

Review

Bench-to-bedside review: Microvascular and airspace linkage in ventilator-induced lung injuryJohn J Marini¹, John R Hotchkiss² and Alain F Broccard³¹Professor, University of Minnesota, Regions Hospital, St Paul, Minnesota, USA²Assistant Professor, University of Minnesota, Regions Hospital, St Paul, Minnesota, USA³Associate Professor, University of Minnesota, Regions Hospital, St Paul, Minnesota, USACorrespondence: John J Marini, marin002@umn.edu

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Abstract

Experimental and clinical evidence point strongly toward the potential for microvascular stresses to influence the severity and expression of ventilator associated lung injury. Intense microvascular stresses not only influence edema but predispose to structural failure of the gas–blood barrier, possibly with adverse consequences for the lung and for extrapulmonary organs. Taking measures to lower vascular stress may offer a logical, but as yet unproven, extension of a lung-protective strategy for life support in ARDS.

Keywords acute respiratory distress syndrome, capillary stress fracture, mechanical ventilation, vascular injury, ventilator-induced lung injury

Introduction

Although ventilator-induced lung injury (VILI) is undoubtedly a complex process that is influenced by many factors, the great majority of investigative attention has been directed at airspace mechanics, as exemplified by tidal volume, plateau pressure, and positive end-expiratory pressure (PEEP). However, because the fragile alveolus serves as the interface between gas and blood, and because the intraluminal pressures applied to the airway epithelium also impact on the vascular endothelium, the potential for pressures and flows within blood vessels to influence the development and/or evolution of VILI also deserves consideration. This overview addresses the experimental evidence linking alveolar and vascular events in the generation of barrier breakdown.

Inflation and pulmonary vascular pressure

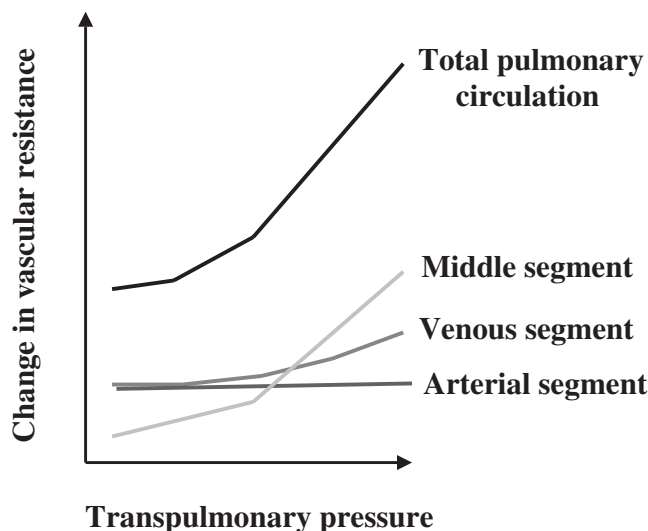
The vascular pathway from pulmonary artery to left atrium can be considered as a series of three functional segments: arterial, 'intermediate' (which includes alveolar capillaries and contiguous microvessels), and venous [1]. Under normal conditions the arterial and venous segments, which are entirely extra-alveolar, contribute most to overall pulmonary vascular resistance. The compliant intermediate or 'middle'

segment, however, is influenced primarily by alveolar pressures, and as a consequence it undergoes the greatest change in overall vascular resistance that occurs during ventilation (Fig. 1).

The behaviors of alveolar and extra-alveolar vessels during lung expansion are fundamentally different. The structural forces of interdependence cause a fall in interstitial pressure during inflation, even during positive pressure ventilation [2]. This reduction in interstitial pressure tends to increase the transmural pressure of the vessels in the immediate environment, thus dilating them; this in turn increases wall tension, in particular in the vessels upstream from the alveoli. Something quite different, however, happens at the alveolar level. During inflation of a normal, fully aerated ('open') lung, the majority of capillaries embedded within the alveolar wall are compressed by the expansion of adjoining alveoli, even as extra-alveolar vessels dilate (Fig. 2).

At all lung volumes above functional residual capacity, the effects of vessel elongation and alveolar capillary compression outweigh the tendency for extra-alveolar vessels to dilate, so that pulmonary vascular resistance rises monotonically.

Figure 1



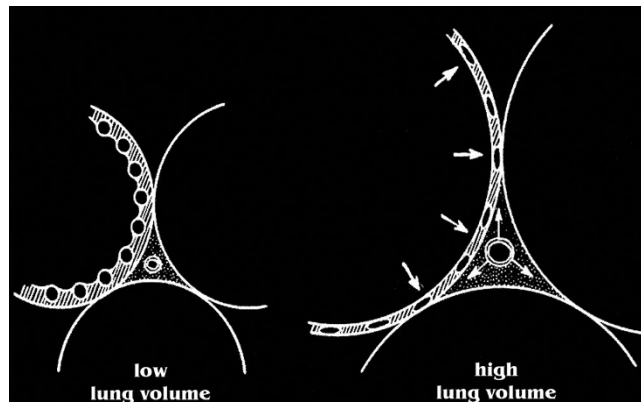
Relative contributions of pulmonary vascular segments to overall pulmonary vascular resistance in the normal lung as a function of transpulmonary pressure (and lung volume). The middle segment that bridges the alveolus accounts for a progressively greater proportion of the total as the lung distends.

