CHEST

# High-Frequency Oscillatory Ventilation in Adults With ARDS

## Past, Present, and Future

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High-frequency oscillatory ventilation (HFOV) is a unique mode of mechanical ventilation that uses nonconventional gas exchange mechanisms to deliver ventilation at very low tidal volumes and high frequencies. The properties of HFOV make it a potentially ideal mode to prevent ventilator-induced lung injury in patients with ARDS. Despite a compelling physiological basis and promising experimental data, large randomized controlled trials have not detected an improvement in survival with the use of HFOV, and its use as an early lung-protective strategy in patients with ARDS may be harmful. Nevertheless, HFOV still has an important potential role in the management of refractory hypoxemia. Careful attention should be paid to right ventricular function and lung stress when applying HFOV. This review discusses the physiological principles, clinical evidence, practical applications, and future prospects for the use of HFOV in patients with ARDS.

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**KEY WORDS:** ARDS; mechanical ventilation; respiratory failure

## Historical Background

High-frequency oscillatory ventilation (HFOV), like many seminal discoveries in science, was stumbled on by chance.[1,2] While using the forced oscillation technique to examine the effects of neuromuscular blockers on lung impedance, the eminent physiologist and pediatric intensivist A. Charlie Bryan noticed that $CO_2$ was detected at the mouthpiece of the apparatus with each loudspeaker beat. This seemed counterintuitive, as each oscillation of the loudspeaker generated a tidal volume ($V_T$) far smaller than his own dead space volume of 150 mL (Bryan was himself one of the experimental subjects). Alveolar ventilation should have been impossible. Although he initially disregarded the observation, Bryan later discovered that facilitated diffusion of $CO_2$ could account in part for the observed alveolar ventilation, and he began to explore HFOV as a ventilatory technique.[3]

The use of HFOV rapidly progressed from healthy volunteers to animal models and then to critically ill adults and neonates.[4,5] The first multicenter randomized trial of HFOV (1989) to treat neonatal respiratory

**ABBREVIATIONS:** CMV = conventional mechanical ventilation; HFOV = high-frequency oscillatory ventilation; HFPV = high-frequency percussive ventilation; LOVS = Lung Open Ventilation Study; mPaw = mean airway pressure; PBW = predicted body weight; PEEP = positive end-expiratory pressure; P/F = $Pao_2/Fio_2$; RV = right ventricular; VILI = ventilator-induced lung injury; $V_T$ = tidal volume

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distress syndrome[6] was stopped early due to an unexpectedly high rate of intraventricular hemorrhage in the HFOV group, possibly related to altered cerebral hemodynamics.[7] Despite early negative results, HFOV was tested in a number of subsequent randomized trials in both pediatric and adult patients with respiratory failure with mixed results. Two recent multicenter trials of HFOV vs conventional mechanical ventilation (CMV) in adult patients with ARDS found no significant benefit and even a signal for harm. These findings were disappointing in view of the extremely promising biological rationale in support of HFOV. In this review, we discuss the physiological mechanisms of gas exchange under HFOV, the basis for its theoretical benefit as a lung-protective ventilation strategy, the clinical data, and potential future avenues for research and treatment.

## Mechanics of HFOV

HFOV consists of a simple circuit in which oxygenated humidified gas (bias flow) is passed across the path of an oscillating membrane at a set frequency (usually 3-15 Hz) generating $V_T$ that is far less than anatomic dead space (typically 1-3 mL/kg predicted body weight [PBW]) (Fig 1). In HFOV, oxygenation ($Pa_{O_2}$) and ventilation ($Pa_{CO_2}$) can be manipulated independently. $Pa_{O_2}$ is determined by $F_{IO_2}$ and the mean airway pressure (mPaw). $Pa_{CO_2}$, in contrast, is regulated by the oscillation frequency, the pressure amplitude of the oscillations (power, $\Delta P$), and the inspiratory time.[8] $CO_2$ clearance is enhanced by increasing $\Delta P$ and is decreased (somewhat counterintuitively) by increases in frequency.[9] HFOV differs from high-frequency percussive ventilation (HFPV), which combines high-frequency oscillations with conventional inspiratory and

