

High-frequency oscillatory ventilation and ventilator-induced lung injury

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Introduction: Although mechanical ventilation is lifesaving for patients with acute respiratory distress syndrome, it can cause ventilator-induced lung injury. To minimize ventilator-induced lung injury, different ventilatory strategies have been developed. One of the strategies is the use of high-frequency oscillatory ventilation (HFOV).

Theoretical Backgrounds of Ventilator-Induced Lung Injury and HFOV: Because of the novel gas exchange mechanisms, HFOV can provide adequate gas exchange using extremely small tidal volumes and maintain high end-expiratory lung volume without inducing overdistension, which should result in minimization of ventilator-induced lung injury.

Studies of HFOV and Lung Injury: There are convincing clinical and animal data indicating that HFOV is an ideal lung-protective ventilatory strategy, particularly in the setting of neonatal respiratory failure, if lung volume recruitment is performed.

Clinical Implication of HFOV in Adult Acute Respiratory Distress Syndrome: A recent clinical trial demonstrated early (<16 hrs) improvement in oxygenation with HFOV and a 30-day mortality of 37% with HFOV vs. 52% with pressure-controlled ventilation ($p = .102$), suggesting that HFOV is as effective and safe as the conventional strategy in adult acute respiratory distress syndrome. Future studies examining optimal algorithms of HFOV using clinically relevant animal models, and patients with acute respiratory distress syndrome, are imperative to determine whether the wide-spread application of HFOV is warranted in adult acute respiratory distress syndrome. (Crit Care Med 2005; 33[Suppl.]:S129-S134)

KEY WORDS: high-frequency oscillatory ventilation; ventilator-induced lung injury; acute respiratory distress syndrome; animal models

Acute respiratory distress syndrome (ARDS) is the most severe form of acute lung injury and has a mortality rate of at least 30%. No effective drugs exist to treat ARDS, and therapy is largely supportive with mechanical ventilation. Although mechanical ventilation is often lifesaving for patients with ARDS, mechanical ventilation can cause lung injury, a concept that has been termed ventilator-induced lung injury (VILI). In an attempt to minimize the detrimental consequences of VILI, scientists and clinicians have been studying different ventilatory strategies. One form of ventilation that has garnered significant interest is the use of high-frequency oscillatory ventilation (HFOV) in patients with various forms of respiratory distress syndrome. This article will review a number of concepts related to VILI and, specifi-

cally, how HFOV might fit into the clinician's armamentarium for the ventilation of patients with respiratory distress syndrome.

VILI and HFOV: Theoretical Considerations

There are a number of mechanisms that can lead to development of VILI, including gross air leaks (barotrauma), diffuse alveolar injury due to overdistension (volutrauma), injury due to repeated cycles of recruitment/derecruitment (atelectrauma) (Fig. 1), and the most subtle form of injury due to the release of mediators from the lung (biotrauma) (Fig. 2) (1-3). Lungs of patients with ARDS are heterogeneously damaged, and hence, mechanical ventilation with normal or even low tidal volumes can lead to regional lung injury. Recruitment/derecruitment denotes the situation whereby alveolar units open during inspiration and collapse again during expiration. The repetitive cycling in which lung units open and collapse again during expiration results in high shear stress, which can further injure the lungs. Reducing the magnitude of these cyclic fluctuations and application of higher positive end-expiratory pressure (PEEP) levels can

minimize VILI (4, 5). Based on these concepts, various "lung-protective" strategies have been developed to minimize VILI. One strategy uses relatively small tidal volumes and PEEP titrated to a few centimeters of H₂O above the lower inflection point (P_{inf}) on the pressure-volume curve (6, 7). In 2000, the ARDS Net investigators reported a 9% decrease in absolute mortality of patients with ARDS using a lung-protective strategy using a small tidal volume (6 mL/kg predicted body weight) with a PEEP that averaged ~10 cm H₂O (8).

