Does High-Frequency Ventilation Offer Benefits Over Conventional Ventilation in Adult Patients With Acute Respiratory Distress Syndrome?

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High-frequency ventilation is the application of mechanical ventilation with a respiratory rate > 100 breaths/min. High-frequency oscillatory ventilation (HFOV) is the form of high-frequency ventilation most widely used in adult critical care. The principles of lung-protective ventilation have matured in parallel with the technology for HFOV. The 2 basic principles of lung-protective ventilation are the use of small tidal volume and maintenance of adequate alveolar recruitment. Research in animal models and humans demonstrate that HFOV can support gas exchange with much smaller tidal volume than can be achieved with conventional ventilation. HFOV also provides more effective lung recruitment than conventional mechanical ventilation. However, at present,

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evidence is lacking that survival in adults with acute respiratory distress syndrome is improved by HFOV. Although HFOV may improve P_{aO_2} in some patients, this improvement is often transitory. Available evidence does not support that pulmonary inflammation is reduced with HFOV in adult acute respiratory distress syndrome. Heavy sedation and often paralysis are necessary. The promise of HFOV as a lung-protective ventilation strategy remains attractive, but additional clinical trials are needed to determine whether this approach is superior to lung-protective ventilation with conventional mechanical ventilation. *Key words: acute lung injury, acute respiratory distress syndrome, high-frequency oscillatory ventilation, high-frequency ventilation, lung-protective ventilation, mechanical ventilation.* [Respir Care 2007;52(5):595–605. © 2007 Daedalus Enterprises]

Introduction

High-frequency ventilation can be generically defined as any application of mechanical ventilation with a respiratory rate that exceeds 100 breaths/min. This may be achieved with small tidal volume (V_T) and rapid respiratory rate with a conventional mechanical ventilator, high-frequency percussive ventilation, various forms of external chest oscillation, high-frequency jet ventilation, or high-frequency oscillatory ventilation (HFOV). High-frequency jet ventilation and HFOV are the most technically mature. In particular, HFOV is currently the form of high-frequency ventilation most widely used in adult critical care, and probably the most widely studied. A ventilator that provides HFOV has been U.S. Food and Drug Administration approved and sold in the United States since 2001. Therefore, this debate will focus on HFOV.

Studies of high-frequency ventilation in its various formats have been carried out for over 30 years. During the 1980s there was intensive study of the mechanisms of gas exchange when the V_T is smaller than the anatomic dead space, as it often is during high-frequency ventilation. Clinical studies in adults at that time were mostly small physiologic studies or clinical case series.[1–4] The science of clinical application advanced somewhat more rapidly in neonatology, where several large multicenter randomized controlled trials were completed in the 1980s and early 1990s.[5–8] Many of these early trials, most notably the High-Frequency Ventilation in Premature Infants trial,[5] were undertaken in an era in which high-frequency ventilation was attractive primarily for its ability to correct hypoxemia. There was relatively little appreciation of the role of ventilator-induced lung injury[9] in the genesis or perpetuation of multiple-organ system failure and mortality in acute respiratory distress syndrome (ARDS). The concepts and principles of lung-protective ventilation have since matured in parallel with the technology for HFOV. Only recently have those principles become foremost in the design of clinical trials of high-frequency ventilation.[10]

Strategies for lung-protective ventilation are designed to respect 2 principles. First, it has been well established on the basis of numerous animal and human trials that alveolar overdistension will induce injury.[11–16] Overdistension can induce injury in normal alveoli[12,14] and can also exacerbate injury or prevent recovery in lungs already injured by another insult.[16,17] Alveolar injury can also be amplified or perpetuated when injured lung regions are allowed to close and reopen during tidal breathing.[12,16,17] Thus, the second principle of lung-protective ventilation is to avoid repetitive closure and opening of alveoli. This may be achieved through procedures that attempt to recruit alveoli and maintain recruitment, a strategy that has been termed an "open lung approach."[18,19]

The biomechanical forces that cause alveolar injury, either from overdistension or from repetitive opening and closing, also prompt an inflammatory response.[16,20,21] This response is systemic and contributes to failure of other organ systems and ultimately to mortality. Thus, the goal of lung-protective ventilation is not merely improved gas exchange, but, rather, the clinically important outcomes of improved organ function, decreased time on mechanical ventilation, and improved survival.

