

Clinical use of high-frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome

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Objective: High-frequency oscillatory ventilation (HFOV) is an emerging ventilatory strategy for adults that has been used successfully in the neonatal and pediatric population. This modality utilizes high mean airway pressures to maintain an open lung and low tidal volumes at a high frequency that allow for adequate ventilation while at the same time preventing alveolar overdistension. With the current understanding that excessive lung stretch and inadequate end-expiratory ventilatory volume may be injurious to the lungs, HFOV seems to be the ideal lung-protective ventilatory mode. During the past 8 yrs, there have been increasing numbers of studies describing its use in adult patients with acute respiratory distress syndrome. This article aims to review the published studies of HFOV in adults with acute respiratory distress syndrome with regard to its safety and efficacy.

Data Source: To assist us with our review, we did a search of MEDLINE (from 1966 to present) and EMBASE (1980 to present) databases to identify adult, clinical, English-language, research articles related to HFOV use. In addition, we reviewed relevant animal and mechanical ventilation studies. We did not perform a formal systematic review.

Data Synthesis: The application of HFOV was mainly reported as a rescue ventilatory mode in adult patients with acute respiratory distress syndrome who were thought to have failed conventional ventilation. In these patients, HFOV has consistently

been shown to improve oxygenation without obvious increases in complications measured. There was only one randomized, controlled trial comparing HFOV with conventional ventilation. This study showed that there was a nonsignificant trend toward a lower mortality rate in the HFOV group. In addition, HFOV was as effective and safe as conventional ventilation. Although there are limitations, multiple studies have shown that earlier initiation of HFOV in patients with severe acute respiratory distress syndrome may also be associated with a lower mortality.

Conclusions: HFOV seems to be safe and effective for adults with severe acute respiratory distress syndrome who have failed conventional ventilation. Further research is needed to determine the ideal patients, timing, and optimal technique with which to provide HFOV. When considering HFOV as an early, lung-protective mode of ventilation, there is still a need to perform an adequately powered, randomized, controlled trial comparing it with the best available form of conventional ventilation. However, we believe that such a trial should wait until we have a better understanding of HFOV in adults. (Crit Care Med 2005; 33[Suppl.]:S170–S174)

KEY WORDS: acute respiratory distress syndrome; high-frequency ventilation; high-frequency oscillatory ventilation; mechanical ventilation; respiratory failure; ventilator-induced lung injury; mortality; recruitment maneuver

With the publication of a randomized, controlled trial documenting the efficacy of a low-tidal volume (\dot{V}_T) ventilatory strategy in reducing mortality compared with a higher \dot{V}_T strategy, there has been renewed appreciation that mechanical ventilation in a patient with acute respiratory distress syndrome (ARDS), although necessary, is often injurious and may contribute to further lung damage (1, 2). Positive-pressure ventilation may injure the lung via several different mechanisms, includ-

ing alveolar overdistension (volutrauma), repeated closing and opening of collapsed alveolar units (atelectrauma), and oxygen toxicity (3). In addition, these mechanisms seem to lead to the release of proinflammatory cytokines, which further perpetuate the ongoing lung damage and may have a role in multiple organ dysfunction syndrome, which is often encountered in these patients (4, 5).

An understanding of these processes has led to the search for ventilatory strategies that are “lung-protective” (i.e., further lung injury is minimized while still maintaining adequate oxygenation and support to off-load the respiratory muscles). This involves the use of limited \dot{V}_T to avoid alveolar overdistension, adequate end-expiratory lung volumes utilizing positive end-expiratory pressure (PEEP), and higher mean airway pressures (maws) to minimize atelectrauma and

improve oxygenation. In a randomized, controlled trial conducted by the National Institutes of Health’s ARDS Network, a ventilatory strategy using conventional ventilation (CV), low tidal volumes ($\dot{V}_T \leq 6$ mL/kg predicted body weight) and limited inspiratory plateau pressures (≤ 30 cm H₂O) was associated with an absolute reduction in mortality of 9% when compared with a larger \dot{V}_T strategy (target, 12 mL/kg) (2). Although this is exciting, there are still patients with ARDS who are unable to achieve adequate gas exchange while receiving CV, and the mortality rate of these patients remains high (6).