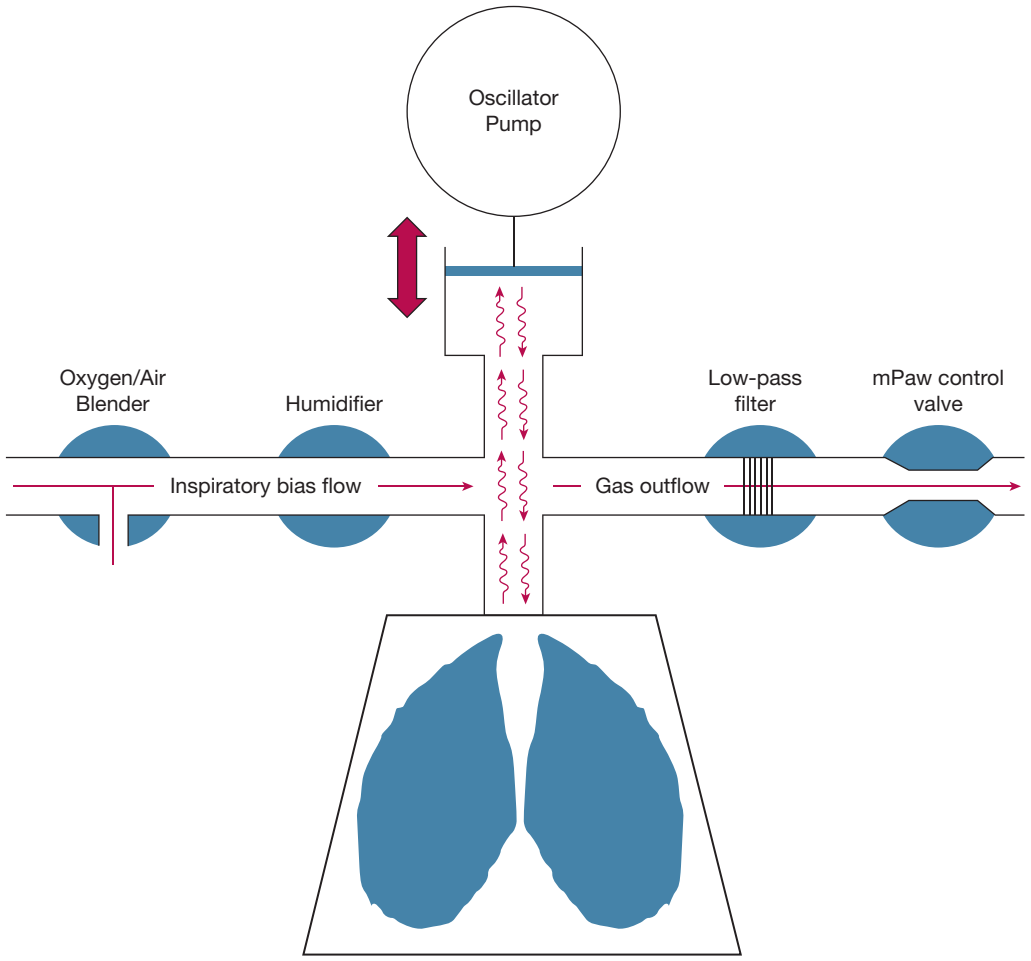


Figure 1 – *Schematic diagram of a high-frequency oscillatory ventilator. A humidified mixture of air and oxygen flows continuously across the ventilator circuit (bias flow, typically 40 L/min). At the same time, gas flowing out of the circuit crosses a low-pass filter (to preferentially remove high-frequency currents). A valve on the outflow limb controls the outgoing flow rate. Mean airway pressure is increased by increasing the bias flow or by increasing the resistance to expiratory flow. High-frequency oscillations are generated by a piston-driven pump that actively pushes gas into the circuit during the inspiratory phase and actively pulls gas out of the circuit during the expiratory phase. mPaw = mean airway pressure.*

expiratory pressure swings at conventional respiratory frequencies.[10] Because of the conventional swings in airway pressure, HFPV may be superior regarding secretion clearance and sedation requirements. However, the same conventional swings in airway pressure increase peak lung stress and limit the mPaw that can be applied; consequently, HFPV has received less attention as a lung-protective mode.

As a nonconventional mode of ventilation, HFOV is ideally managed in centers with prior training and experience in its use. Experts generally recommend against HFOV in patients with intracranial hypertension and known severe airflow limitation.[11] Different approaches to initial setup and titration of HFOV settings are summarized in a roundtable consensus document[11] and in Table 1.

## Mechanisms of Gas Exchange in HFOV

The possibility of ventilation at very low $V_T$ is both counterintuitive and fascinating. During HFOV, alveolar ventilation varies inversely with frequency and increases exponentially with $V_T$. Increases in frequency dampen pressure delivery and decrease $V_T$, leading to a net decrease in $CO_2$ clearance. Some mammalian species routinely rely on small frequent $V_T$ to achieve gas exchange. Panting dogs maintain acceptable gas exchange even though the $V_T$ of each "pant" is much less than dead space.[12] Similarly, hummingbirds—breathing with very low $V_T$ at a rate of 250 breaths/min—maintain effective alveolar ventilation despite a high metabolic rate.[13] Several mechanisms have been identified that may explain in part how adequate gas exchange can occur at very low $V_T$ (Fig 2).[14-19]

Bulk convection is the major mechanism of gas exchange during CMV, and it also plays a role in HFOV, particularly in the most proximal gas exchange units.[15] Its importance was demonstrated in an anesthetized canine model in which investigators showed that when volume delivered per oscillation was decreased to levels less than the rebreathing circuit volume, alveolar carbon dioxide tension ($Paco_2$) rose significantly.[20] In clinical practice, $V_T$ delivered by HFOV may be greater than expected, sometimes as high as 200 mL per oscillation depending on the applied frequency.[21]

During HFOV, convective gas transport is achieved by the formation of asymmetrical velocity profiles of gas flow in the airway. Because the spatial distribution of inspired gas flow differs from the spatial distribution of expired gas flow, the net result is opposing currents of convection within the same airway (Fig 2). This mechanism is likely more pronounced at airway bifurcations, where inhaled fresh gas streams along inner airway walls, whereas exhaled gas streams from alveoli along outer walls, giving rise to convective gas exchange.[22]

