Intensive Care Med
DOI 10.1007/s00134-015-4111-8

EDITORIAL

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Does high-pressure, high-frequency oscillation shake the foundations of lung protection?

Received: 16 October 2015
Accepted: 16 October 2015

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There is a strong temptation to take a reductionist approach that would permit us to assign a single mechanistic cause for ventilation-induced lung injury (VILI) and thereby identify a simple bedside intervention to avoid its consequences. However, convincing investigations have uncovered at least three ways in which adverse tidal cycling pressures may injure the lung: (1) over distension of already inflated alveoli, with cellular distortion, epithelial wounding, and capillary stress fracture [1]; (2) tidal opening and closure with attendant (or causal) surfactant dysfunction, liquid bridge disruption, and high interfacial surface forces [2]; and (3) stress focusing/shear at points of micromechanical heterogeneity [3]. Over the years each has had a spokesperson for its primacy, backed by an impressive body of supportive scientific literature.

Whatever the emphasized viewpoint, however, consensus exists that attaining high peak transpulmonary cycling pressures is an essential precondition for VILI. Excessive transpulmonary forces reflect the reduced capacity of the 'baby lung' to accept its distending and tidal volumes [4]. But with such critical elements respected and most unstable units held open, it seems reasonable that high-frequency oscillation (HFO), a strategy that targets reduced tidal volume and open lung, should be nearly ideal as a lung-protective methodology. It was therefore upsetting that a rigorously designed and executed clinical trial demonstrated that HFO could increase mortality risk [5].

In this issue of *Intensive Care Medicine*, pioneering contributors to VILI research (Didier Dreyfuss and colleagues) present a cogent, detailed, and deliberately provocative argument that the cause of this unexpected result might be violation of the basic directive to avoid high airway pressures, with the *likely* mechanism being sustained and excessive tissue stretch [6]. The implication is that opening/closure and stress focusing, though acknowledged contributors to VILI at conventional ventilation frequencies, have received disproportionate attention. To evaluate the plausibility and vulnerability of this argument, the challenging complexity of VILI must be appreciated.

VILI is a multifaceted process influenced by mechanical and non-mechanical factors. From the mechanical side, two factors are keys: maximal alveolar pressure and excursion of alveolar pressure. This duo is estimated clinically as the plateau and driving pressures (DP = VT/C or plateau minus PEEP), and both are important. There appears to be a fuzzy threshold of maximal applied *transpulmonary* pressure below which generation of extensive tissue damage is unlikely and above which the risks for cellular distortion and wounding, increased vascular permeability, and inflammation rise in nonlinear fashion [1, 7]. Once above threshold, frequency of breath delivery becomes increasingly important, in part because native repair processes have inadequate time to mend cell membranes between cycles [8]. A persuasive case has been made for the primacy of surfactant loss in the initiation, extension, and progression of VILI [2]. With pressure thresholds exceeded and functional surfactant depleted, adequate PEEP and/or prone position de-amplify shear and reduce surface forces.

High peak transpulmonary stretching pressure, though essential, does not act alone. Sustained high alveolar pressure distorts but does not dramatically injure epithelium until it cycles sufficiently often to lower pressure [9]. Moreover, VILI tends to propagate from points of mechanical heterogeneity, wherever they occur [3]. Thus, experimental VILI concentrates in gravitationally

Published online: 23 October 2015

dependent zones, which are subject to less transpulmonary pressure but greater stress focusing and wider swings of transpulmonary DP [10]. Finally, although the static airway driving pressure may dominate over its individual *static* determinants (PEEP and plateau pressure) as a contributor to adverse clinical outcome [4], certain *dynamic* characteristics of the tidal cycle should also generate high interest as VILI culprits, e.g., the interaction among tissue viscoelastance, speed, and contour of the DP rise (as regulated by flow amplitude and profile). One unifying theory incriminates intensity of energy delivery per unit time (power) as the actual VILI motor that incites inflammation [11]. But even this attractive idea, which fuses the effects of frequency, transpulmonary DP, and strain, may prove imprecise, as it underestimates the *local* dissipation of energy at points of stress focusing. Importantly, underemphasized non-ventilatory conditions set the background for VILI expression. For identical ventilation patterns, tissue edema, airway biofluids, and different vascular pressure and flow gradients strongly influence the damage that results [12]. In theory, fragile interstitial microvessels are strained at high volumes, causing stress fractures and dissipating energy along the vascular endothelium.

When equating VILI to mortality risk from ventilation strategy, it is sobering to remember that the precise causative link to adverse outcomes has not yet been determined. Why *did* these HFO patients die at a higher rate? Excessive right ventricular strain and multi-organ failure due to hypoperfusion is perhaps the strongest possibility; however, blood flowing through the injured lung encounters progressively steeper gradients (waterfalls) as mean alveolar pressure rises [13]. Could such *endothelial* shear stress generate mediators even as the bloodstream transports preformed inflammatory products (whatever their source) to systemic vital organs? Pure speculation, but operating HFO at high mean airway pressure would do little to abrogate such a process.

Occult VILI could have developed during OSCILLATE for dynamic reasons that relate only indirectly to static 'stretch' mechanisms. Global tidal volumes during HFO may range from <100 ml to >400 ml, varying inversely with cycling frequency. Alveolar pressure excursions remain unmeasured. At a frequency of 5 Hz (300 cycles/min), *total* ventilation and rate of alveolar energy delivery would be extremely high—especially for a 'baby lung'. Effective inspiratory time fractions of 1:2 would put inspiratory flow at three times the minute ventilation—producing a very high strain *rate*. Moreover, when the clinical need for alveolar ventilation increased, the OSCILLATE protocol understandably suggested slower frequency, upping the transalveolar DP and dissipated power [5]. It is not difficult to envision propagating injury and a downward spiral once things start to go bad for a 'baby lung' of diminishing size. Note that when the lungs of healthy animals are reduced surgically to <1/4 to of their original volume, death from pulmonary edema, hemodynamic compromise, and/or unsupportable gas exchange is almost inevitable [14]. Neither the data presented in the original report nor those in the online supplement allow determination of whether lung function deteriorated as the result of ventilation management.

We now can state confidently that *both* high 'stretch' conditions and repeated cycling with wide excursions of transpulmonary pressure contribute to VILI and are to be avoided at all frequencies. We also know that minimizing contributors to stress amplification—mechanical heterogeneity (e.g., with adequate PEEP and prone positioning) is likely to pay dividends, especially when transpulmonary forces are high and background conditions are conducive to VILI expression. Dreyfuss and colleagues [6] are quite correct in asserting that one of the key principles of lung protection—avoidance of high transalveolar pressure—was compromised by OSCILLATE's focus on open lungs and small tidal volumes. But whether tissue tensions, DPs, and delivered power were lung damaging has not been settled. The lesson we have been slow to learn in bedside management is that reducing the *demands* for ventilation, oxygen consumption, and cardiac output helps downregulate key VILI risk factors and represents perhaps the highest-yield strategy of all for ensuring effective lung protection.

Compliance with ethical standards

Conflicts of interest None.

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