High-frequency oscillatory ventilation (HFOV) is a unique mode of mechanical ventilation first used successfully in the neonatal population (7–9). It is characterized by rapid oscillations of a reciprocating diaphragm, leading to high-

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respiratory cycle frequencies, usually between 3 and 9 Hz in adults, and very low \dot{V}_T . Although no data in adult patients with ARDS exist as yet, measurements in a sheep model of ARDS suggests that \dot{V}_T delivered during HFOV is about 1–4 mL/kg, depending on the frequency (10). HFOV is conceptually very attractive, as it achieves many of the goals of lung-protective ventilation. The application of a constant mPaw maintains an “open lung” and optimizes lung recruitment. Ventilation in HFOV is primarily achieved by oscillations of air around the set mPaw, usually at much lower \dot{V}_T s than those achieved with CV, thus theoretically avoiding alveolar overdistension. The mechanism of ventilation during high-frequency ventilation is significantly different from CV and is described elsewhere (11). Importantly, unlike other forms of high-frequency ventilation, expiration is active during HFOV. This is likely an essential mechanism in the prevention of gas trapping and the optimization of ventilation.

Comparative studies in animals indeed suggest that HFOV reduces ventilator-induced lung injury (12, 13). Imai et al. compared pathophysiologic and biochemical markers of acute lung injury in a saline-lavaged rabbit model of ARDS with different ventilatory strategies: a control group utilizing CV with moderate \dot{V}_T (10–12 mL/kg) and three different lung-protective strategies: 1) low \dot{V}_T (5–6 mL/kg) with PEEP 2–3 cm H₂O higher than the lower inflection point utilizing CV, 2) low \dot{V}_T with PEEP of 8–10 cm H₂O, and 3) HFOV (12). The group utilizing HFOV had lower neutrophil infiltration, lower levels of tumor necrosis factor, and decreased pathologic changes in the alveolar spaces when compared with the other lung-protective groups.

In addition, as higher mPaws are achievable with HFOV when compared with CV, HFOV could theoretically lead to improvements in oxygenation and, in turn, a reduction in F_{IO_2} . Certainly, in the neonatal literature, the use of HFOV has been associated with improvements in oxygenation, a decrease in surfactant use, and possibly, a decrease in lung injury as assessed by a reduction in the need for supplemental oxygen and a lower roentgenographic score at 30 days (7, 9).

In view of the success of HFOV in the neonatal and pediatric population and of its theoretical physiologic advantages in regard to lung-protective ventilation, there has been accumulating interest in

the application of this ventilatory mode in adult patients with ARDS. This article aims to review the published experience with HFOV in adult patients with ARDS. We will describe the safety and efficacy of this relatively new mode of ventilation in terms of its complications and clinically relevant outcomes.

Clinical Studies of HFOV in Adult Patients

The first study we reviewed described HFOV use in 17 adult patients with ARDS, mainly due to sepsis and pneumonia, who failed CV (14). Failure of mechanical ventilation was defined by any one of the following criteria: an F_{IO_2} of ≥ 0.7 with a P_{aO_2} of ≤ 65 mm Hg, a peak inspiratory pressure of >65 cm H₂O, or a PEEP of ≥ 15 cm H₂O. The patients had a mean P_{aO_2}/F_{IO_2} ratio of 68.6 mm Hg, a mean oxygenation index ($OI = F_{IO_2} \times mPaw \times 100/P_{aO_2}$) of 48.56, and a mean Acute Physiology and Chronic Health Evaluation (APACHE) II score of 23.3. Thirteen of the patients had an improvement in the P_{aO_2}/F_{IO_2} ratio and the OI. At 30 days, nine patients did not survive (53% mortality), with four patients dying of respiratory failure.

Subsequent to this study, a number of other authors published their experience with HFOV (Table 1) (15–19). All of these studies have several similar characteristics. First, the number of patients was generally small, ranging between 5 and 42. Second, most of the patients had ARDS secondary to pneumonia or sepsis, although two of the studies looked specifically at patients with multiple trauma and burns, respectively (15, 17). Third, HFOV was primarily employed as a rescue mode of ventilation for patients who had failed CV. As such, the severity of lung injury was higher than that reported in other studies of ventilatory modes in ARDS, with P_{aO_2}/F_{IO_2} ratios ranging from 68.6 to 114 (2, 4, 20). Fourth, the strategies used to implement HFOV were similar; the mPaw was set at 5 cm H₂O above the last mPaw measured while receiving CV, the mPaw was then titrated upward at 2–3 cm H₂O increments until an F_{IO_2} of ≤ 0.6 or Sp_{O_2} of $\geq 92\%$ was achieved with a reasonable mPaw, and initial frequency was at 4–5 Hz and bias flow at between 30–40 L/min.