HFOV appears ideally suited to support these principles of lung-protective ventilation. It provides a relatively high mean airway pressure, which may recruit the lung more effectively than positive end-expiratory pressure (PEEP) as typically set on a conventional ventilator. It also provides very small V_T. This should both minimize the risk of overdistension during inspiration and minimize the opportunities for derecruitment during expiration. The idealized, hypothetical application of HFOV is one in which small V_T occur within a zone of safe lung volumes, where risks of both derecruitment and overdistension are minimal.[22]

Nevertheless, controversy persists over whether the goals of lung-protective ventilation and the desired outcome of improved survival can be achieved with HFOV. There are several reasons why this uncertainty lingers. First, V_T is technically difficult to measure[23,24] and is not monitored during HFOV. Although it is assumed that V_T are smaller than during lung-protective use of a conventional ventilator, the extent to which this is true with the HFOV adult ventilator in clinical use is not known quantitatively. Furthermore, even if V_T is smaller, the V_T is applied several hundred times per minute. It is assumed that the greater

safety of smaller breaths is not countermanded by their greater frequency. In addition, HFOV is commonly used in adults with ARDS at relatively high mean airway pressure.[10,25–28] While this favors the goal of recruitment, it often subjects injured lungs at the midpoint of the HFOV respiratory cycle to a pressure that would be considered dangerous at end-inspiration of a conventional ventilator cycle. Finally, the epiphenomena of HFOV include the potential for circulatory depression from high airway pressure and the need for heavy sedation or paralysis during HFOV. Even if HFOV decreases ventilator-induced lung injury, these or other lugubrious effects may outweigh its benefits.

The net balance of the potentially beneficial and potentially harmful aspects of HFOV would be easily settled if there were large definitive clinical trials in adults with ARDS. However, such trials are lacking, and the literature on HFOV in adults is largely case series and physiologic studies.[10,25–28] There are more extensive data in neonatology, where numerous randomized clinical trials have been completed over the past 25 years. However, data from neonatology cannot be extrapolated with confidence to adult medicine because of the dissimilarity of disease states (respiratory distress of a newborn vs ARDS) and different ventilator settings and respiratory care equipment. The neonatal literature has been the subject of 2 recent meta-analyses.[29,30] Study designs have been heterogeneous, and even superficially similar studies have had subtle protocol differences that may have led to differing findings.[31,32] There has also been substantial evolution of nonventilatory care in neonatology during this period, including the widespread use of surfactant replacement. The meta-analyses of studies in neonatology have shown no effect on mortality and only modest improvement in the prevalence of chronic lung disease at full gestational age.[29,30] To the extent that these findings may foreshadow those in adult critical care, the benefits of HFOV compared to lung-protective conventional ventilation may be slight, and may require large and carefully planned studies to demonstrate.

In the absence of definitive human data, it is necessary to extrapolate from animal studies. However, in addition to inter-species differences, different models of lung injury may be more or less susceptible to aggravation by mechanical ventilation. Some models, such as saline lavage, are highly recruitable, and that may minimize differences between ventilator modes. Adding further complexity, it is clear that HFOV may be applied in such a way as to minimize its beneficial effects,[33] and conventional ventilation may be applied in such a way as to mimic many of the putative advantages of HFOV.[34] Thus, the question of whether high-frequency ventilation offers benefits over conventional ventilation remains open to debate.

Pro: HFOV Offers Benefits Over Conventional Ventilation in Adult Patients With ARDS

Principles of Lung-Protective Ventilation

While definitive clinical trials in adults await completion, there are nevertheless substantial data that HFOV is lung-protective, and more lung-protective than the best-practice application of conventional ventilation. The principles of lung-protective ventilation are to decrease the V_T, improve lung recruitment, and thereby decrease lung inflammation and injury. The literature clearly shows that each of these goals is achieved with HFOV.

Small V_T

The importance of smaller V_T is most definitively supported by the study of the ARDS Network, which compared 2 V_T during conventional ventilation.[16] A V_T of 6 mL/kg predicted body weight decreased mortality in adult ARDS, compared to a V_T of 12 mL/kg predicted body weight. Although that study made no attempt to ferret out the ideal V_T, a reasonable and rational conclusion is that smaller V_T are better than larger V_T. That is a fundamental assumption upon which rests the current interest in HFOV. The first step in that chain of logic is to prove that HFOV V_T are actually smaller than those used with lung-protective conventional ventilation.

Many of the available human data on delivered V_T during HFOV are from studies of neonates.[23,35,36] However, neonates are ventilated through small and uncuffed endotracheal tubes. Neonates are typically ventilated at very much higher frequencies (10–15 Hz) than used in adults (3–6 Hz), and they have very different lung and chest wall mechanics than adults. Therefore, the very small V_T reported in neonates could well be irrelevant to adult medicine.

