP 50 cmH_2O) to that with low V_t (10 ml/kg, PIP 15–20 cmH_2O) . Interestingly, they found that all sheep subjected to the high V_t strategy died with multiple organ system dysfunction within 48 h.

In 1998 we hypothesized that biotrauma and the translocation of mediators can lead to the development of multisystem organ dysfunction [35] (*N*=185). Supportive of this hypothesis, several investigators have demonstrated that the increased alveolar capillary membrane permeability observed with high V_t ventilation allows translocation of various alveolar inflammatory mediators or bacteria into the systemic circulation. For example, using in an isolated perfused lung model von Bethmann et al. [36] (*N*=122) showed that high V_t ventilation produces increased levels of TNFα and IL6 in the perfusate; and in an acid aspiration rat model Chiumello et al. observed increased serum TNF-a levels in the group ventilated with zero PEEP and high V_t [37] (*N*=130). Similarly, using an in vivo dog model Nahum et al. [38] (*N*=85) demonstrated translocation of *Escherichia coli* from the lungs into the

bloodstream of most dogs ventilated with high V_t and low PEEP (transpulmonary pressure of 35, equivalent to 76 ml/kg, 3 cmH_2O PEEP). In contrast, bacterial translocation was only found in one of six dogs ventilated at the same end-inspiratory pressure (35 cmH_2O) and 10 cmH_2O PEEP, and in none of the dogs ventilated with V_t 15 ml/kg and 3 cmH_2O PEEP. Subsequent studies have provided further evidence of ventilation-induced "spillover" of a number of other intra-alveolar pathogens (e.g., *Klebsiella* [39], LPS [40]) and inflammatory mediators into the circulation. In addition, recent studies have shown that ventilatory strategy can also have a wide range of effects on remote organs, including increased ileal permeability [41], increased renal and small intestine apoptosis [42], changes in the peripheral immune response and host susceptibility to infection, and the development of systemic capillary leak [32, 43].

Strengths and weakness of the bench studies

As alluded to above, bench studies have a number of limitations that prevent direct extrapolation to the clinical arena. Although in vitro and ex vivo models are indispensable for addressing questions regarding the effect of cell stretch or ventilation on particular cells or signal transduction pathways in the absence of confounding systemic sequelae (such as hypotension due to high mean pleural pressure), the findings from such models may not be representative of the events occurring in vivo. In addition, although animal models may minimize differences between study participants, there are genetic and species-specific susceptibilities and responses to certain stimuli which may or may not be representative of the human response. Furthermore, with few exceptions the majority of laboratory studies of VILI to date have involved only brief periods of ventilation (hours) and used fairly extreme ventilatory settings to produce injury, leading some to question the clinical relevance of such studies.

Seminal *bedside* studies on ventilation-induced lung injury

From a clinician's perspective the key question is whether VILI contributes to patient morbidity and mortality, and if so, how can it be avoided. Although underlying lung injury is known to be a confounding factor present in many patients on ventilatory support, the laboratory studies have suggested that, if anything, this places the patients at increased risk of VILI as: (a) these patients often require higher pressure/volume to oxygenate/ventilate, and (b) many of these patients have factors known to increase susceptibility to VILI (such as surfactant dysfunction, malnutrition, endotoxemia).

In a series of publications Gattinoni et al. used computed tomography to demonstrate the effect of different ventilation strategies on the lungs of patients with acute lung injury (ALI). In a highly cited study Gattinoni et al. [44] (*N*=318) examined the effect of ventilation with different levels of PEEP (5, 10, and 15 cmH_2O) on lung compliance, lung volumes (as measured by helium dilution), and the computed tomographic appearance of the lungs in 20 patients with ALI. The key finding of this study was the visual evidence that lung inflation in ALI is extremely heterogeneous, with dependent regions being flooded or atelectatic, and often only a low volume of aerated nondependent lung. In addition, ventilation in these patients with ALI appears to be distributed principally to this low volume of aerated nondependent lung with relatively normal compliance (which the authors termed "baby lung," due to its low volume) [44, 45]. These computed tomography studies also suggested that the pressure-volume curve of the patients is representative of only the healthy aerated zones of the lung, and that optimal lung recruitment (i.e., opening up of lung units without significant overdistension) coincides with the PEEP at which optimal lung compliance was measured. Thus, in keeping with the speculations of Webb and Tierney [10] and others decades earlier, the studies by Gattinoni et al. demonstrated how mechanical ventilation of heterogeneously injured lungs with even relatively low V_t can produce significant regional overdistension. For example, in a lung with only 25% of alveoli ventilated, a ventilator set to deliver a V_t of 10 ml/kg would actually deliver approx. 40 ml/kg to the patient's "baby lungs"—a volume associated with significant lung injury in laboratory studies.