All of these studies showed that the utilization of HFOV led to an improvement in oxygenation. This was not entirely surprising, as one of the main ad-

vantages of HFOV over CV is the ability to employ higher mPaws, leading to higher end-expiratory lung volumes and better recruitment. Despite the ability to improve gas exchange, mortality rates were relatively high, ranging from 20% to 83.3%. Given that these studies were uncontrolled, it is difficult to make conclusions from these rates. Certainly, a high mortality rate is not surprising because failure to respond to CV reflects a patient population with a greater severity of illness. For example, the mean APACHE II scores in the studies by Mehta et al. (16) and David et al. (19) were 21.5 and 28, respectively. In addition, two of the studies had patients with severe burns or were recipients of bone-marrow transplants, factors associated with an increased mortality (16, 17). Indeed, combining these two studies, patients with severe burns had a 90.9% mortality rate. Consistent with other studies of outcomes in ARDS, only a minority of patients receiving HFOV died because of respiratory failure (21). Nevertheless, this observation may be impressive when one considers the fact that most of these patients had failed CV.

The largest case series so far was published recently by Mehta et al (22). They retrospectively reviewed the experience with HFOV in 156 adult patients with severe ARDS at three academic, teaching hospitals. The patients had a mean age of 48 yrs, were severely ill (mean APACHE II, 23.8), and had severe ARDS (mean P_{aO_2}/F_{IO_2} ratio of 91 mm Hg and OI of 31). Again, HFOV was generally employed as a rescue therapy. They found significant improvements in the P_{aO_2}/F_{IO_2} ratio and the OI, but they had a 30-day mortality rate of 61.7%. Independent predictors of mortality on multivariate analysis were older age, higher APACHE II score, lower pH, and a greater number of days receiving CV before HFOV. Twenty-six percent of patients had HFOV discontinued because of difficulties with oxygenation, ventilation, or hemodynamics. Importantly, we believe this study demonstrates that similar results can be obtained in multiple centers.

Thus far, there has only been one prospective, randomized trial comparing the safety and efficiency of HFOV with CV in adults with ARDS. Derdak et al. (23) randomized 148 adults, in 13 university-affiliated medical centers, with ARDS to HFOV or CV utilizing pressure-controlled ventilation. Patients had a mean age of 49.5 yrs, APACHE II score of 22, and

Table 1. Comparison of studies evaluating the use of high-frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome

Author (Reference No.)	Study Design	Patients	Mortality	Death Due to Respiratory Failure, %	Selected Complications
Fort et al. (14)	Prospective, observational	17 patients Mean age, 38 yrs PaO ₂ /FIO ₂ ratio, 68.6 OI, 48.6 APACHE II score, 23.3	30-day mortality rate, 53%	33.0	3 (17.6%) patients withdrawn from HFOV because of hypotension
Claridge et al. (15)	Prospective, observational	5 patients (all trauma) Mean age, 36.6 yrs PaO ₂ /FIO ₂ ratio, 52.2 APACHE II score, 28.5	Mortality rate, 20%	0	None reported
Mehta et al. (16)	Prospective, observational	24 patients Mean age, 48.5 yrs PaO ₂ /FIO ₂ ratio, 98.8 OI, 32.5 APACHE II score, 21.5	30-day mortality rate, 66%	6.25	2 patients (8.3%) had pneumothoraces
Cartotto et al. (17)	Retrospective	6 patients (all burns) Mean age, 34 yrs PaO ₂ /FIO ₂ ratio, 92 OI, 32 APACHE II score, 16	Mortality rate, 83.3%	0	Not reported
Derdak et al. (23)	Randomized, controlled trial	148 patients Mean age, 49.5 yrs PaO ₂ /FIO ₂ ratio, 112.5 OI, 25.2 APACHE II score, 22	30-day mortality was 37% in the HFOV group and 52% in the CV group	16.0 in both arms	Similar in both groups
Andersen et al. (18)	Retrospective	16 patients Mean age, 38.2 yrs PaO ₂ /FIO ₂ ratio, 92 OI, 28.1 SAPS II, 40.3	Mortality rate, 31.2% at 3 mos	Not reported	1 patient (6.3%) had a pneumothorax
David et al. (19)	Prospective, observational	42 patients Median age, 49 yrs PaO ₂ /FIO ₂ ratio, 94 OI, 23 APACHE II score, 28	30-day mortality rate, 43%	33.3	1 patient (2.4%) had a pneumothorax
Mehta et al. (22)	Retrospective	156 patients Median age, 47.8 yrs PaO ₂ /FIO ₂ ratio, 91 OI, 31.2 APACHE II score, 23.8	30-day mortality rate, 61.7%	Not reported	34 patients (21.8%) had a pneumothorax