Large animal studies may provide a more suitable comparison. Sedeek et al[37] used the commercially available adult high-frequency oscillator to ventilate sheep that averaged 29 kg, through an 8 mm endotracheal tube. The lungs were injured with saline lavage, and a recruitment maneuver was used prior to oscillation. With a pressure amplitude of 60 cm H_2O and a frequency of 4–6 Hz, the measured V_T was 3–4 mL/kg body weight. Though that V_T is small, it approaches the V_T that may be used during lung-protective ventilation with a conventional ventilator. Direct extrapolation to human ARDS is limited by the highly recruitable nature of the lung injury model and the limited range of pressure amplitudes tested, which did not exceed 60 cm H_2O. However, these V_T substantially exceeded the 25–50 mL V_T range that was studied with early generations of high-frequency ventilators in which V_T could be controlled.[2] If V_T as large as these routinely occur

during HFOV in adults, then one of the putative benefits of this mode may be only slightly better than conventional approaches.

With a mechanical lung model in which compliance and resistance could be altered, Hager et al conducted bench testing of how various patient characteristics and ventilator settings affect V_T during HFOV.[38] V_T was measured with a heated-wire anemometer that had been carefully calibrated and validated for use with the high-frequency oscillator.[24] Measured V_T varied with the pressure amplitude and varied strongly with the frequency. At a pressure amplitude of 90 cm H_2O and a frequency of only 4 Hz, V_T was 200 mL. At 10 Hz, the V_T fell to about 80 mL, even at the pressure amplitude of 90 cm H_2O. Additional measurements were made in 6 patients with severe ARDS who were receiving HFOV. Among the patients studied, pressure amplitude varied from 50 cm H_2O to 100 cm H_2O, and frequency ranged from 3 Hz to 14 Hz. The largest V_T measured under any condition was seen in one patient whose settings were increased to 100 cm H_2O and 3 Hz. This V_T was less than 180 mL. Among all the patients, V_T ranged between 50 mL and 130 mL with the settings (chosen by the treating physicians) that had provided acceptable gas exchange. Thus, data both from the lung model and from adults with ARDS showed that V_T during HFOV is substantially less than the V_T used during lung-protective conventional ventilation. The V_T were in the range of 1–2 mL/kg predicted body weight, which is a V_T that could not be delivered at conventional rates without an unacceptable level of respiratory acidosis. These small V_T are favored if HFOV is used at high frequencies, higher than typically suggested.[10,25,26,28] If one accepts the premise that smaller V_T is preferred, then HFOV would be the preferred mode of delivering smaller V_T.

Improved Alveolar Recruitment

The second key principle of lung-protective ventilation is alveolar recruitment. This may also be achieved quite effectively with HFOV. One of the early studies that demonstrated this was by McCulloch et al in 1988.[33] They studied rabbits with lavage-injured lungs. The animals were divided into 3 groups. The conventional ventilation group was ventilated with a peak airway pressure that averaged 32 cm H_2O and 8 cm H_2O PEEP. This would correspond to a plateau pressure that some would argue falls within a safe range,[39] and a PEEP that is commonly used in patients with ARDS.[16] HFOV was used in 2 groups of animals. The first group was set at a relatively high pressure, targeting a high P_{aO_2}. The mean airway pressure in that group averaged 18 cm H_2O, and was nearly identical to the mean airway pressure in the group that received conventional ventilation. The second HFOV group targeted a lower P_{aO_2} goal, and achieved that with a mean airway pressure of only about 10 cm H_2O. All 3 groups were treated with identical recruitment maneuvers whenever oxygenation fell below the established target. At the end of the period of mechanical ventilation, the end-expiratory lung volume was measured relative to the functional residual capacity (FRC) at zero PEEP. This quantified the extent of recruitment. The group that received conventional mechanical ventilation with a mean of about 8 cm H_2O PEEP had an end-expiratory lung volume 4 mL/kg above FRC. The group that received HFOV at a low mean airway pressure, despite that low mean airway pressure, had an end-expiratory lung volume that was 8 mL/kg above FRC. The HFOV group ventilated at a higher pressure (but at mean airway pressure that would still be low compared to typical patients with ARDS on HFOV) had an end-expiratory lung volume 23 mL/kg above FRC. Many other studies in animals have confirmed that HFOV, set at a mean airway pressure comparable to conventional mechanical ventilation, results in greater alveolar recruitment (based on measurement of oxygenation, compliance, or volume).[40–45] Furthermore, in clinical use, mean airway pressure on HFOV is typically set above its value during conventional ventilation.[10,25,28] This should yield still better recruitment.