Pendelluft (literally "swinging air") describes the movement of gas within the lung because of dynamic pressure gradients between lung units arising through differences in the timing of inflation and deflation.[23] Regional differences in inertance and compliance of the peripheral airways and lung units[24]—and hence differences in local respiratory time constants—result in differences in the timing of inflation and deflation at steady state during HFOV. Lung units that are inflating even as others are deflating may receive gas from the deflating lung units. This interregional airflow increases gas mixing and enhances gas exchange.[25,26]

Cardiac contractions enhance gas mixing and contribute to gas exchange during HFOV.[27] The strong contractions of the heart act as a percussive force for gas mixing. Indeed, during apneic ventilation, cardiac oscillations may account for > 50% of oxygen uptake and nearly 40% of $CO_2$ clearance.[27,28]

## HFOV in ARDS

### *What Makes HFOV Ideally Suited to ARDS?*

Ventilator-induced lung injury (VILI) has traditionally been thought to result from two key mechanisms: excess mechanical stress and strain within lung regions participating in ventilation (volutrauma) and cyclic tidal recruitment at the interface between collapsed and recruited lung (atelectrauma).[29] Mechanical forces applied to the pulmonary epithelium lining the distal airways and alveoli initiate an inflammatory response within the lung[30] that can spread through the circulation to distal organs—a mechanism of multiorgan failure referred to as biotrauma.[31] The benefits of avoiding volutrauma were demonstrated in the landmark Acute Respiratory Distress Syndrome Network (ARDSNet) trial[32] that demonstrated a significant reduction in mortality in patients receiving lower $V_T$ (6 mL/kg PBW). The role of lung stress during tidal ventilation is further supported by a recent study demonstrating that driving pressure (a surrogate for tidal stress) is a key determinant of benefit in lung-protective ventilation trials.[33] Conversely, several trials of higher PEEP ventilation strategies used with the aim of avoiding atelectrauma failed to demonstrate a significant

**TABLE 1** ] Characteristics of the Major Clinical Trials of HFOV in Adult Patients With ARDS

| | | HFOV | | | Conventional Mechanical Ventilation | | |
|---|---|---|---|---|---|---|---|
| Study/Year | No. of Patients | Frequency Titration Strategy | mPaw Titration Strategy | ΔP Titration Strategy | Mode | Target Tidal Volume (Actual on Day 1) | PEEP Titration Strategy |
| Ferguson et al[45]/2013 | 548 | Set between 3 and 12 Hz, targeted maximum value that maintained pH > 7.25 | Initiated at 30 cm $H_2O$ mPaw—$F_{IO_2}$ table | Set at 90 cm $H_2O$ | PCV | 6 mL/kg PBW (6.1 mL/kg) | LOVS[a] PEEP— $F_{IO_2}$ table |
| Young et al[44]/2013 | 795 | Initially 10 Hz, titrated to keep pH > 7.25, minimum 5 Hz | Initiated at 5 cm $H_2O$ greater than mean airway pressure under CMV | Cycle volume titrated to keep pH > 7.25 | PCV | 6-8 mL/kg PBW (8.3 mL/kg) | ARDSnet[b] lower PEEP— $F_{IO_2}$ table |
| Mentzelopoulos et al[49]/2012 | 64 | TGI flow to 50% of previous CMV minute ventilation; frequency set to 4 Hz | Applied with tracheal gas insufflation; target was to get P/F > 150 mm Hg | Set ΔP = $Paco_2$ (on CMV) + 30 | . . . | 5.5-7.5 mL/kg PBW (6.4 mL/kg) | ARDSnet lower PEEP— $F_{IO_2}$ table |
| Bollen et al[48]/2005 | 61 | 5 Hz | Set mPaw 5 cm $H_2O$ higher than mean airway pressure under CMV | Titrated to chest wall vibration and $Paco_2$ | PCV | PIP maximum 40 cm $H_2O$ (9 mL/kg) | PEEP up to 15 cm $H_2O$ |
| Shah and Findlay[46]/2004 | 38 | 5 Hz | Set mPaw 5 cm $H_2O$ higher than mPaw under CMV | Titrated to achieve vibration from chest wall to midthigh | . . . | 7-8 mL/kg PBW (8 mL/kg) | Not reported |
| Derdak et al[47]/2002 | 148 | 5 Hz | Set mPaw 5 cm $H_2O$ higher than mPaw under CMV | Titrated to achieve chest wall vibration | PCV | 6-10 mL/kg (8 mL/kg) | ≥10 cm $H_2O$ |

CMV = conventional mechanical ventilation; HFOV = high-frequency oscillatory ventilation; LOVS = Lung Open Ventilation Study; mPaw = mean airway pressure; PBW = predicted body weight; PCV = pressure controlled ventilation; PEEP = positive end-expiratory pressure; P/F = $Pao_2/F_{IO_2}$; PIP = peak inspiratory pressure; RCT = randomized controlled trial; TGI = tracheal gas insufflation.