OI, oxygenation index (FIO₂ × mean airway pressure × 100/PaO₂); APACHE, Acute Physiology and Chronic Health Evaluation score; HFOV, high-frequency oscillatory ventilation; SAPS, Simplified Acute Physiology Score, CV, conventional ventilation.

similar PaO₂/FIO₂ ratios (114 ± 37 in the HFOV group and 111 ± 42 in the CV group). The authors found an earlier improvement in the PaO₂/FIO₂ ratio (<16 hrs) in the HFOV group; however, this difference did not persist beyond 24 hrs. There were a similar number of adverse events in both groups (intractable hypotension, 0% in the HFOV group and 3% in the CV group; air leak, 9% and 12%; mucus-plugged endotracheal tube, 5% and 4%, respectively). It was interesting

that there was a nonsignificant trend toward a lower 30-day mortality in the HFOV group (37% vs. 52%, *p* = .102). It would be attractive to postulate that the mortality difference could be due to the reduction in ventilator-induced lung injury among the patients receiving HFOV. However, as this study was primarily a safety and efficacy study, it was not adequately powered to detect a mortality difference. The authors have also been criticized for using relatively large \dot{V}_T s (of up

to 10 mL/kg) that led to high Paws (38 ± 9 cm H₂O at 48 hrs) in the control group, in comparison with \dot{V}_T s of 6 mL/kg, now considered a standard of care (3). It is important to bear in mind that this study was conducted before the publication of the ARDS Network trial, which demonstrated a survival benefit among patients ventilated with a lower \dot{V}_T strategy (2).

Adjunctive Therapies to HFOV. If HFOV fails to improve oxygenation in the adult patient with ARDS or the patient

subsequently deteriorates, other adjunctive therapies, including prone positioning and inhaled nitric oxide, have been reported to be used successfully to improve gas exchange (24, 25). In a study of 23 adults with ARDS by Mehta et al. (24), titrated inhaled nitric oxide at doses between 5 and 20 ppm during HFOV increased $\text{PaO}_2/\text{FiO}_2$ by 38% at 30 mins in 19 of those patients (83%). The intensive care unit survival was only 39%, an observation that may not be surprising considering that these patients had been deemed to fail CV and were also deteriorating while receiving HFOV.

Recently, recruitment maneuvers in combination with HFOV have been shown to be safe and result in rapid and sustained improvements in oxygenation when compared with CV (26). Furthermore, because of the earlier improvement in oxygenation when compared with other studies of HFOV, it is possible that the effects of recruitment maneuvers are, at the very least, additive.

Overall, the effect of these adjunctive therapies on further ventilator-induced lung injury, duration of mechanical ventilation, and mortality remains to be defined. Further research also needs to be done on patient selection and ideal timing in applying these adjuncts to HFOV.

Predictors of Mortality Among Patients Receiving HFOV. Many of the studies showed that a delay in initiating HFOV was a predictor of death (14, 16, 19, 22). For example, in the study by Fort et al. (14), the mean duration of CV in the survivors was 2.5 days, as compared with 7.2 days in the nonsurvivors ($p < .09$). A similar finding was later reported by Mehta et al. (16) (1.6 days vs. 7.8 days, respectively). In addition, David et al. (19) found a greater 30-day mortality in patients ventilated with CV for ≥ 3 days before commencing HFOV (64% vs. 20%). A subsequent study involving 156 patients also found that a higher number of days receiving CV before HFOV independently predicted mortality in a multivariable analysis (22). It is possible that these observations may have been confounded by both a greater severity of illness and lung injury in the nonsurvivor group. For instance, in the study by Fort et al. (14), nonsurvivors had higher mean APACHE II scores (27.17 vs. 20.0 in the survivor group), OI (60.0 vs. 34.0), and Lung Injury Scores (3.92 vs. 3.69) at baseline. However, Mehta et al. (16) found similar baseline APACHE II and Lung Injury Scores in both groups.

Multiple animal studies have also shown that exposure to excessive \dot{V}_T s and insufficient PEEP to prevent repeated alveolar collapse could further exacerbate the ongoing lung injury (27–29). In addition, exposure to excessive airway pressures has been shown to increase the levels of proinflammatory cytokines and has been implicated in the development of multiple organ failure (4, 5). Thus, it is attractive to postulate that a longer duration of exposure to CV could have led to worsening lung injury, perhaps multiple organ failure, and hence, a higher mortality. As mentioned before, in the randomized trial by Derdak et al. (23) comparing the safety and efficacy, there was a trend toward a lower mortality in the HFOV group. Nevertheless, the reader needs to bear in mind that patients with ARDS who have severe illness early in their intensive care unit course (and thus need HFOV earlier) may have an entirely different prognosis than those who have severe illness later. Clearly, the hypothesis that patients with severe ARDS may derive benefit from earlier intervention with HFOV is worthwhile in testing in a prospective, randomized fashion.