cally as a function of lung volume [3]. The so-called ‘corner’ vessels, which are located at the junctions of three or more alveolar septae, are simultaneously influenced by competing stresses arising from alveolar and interstitial pressures and do not behave as the wall-embedded capillaries do. Functionally, they behave like extra-alveolar vessels. Indeed, they may serve as a conduit for some blood to flow through the intermediate segment, even when alveolar pressure exceeds pulmonary arterial pressure [4]. With reference to the vascular contribution to VILI, it is important to consider that, even for the normal lung, inflation imposes competing vascular stresses on different classes of microvessels. As discussed below, these competing forces are amplified by the heterogeneity of acute lung injury (ALI).

Interactions between airway and pulmonary vascular pressures

The normal lung exhibits up to three perfusion zones, depending on the relationship between alveolar pressure and pulmonary arterial and pulmonary venous pressure. According to the familiar conceptual model popularized by West [5], gas pressures within aerated alveoli are everywhere equivalent under static conditions, whereas vascular pressures are influenced by gravity. Zone III conditions, under which both arterial and venous macrovascular pressures exceed alveolar pressure, allow flow to be governed by vascular pressure gradients and resistances. These conditions are most likely to be observed in dependent regions during positive pressure ventilation. When alveolar pressure exceeds both arterial and venous pressures, little blood flow occurs (except through

Figure 2



Influence of lung expansion on alveolar and extra-alveolar vasculature. Inflation compresses wall-embedded capillaries but dilates extra-alveolar microvessels.

corner vessels). Zone II exists where alveolar pressure exceeds pulmonary venous pressure (but not arterial pressure), allowing flow to occur as regulated by the pressure gradient between arterial and alveolar pressures. These latter zones tend to develop in less dependent areas, where hydrostatic pressures are lower.

Unfortunately, the application of these potentially useful concepts to the problem of the acutely injured lung is not straightforward. Indeed, their validity for this circumstance – in which collapsed, edematous, inflamed, and even fibrotic lung units may coexist in the same micro-environment – can rightfully be questioned. In the setting of ALI, both alveolar and pulmonary arterial pressures are considerably greater than they are under normal conditions. Moreover, a variety of perfusion states are likely to exist, even along the same transverse plane. Filling of the small airways, and alveolar and interstitial spaces with cells and fluid alters the normal relationships among the pressures and flows of gases and blood. Independently of any variations in local pathology, increased lung tissue density and accentuated pleural pressure gradients tend to collapse dependent lung units, developing shunt and/or extending zone II conditions to more caudal levels as the interstitial pressures surrounding the microvasculature rise. Finally, the hemodynamics of the microvascular environment are almost certain to vary, depending on ventilation mode. Although the lung is a passive structure, the pressure drop occurring across the pulmonary circulation is greater for a positive pressure than it is for a negative pressure breath (Fig. 3).

Under the high permeability conditions of the first stage of ALI, even minor increases in pulmonary microvascular pressure will increase edema formation dramatically. Moreover, unlike in healthy tissue in which the blood–gas barrier is intact, there is no clear pressure threshold for edema forma-

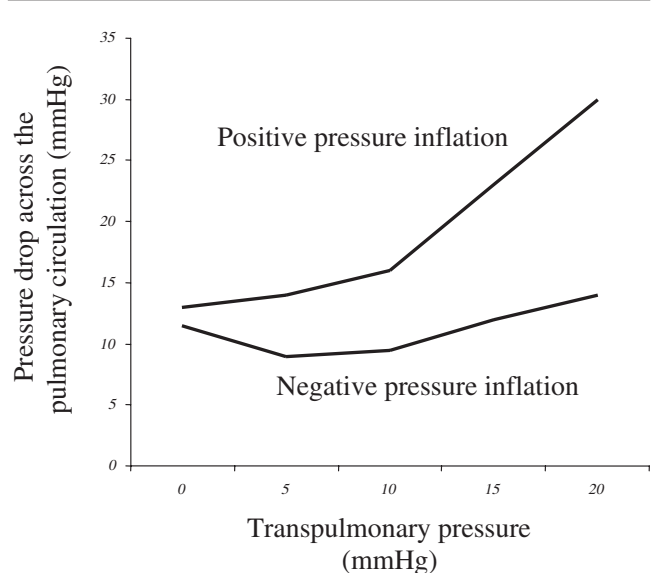
tion in lung tissue undergoing ALI [6]. The physiologic consequences of pulmonary edema are well understood; alveolar edema compromises gas exchange, and edematous airways impede airflow and secretion clearance. From the standpoint of VILI, however, alveolar flooding may produce competing effects. A well known if simplistic model of interdependence proposed by Mead (see below) suggests that collapsed alveoli are subjected to shearing forces that are proportional to the disparity in alveolar dimensions between the collapsed alveolus and its distended neighbors [7]. Therefore, completely fluid-filled (flooded) alveoli theoretically are subjected to lower shearing stresses than are atelectatic units, as the gas-liquid interface is eliminated and alveolar dimensions increase. On the other hand, elimination of surface tension would cause capillaries that are fully embedded in the alveolar walls to bulge further into the interior, encouraging their rupture [8], and the increased weight of the edematous lung may encourage small airway compression and accentuate the tendency for tidal opening and closure to occur. Which of these competing effects predominates cannot be stated with certainty. Thus, although the influence of preformed edema on lung mechanics and gas exchange is reasonably well described, the importance of the microvasculature to the generation of VILI is less well understood. The remainder of the present brief review focuses on what is currently known regarding the interactions between airway pressures and vascular pressures in the generation and maintenance of VILI.