[a]LOVS = Lung Open Ventilation Study RCT.[34]

[b]ARDSnet = RCT of lower tidal volume ventilation.[32]

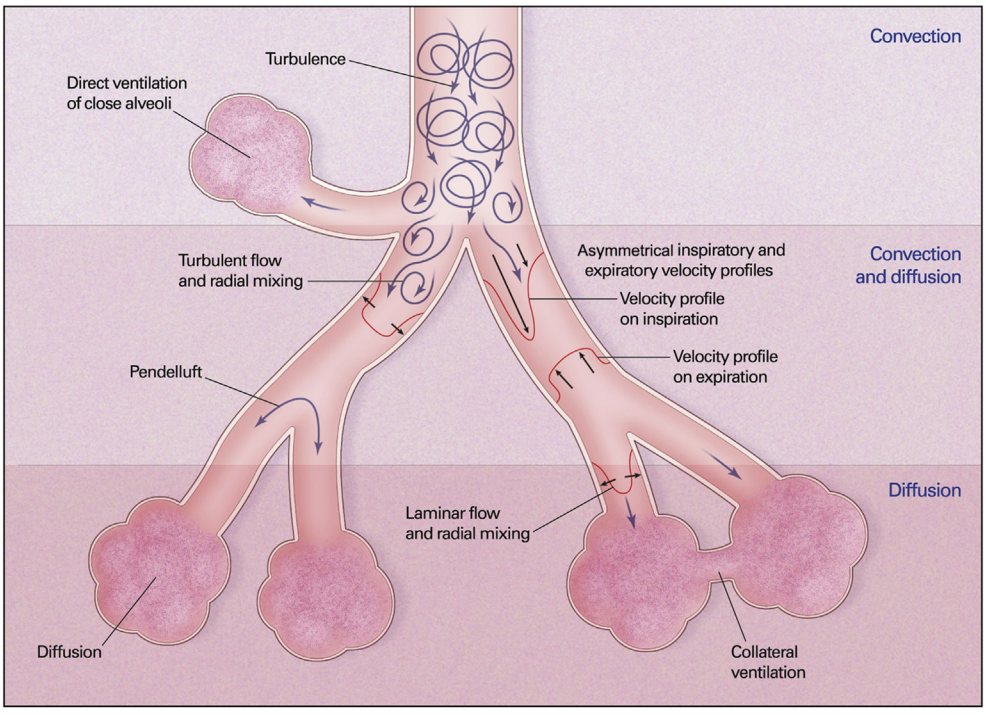


Figure 2 – *Mechanisms of gas exchange during high-frequency oscillation. The rapid oscillations in airway set up multiple mechanisms that promote gas exchange. Proximally, conventional bulk convection moves gas in and out of the lung. Several unique gas mechanisms are set up in more distal airways, including asymmetrical flow profiles, pendelluft, and gas mixing promoted by cardiac motion. (Reprinted with permission from Slutsky and Drazen.[14])*

improvement in outcome (although there was a signal for benefit in patients with more severe hypoxemia).[34-38] Concerns about volutrauma and atelectrauma undergirded the formulation of the "open lung" hypothesis,[39] which stipulated that clinicians should "open the lung and keep it open."

HFOV is ideally suited to achieving this goal. By delivering very small $V_T$ around a relatively constant mPaw, HFOV can substantially reduce the mechanical stress and strain applied during each tidal breath.[40] These very small $V_T$ limit swings in alveolar pressure, particularly since airway pressures are significantly dampened in the distal airways,[15] allowing the application of a relatively high mPaw (closer to the value of plateau airway pressure in CMV) to prevent atelectrauma.[40] Furthermore, these higher airway pressures can recruit more severely noncompliant collapsed regions, increasing lung volume and potentially reducing ventilatory strain.[41] These putative benefits of HFOV were strongly supported by a large body of experimental evidence showing that HFOV improves oxygenation and compliance, reduces pulmonary and systemic inflammation, and reduces histologic evidence of lung injury.[42]

## HFOV for Rescue Therapy in Refractory Hypoxemia

HFOV was initially used in adult patients with respiratory failure as a rescue therapy in refractory hypoxemia. A large retrospective study from three academic ICUs described the use of HFOV for refractory hypoxemia in 156 patients.[43] These patients had a mean ($\pm$ SD) $Pao_2/Fio_2$ (P/F) ratio of 91 $\pm$ 48 mm Hg and had been receiving CMV for 5.6 $\pm$ 7.6 days. Following HFOV application, oxygenation improved considerably (mean increase in P/F ratio, 60 mm Hg) with a concomitant reduction in $Fio_2$. In large multicenter trials, HFOV consistently improved oxygenation (Oscillation in ARDS [OSCAR] trial: day 3 P/F ratio of 217 $\pm$ 69 vs 166 $\pm$ 63 mm Hg)[44] and reduced the rate of refractory hypoxemia (Oscillation for Acute Respiratory Distress Syndrome Treated Early [OSCILLATE] trial: relative risk [RR], 0.50; 95% CI, 0.29-0.84).[45]

## Lung-Protective Ventilation

Given the theoretically ideal lung-protective features of HFOV discussed earlier, there has been great interest in establishing whether using it as an early lung-protective ventilation strategy in ARDS (as opposed to reserving it for rescue therapy) would reduce mortality. HFOV has

been compared against CMV in patients with ARDS in several randomized controlled trials (Table 1).[44-49]