Based on the above, and mounting experimental evidence of potential adverse sequelae of mechanical ventilation with greater than physiological volumes, clinical investigators began to question whether mechanical ventilation using "conventional" V_t of 10–15 ml/kg to maintain normal arterial oxygenation and ventilation is necessary or harmful, particularly in patients with ARDS and "baby" lungs. After all, in patients with status asthmaticus a ventilatory approach that uses lower peak pressures and allows higher $PaCO_2$, a technique termed "controlled hypoventilation," appeared to be well tolerated and associated with improved outcomes [46, 47].

In 1990 Hickling et al. [48] (*N*=368) published a landmark study showing that the use of a "protective" ventilation strategy that limits PIP (<40 or <30 cmH_2O if possible, corresponding to V_t of 4–7 ml/kg) and allowed hypercapnia and a slight deterioration in oxygenation, appeared to reduce mortality by 60% in 70 patients with severe ARDS compared to mortality predicted by Acute Physiology and Chronic Health Evaluation II score (i.e., 16% vs. 40%). This seminal study suggested a promising new approach for ventilation in ARDS. A major weakness of the study, however, was the absence of a concurrent

control group. In addition, the study was only a retrospective case series from a single institution, which despite showing an apparent survival advantage did not observe a difference in either gas exchange or signs of lung injury between survivors and nonsurvivors. These weaknesses, however, do not diminish the importance of this study which helped to change the prevailing philosophy at the time that normal arterial blood gases should be a major goal of ventilatory support.

To circumvent the inherent limitations of retrospective and nonrandomized trials, prospective randomized trials examined whether a ventilation strategy with lower vs. higher lung volume improves patient outcome. In 1995 Amato et al. [49] (*N*=238) published a positive trial that further fueled debate. In this study 28 patients with ARDS were randomized to either a low V_t/high PEEP strategy (V_t <6 ml/kg, PIP<40 cmH_2O, permissive hypercapnia, PEEP 15–20 cmH_2O, and a goal of a plateau pressure, P_{plat}, <30 cmH_2O) or a high V_t strategy (V_t 12 ml/kg, PEEP 6–8 cmH_2O, P_{plat} of approx. 46 cmH_2O). The low V_t strategy was associated with improved survival (40% relative reduction in mortality at 28 days). The benefits of the low V_t/high PEEP strategy were confirmed by extending the study to 53 patients at which point the study was stopped because an interim analysis revealed a significant survival difference (28-day mortality of 38% with the low volume/high PEEP strategy vs. 71% with the high V_t strategy; $p<0.001$) [50] (*N*=678). In addition to a survival advantage, at 28 days more patients in the "protective" ventilation strategy arm had been weaned from ventilation (66% vs. 29%), and there was a lower incidence of barotrauma (7% vs. 42%). However, the Amato et al. study was criticized for having higher than predicted mortality in the control group. Furthermore, three other small prospective randomized trials failed to find a survival advantage of low vs. high V_t ventilation strategy [51, 52, 53] (*N*=258, 182, 102, respectively). These smaller negative trials, however, were criticized for having only a small difference in V_t between study groups, insufficient statistical power to detect a difference, the presence of uncorrected acidosis in the low volume arms, as well as the fact that the conventional ventilation arms in all the negative trials had a P_{plat} less than 32 cmH_2O (i.e., had relatively low end-inspiratory lung volumes more in keeping with ventilatory strategies found to be noninjurious in laboratory studies).

To overcome the limitations of these small studies the National Institutes of Health (NIH) sponsored a consortium (ARDSNet) to carry out a large multicenter prospective randomized trial in which patients with ALI or ARDS were randomized to either: (a) "traditional" V_t of 12 ml/kg predicted body weight (using a formula based on gender and height rather than actual weight) and a P_{plat} of 50 cmH_2O or lower, or (b) V_t of 6 ml/kg predicted body weight and a P_{plat} of 30 cmH_2O or lower [54] (*N*=1027). Although the study was conceived with a patient population of approx. 1000, the trial was stopped early after an interim analysis revealed a 22% relative survival advantage with the low V_t strategy (*n*=861; mortality of 31% vs. 39.8%). In addition to improved survival, patients in the low V_t strategy were also found to have more days free of ventilatory support during the 28 days following randomization (12±11 vs. 10±11). Of note, the mean P_{plat} s of the low and high V_t strategy were 25±6 vs. 33±8 cmH_2O respectively (a greater difference between groups than that of the small, negative trials). Furthermore, in keeping with the animal studies suggesting that ventilation affect systemic inflammation, the low V_t strategy also resulted in lower plasma IL-6 levels (on day 3) as well as fewer nonpulmonary organ failures (circulatory, renal, coagulation).