Within this context, HFOV can be viewed as providing alveolar ventilation with very small tidal volumes and thus, theoretically, could be viewed as providing the optimal lung-protective ventilatory strategy. HFOV has novel gas exchange mechanisms that contribute to better oxygenation and CO₂ removal. Bulk convection and diffusion are the main mechanisms of gas exchange during conventional mechanical ventilation (CMV), whereas interregional gas mixing between units with different time constants (pendelluft), convective transport attributable to asymmetry between inspiratory and expiratory velocity profiles, and longitudinal dispersion due to interaction between the axial velocity profile

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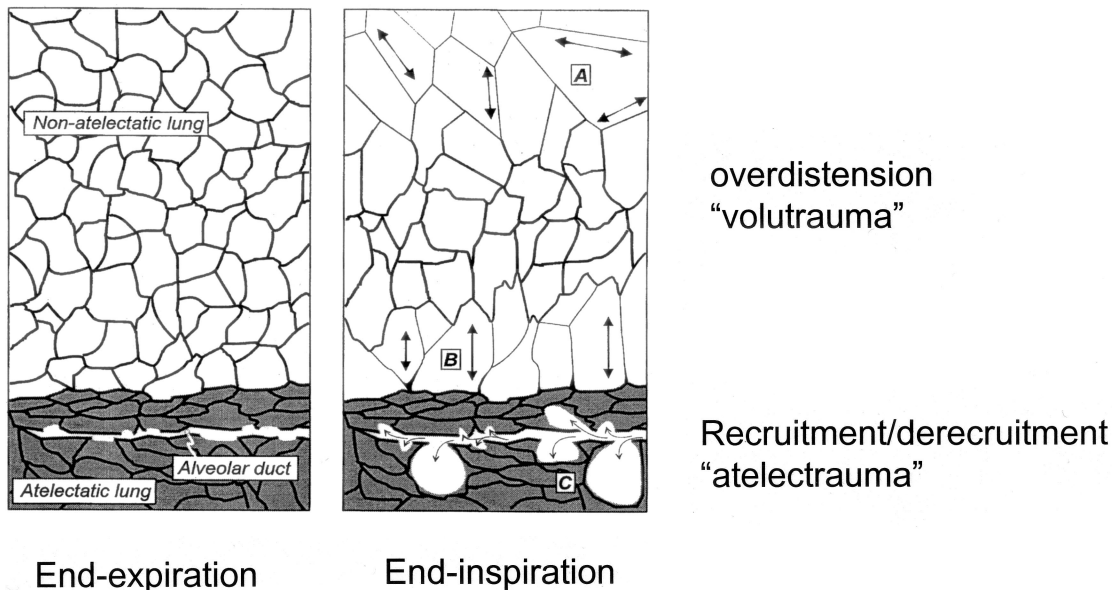


Figure 1. Overdistension (volutrauma) and recruitment/derecruitment (atelectrauma). Overdistension (volutrauma) develops when inspired air preferably distributes to the areas with higher compliance (nonatelectatic regions). Recruitment/derecruitment denotes the situation whereby alveolar units open during inspiration and collapse again during expiration in atelectatic regions. This cycle of repeated opening and collapse results in high shear stress that can further injure the lungs (atelectrauma), in particular at end-expiration. Reproduced with permission from Frank JA, Imai Y, Slutsky AS: Pathogenesis of ventilator-induced lung injury. *Physiological Basis of Ventilatory Support* [Marcel Dekker] 2003.