What disrupts the blood-gas barrier during ventilator-induced lung injury?

Clinicians have long been aware that certain inflammatory conditions of the lung produce tissue hemorrhage in the absence of ventilatory stress. These vessel-disrupting inflammatory injuries may originate either from the alveolar side (e.g. pneumonia, abscess) or from the vascular side of the blood-gas interface. Inflammatory conditions such as Wegener's granulomatosis, Goodpasture's syndrome, and pulmonary embolism are examples from the latter category. Each disrupts the delicate barrier between gas and blood, allowing erythrocytes to breach their vascular confines and migrate into the interstitium and airspaces.

Although inflammation is of potential importance to the breakdown of the lung's structural architecture, simply elevating transmural pulmonary vascular pressure to high levels may cause vascular rents or tears. Perhaps the clearest example in this category occurs in severe mitral stenosis, a condition in which pulmonary venous and capillary pressures can exceed 35–40 mmHg. Acute edema that forms in this setting is typically blood tinged, and the presence of hemosiderin-laden macrophages in expectorated or lavaged samples strongly suggests that this process originates at the alveolar level from the pulmonary circulation (rather than the bronchial circulation). Another circumstance under which elevating transmural vascular pressures may cause hemoptysis in the absence of pre-existing inflammation occurs during extreme

Figure 3



Pressure gradient along the normal pulmonary vascular bed as a function of transpulmonary pressure generated by positive and negative distension. Note that the pressure drop is greater during positive pressure breathing, especially at higher lung volumes.

exertion, when blood flows through the lung are extremely high and excursions of alveolar pressure are unusually large. Postexertional lung hemorrhage is a well described occurrence in racehorses [9], and hemoptysis has been reported after heavy exertion in elite human athletes as well [10]. Finally, forceful inspiratory efforts made during upper airway obstruction may produce transvascular pressures of sufficient magnitude to cause hemorrhagic pulmonary edema [11].

In elegant experiments undertaken in the laboratories of West and colleagues [12–15], electron microscopy was used to demonstrate the potential for mechanical disruption of the microvasculature – ‘capillary stress fracture’ – to occur when microvascular pressures are elevated to very high levels relative to their usual operating conditions. The pressures necessary to cause capillary stress fracture vary among species, with disruption being observed in healthy small animal lungs (e.g. rabbits) at pressures as low as 40 mmHg. Larger animals, such as dogs, withstand much higher microvascular pressures without losing the structural integrity of the capillary network [14]. Experimental studies reporting capillary stress fracture in animals have largely been undertaken in static preparations in which the airway pressure was held constant and the intraluminal vascular pressures upstream and downstream of the alveolus were equivalent. Under such conditions, structural breakdown is more likely to be seen at high lung volumes relative to resting conditions [15]. Although the range of microvascular pressure applied in these studies might appear to preclude their physiologic relevance, much lower vascular pressures might be required if

the framework of the lung were degraded by inflammation. Moreover, there is excellent reason to believe that regional transmural vascular forces may be dramatically different when mechanically heterogeneous lungs are ventilated with adverse ventilatory patterns.

Experimental evidence linking vascular pressure to ventilator-induced lung injury

Just as with inflammation, mechanical forces that tear the delicate alveolar–capillary membrane can originate on either side of the boundary. That the alveolar epithelium can be disrupted by sufficient airway pressure is evident when barotrauma develops. Clinicians recognize this damage radiographically as air that leaks into the interstitial spaces to cause intrapulmonary gas cysts, mediastinal emphysema, pneumothorax, and systemic gas embolism [16]. It is equally clear that the vasculature can lose its integrity in advance of epithelial fragmentation. Postmortem examination of tissues from patients with acute respiratory distress syndrome often reveals areas of interstitial and alveolar hemorrhage, findings that have generally been attributed to the underlying inflammatory process. However, in both small and large animal models, the application of adverse ventilatory patterns to previously healthy lungs not only causes formation of proteinaceous edema but it also stimulates neutrophil aggregation and hemorrhage [17,18]. Studies conducted in our laboratory strongly indicate that, in the supine position, hemorrhagic edema forms preferentially in dependent areas [18,19]. This proclivity is not subtle, and has been corroborated by the work of other investigators using different injury models [20]. It is worth emphasizing that our experiments demonstrated that purely mechanical forces originating within the alveolus inflict hemorrhagic injury in the absence of pre-existing inflammation. It is somewhat counter-intuitive that tissue disruption should occur in areas where transmural stretching forces (as defined by plateau pressure minus pleural pressure) are least. That is to say, 'alveolar stretch' is greatest in the nondependent regions, which are spared both the hemorrhagic infiltrate and most signs of inflammation. Why might this occur?