Several early trials yielded inconsistent and inconclusive results. Bollen et al[48] and Derdak et al[47] randomized patients with moderate or severe ARDS to HFOV or CMV and reported a nonsignificant effect of HFOV on mortality in opposing directions (Bollen et al: RR, 1.30; 95% CI, 0.66-2.55; Derdak: RR, 0.72; 95% CI, 0.5-1.03). Statistical power was low in both trials, and these disparate treatment effects were situated within the 95% CIs of each trial. Shah and Findlay[46] conducted a small randomized trial comparing HFOV to CMV in patients with ARDS; the study was underpowered to detect clinically important treatment effects (RR, 0.87; 95% CI, 0.37-2.04). Mentzelopoulos et al[49] tested the efficacy of HFOV in combination with tracheal gas insufflation as a type of prolonged lung recruitment maneuver that was applied daily for several hours until prespecified oxygenation targets were achieved, at which point CMV was resumed. They reported that HFOV was associated with significant improvements in oxygenation, lung compliance, and lower mortality (RR, 0.59; 95% CI, 0.41-0.85).

A meta-analysis of these early trials reassuringly found that rates of barotrauma and hemodynamic instability were not significantly different between HFOV and CMV.[50] Complications related to severe hypercapnia and acidosis, as well as endotracheal tube obstruction consequent to accumulation of airway secretions, were no more frequent with HFOV, and HFOV was associated with an overall significant decrease in pooled mortality risk across these trials. Importantly, however, CMV management in some of these trials (published before the advent of lung-protective ventilation) was suboptimal, as $V_T$ limitation was not carefully specified.

OSCILLATE and OSCAR were large multicenter randomized trials carefully designed to rigorously evaluate whether HFOV improved survival in ARDS compared with optimal CMV. OSCILLATE enrolled adults with moderate or severe ARDS from 39 ICUs in several countries. HFOV was applied using recruitment maneuvers and relatively high mPaw (mean, 31 cm $H_2O$ on day 1) titrated according to the severity of hypoxemia. The CMV protocol used a low $V_T$ and a high PEEP strategy according to the Lung Open Ventilation Study (LOVS) protocol.[34] OSCILLATE was halted early after enrolling 548 of a planned 1,200 patients because mortality was significantly higher in the HFOV group compared with the group who received CMV (47% vs 35%; RR, 1.33; 95% CI, 1.09-1.64). Vasopressor use and net fluid balance was higher in the HFOV arm, suggesting that the HFOV strategy may have significantly impaired hemodynamics, which may possibly have contributed to the worsened outcome.

The OSCAR trial[44] enrolled 795 patients with moderate to severe ARDS in 29 ICUs (many of which had no prior experience with HFOV) in the United Kingdom. HFOV was titrated according to a complex algorithm with overall goals that were similar to those of OSCILLATE: lung recruitment for oxygenation and frequency reductions as needed to improve $CO_2$ clearance. mPaw was lower in OSCAR on study day 1 (mean, 26.9 cm $H_2O$) compared with OSCILLATE. Unlike OSCILLATE, OSCAR used a lower PEEP strategy in the CMV arm. There was no significant difference in mortality (41.7% in HFOV vs 41.1% in CMV; RR, 1.02; 95% CI, 0.86-1.20) and no significant difference in vasopressor requirements.

In an individual patient data meta-analysis of four trials of HFOV vs CMV (N = 1,552 patients),[51] the effect of HFOV on mortality varied with the baseline severity of hypoxemia. HFOV was associated with increased mortality in mild to moderate ARDS and a possible signal toward benefit in patients with the most severe hypoxemia (P/F ratio < 65 mm Hg). This finding supports the utility of HFOV as rescue therapy in patients with refractory hypoxemia. Of note, the same meta-analysis found that HFOV was associated with an increased risk of barotrauma as applied in those trials; high mPaw should generally be avoided and applied only with great caution and care.

## Why Did HFOV Fail to Reduce Mortality?

In view of the plausible biological rationale in favor of HFOV as a lung-protective strategy, the findings of OSCILLATE and OSCAR are both surprising and disappointing. Several explanations may be offered for the apparent discordance between experimental evidence and clinical outcomes.

### *Worsened Volutrauma*

The central appeal of HFOV is the possibility of applying a very small $V_T$ to limit mechanical stress and strain during ventilation. However, real-world delivery of HFOV does not always result in extremely low $V_T$. Hypercapnia and acidosis may mandate reductions in frequency that increase $V_T$ to levels approximating those applied during CMV.[21] Mean frequency in OSCILLATE was only 5.5 Hz and sometimes lower. Moreover,

applying $V_T$ in the range of 1 to 3 mL/kg PBW at these very high frequencies may actually increase the total energy delivered to the lung and propagate increased injury. Recent studies of the mechanical power on VILI suggest that respiratory frequency may be an underappreciated contributor to lung injury.[52] Despite very low $V_T$, high respiratory frequency (and consequently high energy levels) as applied with HFOV can cause cellular injury by influencing the elastic and frictional properties of pulmonary epithelium, leading to increased local stress,[53] edema formation,[54] and fracture of liquid bridges in airspaces.[55]

High mPaw is applied during HFOV to recruit the lung and improve oxygenation while reducing tidal mechanical stress by recruiting collapsed lung. Although experimental models generally exhibit significant and uniform recruitability, lung recruitment varies widely among patients in the clinical setting.[56] If high mPaw applied using HFOV fails to recruit atelectatic lung, the stress applied to lung regions already participating in ventilation greatly increases.[57,58] Basing HFOV titration on the open lung concept may therefore actually worsen VILI in patients with limited lung recruitability. Therefore, the effect of HFOV on outcome is likely dependent on the strategy for selecting mPaw.