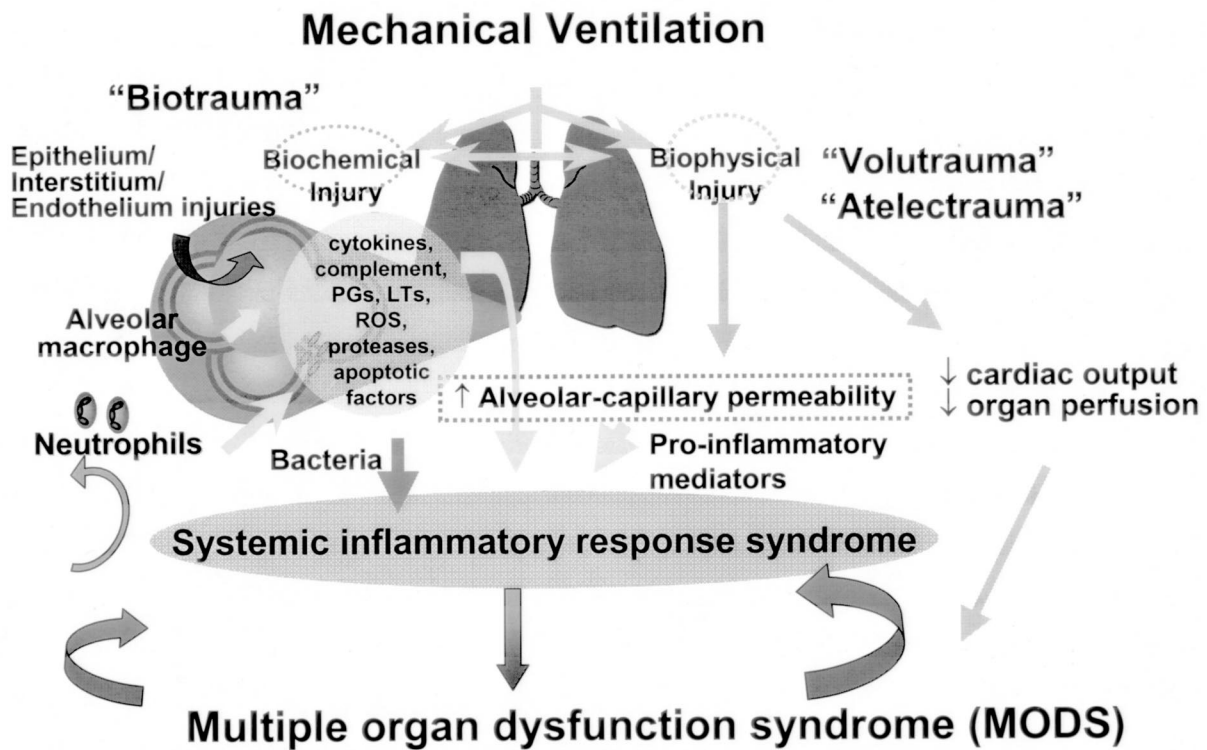


Figure 2. Postulated mechanisms whereby volutrauma, atelectrauma, and biotrauma caused by mechanical ventilation contribute to multiple organ dysfunction syndrome (MODS). The potential importance of biotrauma is not only that it can aggravate ongoing lung injury, but also that it can contribute to the development of MODS, possibly through the release of proinflammatory mediators from the lung. Adapted with permission from Slutsky and Tremblay (2).

and radial concentration gradient (Taylor's dispersion) also play an important role during HFOV (Fig. 3) (9–11). Because of these mechanisms, adequate gas exchange during HFOV is possible with

extremely small tidal volumes, often less than the anatomic dead space (1–3 mL/kg). In addition, during HFOV, it is possible to maintain relatively high end-expiratory lung volume, without inducing overdisten-

sion. HFOV may have a larger margin of safety in keeping the lung open within the desired target range of alveolar overdistension in heterogeneously injured ARDS lungs (12) (Fig. 4).