The tendency for hemorrhage to occur preferentially in the most dependent regions of the lung may have several explanations. One compelling reason to expect microvascular disruption to occur there is that the mechanical stresses applied by the tidal inflation cycle are greatly amplified at the interface of opened and closed lung tissues. More than three decades ago, Mead and coworkers [7] described a simplified model of alveolar mechanics in which they proposed that an alveolus attempting to close in an environment in which it was surrounded by inflated tissue would experience traction forces that are amplified in nonlinear proportion to the alveolar pressures existing in the open units. According to their reasoning, the coefficient linking effective pressure (P_{eff}) to that actually applied (P_{app}) is the ratio between the alveolar volume that corresponds to alveolar pressure (V) and the volume of the collapsed alveolus (V_0) raised to the power of 2/3:

$P_{\text{eff}} = P_{\text{app}} \times (V/V_0)^{2/3}$. That admittedly oversimplified geometric argument suggested that at 30 cmH₂O alveolar pressure, for example, the effective stress applied at the junction of closed and open tissue might approximate a value 4.5 times as great as that experienced in the free walls of the open alveolus.

Whatever its quantitative accuracy, a similar line of reasoning might apply when tissues are already atelectatic and the lung is exposed to high ventilating pressures, as in acute respiratory distress syndrome. Extrapolating from the Mead equation presented above, the traction forces applied to junctional tissues when alveolar pressure is 30 cmH₂O could approximate 140 cmH₂O, or about 100 mmHg. Thus, transvascular microvascular forces during tidal ventilation could be in the range that West and colleagues [14] suggested necessary for a stress fracture to occur in large animals (dogs). Clearly, such theoretic arguments are widely open to criticism. However, it does appear reasonable to assume that mechanical shearing forces experienced in 'junctional' tissues are likely to exceed those elsewhere in the lung. Moreover, even within fully inflated regions, the competing forces of capillary compression and extraalveolar vessel dilatation/elongation would be amplified when both lung volumes and vascular pressures are high. These stresses would tug at the microvascular conduit that links the alveolar and extra-alveolar vessels with potentially damaging force. It is not difficult, therefore, to envision vascular rupture from ventilatory pressure under the pathologic conditions of ALI. Although unstudied, surfactant depletion and inflammatory weakening of the interstitial structure could amplify the impact of such forces, whereas other changes of the microenvironment (e.g. flooding by edema) could abrogate the mechanical stresses experienced in distal lung units.

Another intriguing possibility that may explain disproportionate vascular disruption in dependent lung regions is that dorsally situated tissues receive a majority of the lung's total blood flow and are subjected to greater hydrostatic pressures in the supine position. These higher intraluminal vascular pressures or flows might amplify tensile forces external to the microvessels or give rise to shearing stresses within the vascular endothelium that initiate inflammation-mediated tissue breakdown. There are hints in the early experimental literature for VILI that vascular pressure could play an important if not pivotal role in VILI development or expression. Dreyfuss and Saumon [21], for example, found that ventilation with negative pressure caused damage more severe than that caused by positive pressure, implicating involvement of increased blood flow in ventilation-related damage. Those same investigators provided further support for this hypothesis by showing that rats given dopamine to increase cardiac output suffered increased albumin leak when ventilated with high pressure, and ascribed a major portion of the protective effect of PEEP in the setting of high pressure ventilation to its reduction of pulmonary perfusion [22].

Our group also explored the vascular contribution to VILI in a series of experiments using isolated, ventilated, and perfused (IVP) rodent lungs [23–26]. The IVP system offers numerous advantages for the investigation of the interactions between alveolar and vascular pressures. The progress of edema formation can be monitored by continuously weighing the heart–lung block suspended from a strain gauge. Breakdown of the alveolar capillary barrier can be inferred from the filtration constant (K_f) derived from the weight–time relationship. Inflow and outflow vascular pressures and perfusion rate can be precisely measured and/or regulated. Finally, the composition and physical properties of the perfusate can be adjusted.

In the experiments described below, each heart–lung block was perfused with Krebs-Henseleit solution, doped with a small quantity of autologous blood to provide a histologically visible marker of overt vascular rupture. Sufficient albumin was added to achieve physiologic tonicity. The cumulative results of this work demonstrate unequivocally that variations in vascular pressure and flow have the potential to modulate the nature and severity of VILI.

Pressure or flow: which is the key variable?

In our first experiment we exposed isolated rabbit lungs to perfusion levels that were equivalent to or about 50% greater or less than the normal resting blood flow of that animal species [23]. All lungs were ventilated identically with airway pressures that proved damaging *in vivo*. In this model of VILI we demonstrated that perfusion amplitude contributed to the reduced lung compliance resulting from an adverse ventilatory pattern and promoted both lung edema and hemorrhage. We also found a strong correlation between indices of lung injury and the vascular pressure changes resulting from the interaction between ventilation and perfusion [23]. Although data from that experiment strongly suggested the primacy of perfusion pressure, it was not possible in that initial experiment to determine definitively which of those two variables was more important in modulating VILI, because vascular pressure increased in parallel with flow.