### Revisiting the Atelectrauma Hypothesis

The use of high mPaw during HFOV is predicated on the goal of avoiding cyclic opening and closing of collapsed alveoli during ventilation. The small $V_T$ delivered by HFOV permits very high $mP_{aw}$ that almost certainly precludes end-expiratory derecruitment—this is a key "selling point" for HFOV.[42] However, as discussed earlier, the degree to which atelectrauma contributes to VILI is debated by experimentalists,[59] with conflicting evidence regarding the effect of high PEEP and outcomes for patients with ARDS.[34-36,38,60] The benefit of higher PEEP ventilation may be largely attributable to its effects on tidal lung stress (driving pressure).[33] Histologic and imaging studies suggest that lung injury and inflammation predominate in ventilated lung regions rather than at the interface between collapsed and ventilated regions.[61-63] Recent work suggests that the pressures required to avoid atelectrauma are sufficiently high to necessarily result in volutrauma[60]—the results of HFOV trials based on the open lung concept may serve as a case in point. These considerations call into question the relative importance of atelectrauma and suggest that the focus of HFOV delivery should be to minimize both static (end-inspiratory) and dynamic (tidal) stress.

### Deleterious Hemodynamic Effects of HFOV

HFOV can impair hemodynamics by decreasing preload and worsening right ventricular (RV) dysfunction (defined by Guervilly et al[64] as a RV end-diastolic area/left ventricular [LV] end-diastolic area [RVEDA/LVEDA] $> 0.6$ during HFOV).[44,45,65] Applying HFOV at a mPaw of 30 cm $H_2O$ increases right atrial pressure within 5 min of transition from CMV to HFOV, and after 30 min, pulmonary capillary wedge pressure is increased, whereas cardiac index and stroke volume are significantly decreased.[65] Elevated intracardiac pressures likely result from increased pleural pressure transmitted from the airways rather than a rise in transmural vascular pressure due to cardiac failure. These hemodynamic effects are primarily related to the airway pressures applied rather than to the mode of ventilation per se.[66]

High mPaw applied by HFOV has been shown to worsen RV function, as assessed by the ratio of RVEDA/LVEDA.[64] The importance of this adverse effect of HFOV is supported by the significant increase in vasopressor use and fluid balance with HFOV in the OSCILLATE trial, which may explain the increase in mortality with HFOV observed in that trial.[45] These reasons further suggest that the effect of HFOV on outcome depends on the strategy for selecting mPaw.

### Resonance Frequency of the Lung

To date, the consensus approach to HFOV aims to maximize frequency to minimize delivered $V_T$ and hence minimize mechanical stress and strain. Recent work suggests that the impact of high-frequency ventilation on dynamics of alveolar ventilation and gas transport in the lung may be considerably more complex than previously appreciated.[67] The lung exhibits a resonance frequency at which point gas transport becomes dependent on local tissue inertance rather than tissue elastance. Above this resonance frequency, ventilation heterogeneity can significantly increase, potentially worsening ventilation-perfusion mismatch and exacerbating hypoxemia[68]; this in turn may lead to increased airway pressure and $F_{IO_2}$ requirements (and possibly worsened VILI). Furthermore, applying HFOV at the lung resonance frequency may amplify the delivered $V_T$.[69] Lung resonant frequency likely varies between patients[70] and according to the severity of lung

injury; this factor may need to be considered to enhance the efficacy and safety of HFOV.

## Moving Forward: Using HFOV in 2017

Current evidence suggests no benefit in applying HFOV as an early strategy to prevent VILI in ARDS, and it is possibly even harmful. Given the specialized nature of the technique and the lack of evidence in support of benefit, its low rate of use worldwide (approximately 1% of cases) is unsurprising.[71] However, lessons learned from the foregoing discussion may be applied at the bedside to maximize the benefit of HFOV when applied as rescue therapy and may also suggest avenues of future investigation of HFOV as a lung-protective strategy (Table 2).[72-74]

First, HFOV is indisputably effective at improving oxygenation. This finding has been confirmed repeatedly in clinical trials. Accordingly, in clinical situations in which severe or refractory hypoxemia is thought to present a serious threat to life, the use of HFOV as rescue therapy should be considered. This recommendation is supported by the recently published individual patient data meta-analysis, suggesting that a mortality benefit exists for patients with a P/F ratio < 65 mm Hg.[51] HFOV should be considered only after (or in combination with) other interventions, such as prone ventilation and neuromuscular blockade, for which there is evidence of benefit.[75,76] HFOV should be applied with caution in patients with severe respiratory acidosis (pH < 7.23), as these patients are less likely to respond favorably.[77] Alternative rescue techniques, including extracorporeal membrane oxygenation, should be considered in such situations.