Although oxygenation typically changes in parallel with recruitment when airway pressure is changed, the relationship between P_{aO_2} and lung volume is highly nonlinear, and oxygenation will not reveal areas where overdistension may be occurring. A more direct and detailed way to measure lung recruitment is volumetric computed tomography. Unfortunately, there are no complete publications of recruitment measured with computed tomography during HFOV. However, Luecke et al reported some preliminary findings in a review article on the topic.[46] They studied 8 patients with ARDS (4 from pneumonia and 4 from sepsis). Patients were ventilated at baseline with pressure-controlled ventilation, with a peak airway pressure $\leq$ 35 cm H_2O and a PEEP of 15 cm H_2O. No recruitment maneuver was performed. Patients were begun on HFOV an average of 4.4 days into their course of ARDS. HFOV was initiated without a recruitment maneuver, at an average mean airway pressure of 28 cm H_2O and a frequency of 5 Hz. The computed tomograms were obtained during an end-inspiratory hold, while on conventional ventilation (the point in the respiratory cycle when recruitment would be maximum). Scanning was repeated on HFOV after 48 hours. This study showed substantial increases in the total lung volume, and particularly in the volume of normally aerated lung tissue, which increased by nearly a liter. There was a significant decrease in the volume of poorly aerated lung tissue. There were small (approximately 50 mL), nonsignificant increases in the volume of overinflated lung. Thus, the limited available data in adults with ARDS show that 48 hours of HFOV are much more effective at recruiting the lung, without causing overinfla-

tion, than are 4 days of conventional ventilation with a relatively generous level of PEEP.

Decreased Lung Inflammation

Smaller V_T and better recruitment are only the first links in the chain leading to improved ARDS survival. The next steps are to show that HFOV results in less lung inflammation and injury. This has also been demonstrated in numerous studies. These studies have included measurement of hyaline membranes or bronchiolar epithelial injury,[33,40] and inflammation, such as polymorphonuclear influx and activation.[44,45] However, many of these studies used conventional mechanical ventilation and HFOV matched for mean airway pressure. Inevitably, this results in a relatively low PEEP during conventional ventilation, which may unfairly bias such studies toward HFOV, since they do not replicate the contemporary lung-protective use of conventional ventilation with more generous PEEP.

However, 2 studies have attempted to compare the ventilation modes while using the conventional ventilator to its best advantage. Sedeek et al studied adult sheep injured with saline lung lavage.[34] Following injury, all the animals had aggressive recruitment maneuvers to 50 cm H_2O, which were repeated until the P_{aO_2} on 100% oxygen exceeded 400 mm Hg. This assured a baseline degree of alveolar recruitment. To sustain that recruitment, PEEP (on conventional ventilation) or mean airway pressure (on HFOV) was carefully titrated to the minimum level that preserved oxygenation. This was assumed to represent a "shoulder" on the lung-deflation pressure-volume relationship, below which derecruitment would rapidly occur. After the titration was complete, the conventionally ventilated animals received pressure-controlled ventilation with a peak pressure maintained below 35 cm H_2O, and approximately 20 cm H_2O PEEP. These settings yielded a V_T of 9 mL/kg. The animals that received HFOV had a mean airway pressure of 20 cm H_2O, which is close to the PEEP level in the conventionally ventilated group. This is not unexpected, since the end-expiratory alveolar pressure during HFOV was probably only slightly less than the mean airway pressure. They were ventilated at 8 Hz with a pressure amplitude of 50 cm H_2O, which yielded V_T of approximately 2 mL/kg. After 4 hours of mechanical ventilation, the animals underwent lung mechanics studies, detailed quantitative histological examination of lung samples, and regional bronchoalveolar lavage in dependent and nondependent lung regions for cell counts and measurement of interleukin-1 and interleukin-8.

Using conventional ventilation in this fashion to aggressively maximize lung recruitment reduced many of the differences between the ventilator modes. There was no significant difference between conventional ventilation and HFOV in measures of oxygenation, lung compliance, leukocyte or polymorphonuclear cell counts, or cytokine levels. However, the lungs of animals ventilated with HFOV showed significantly less interstitial hemorrhage and alveolar septal expansion. There were also trends toward less alveolar hemorrhage, proteinaceous exudate, and granulocytes. Thus, aggressive efforts at lung recruitment with a conventional ventilator can attenuate some of the differences between modes. However, the high-frequency oscillator still produces less histological injury after only 4 hours of use.

