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WHAT'S NEW IN INTENSIVE CARE

Inspiratory preload obliteration may injure lungs via cyclical "on–off" vascular flow

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Introduction

Mechanical ventilation is the mainstay of supportive treatment for acute respiratory distress syndrome (ARDS) and high tidal volumes worsen outcome [1, 2]. The current paper considers how the pulmonary vasculature might participate in the development of ventilator-associated lung injury, and how recent research insights might ultimately be exploited in practice.

Vascular contributions to VILI

The status of the pulmonary vasculature can directly impact the development of ventilator-induced lung injury (VILI) via several mechanisms. Elevated pulmonary artery pressure, flow, or pulse frequency [3] can each potentiate VILI. Also, increased hydrostatic pressure in the microvasculature augments edema formation, and if permeability is also increased, the impact is synergistic. In addition, higher flow and hydrostatic pressure potentiate injury, as dopamine, administered to increase flow and pressure, caused injury despite "protective" ventilation [4].

Increased perfusion and stretch *each* cause injury, as injury is greater following negative-pressure (increased perfusion) vs. positive-pressure (decreased perfusion) ventilation, despite equal lung distension [4]. In contrast, remodeled vasculature may be less susceptible to stretch-induced permeability [5].

Ventilation and endothelial injury

Several findings suggest that the endothelium (vs. epithelium) may be responsible for initiation or propagation of injury [6]. First, in a classic model of VILI, disruption of the endothelium occurs *before* epithelial injury [4]. Lung overventilation (signaling due to mechanical stress) initiates pro-inflammatory events on lung microvascular endothelial cells (e.g., expression of adhesion molecules, deposition of leukocyte/platelet-binding proteins). In parallel, lung overventilation triggers endothelial Ca^{2+} signaling which in turn increases vascular permeability and inflammatory responses [7]. Endothelial dysfunction impairs transcytotic and paracytotic transport and increases permeability [6], leading to alveolar flooding; indeed, increased microvascular permeability is universal in experimental VILI [8], and is presumed in the current ARDS definition.

While modest changes in airway pressure can amplify focal force in the lung parenchyma via tissue interdependence [9] and induce cell stress failure [8], increases in transmural pressure (across the vessel walls) could fracture capillaries and cause hemorrhagic pulmonary edema [10]. Less recognized is vascular shear stress produced by turbulent (or rapidly changing) blood flow; this can cause endothelial dysfunction and injury and induce inflammation and vascular leak, as demonstrated during reperfusion following ischemia. Endothelial disruption will increase pulmonary vascular resistance, and may cause right ventricle (RV) strain, which in clinical ARDS is associated with worse outcome.

Tidal volume and vascular injury

The classic experiments of Webb and Tierney [11] demonstrated that high V_T and zero PEEP caused overwhelming lung injury; this in vivo experiment largely prompted a generation of work on VILI that ultimately changed practice. On the basis of these experiments it was discovered that increased microvascular permeability [4] and hydrostatic pressure were responsible for the associated edema.

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Recent observations advance this interpretation, because the (same) combination of high V_T and zero PEEP caused cycles of obliteration of perfusion during inspiration and increased perfusion during expiration [12] (Fig. 1; see animated figure in online supplement). This cyclic pattern of altered perfusion was not due to microvascular compression at peak inspiration (from very high alveolar pressure); instead, it was due to abolition of right ventricular preload in inspiration and (compensatory) greater ventricular filling in expiration. During high V_T ventilation, at peak inspiration the pleural pressure exceeds the pressure in large veins and right atrium, resulting in their collapse, abolition of venous return, and absent right ventricular filling. This in turn interrupts pulmonary artery flow and pressure, and therefore pulmonary capillary pressure becomes very low.

At this point the lung enters West zone I condition (ventilation, no perfusion); however, this is because of cyclic inspiratory interruption of RV preload, rather than excessive alveolar pressure. During expiration the reverse occurs, and the pulmonary artery flow and pressure increase, briefly exceeding normal values.

Similar effects of ventilation have been observed in a computational study [13], and interruption of pulmonary blood flow due to cyclic changes in *afterload* has been reported in patients with ARDS [14]. This pattern over time caused progressive RV failure, presumably due to repetitive microvascular injury from cycles of absent/excessive vascular flow (vascular shear stress). If this mechanism is confirmed, it would represent an entirely new form of VILI, with specific implications for trial design and management.

Airway and hemodynamic forces act in concert, changing cyclically during superimposed cardiac and respiratory cycles. The alveolus and microvasculature are stretched in inspiration, and at peak inspiration (due to absent preload) the blood flow is reduced; during expiration, the alveolus shrinks but perfusion (and transmural pressure) is maximal. Thus, both cell types are exposed to injurious stress [8, 10]. At the molecular level, overventilation, hydrostatic pressure, and microvascular flow act through similar mechanosensory mechanisms (e.g., transient receptor potential vanilloid 4 cation channels on the endothelial barrier [7]) therefore acting synergistically.