Some of the studies have also identified the OI as a predictor of mortality (14, 22, 23). Fort et al. (14) found that a baseline OI > 47 was predictive of death, with 100% sensitivity and 100% specificity. In addition, both Derdak et al. (23) and Mehta et al. (22) found that the posttreatment OI was also important. For example, in a multivariable analysis, the OI at 24 hrs after commencing HFOV was found to be the most significant predictor of mortality (22). This is not entirely unexpected, as the OI has also been found to be an independent predictor of mortality in the pediatric literature studying the utility of HFOV and in adult patients receiving CV (7, 30, 31). The OI may be more powerful than traditional indices like the $\text{PaO}_2/\text{FiO}_2$ ratio, as it assesses the “pressure cost” of oxygenation.

Other variables that have been shown to correlate independently with survival include the age of the patient, pH, and the APACHE II score (22, 23). Unfortunately these predictors of poor outcome have not been substantiated to the point that they can be incorporated into decisions around ongoing care.

Complications of HFOV. The complications reported with the use of HFOV are generally low (Table 1). These are usually related to barotrauma or hemodynamic compromise. For example, in

the series by Mehta et al. (16), two patients (8.3%) had pneumothoraces. In one of these patients, the pneumothorax could possibly be related to a right main bronchus intubation. However, in a later retrospective study involving a larger group of patients, again by Mehta et al. (22), they found a much higher prevalence of pneumothoraces (21.8%). This rate is higher than that reported in other studies evaluating HFOV and also in studies evaluating conventional ventilatory strategies (2, 14–19, 23, 32). The reason for the higher rate remains unclear. There were no obvious differences in the way HFOV was employed compared with the other studies. Differences in ventilatory strategies and patient populations across the different centers may have led to greater barotrauma.

The higher mPaws utilized during HFOV could conceivably impede venous return and lead to hypotension. However, this complication seemed to be uncommon, and only one study documented significant hypotension after the initiation of HFOV (14). In this study, HFOV was withdrawn from three patients (17.6%) because of hypotension. In one of these patients, the hypotension was attributed to postoperative bleeding. In patients with a pulmonary artery catheter *in situ*, the utilization of HFOV has been associated with an increase in central venous pressure and pulmonary artery occlusion pressure and a small decrease in cardiac output (14, 16, 22, 23). As an example, in the randomized study by Derdak et al. (23), the central venous pressure increased from 14 mm Hg at baseline to 16 mm Hg at 2 hrs. The corresponding values for the pulmonary artery occlusion pressure were 16 mm Hg and 18 mm Hg. For cardiac output, they were 7.4 L/min and 7.0 L/min. Most of these changes were transient, as only the pulmonary artery occlusion pressure remained significantly increased after 3 days. The increase in central venous pressure and pulmonary artery occlusion pressure likely reflected the increase in mPaw. The relevance of the small decrease in cardiac output is unclear, particularly given that the cardiac output remained within normal or supernormal range, and it did not seem to be associated with a decrease in mean arterial pressure or increase in heart rate (22, 23). However, in our experience, clinicians do need to be aware that as the mPaw increases, techniques to improve the cardiac output (e.g., intravascular

volume loading) may need to be employed.

Mucus inspissation is a potential problem, which could cause endotracheal tube obstruction and refractory hypercapnia (6). It should be suspected in an otherwise stable patient who has had a sudden increase in PCO_2 . Fortunately, the prevalence of this complication is relatively low (4–5%) and not reported by all the studies (14, 16). The extent that frequent airway suctioning, chest physiotherapy, or fluid instillation into the airway ameliorates this is uncertain. In the randomized study by Derdak et al. (23), the frequency of endotracheal tube occlusion requiring a tube change was similar in both the HFOV and the CV groups, at about 5% and 4%, respectively.

Conclusions

HFOV has been shown to be a safe and effective mode of ventilation in adult patients with severe ARDS who have failed CV. Earlier initiation of HFOV in adult patients with ARDS seems to be at least as safe as CV, and preliminary data suggest that there may be a survival advantage. Future research should be geared toward identifying patients who may benefit from early initiation of HFOV and the best technique with which to utilize it. Finally, although we are encouraged by the data we have reviewed, HFOV for adults with ARDS is still in its infancy, and we look forward to its continued evaluation.

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