In a second IVP lung experiment designed to address that question, we varied airway pressure profiles to allow arterial pulmonary pressure to vary while blood flow was held constant [24]. Our results indicated that mean airway pressure had greater impact than did tidal excursion amplitude in determining the severity of lung hemorrhage and lung permeability alterations resulting from an adverse pattern of mechanical ventilation. Histologic injury scores were virtually identical for large and small tidal volumes when high mean airway pressures were achieved, whether by lengthening inspiratory time or by increasing PEEP. A key difference between high mean airway pressure and low mean airway pressure preparations was the magnitude of the pulmonary arterial pressure and the length of time over which it was sustained. The results of those experiments emphasized the potential for deleterious interactions to occur between lung

volumes and pulmonary hemodynamics. Taken together, our initial two studies demonstrated that modifications of vascular pressure within and upstream from the intermediate segment could influence the severity of VILI inflicted by an unchanging adverse pattern of ventilation.

How does the number of ventilatory cycles influence the expression of ventilator-induced lung injury?

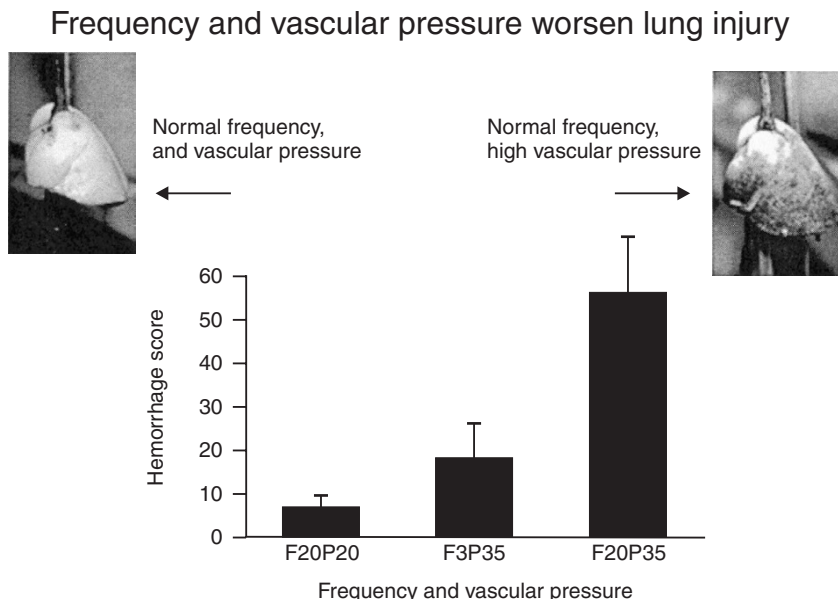
Although ventilation is the product of tidal volume and frequency, surprisingly little attention has been directed at the role of the latter in the generation of VILI. Therefore, having concluded that upstream microvascular pressure might be an important cofactor in the development of VILI, we next addressed the question of how the number of ventilatory cycles occurring over a timed interval influences the rate of edema formation or severity of histologic alterations when maximum, minimum, and mean airway pressures are held identical.

Almost 15 years ago, Bshouty and Younes [27] reported that, for the same minute ventilation target, raising tidal volume at a constant frequency and raising frequency at a constant tidal volume produced similar degrees of edema in canine lobes perfused *in situ* at elevated hydrostatic pressures. At about the same time, Kolobow and colleagues [28,29] demonstrated that sheep ventilated over many hours with high and moderate airway pressures sustained more lung injury than did those examined earlier, suggesting the potential for cumulative damage to occur under adverse ventilatory conditions.

We used our IVP model in experiments testing the hypothesis that cumulative damage occurs as a function of the number of stress cycles as well as stress magnitude. In these experiments, the pressure controlled mode with a peak pressure of 30 cmH₂O and a PEEP of 3 cmH₂O was used in each preparation [25]. Each experiment was conducted over 30 min. In one of three experimental groups of isolated and perfused rabbit lungs, a pulmonary artery peak pressure of 20 mmHg was matched to a ventilatory frequency of 20 cycles per minute to serve as our control. In a second set of perfused lungs, pulmonary artery pressure was allowed to rise to a maximum of 35 mmHg with each tidal cycle, at a frequency of 20 breaths per minute. In the third group peak pulmonary artery pressure was again capped at 35 mmHg, but ventilator frequency was reduced to three cycles per minute with the same inspiratory time fraction as in the other two groups. Thus, mean airway pressure was identical for both high-pressure ventilatory patterns. The pH characteristics did not vary significantly among the groups.