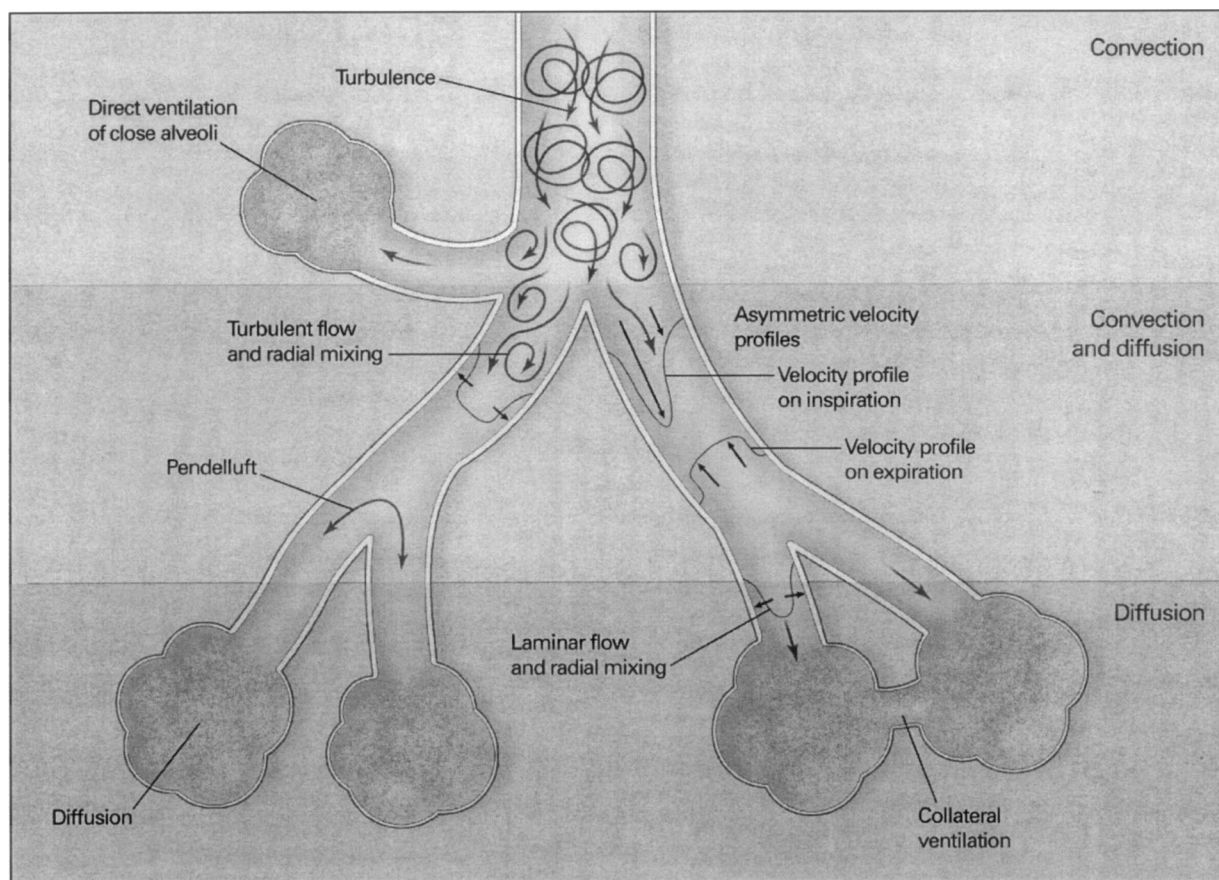


Figure 3. Gas transport mechanisms during high-frequency oscillatory ventilation. Bulk convection and diffusion are the main mechanisms of gas exchange during conventional mechanical ventilation. Interregional gas mixing between units with different time constants (pendelluft), convective transport attributable to asymmetry between inspiratory and expiratory velocity profiles, and longitudinal dispersion due to interaction between the axial velocity profile and radial concentration gradient (Taylor's dispersion) also play a important role during HFO ventilation. Reproduced with permission from Slutsky and Drazen (11).

Venegas and Fredberg (13) developed a theoretical model to determine the optimal ventilatory variables in patients with lung disease. They formulated the problem of developing an optimal ventilatory strategy by dividing it into two simpler problems: 1) examination of the factors related to pressure cost per unit of convective oscillatory flow and 2) the convective flow cost necessary to achieve a unit of alveolar ventilation. They obtained simple solutions for these two functions. Their model included models of gas exchange and lung mechanics, including the effects of lung inflation tidal volume and respiratory frequency in alveolar ventilation, nonlinear lung tissue compliance, and alveolar recruitment and derecruitment. They then determined the putative detrimental effects of high-frequency ventilation as a function of the ventilatory settings and the pathophysiologic variables of the patient. Their model predicted that for respiratory distress syndrome (RDS) in neonates, the selected PEEP level was critical because detrimental consequences were increased at both high