Second, the physiological response to HFOV should be carefully monitored, and these responses may be helpful to guide safer application of HFOV. We argued earlier that lung recruitment and RV loading are critical determinants of harm from HFOV. RV function can be monitored by echocardiography while applying HFOV. If evidence of RV strain or dysfunction develops (ie, decreased tricuspid annular plane systolic excursion, increased ratio of RVEDA to LVEDA), mPaw should be adjusted to avoid excess RV loading. A careful hemodynamic assessment and monitoring plan (including markers of tissue perfusion) are critical when applying HFOV, and clinicians should ensure that

**TABLE 2** ] Strategies to Monitor Important Physiological Responses to HFOV at the Bedside

| Effect of HFOV | Clinical Variable to Monitor | HFOV Setting to Modify |
|---|---|---|
| Lung recruitment | Improvement in $Pao_2/ F_{IO_2}$ within 3 h after HFOV application[43-45,72]<br>Lung ultrasonography[73]—resolution of consolidated lung fields after HFOV application | If inadequate improvement in $Pao_2/ F_{IO_2}$, consider increasing mPaw to a maximum of 30 cm $H_2O$ (bearing in mind possible hemodynamic effects)<br>If no improvement in $PaO_2/ F_{IO_2}$ at maximum tolerable mPaw within 3 h, consider returning to conventional ventilation |
| Excess right ventricular afterload | Transthoracic echocardiography—RVEDA/LVEDA > 0.6, decreased tricuspid annular systolic excursion, septal dyskinesis[64,66] | Consider lowering mPaw as tolerated by oxygenation to reduce right ventricular afterload |
| Decreased cardiac preload and cardiac output | Cardiac output response to passive leg raising[74] to assess intravascular volume status before applying HFOV<br>Markers of tissue perfusion include mixed or central venous oxygenation or lactate clearance | Consider lowering mPaw as tolerated by oxygenation to improve venous return<br>Consider fluid bolus or vasopressor infusion to maintain adequate venous return at increased mPaw |
| Excess pulmonary stress and strain | Potentially helpful to measure transpulmonary pressure[80]; if using esophageal manometry, we suggest targeting mPaw during HFOV to maintain mean quasi-static mean transpulmonary pressure between 0 and 15 cm $H_2O$ to avoid overdistending the lung while preventing significant atelectasis[80,81a] | Consider lowering or raising mPaw to achieve target quasi-static mean transpulmonary pressure |

RVEDA/LVEDA = right ventricular end diastolic area/left ventricular end diastolic area. See Table 1 legend for expansion of other abbreviations.
[a]Mean quasi-static transpulmonary pressure should be measured during an inspiratory hold; this target transpulmonary pressure range is intended to prevent atelectasis while maintaining lung volume at less than total lung capacity (to avoid overdistention) in the absence of specific data on optimal transpulmonary pressure targets.

intravascular volume status is corrected before applying HFOV. We suggest transitioning back to conventional ventilation if there is no improvement in oxygenation or deterioration in hemodynamics, or both.

The degree of lung recruitment obtained by applying HFOV should also be monitored. A variety of modalities for monitoring lung recruitment are available, although few have been evaluated in the context of HFOV. One simple approach is to track the magnitude of improvement in oxygenation after applying HFOV. The oxygenation response to increased PEEP has been shown to predict mortality in ARDS,[78] possibly because it reflects lung recruitment.[79] The oxygenation response to HFOV application also predicts mortality.[77] This improvement in oxygenation may reflect lung recruitment with attendant beneficial effects on the determinants of VILI. The absence of a favorable physiological response within 3 to 4 hours of initiating HFOV should prompt consideration of other ventilation adjuncts for severe hypoxemia.

Third, although carefully conducted multicenter trials designed to test the effect of HFOV on VILI in ARDS failed to demonstrate improved survival, the lung-protective potential of HFOV cannot be entirely ruled out, especially among severely hypoxemic patients.[51] As the importance of atelectrauma is debated, HFOV titration might be reconfigured to pay greater attention to limiting both dynamic and static strain while also considering lung resonance and hemodynamic function. Indeed, it seems prudent to avoid high mPaw in general when applying HFOV (ie, > 28-30 cm $H_2O$). One approach might be to titrate HFOV to target accepted limits of transpulmonary pressure (Fig 3). The feasibility of monitoring transpulmonary pressure was demonstrated in a recent study.[80] In this study, Guervilly et al[80] compared plateau transpulmonary pressure during conventional ventilation to mean transpulmonary pressure during HFOV at three different mPaw levels (5, 10, or 15 cm $H_2O$ greater than the $mP_{aw}$ obtained during conventional ventilation). Mean transpulmonary pressure was as high (or higher)