The second study was performed in saline-lavaged rabbits, all of which also received a recruitment maneuver before being randomized to one of 3 mechanical ventilation groups.[43] One conventionally ventilated group received generous V_T of 10–12 mL/kg with low PEEP (4–5 cm H_2O). The second conventionally ventilated group received V_T of 5–6 mL/kg and 9–10 cm H_2O PEEP. This group protocol was designed to mimic the lung-protective mechanical ventilation applied in the small-V_T arm of the ARDS Network trial.[16] The authors also attempted to study a third conventionally ventilated group of rabbits, in which PEEP was set to exceed the lower inflection point on the lung pressure-volume relationship. However, this style of lung-protective ventilation resulted in shock or barotrauma in most of the animals, and had to be abandoned. The final group studied was HFOV, at a frequency of 15 Hz and a mean airway pressure of 15 cm H_2O. Measured outcomes included gas exchange, lung compliance, bronchoalveolar lavage fluid (BALF) cell counts, cytokines, and lung histology. Respiratory-system compliance was better preserved in the group that received HFOV than in the group that received small V_T and high-PEEP conventional mechanical ventilation. In the HFOV group, the BALF tumor necrosis factor alpha level and the polymorphonuclear cell count was lower than in either of the conventionally ventilated groups. There was also less histological alveolar and bronchiolar injury. Thus, even compared to the best lung-protective application of conventional mechanical ventilation, HFOV consistently showed less lung injury and inflammation.

Summary of the Pro-HFOV Position

In summary, 2 decades of research in animal models and humans demonstrate that HFOV can support gas exchange with much smaller V_T than can be achieved with a conventional ventilator. It also provides much more effective lung recruitment than conventional mechanical ventilation. These are the 2 basic principles of lung-protective ventilation. As one would expect, based on those basic mechanical factors, 2 decades of research have consistently shown less lung inflammation and injury with HFOV. Although we eagerly await the definitive clinical trials, available data clearly demonstrated that high-frequency

ventilation offers benefits over conventional ventilation in adult patients with ARDS.

Con: HFOV Offers No Benefit Over Conventional Ventilation in Adult Patients With ARDS

Strength of the Evidence

Much of the evidence related to the use of HFOV in adults is in the form of small observational trials.[25,26,28,47–56] These are simple single-center retrospective or prospective uncontrolled reports. Observational studies are generally not considered reliable, high-level evidence. Although these studies suggest that HFOV *can* be used in adult patients with ARDS, the absence of a control group means these studies do not provide sufficient evidence that HFOV *should* be used in this patient population. In addition to the observational studies, there is one well-done human physiologic study of the effects of HFOV on alveolar inflammation.[57] There are only 2 randomized controlled trials of HFOV versus conventional ventilation.[10,27] Thus, the evidence base that supports HFOV in adults with ARDS is, at best, modest.

Rescue Therapy

In the observational trials, HFOV was typically used in the setting of "failed conventional ventilation." But, on closer inspection, it becomes clear that this means no more than failure to meet the oxygenation targets set by the authors. For example, Mehta et al[51] considered use of HFOV in patients with ARDS who had $P_{aO_2} \leq 65$ mm Hg with fraction of inspired oxygen (F_{IO_2}) ≥ 0.6, or plateau pressure ≥ 35 cm H_2O. Fort et al[25] used HFOV in patients with ARDS when F_{IO_2} was ≥ 0.7 with a $P_{aO_2} \leq 65$ mm Hg, a peak inspiratory pressure of ≥ 65 cm H_2O, or PEEP ≥ 15 cm H_2O. Thus, "failed mechanical ventilation" was, more precisely, merely a relative failure of oxygenation.

The benefit of measures intended to improve the P_{aO_2} of patients with ARDS and poor oxygenation is debatable. There are numerous examples of therapies that successfully improved oxygenation but failed to improve survival rate. These include inhaled nitric oxide,[58] prone positioning,[59–61] and higher (compared with moderate) levels of PEEP.[62] Moreover, in the ARDS Network trial of high versus low V_T, the patients who received a high V_T had a higher P_{aO_2}/F_{IO_2}, but nevertheless also had a lower survival rate.[16] The benefit of using recruitment techniques for the purpose of reducing F_{IO_2} is also debatable, in that evidence for clinically important oxygen toxicity in humans is slim. Thus, as bedside clinicians we may interpret an intervention that raises P_{aO_2} as reflecting some underlying physiologic improvement, but there is little evidence that this predicts survival.

In the observational studies of HFOV, the term "rescue therapy" is commonly used. In everyday use, "rescue" implies the heroic release from some danger or evil. In the case of HFOV, the implied intent is to rescue the patient from the danger (evil) of oxygenation failure. However, in many of these studies (Table 1), the mortality rate remains high despite intervention with HFOV. Thus, despite their "rescue," a high percentage of patients die. In the absence of a control group ventilated conventionally, the designation of HFOV as a form of rescue is self-serving.