and low values of PEEP. Of interest, in the infant respiratory distress syndrome patient, the choice of which respiratory frequency to use was not as critical for frequencies of >10 Hz. The analysis supported the use of high-frequency ventilation in infant respiratory distress syndrome and of ensuring adequate end-expiratory pressure. Their model predicted that the range of "safe" frequency-PEEP combinations would be relatively narrow and move to higher frequencies as lung compliance decreases. Also, if similar tidal volumes and levels of PEEP were applied at conventional frequencies (<50 breaths/min), CO_2 clearance would be compromised. These data provide a theoretical background for the putative advantages of HFOV in the treatment of patients with ARDS.

HFOV and Studies of Lung Injury

There are a number of animal studies demonstrating reduced VILI with HFOV. A

number of studies that laid the groundwork for our current understanding of HFOV and VILI were published in the 1980s and early 1990s by the Toronto group led by Bryan and Froese. Kolton et al. (14) examined CMV and HFOV in models of oleic acid injury and lung lavage. They found that when HFOV was combined with a sustained inflation (i.e., recruitment maneuver), there were larger mean lung volumes and improved oxygenation with HFOV. They suggested that this approach of a recruitment maneuver and high mean airway pressures during HFOV could "more fully exploit the pressure volume hysteresis of unstable lung units than CMV." Hamilton et al. (15) examined oxygenation and lung pathology in rabbits with saline lavage-induced lung injury, ventilated with HFOV or CMV. HFOV provided marked improvements in oxygenation over 5 hrs, and most importantly, the animals treated with HFOV had markedly attenuated lung injury as assessed by hyaline membranes. They concluded that "avoidance of low lung volume and large pressure-volume changes

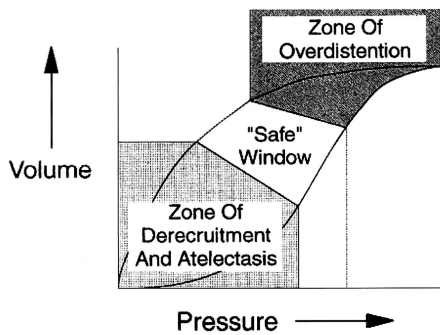


Figure 4. Pressure–volume curve of a moderately diseased lung, such as one with adult acute respiratory distress syndrome. Two hazard zones exist; overdistension and derecruitment and atelectasis. High end-expiratory pressures and small tidal volumes are needed to stay in the “safe” window. High-frequency oscillatory ventilation may have a larger margin of safety in keeping the lung open within the desired target range of alveolar overdistension. Reproduced with permission from Froese (12).

through the use of HFOV results in reduced pulmonary damage.” This critical concept in the use of HFOV to mitigate VILI is still valid today.

McCulloch et al. (16) addressed the issue of whether the use of high mean airway pressures was important during HFOV. They ventilated rabbits after lung lavage using three different strategies: HFOV at high mean lung volume, HFOV at low mean lung volume, and CMV at a low mean lung volume. The latter two groups ventilated at low lung volumes had lower respiratory system compliance, more hyaline membranes, and more severe airway epithelial damage. These data demonstrated that maintenance of an adequately high mean lung volume is critical to minimize the lung injury caused by mechanical ventilation, and they also emphasized the importance of appropriate lung recruitment during HFOV.

In 1987, Delemos et al. (17) used a very clinically relevant model of premature baboons with hyaline membrane disease and reported that HFOV at 10 Hz resulted in decreased pulmonary barotrauma compared with CMV. Meredith et al. (18) used the same premature baboon model and reported that application of HFOV for 24 hrs protected animals from lung injury as assessed by gas exchange, lung mechanics, morphologic findings, and measurements of platelet-activating factor compared with CMV (peak inspiratory pressure, 31.4–45.0 cm H₂O; PEEP, 4.0–6.9 cm H₂O). Using saline-lavaged adult rabbits, Matsuoka et al. (19) dem-

