Point:Counterpoint: High-frequency ventilation is/is not the optimal physiological approach to ventilate ARDS patients

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Before we can agree (or disagree) on whether high-frequency ventilation is the optimal physiological approach for ventilating patients with acute respiratory distress syndrome (ARDS), we must first define exactly what we mean by an optimal physiological approach. In this regard, we are not talking about restoring a “normal” physiological pattern of breathing nor even necessarily achieving “normal” blood gases. The goals of mechanical ventilation in ARDS have changed markedly over the last 10–15 years; we now define an optimal physiological approach as that which preserves “acceptable” gas exchange while simultaneously minimizing further lung injury caused by the ventilator, termed ventilator-induced lung injury (VILI; Ref. 4). This focus on VILI avoidance is justified by a wealth of preclinical data (briefly discussed below), along with several clinical trials demonstrating decreased mortality with lung-protective ventilation strategies (24, 28).

VILI occurs through various mechanisms, including oxygen toxicity, volutrauma, atelectrauma, and biotrauma (4, 27). Relatively early research documented oxygen toxicity—the deleterious effects of high levels of oxygen on lung tissue (14). Volutrauma refers to lung injury arising from pulmonary overdistension (5). ARDS is a heterogeneous disease; the least damaged (most compliant) regions of lung receive a disproportionate fraction of the inspired volume and are at particularly high risk of volutrauma. There is surfactant deficiency and alveolar instability resulting in repetitive alveolar collapse (atelectasis) and reopening, which generates shear forces that accentuate lung injury: so-called atelectrauma (20). Limiting alveolar collapse (by adequate positive end-expiratory pressure [PEEP]) can mitigate atelectrauma (13, 23, 25, 27, 30). These three mechanisms of ventilator-induced lung injury can all contribute to biotrauma with release of inflammatory mediators [e.g., interleukins, tumor necrosis factor (TNF)-α, . . . ; Refs. 4, 26]. These mediators can translocate into the circulation (15, 25–27), potentially contributing to multi-organ dysfunction, the major cause of ARDS mortality. As demonstrated below, high-frequency oscillation (HFO) addresses all of these major mechanisms of injury while providing adequate gas exchange; hence, from a physiological perspective, it is the ideal way to ventilate patients with ARDS.

HFO is a subtype of high-frequency ventilation that provides pressure oscillations around a relatively constant mean airway pressure, delivering very small tidal volumes (VT) at high respiratory rates (frequencies) of 3–15 Hz. The key to the lung protective potential of HFO are these very small VT. Not only will they directly limit tidal overdistension and volutrauma, but equally importantly they facilitate the safe use of higher mean airway pressures to mitigate atelectrauma. With minimal tidal excursions, the mean airway pressure on HFO can be thought of as being similar to positive-end expiratory pressure (PEEP) on conventional ventilation. CO2 removal is achieved through a number of mechanisms including bulk convection, convective streaming, pendelluft, cardiogenic mixing, and diffusion (21). Because cyclic alveolar stretch is minimal, volutrauma can be avoided even when the mean airway pressure is set to higher levels than can be reasonably set with PEEP on conventional ventilation. Indeed, to the extent that these higher mean airway pressures are able to recruit previously atelectatic lung, the potential for volutrauma may be further decreased by increasing the size of the “baby lung.” (7) and the potential for oxygen toxicity may be reduced as lower FIO2s are required.

This lung-protective potential of HFO has been examined in numerous animal studies. In addition to older studies that demonstrated benefits of HFO versus traditional ventilation (i.e., with higher VT than currently used), the majority of more recent studies that have compared HFO with a lung-protective conventional strategy have continued to demonstrate the superiority of HFO on physiological (e.g., oxygenation, compliance), inflammatory (e.g., TNF-α, IL-6, neutrophil counts in broncho-alveolar lavage), and pathological evidence of lung injury (11, 12, 17, 19, 29). Thus there are strong animal data supporting the concept that HFO is better than conventional lung-protective ventilation.

These physiological advantages of HFO would be meaningless if HFO were not effective in humans. Clinically, HFO was first introduced in the neonatal ICU; whereas there are important differences in characteristics, pathology, and management between neonates with respiratory distress syndrome and adults with ARDS, some important inferences can still be drawn from this population. In general, randomized controlled trials (RCTs) that have employed a lung recruitment strategy in the HFO arm have shown better oxygenation and lung mechanics in the HFO group, with some showing significant improvement in outcomes (e.g., chronic lung disease; Ref. 10). Even with all the advances made in the care of neonatal respiratory distress in the last two decades, a cumulative meta-analysis continues to demonstrate benefit with HFO (1).

Adult HFO has been commercially available for only 10 years, so this body of literature is understandably smaller. The largest of two published RCTs comparing HFO with conventional ventilation showed an impressive trend toward decreased mortality with HFO (absolute risk difference 16%; R-R 0.72; 95% confidence interval 0.50–1.04; Ref. 3). The smaller RCT did not demonstrate a mortality trend in either direction, but these results are confounded by an almost 20% crossover rate and by large baseline differences favoring the control group (2). We readily admit that data from these trials are not definitive. There are methodological issues: small sample sizes and the use of now dated, potentially injurious conventional ventilation strategies in the control arms; they do, however, provide supporting data that are consistent with our physiological framework supporting HFO. It is important to point out that the purpose of this debate is not to demonstrate that HFO is better clinically, but rather that it represents the “optimal physiological” ventilatory approach that is currently available. Of course, the most important issue for patients is clinical outcomes, but unfortunately there are insufficient data in the literature to adequately address this point (if these existed, there would be no debate).

We stated earlier that the very small VTs on HFO are the cornerstone of this physiological framework. It is true, however, that VT is not routinely measured with currently available oscil-
lators; as such, one might argue that the Vrs on HFO are really not as small as we suggest. Vr during HFO is inversely related to frequency (because of decreasing inspiratory time with increasing frequency; Ref. 22); however in adults, respiratory frequencies are often lower than those used in neonates (3–6 vs. 12–15 Hz). Work from our worthy opponent’s laboratory questions whether delivered Vrs are in fact small; Sedeek and colleagues (198) measured Vrs of up to 4 ml/kg at high-pressure amplitudes and low frequencies in an ovine model. Unfortunately, for technical reasons, these Vr measurements may be overestimated (8), but importantly they have prompted further investigation. HFO in frequencies in an ovine model. Unfortunately, for technical reasons, these Vr measurements may be overestimated (8), but importantly they have prompted further investigation. HFO in adults can in fact be set to deliver very small Vrs in adults, particularly when the strategy focuses on using the highest frequency possible (6). Recent work shows that HFO Vrs in adult patients [measured using a hot-wire anemometer) are reassuringly small; Sedeek and colleagues (198) measured VTs from our worthy opponent’s laboratory questions whether delivered VTs are in fact small; Sedeek and colleagues (198) measured VTs of up to 1.5 ml/kg (16). This is in accord with early data demonstrating that normocapnic levels of PaCO2, can be achieved with HFO using VTs averaging 1.5 ml/kg (16).

In summary, by allowing greater end-expiratory volume while simultaneously minimizing cyclic end-inspiratory stretch, HFO is theoretically better suited than any conventional ventilation strategy for avoiding ventilator-induced lung injury, an important contributor to the high mortality observed in ARDS patients. The strong physiological rationale, experimental data from animal studies, and encouraging clinical findings all point toward HFO being an ideal mode for lung-protection in patients with severe ARDS. All that awaits is clinical confirmation by a definitive RCT—an issue that we are currently in the process of addressing.

REFERENCES


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