Our main findings were that lungs ventilated at low frequencies and high peak pulmonary artery pressures formed less edema and exhibited markedly less perivascular hemorrhage than did those ventilated at higher frequencies but identical peak pulmonary artery pressures. In addition, lungs ventilated

Figure 4



Damaging effect of high vascular pressure and repeated cycling on isolated, ventilated, and perfused rabbit lungs. For identical airway pressure profiles (plateau, mean, and end-expiratory pressures), higher peak inflow pressure (35 mmHg) was associated with greater damage, as compared with the control value of 20 mmHg. Reducing cycling frequency from 20 to 3 cycles per minute while holding airway and vascular pressures constant reduced injury severity. Adapted with permission from Hotchkiss and coworkers [25].

with high peak pulmonary artery pressures and flows exhibited more extensive histologic alterations and edema formation than did those subjected to the same ventilatory pattern but at lower peak vascular pressures and flows [25] (Fig. 4). Only a very small fraction of this difference was attributable to differences in mean hydraulic pressure. These data strongly indicated not only that the characteristics of the tidal cycle and vascular pressures are of fundamental importance to VILI, but also that minute ventilation, reflecting the number of stress cycles of a potentially damaging magnitude per unit time or their cumulative number, might be as well.

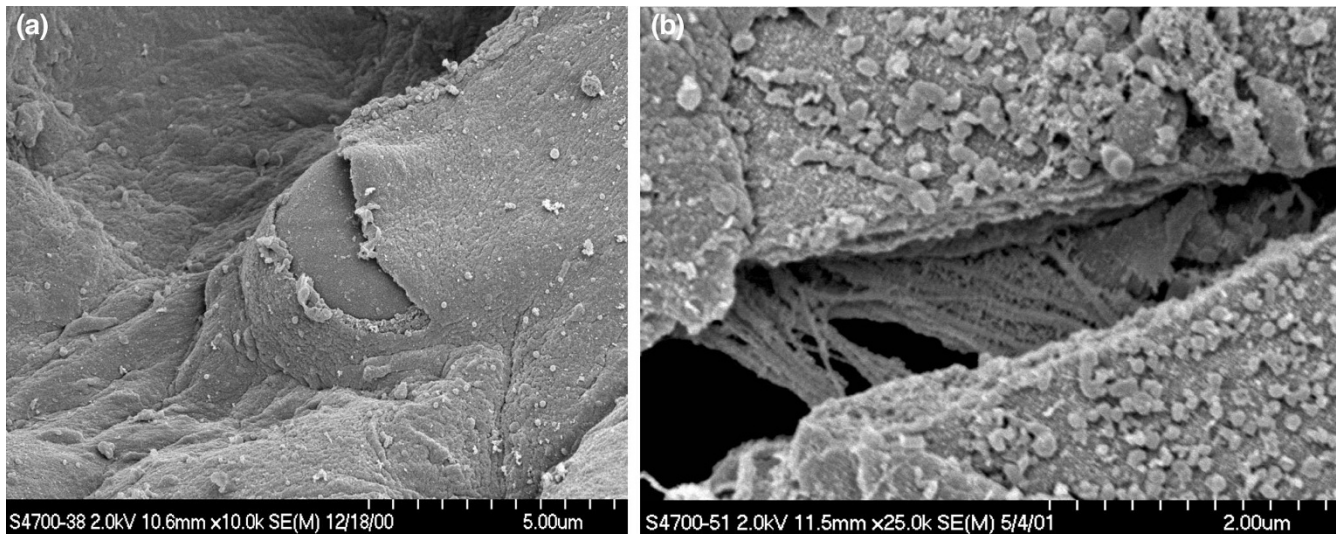
Whereas dependence of edema formation on minute ventilation was previously noted in the aforementioned experimental study conducted by Bshouty and Younes in isolated dog lobes [27], their experiments differed from ours in four notable ways. First, whereas their study was conducted with a physiologic ventilatory pattern, we employed ventilatory patterns known to be potentially injurious. Second, vascular pressure in the study by Bshouty and Younes was elevated by raising outflow (left atrial) pressure, thereby increasing pressure along the entire vascular tree (a simulation of left sided congestive heart failure). We held outflow pressure constant at a physiologically normal value while raising pressure selectively in those regions proximal to the intermediate vascular segment. Third, we used considerably higher vascular flows on a per-gram-of-lung basis than did Bshouty and Younes [27]. Finally, we not only measured

edema and but also assessed histologic changes, as reflected by lung hemorrhage.

Several mechanisms come to mind that may explain the diminution of lung edema formation and perivascular hemorrhage that we observed by decreasing respiratory frequency. A higher ventilatory frequency could have depleted surfactant more efficiently, thereby increasing alveolar surface tension, lowering end-expiratory extravascular pressure, and promoting alveolar flooding. Upstream, the increased transvascular pressure gradient across extra-alveolar vessels would also favor fluid transudation, vessel disruption, and perivascular hemorrhage. Conceivably, the larger number of stress cycles imposed on the groups receiving 20 breaths per minute could have induced cumulative damage in a manner similar to that experienced in a variety of biomaterials that are subjected to sufficient repeated stress [30]. Overt stress fractures similar to those found by West and colleagues [13–15] were demonstrated by scanning electron microscopy in our laboratory to occur in the setting of VILI (Fig. 5), as well as in a recently reported human patient [31]. A type of ‘materials failure’ of structural elements seems an attractive explanation, in that we found that both reducing stress application frequency (respiratory rate) and stress amplitude (pulmonary artery peak pressure) effectively limited VILI.