onstrated that HFOV led to decreased respiratory burst of neutrophil activation compared with CMV (peak inspiratory pressure, 25 cm H₂O; PEEP, 5 cm H₂O). Imai et al. (20) used the same model and found that HFOV, as opposed to CMV (peak inspiratory pressure, 25 cm H₂O; PEEP, 5 cm H₂O), led to decreased production of platelet-activating factor and thromboxane-A₂ in lung. Furthermore, Takata et al. (21) confirmed that only 1 hr of HFOV produced less tumor necrosis factor- α messenger RNA in intra-alveolar cells compared with CMV (peak inspiratory pressure, 28 cm H₂O; PEEP, 5 cm H₂O) in the same model. Very recently, using a surfactant-depleted piglet model, von der Hardt et al. (22) demonstrated that messenger RNA expression of cytokines (interleukin [IL]-1 β , IL-6, IL-8, and IL-10), transforming growth factor- β 1, endothelin-1, and adhesion molecules (E-selectin, P-selectin, intercellular adhesion molecule-1) in lung tissue and IL-8 expression in microdissected alveolar macrophages were highly reduced with HFOV compared with CMV (peak inspiratory pressure, 38 cm H₂O; PEEP, 8 cm H₂O), suggesting HFOV can reduce pulmonary inflammatory response.

All of these data from various animal studies indicate that HFOV can reduce VILI compared with CMV with conventional ventilatory strategies (nonprotective ventilatory strategies). However, early clinical trials targeting neonates were unable to demonstrate the superiority of HFOV over CMV, even when CMV was used with a nonprotective ventilatory strategy (23). There was no benefit of HFOV in the High-Frequency Intervention (HIFI) study (23), and HFOV was associated with an increased prevalence of air leak, intracranial hemorrhage, and periventricular leukomalacia. It was suggested that this lack of benefit was related to the lack of an adequate volume recruitment strategy inherent in the protocols (24). Later studies using a volume recruitment strategy demonstrated improved gas exchange, reductions in barotrauma, and overall improved outcome in neonatal patients receiving HFOV (25–27). Using volume recruitment maneuvers, HFOV maintains end-expiratory lung volume higher up on the deflation pressure–volume relationship without inducing simultaneous overdistension because of the much smaller tidal volume used. This should result in minimal stretch injury generated by the pressure amplitude excursions.

Many of the animal studies described above were performed before the widespread use of protective ventilatory strategies using CMV, so a critical question is: does HFOV have a protective advantage from VILI over CMV with protective ventilatory strategies? To address this issue, we conducted a study using a rabbit-lung lavage model (28). Because there is no consensus on what constitutes the optimal (protective) strategy with CMV, we chose two strategies that have been shown to decrease mortality in two recent randomized, controlled trials: 1) a strategy similar to that used by Amato et al. (6) in which the PEEP was set 2–3 cm H₂O greater than the lower P_{inf} base on the inflation limb of the pressure–volume curve (6, 7) and 2) a strategy similar to the ARDSNet trial (8) using small tidal volumes and PEEP of \sim 10 cm H₂O. The first strategy that used PEEP > P_{inf} led to hypotension and barotraumas, suggesting that a strategy with PEEP above P_{inf} may not be always possible during CMV because of hemodynamic compromise and possible barotrauma. In addition, the validity of this approach has been questioned because the lung is often not fully recruited, even if PEEP > P_{inf}, and it does not take into account the effect of the chest wall on P_{inf}. The second strategy that was similar to that used in the ARDSNet trial (8) fulfilled two criteria for an adequate lung-protective strategy: plateau pressure of <30 cm H₂O and PaO₂ of >300 Torr, indicating adequate recruitment. We found that HFOV attenuated the decrease in pulmonary compliance, lung inflammation assessed by polymorphonuclear leukocyte infiltration and tumor necrosis factor- α concentration in the alveolar space, and pathologic changes of the small airways and alveoli, whereas CMV, with a strategy similar to the ARDSNet trial, only attenuated the decrease in oxygenation and pulmonary compliance (Fig. 5). These data suggest that HFOV may have a larger margin of safety in keeping the lung open within the desired target range of alveolar overdistension, and thus, HFOV may have advantages over CMV with respect to VILI, even when CMV is used with a protective ventilatory strategy.