As seen in Table 1, the peak inspiratory or plateau airway pressure during conventional ventilation, before patients were switched to HFOV, was quite high. There is strong evidence that such high airway pressure (and V_T) is injurious, and that lower pressure (and V_T) reduces the mortality rate.[16,63] Evidence is also accumulating that high V_T and airway pressure are risk factors for development of acute lung injury in patients who do not have it at the time of intubation.[64–66] Thus, one may speculate that the oxygenation failure in these observational trials may have been iatrogenic. Lung-protective conventional ventilation earlier in the course might have ameliorated the extent of acute lung injury and averted the need for rescue therapy later. If the use of HFOV in these observational studies was a rescue, it may have only saved the patients from extension of their suboptimal conventional ventilation.

Effect of HFOV on Inflammation

If HFOV is to improve outcomes, it should prevent the pro-inflammatory effects of mechanical ventilation that have been associated with poor outcomes when harmful ventilator strategies are used. Thus, it is important to understand the effect of HFOV on lung inflammation. Papazian et al[57] compared the physiologic and inflammatory effects of HFOV, prone positioning, or their combination in severe ARDS. This was a prospective randomized study that enrolled 39 ARDS patients with a $P_{aO_2}/F_{IO_2} < 150$ mm Hg at PEEP > 5 cm H_2O. After 12 hours on conventional lung-protective mechanical ventilation (V_T of 6 mL/kg, plateau pressure not to exceed the upper inflection point of the pressure-volume curve, and a maximum plateau pressure of 35 cm H_2O, with supine conventional ventilation), patients received conventional lung-protective mechanical ventilation in prone position, HFOV in supine position, or HFOV in prone position. P_{aO_2}/F_{IO_2} increased with prone conventional ventilation (from 138 ± 58 mm Hg to 217 ± 110 mm Hg, $p < 0.001$) and with prone HFOV (from 126 ± 40 mm Hg to 227 ± 64 mm Hg, $p < 0.001$). With supine HFOV, however, P_{aO_2}/F_{IO_2} did not significantly change (from 134 ± 57 mm Hg to 138 ± 48 mm Hg). BALF interleukin-8 was significantly higher in both the supine and prone HFOV groups than in the prone or supine conventional

Table 1. Summary of Observational Studies of High-Frequency Oscillatory Ventilation

First Author, Year	Design	Patients	Conventional Ventilation (d)	HFOV (d)	*n*	PIP (cm H_2O)	P_{plat} (cm H_2O)	PEEP (cm H_2O)	Paralysis (%)	HFOV Failure (%)	Mortality (%)
Fort[25] 1997	Prospective	Severe ARDS	5.1 ± 4.3	1.5 h–6 d	17	54 ± 13	ND	18 ± 7	100	24	53
Claridge[54] 1999	Prospective	Severe ARDS; trauma	1.5 ± 1.4	6 ± 2.4	5	52 ± 3	ND	ND	100	0	20
Cartotto[47] 2001	Retrospective	ARDS; severe burns	6 ± 3.5	6.1 (range 2–12)	6	43 ± 3	ND	15 ± 3	100	0	83
Mehta[51] 2001	Prospective	$P_{aO_2} < 65$ mm Hg, $F_{IO_2} > 0.6$, or $P_{plat} > 35$ cm H_2O	5.7 ± 5.6	1 to > 10	24	ND	37 ± 4	15 ± 2	62	4	67
Andersen[49] 2002	Retrospective	Mainly pneumonia and burns	7.2 ± 4.6	6.3 ± 2.9	16	36 ± 5	ND	12 ± 3	69	0	31
David[26] 2003	Prospective	$P_{aO_2}/F_{IO_2} < 200$ after 2 h of PCV	3 (IQR 0.7–9.1)	1.2 (IQR 0.3–2.3)	42	35 (IQR 30–38)	ND	15 (IQR 10–16)	0	7	43
Mehta[52] 2003	Prospective	Combined use of inhaled nitric oxide and HFOV	3.1 ± 4	ND	23	ND	37 ± 5	15 ± 3	"majority"	ND	61
Mehta[50] 2004	Retrospective	Severe ARDS	5.6 ± 7.6	5.1 ± 6.3	156	ND	36 ± 7	14 ± 3	90	26	62
Cartotto[48] 2004	Retrospective	Burn and inhalation injury	4.8 ± 4.4	6.1 ± 5.8	25	37 ± 5	ND	14 ± 4	100	0	32
David[53] 2005	Retrospective	ARDS; traumatic brain injury	10 (range 7–11)	3 (range 0.3–10.3)	5	35	ND	15 (range 13–15)	0	0	20
Ferguson[28] 2005	Prospective	Early ARDS and severe oxygenation failure	0.5 (IQR 0.2–2.1)	ND	25	32 (IQR 30–34)	ND	10 (IQR 10–15)	ND	ND	44
Finkielman[56] 2006	Retrospective	Severe ARDS	1.8 (IQR 0.7–3.0)	3.2 (IQR 0.9–6.5)	14	37 ± 10	35 ± 11	14 ± 4	93	13	57
Kao[55] 2006	Prospective	Severe oxygenation failure with ARDS	1.6 ± 1	1.7 (range 0.5–4)	16	34.4 ± 4.2		12.8 ± 2.2	"majority"	19	62