Subsequent reports, however, have brought to light a number of caveats regarding the ARDSNet study. First, some have argued that the study demonstrated the increased mortality of a high V_t strategy resulting in a high P_{plat} (33 cmH_2O) rather than a survival advantage to using V_t of 6 ml/kg. Of note, the P_{plat} in all of the smaller negative studies was less than 32 cmH_2O in both study groups (i.e., control and less injurious ventilation strategy groups). Second, it has been argued that those in the low V_t group may have developed higher auto-PEEP than those in the conventional ventilation group due to the high respiratory rates used [55]. As such, the survival advantage may have been due to higher PEEP rather that low V_t and/or end-inspiratory lung volume (although the results of a more recent trial argue against this [56]). Third, the study population was restricted to patients with ALI or ARDS and the exclusion criteria included patients with severe chronic respiratory disease, morbid obesity, burns, a contraindication to hypercapnia or hypoxia (such as increased intracranial pressure or sickle cell disease) or a predicted 6 month mortality of more than 50%. Thus the study findings cannot be directly extrapolated to the excluded patient populations or to patients with less injured or normal lungs. Fourth, the low V_t group developed hypercapnia and received bicarbonate to treat acidosis (note: bicarbonate was not used in the smaller negative trials). Thus it is unclear to what extent bicarbonate contributed to the survival difference. Fifth, the higher number of ventilator-free days was due to reduced mortality (i.e., no significant difference was found in ventilator-free days among survivors between the two groups). Nevertheless, despite these limitations this study was the only large interventional study in decades in ARDS patients to show a significant reduction in mortality, and certainly was in keeping with the plethora of laboratory studies showing that high volume lung ventilation strategies are deleterious. Thus this study provided a new "gold standard" ventilation strategy for patients with ARDS or ALI.

Another seminal study in patients that also supported the experimental evidence that ventilation strategy can

have systemic effects on the host inflammatory response was published by Ranieri and colleagues [57] (*N*=360) in 1999. This study, entitled the "Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome—a randomized controlled trial," examined whether a lung protective ventilation strategy in patients with ARDS reduces their pulmonary and systemic inflammatory cytokine response. Fifty-one ARDS patients who had been ventilated for less than 8 h were randomized to either "control" ventilation (V_t 11 ml/kg to produce normal $PaCO_2$) and PEEP (6 cmH_2O) producing best improvement in PaO_2 without worsening hemodynamics; P_{plat} 31 cmH_2O) or V_t and PEEP based on the pressure-volume curve (V_t 7 ml/kg, PEEP 15 cmH_2O, P_{plat} 25 cmH_2O). In the 44 patients who completed the study the concentration of inflammatory mediators 36 h after randomization was found to rise significantly in the control group (i.e., bronchoalveolar lavage levels of IL-1β and IL-6 and as well as bronchoalveolar lavage and plasma levels of TNF-α, IL-6, TNF-α receptors, and IL-1 RA) whereas in patients in the lung-protective strategy group a reduction in bronchoalveolar lavage concentrations of polymorphonuclear cells, IL-1β, TNF-α, IL-8, IL-6, TNF-α receptors, IL-1 RA, and in plasma concentration of IL-6, IL-1 RA, and a TNF-α receptor was found. Of note, this study was not designed to address whether these changes in inflammatory mediators resulted in improved survival or long-term outcomes (i.e., the ventilation protocols were only set for 36–40 h post inclusion, and organ failure and mortality were not primary outcomes). However, a post-hoc analysis revealed more ventilator-free days (over 28 days) in the lung protective group, and a number of subsequent clinical studies have also demonstrated ventilation strategy dependent changes in systemic inflammatory mediators (including the previously discussed NIH trial [54, 58]). Of importance, although there appeared to be an association between mediator levels and patient outcome in several studies, a cause and effect relationship has never been demonstrated.

Recently the NIH consortium published the results of yet another large trial comparing the effect of high vs. low PEEP on lung injury and survival in patients with ARDS. In this study 549 patients with ALI or ARDS were randomized to ventilation with V_t of 6 ml/kg, P_{plat} of less than 30 cmH_2O, and PEEP of either 8.3±3.2 or 13.2±3.5 cmH_2O [56]. The study was stopped early due to futility when an interim analysis revealed no significant differences in either mortality or ventilator-free days in the 28-day period following randomization. Thus, key clinical questions including how much PEEP is ideal, and what is the best way to determine optimal PEEP remain unanswered.

Similarly, to date most of the other promising interventions found to reduce lung injury and improve outcome in animal studies (e.g., prone positioning, surfactant supplementation, nitric oxide, lung recruitment maneuvers) have not been found significantly to improve patient survival or outcome in adult intensive care patients [59, 60, 61, 62]. As such, ongoing investigations at both the bench and bedside continue in the hopes of addressing the reasons for the discrepancies and better understanding the complex interactions of ventilation with the lung/whole organism.

In summary, the study of VILI over the past century exemplifies the "bench to bedside and back to the bench" research approach. This review discusses several of the seminal studies that led to our current understanding of VILI. Understanding these studies is helpful for interpreting and applying current guidelines for ventilation as well as appreciating the need for further studies at both the bench and the bedside to define the precise mechanisms of injury and develop novel approaches to further reduce or abrogate ventilator-induced injury.

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