HFOV: Clinical Implications in Adult ARDS

As described above, there are convincing clinical and animal data indicating that HFOV can lead to reduced VILI, par-

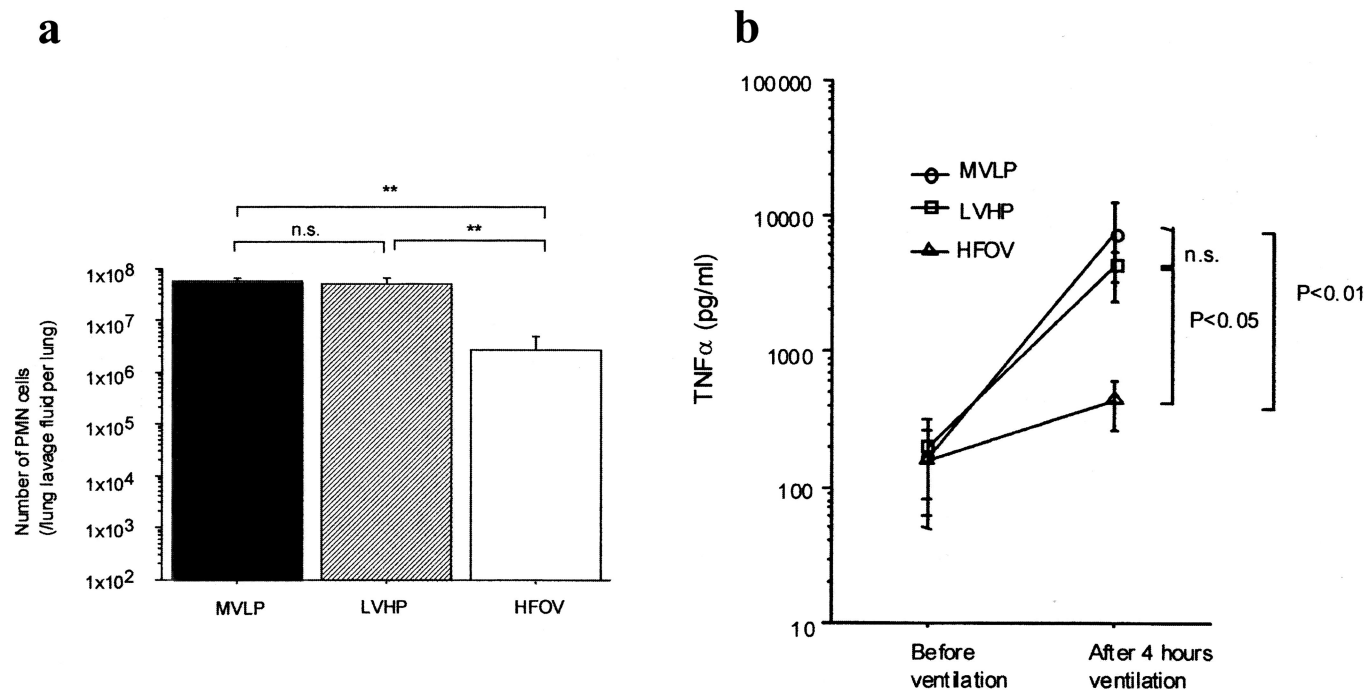


Figure 5. *a*, Numbers of polymorphonuclear leukocyte (PMN) cells in the lung lavage fluid. Values are mean \pm SD. Numbers of PMN cells were significantly higher in the moderate tidal volume and low positive end-expiratory pressure (MVLP) and low tidal volume and high positive end-expiratory pressure (LVHP) groups than in the high-frequency oscillatory ventilation (HFOV) group. $**p < .01$ compared with HFOV group; *n.s.*, not significant. *b*, Levels of tumor necrosis factor- α (TNF- α) in the lung lavage fluid before ventilation and at termination of ventilation in the MVLP, LVHP, and HFOV groups. Values are mean \pm SD. $*p < .05$ compared with HFOV. $**p < .01$ compared with HFOV. Levels of TNF- α after ventilation were higher in the MVLP and LVHP groups than in the HFOV group, and no significant differences were seen between MVLP and LVHP groups. Reproduced with permission from Imai et al (28).