Clinical implications

How can this paradigm help patients? We see two areas of potential impact. First, VILI thought of as "mechanical" injury has increasingly recognized contributions from flow and endothelial injury. However, flow-mediated microvascular injury might be due mainly to cyclic flow interruption (rather than simply high levels of flow), in turn due to major impact of the inspired tidal volume on cardiac preload. While the average preload may be unchanged, monitoring preload might focus on tidal swings (absent to high) due to excessive tidal volume,

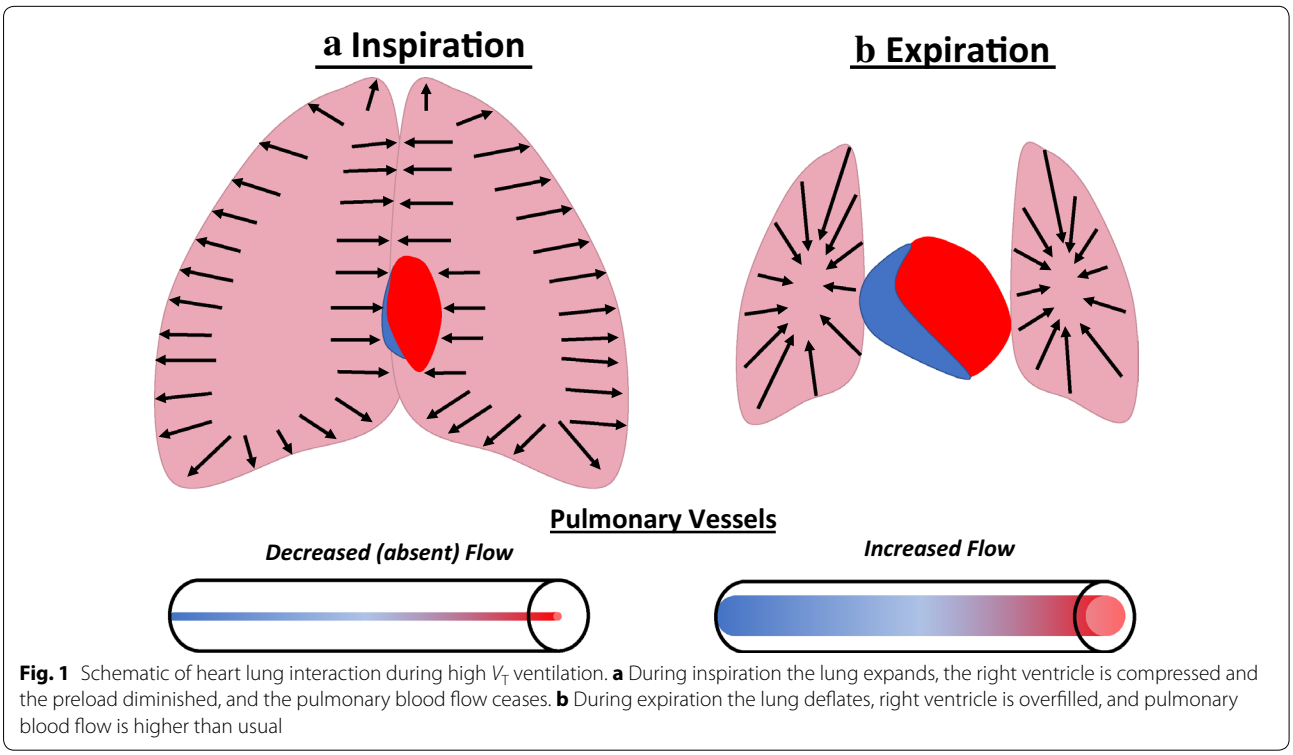

Fig. 1 Schematic of heart lung interaction during high V_T ventilation. **a** During inspiration the lung expands, the right ventricle is compressed and the preload diminished, and the pulmonary blood flow ceases. **b** During expiration the lung deflates, right ventricle is overfilled, and pulmonary blood flow is higher than usual

analogous to tracking "swings" (vs. mean levels) of pleural pressure. Of course, spontaneous breathing in ARDS—which may increase mortality [15]—could amplify such hemodynamic fluctuations and worsen injury.

A second impact may be in ARDS that is propagated by blood-borne mediators (e.g., transfusion, sepsis, reperfusion injury) impacting via the pulmonary endothelium. In addition, vasoactive agents increase pulmonary microvascular flow and pressure, and worsen injury during experimental ventilation [4]—or in patients—from "excessive" resuscitation.

In either case, our ability to monitor the pulmonary microvasculature is increasing. Specific markers of endothelial dysfunction (e.g., von Willebrand factor, angiopoietin-II, endothelial microparticles) are available and with greater specificity and faster response times, monitoring and management of both ventilator and hemodynamics could be tailored to minimize pulmonary vascular harm. Thus, a previously occult component of ventilator-associated lung injury might become a focus of optimized care.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
None of the authors have a financial conflict of interest with the subject matter of this manuscript.

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