If cumulative damage is important, then providing a lower frequency and/or lower pulmonary vascular pressure would both

Figure 5



Electron micrographs of rabbit lungs injured solely by high inflation pressures, low positive end-expiratory pressure, and elevated vascular inflow pressure. **(a)** Capillary stress fracture with incipient extravasation of an erythrocyte. **(b)** Higher power view of stress fracture showing exposure of collagen filaments.

be expected to reduce the tendency for material stress failure. Finally, it is interesting to consider that a low frequency may have allowed sufficient time between adjacent cycles for reparative processes to operate. Surprisingly little time appears to be needed to reseal small disruptions in tissue barriers [32,33].

What are the relative roles of vascular and airspace pressures in ventilator-induced lung injury?

Because rigorous limitation of pulmonary vascular pressures significantly attenuated the damage in lungs exposed to a fixed ventilatory pattern, the work outlined above suggests that elevations in pulmonary vascular pressure arising from interactions between lung volume, pulmonary vascular resistance, and pulmonary vascular flow could worsen ventilator-associated lung injury. Our redirected attention toward the vascular side of the alveolar capillary barrier stimulated us to ask whether the mechanism by which pulmonary artery pressure is phasically increased can influence the severity of lung damage during exposure to high alveolar pressure. In other words, is periodic inflation a necessary component of the vascular injury that is incurred during VILI?

Knowing that the frequency of ventilation is an important determinant of VILI, we reasoned that a lung exposed to pulsatile vascular pressure but not ventilated might experience significant injury, even without fluctuations in airway pressure. In an experiment designed to test this, we applied a damaging pattern of airway pressure (plateau 30 cmH₂O, PEEP 5 cmH₂O) to one of three sets of lung preparations and allowed others to remain motionless [26]. In the ventilated

group, peak pulmonary artery pressure was allowed to rise to 35 mmHg. Left atrial pressure was held at 10 mmHg and mean airway pressure at 17.5 cmH₂O. This set of ventilated preparations was compared with two unventilated groups held without tidal fluctuations in airway pressure (continuous positive airway pressure 17.5 cmH₂O) in which all key hemodynamic pressures – peak, mean, and nadir – were identical to their ventilated counterparts. In the latter two groups a vascular pump applied pulsatile pulmonary artery pressure to the motionless lungs at frequencies of 3 or 20 pulses per minute. Each vascular stress cycle, whether generated by ventilation or by the vascular pump, was characterized by identical peak, mean, and nadir values.

Our main findings were that lungs exposed to cyclic elevations in pulmonary artery pressure in the absence of ventilation formed less edema and exhibited less perivascular and alveolar hemorrhage than did ventilated lungs exposed to similar peak and mean pulmonary artery pressures and mean airway pressure [26]. Interestingly, under conditions of static continuous positive airway pressure, the higher pulsing frequency was associated with a greater degree of perivascular hemorrhage, indicating that the pulsatility of vascular pressure did contribute to VILI. Thus, the effects of respiratory frequency and vascular pressures on VILI are not mediated primarily by pulsatile vascular pressure *per se* but rather by a phenomenon related to cyclic modulation of the vascular microenvironment induced by ventilation. Because alveolar and extra-alveolar microvessels are stressed differently by lung expansion, these experiments focused our attention on the extra-alveolar microvasculature, suggesting the cyclic changes in perivascular pressure surrounding extra-alveolar,

juxtacapillary microvessels might be important in the genesis of VILI.

Should vascular pressures be lowered to avert ventilator-induced lung injury?

Given that elevation in pulmonary vascular inflow pressure accentuated VILI, it seems logical that reduction in postalveolar vascular pressure would also be protective. The merit of reducing left atrial pressure might be expected for at least two reasons. The edematous lungs tend to collapse under their own weight and to develop dependent atelectasis, which could lead to cyclic opening and collapse, intensified shear stresses, and a tendency toward VILI in dependent areas. Moreover, exudation of protein-rich fluid has the potential to inactivate surfactant, further altering membrane permeability by increasing both surface tension and radial traction on pulmonary microvessels. On the other hand, increased left atrial pressure might help to limit VILI by flooding the alveoli of dependent regions, thereby reducing regional mechanical stresses. Reducing capillary pressure could promote cyclic vascular recruitment and derecruitment as the lungs transition from West's zone III to zone II condition during the course of the positive pressure inflation/deflation cycle. Hydrodynamic forces may well be accentuated by the higher velocities and surface shear stresses that occur along the vascular endothelium under such conditions. Reducing outflow pressure also increases the gradient of pressure appearing across the alveoli, and consequently the energy dissipated across the intermediate segment. For these reasons, the impact of selectively reducing pulmonary venous pressure during ventilation with high airway pressure cannot easily be predicted.