ticularly in the setting of neonatal respiratory failure. Can HFOV also reduce VILI in adult patients with ARDS? The limitations of applying the previous studies to adult patients are that the previous animal studies used higher frequency (e.g., 15 Hz), lower ΔP (amplitude), and smaller uncuffed endotracheal tube sizes (e.g., ≤ 4 mm) than are typically used in adult patients. Proximal oscillatory pressure (ΔP) transmitted to the distal alveoli depends on multiple variables, including endotracheal tube diameter, respiratory frequency, percentage of inspiratory time, airway resistance, lung compliance, and gravitational factors (e.g., lower vs. upper lobe). Respiratory mechanics have a significant influence on the intrapulmonary oscillatory pressure (ΔP) during HFOV (29). Low lung compliance can result in significant increases in distal oscillatory pressure transmission, approaching 20–30% of proximal airway pressure amplitudes. Conversely, increases in peripheral airway resistance may decrease oscillatory pressure transmission to the distal alveolar compartment while increasing pressure excursions in the central airways (e.g.,

trachea). Also, changing the percentage of inspiratory time (e.g., from 33% to 50%) may influence oxygenation and ventilation by increasing the distal alveolar pressure and delivered tidal volume. These concepts suggest that development of optimal techniques for achieving oxygenation and ventilation (i.e., frequency, ΔP), percentage of inspiratory time, mean airway pressure) are critical for improving clinical outcomes with HFOV in adult ARDS.

In this perspective, studies to examine the optimal techniques of HFOV using a clinically relevant animal model for adult ARDS (e.g., acid aspiration-induced or cecal ligation/perforation-induced) using large animals (e.g., pig or sheep) are important for clinical application of HFOV to adult ARDS. Clinicians are now faced with the challenge of translating the putative advantages of HFOV into a provable effect on clinical outcome in adult ARDS. Early studies by Fort et al. (30) and Mehta et al. (31) focused on the use of HFOV as a rescue therapy ($n = 17-42$), with patients being administered HFOV only when CMV was observed to be failing. They demonstrated that mean airway

pressure could be safely maintained at a higher level with HFOV and that oxygenation improved with HFOV. These reports also suggested that early initiation (2 days) of HFOV is more likely to result in improved survival than delayed initiation (>7 days). A recently published clinical trial, the Multicenter Oscillatory Ventilation For Acute Respiratory Distress Syndrome Trial (MOAT, $n = 148$), comparing HFOV with a pressure-controlled ventilation strategy (P_{aO_2}/F_{iO_2} ratio of ≤ 200 mm Hg on PEEP of >10 cm H₂O) demonstrated early (<16 hrs) improvement in P_{aO_2}/F_{iO_2} ($p = .008$) in the HFOV group but no significant difference in oxygenation index during the initial 72 hrs of treatment (32). Thirty-day mortality was 37% in the HFOV group and 52% in the conventional ventilation group ($p = .102$). There was no significant difference between treatment groups in the prevalence of barotrauma, hemodynamic instability, or mucus plugging. These studies suggest that HFOV is as effective and safe as the conventional strategy in patients with ARDS. Conclusions

HFOV is a ventilatory technique that can provide adequate gas exchange using

very small tidal volumes. This allows one to ventilate patients at relatively high mean lung volumes, minimizing the risks of volutrauma and of atelectrauma. Animal data are quite convincing that HFOV is an ideal lung-protective ventilatory strategy, but there is a paucity of clinical data supporting this contention in humans, especially in studies in which a protective CMV ventilatory strategy is used. Such studies are required before we fully understand the role of HFOV in the treatment of our most difficult ventilator-dependent patients.

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