HFOV = high-frequency oscillatory ventilation. PIP = peak inspiratory pressure. P_{plat} = inspiratory plateau pressure. PEEP = positive end-expiratory pressure. ARDS = acute respiratory distress syndrome. ND = no data available. F_{IO_2} = fraction of inspired oxygen. IQR = interquartile range. PCV = pressure-controlled ventilation.

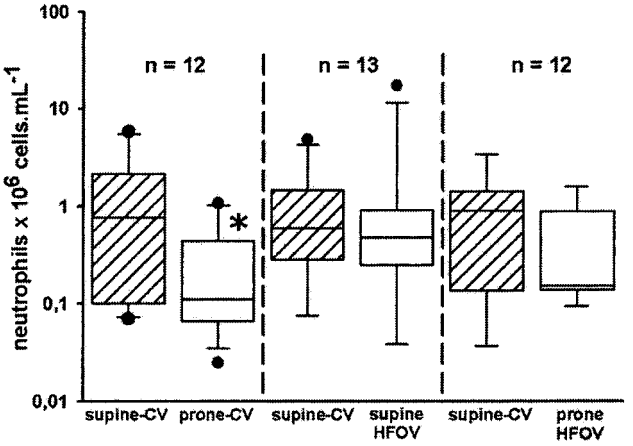

Fig. 1. Neutrophil counts in bronchoalveolar lavage fluid after a 12-hour period of conventional lung-protective mechanical ventilation in the supine position and again after 12 more hours of ventilation in the mode to which the patients were randomized. The median (25th, 50th, and 75th percentiles), largest, and smallest values that are not outliers are reported. Outliers (cases with values between 1.5 and 3 box-lengths from the upper or lower edge of the box) are presented as closed circles. CV = conventional lung-protective mechanical ventilation. HFOV = high-frequency oscillatory ventilation. * $p < 0.05$ versus supine CV, via Wilcoxon signed rank test, and versus supine HFOV, via Mann-Whitney rank sum test. (From Reference 57, with permission.)

ventilation groups. Neutrophil counts were also higher in the supine HFOV group than in the prone conventional ventilation group (Fig. 1). Thus, HFOV in the supine position did not improve oxygenation and was associated with greater lung inflammation. In contrast, the prone position increased oxygenation and reduced lung inflammation in ARDS patients. Prone HFOV produced similar improvement in oxygenation, compared to prone conventional ventilation, but prone HFOV was associated with higher BALF indices of inflammation. These findings are in stark contrast to the selected studies cited in the pro-HFOV portion of this review, which showed less inflammation with HFOV.[33,40,43–45] However, those studies differed in one important respect from that of Papazian et al:[57] they were performed in animal models of ARDS, rather than in ARDS patients. The findings of Papazian et al in adult patients may foreshadow that HFOV-induced improvements in gas exchange, like so many earlier discarded interventions, are dissociated from improved survival.

Randomized Controlled Trials

Derdak et al[10] conducted the largest multicenter randomized controlled trial to date that compared the safety and effectiveness of HFOV with conventional ventilation in adults with ARDS. Seventy-five patients were randomized to HFOV and 73 to conventional ventilation. Although there was an initial improvement (< 16 h) in P_{aO_2}/F_{IO_2} with HFOV ($p < 0.008$), this difference did not persist beyond 24 hours. Mortality at 30 days was 37% in the HFOV group and 52% in the conventional ventilation group ($p = 0.102$). The percentage of patients alive without mechanical ventilation at day 30 was 36% in the HFOV group and 31% in the conventional ventilation groups ($p = 0.686$). There were no significant differences in hemodynamic variables, oxygenation failure, ventilation failure, barotrauma, or mucus plugging between the treatment groups. The authors concluded that HFOV is a safe and effective ventilation mode for the treatment of ARDS in adults. This study provides scant support for the use of HFOV in adults with ARDS. First, the improvement in oxygenation with HFOV was not sustained beyond 24 hours. Second, the V_T in the control group was relatively high (10.6 mL/kg predicted body weight), and patients randomized to conventional ventilation tended to be a bit older and to have had ARDS a bit longer. These factors would all contribute to a relatively excessive mortality in the conventionally ventilated group, and diminish any speculative causality between the use of HFOV and the trend, in those patients, toward lower mortality.