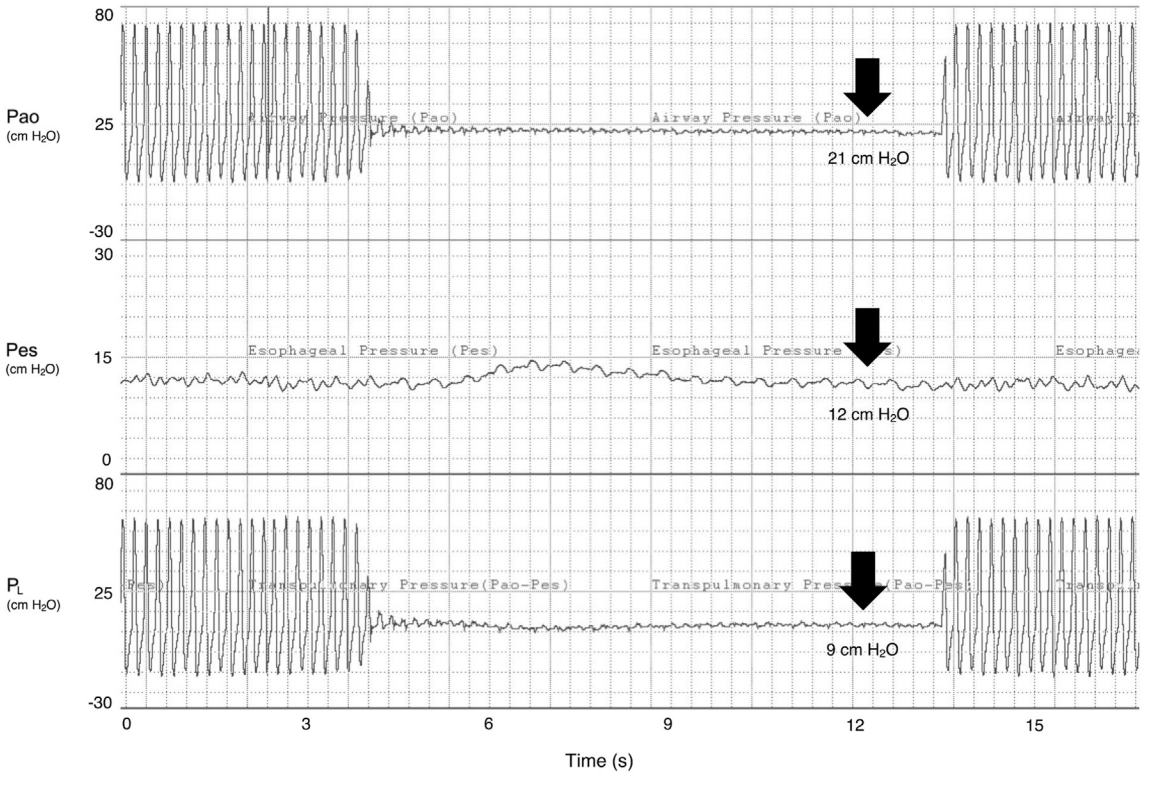


Figure 3 – *Transpulmonary pressure measurement during high-frequency oscillatory ventilation with set mean airway pressure of 26 cm $H_2O$. Airway opening pressure (Pao), esophageal pressure (Pes), and transpulmonary pressure (PL) are recorded after confirming proper balloon placement by the airway occlusion maneuver (not shown). $P_L$ is obtained by online digital subtraction of Pes from Pao. The airway is transiently occluded distal to the site of Pao measurement under relaxed conditions (sedation or paralysis, or both). During the occlusion, Pao is 21 cm $H_2O$ and Pes is 12 cm $H_2O$, giving a PL of 9 cm $H_2O$. Note that Pao measured during the airway occlusion is somewhat lower than the mean airway pressure during oscillation because some of the applied pressure is dissipated by airway resistance. Pao measured under static conditions during occlusion more accurately reflects alveolar pressure. Similarly, fluctuations in Pao during high-frequency oscillation are much higher than fluctuations in alveolar pressure, as evidenced by the relatively stable Pes during oscillation. Pao = pressure at the airway opening; Pes = esophageal pressure; $P_L$ = transpulmonary pressure.*

during HFOV as the plateau transpulmonary pressure obtained during conventional ventilation. In this study, mean transpulmonary pressure always fell to < 25 cm $H_2O$ (the accepted upper limit for lung stress), but these pressures may nevertheless be injurious under HFOV, because this level of lung stress is applied continuously rather than intermittently. Perhaps titrating mPaw sufficiently to merely maintain a positive transpulmonary pressure would reduce lung strain and avoid volutrauma and hemodynamic impairment while achieving acceptable recruitment and oxygenation (Fig 3). The ongoing study, Esophageal Pressure-Guided Optimal PEEP/mPaw in CMV and HFOV: The EPOCH Study (EPOCH)[81] (ClinicalTrials.gov NCT02342756), comparing a strategy of preventing atelectrauma with a transpulmonary pressure of 0 cm $H_2O$ at end expiration to a lung recruitment strategy targeting a transpulmonary pressure of 15 cm $H_2O$ in a cross-over design using both conventional ventilation and HFOV may help address this question. It is noteworthy that such considerations recapitulate the early debate over low vs high pressure strategies for HFOV recounted by Bryan.[1]

## Conclusions

HFOV is a unique and physiologically fascinating mode of ventilation. Studies of HFOV have advanced our understanding of the mechanisms of ventilation and ventilator-induced lung injury. Despite its theoretically ideal features for lung-protective ventilation, high-quality clinical trials do not support the use of HFOV as a lung-protective strategy in ARDS. Nevertheless, HFOV remains an important and effective adjunctive mode of ventilatory support in refractory hypoxemia.[51] When choosing to use HFOV, one must closely monitor cardiorespiratory function and appreciate the risk of barotrauma and hemodynamic impairment associated with the use of high mPaw. Given its complexity, the technique should not be used in the absence of training or local expertise. Clinicians should monitor RV function and other physiological responses and integrate this information with guidance from previously published protocols to titrate HFOV safely.

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