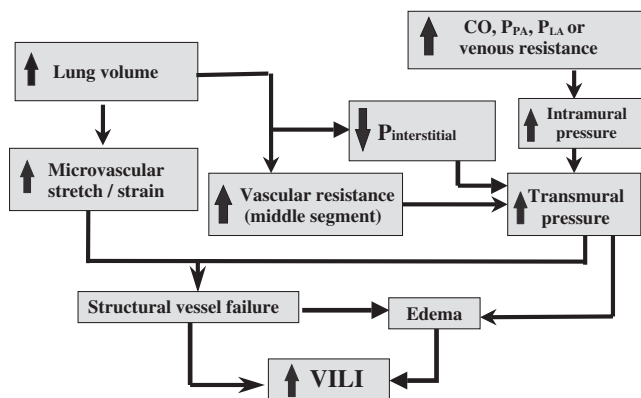
In a recently published comparison of lungs ventilated with moderately high peak alveolar pressures with normal and low left atrial pressures, Broccard and coworkers [34] demonstrated a striking difference in favor of the normal vascular pressure subset. This rather surprising result suggests that cyclic opening and closure of stressed microvessels could be important in the generation of VILI. Alternatively, decreasing outflow pressure might amplify microvascular stresses at or near the alveolar level, presumably acting through interdependence of the pulmonary vascular network. We speculate that direct mechanotransduction of inflammatory signals, increased transalveolar energy dissipation, or materials failure at the stressed boundary could be important linking mechanisms.

Collectively, the results of the laboratory experiments and clinical observations discussed above suggest several pathways by which microvascular hemodynamics may influence the development or expression of VILI (Fig. 6).

Potential clinical implications

Manipulation of cardiac output and vascular pressure is of vital importance in critical care management. The interactions between vascular pressure and ventilation outlined in this review suggest strongly that closer attention should be paid

Figure 6



Possible mechanisms by which hemodynamic parameters may incite or exacerbate ventilator-induced lung injury (VILI). Microvascular strain may be amplified at the junctions of open and closed lung units. CO, cardiac output; P_{LA}, left atrial pressure; P_{PA}, pulmonary artery pressure.

to interventions that impact on vascular pressures, flows, and resistances when high inflation pressures are in use. Because microvascular stresses appear to be a potent cofactor in the development of pulmonary edema as well as lung damage resulting from an injurious pattern of ventilation, the clinician managing ALI should reconcile the competing objectives of ensuring adequate oxygen delivery and minimizing adverse effects. For example, an increase in cardiac output is generally held to be a beneficial consequence of management; however, increases in cardiac output are associated with an increased prealveolar microvascular pressure and a higher vascular pressure gradient across the lung. If increased prealveolar microvascular pressure accentuates a tendency toward VILI, then attempts to raise cardiac output may have unintended consequences. On the other hand, taking steps to reduce oxygen consumption demands could benefit the lung by reducing the pressure gradient developed across the microvasculature. Similarly, a reduction in left atrial pressure with maintained cardiac output is generally believed to benefit lung function, and this perception is almost certainly accurate with respect to hydrostatic edema formation. However, the results of the recent work cited above suggest that excessive reduction in left atrial pressure could amplify the tendency toward VILI [34]. Because reducing ventilation frequency decreases the number of stress cycles, our work would suggest that a reduction in minute ventilation effected either by a decrease in tidal volume or by a decrease in ventilatory frequency might have a salutary effect in reducing the tendency toward VILI.

Reduced minute ventilation is generally associated with increased carbon dioxide retention and hypercapnic acidosis, which until recently was considered an undesirable but necessary consequence of a 'lung protective' ventilation strategy. However, when the lung's gas exchanging properties are not

dramatically altered and carbon dioxide production remains unchanged, recently published experiments by Sinclair and coworkers [35] and by Broccard and colleagues [36] strongly indicate that the generation of hypercapnic acidosis may exert a protective effect on the severity of VILI. (This observation is consistent with elegant work that previously addressed ischemia/reperfusion injury [37].)

Because interventions such as increasing PEEP or extending inspiratory time may redirect blood flow and radically alter the microvascular environment, it is conceivable that both benefit and harm could potentially result from these maneuvers. The body of investigative work reviewed here suggests that a reduction in the demands for cardiac output and ventilation could dramatically reduce the tendency toward VILI, even when using patterns that generate similar values for peak and end-expiratory alveolar pressures. Whether these intriguing possibilities are relevant to the clinical setting will require extensive and careful additional study.

Conclusion

Experimental and clinical evidence point strongly toward the potential for microvascular stresses to influence the severity and expression of ventilator associated lung injury. Increasing pressure upstream from the alveolus not only worsens edema but also predisposes the gas-blood barrier to disrupt in response to high airspace pressures, especially at rapid ventilation frequencies. Paradoxically, reducing venous microvascular pressure (and simultaneously increasing both the pressure gradient and energy dissipated along the pulmonary microvasculature) appears to worsen edema and/or accentuate barrier breakdown. Once disruption occurs, bi-directional interchange between the vascular and gaseous compartments may take place, possibly with adverse consequences for the lung and for extrapulmonary organs. Although it is hazardous to extrapolate from the available data to the clinical setting, taking measures to lower vascular stress (e.g. by reducing the physiologic requirements for ventilation and cardiac output) is a logical, but as yet unproven, extension of a lung-protective strategy for life support in ARDS.

Competing interests

None declared.

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