Bollen et al[27] also conducted a multicenter randomized controlled trial of HFOV ($n = 37$) versus conventional ventilation ($n = 24$) in adults with ARDS. A low-V_T strategy was used with conventional ventilation, and the average V_T was 8 mL/kg predicted body weight. There were no significant differences in survival, therapy failure, or crossover rates. Adjustment by a priori defined baseline characteristics showed an odds ratio of 0.80 (95% confidence interval 0.22–2.97) for survival without oxygen or on the ventilator, and an odds ratio for mortality of 1.15 (95% confidence interval 0.43–3.10) for HFOV, compared with conventional ventilation. The response of the oxygenation index to treatment did not differentiate between survival and death. In the HFOV group, the oxygenation index was significantly higher than in the conventional ventilation group between the first and the second day. A post hoc analysis suggested that there was a relatively better treatment effect with HFOV than with conventional ventilation in patients with a higher baseline oxygenation index. The authors concluded that no significant differences were observed, although the study only had power to detect major differences in survival outcome. In this small study, in which conventionally ventilated patients received a lower V_T than in the study by Derdak et al,[10] there were neither significant differences nor even trends in mortality that favored HFOV.

Cost of HFOV

In the absence of demonstrable benefit, the cost/benefit ratio of HFOV is infinite. However, the costs alone are

substantial. An HFOV ventilator costs approximately $32,000 in the United States. This is the only Food and Drug Administration-approved ventilator that provides HFOV, and HFOV is its only function. This unique ventilator requires substantial staff training, the cost of which has not been quantified. Each single-use ventilator circuit also costs a few hundred dollars. Whether any of this will be repaid in better survival or long-term outcomes is currently unknown. From an economic standpoint, HFOV is hard to justify.

Need for Sedation and Paralysis

Because the HFOV ventilator provides a fixed and rather limited source of fresh respiratory gas, it requires sufficient sedation to suppress virtually all spontaneous breathing effort. In many patients, complete suppression of inspiration requires neuromuscular blockade. One noteworthy aspect of the observational studies of HFOV is the high percentage of patients who received paralysis (see Table 1). In the randomized controlled trial by Derdak et al,[10] all patients who received HFOV were sedated and paralyzed. Paralysis is a risk factor for intensive-care-unit-acquired muscle weakness.[67] Heavy sedation may take time to subside and may delay weaning, even after gas exchange has improved and the patient is returned to conventional ventilation. In contrast, low-V_T ventilation (6 mL/kg), a therapy that has been shown to increase survival,[16] does not increase sedative requirements.[68,69] Thus, even if HFOV proves to decrease lung injury, other barriers may prolong the duration of mechanical ventilation and its associated risks.

Safety of HFOV

In addition to the need for sedation or paralysis, HFOV poses some direct risks. For example, David et al[70] reported that 30 min after the initiation of HFOV, pulmonary arterial occlusion pressure increased ($p = 0.008$), cardiac index decreased ($p = 0.01$), stroke volume index decreased ($p = 0.02$), and both left-ventricular end-diastolic and end-systolic area indices decreased ($p = 0.02$). This is an effect of the higher pleural pressure that occurs when the lungs are recruited with sustained high airway pressure. Restoration of cardiac index would require volume loading. The high airway pressure may also increase the risk of pneumothoraces in injured lungs. In their retrospective review, Mehta et al[50] reported that pneumothorax occurred in 21.8% of patients who received HFOV. A similar high percentage of patients suffered some form of gross barotrauma in the case series and feasibility study of HFOV reported by Ferguson et al.[28]

Summary of the Con-HFOV Position

At present, evidence is completely lacking that survival in adults with ARDS is improved by HFOV. In some patients, but not all, HFOV may improve P_{aO_2} and thereby allow F_{IO_2} to be lowered. However, this improvement in oxygenation is often transitory. In contrast to animal studies, evidence does not show that HFOV reduces pulmonary inflammation in human adult ARDS. Heavy sedation and often paralysis is necessary, and the safety of HFOV itself is uncertain. The Cochrane Collaboration attempted a systematic review and meta-analysis of HFOV in children and adults. Only 2 studies met the quality criteria for inclusion, and there was insufficient evidence for any conclusions, except the need for more study.[71] With the available evidence, the statement that HFOV offers benefits over conventional ventilation in adults with ARDS remains wishful thinking.

Conclusions

The results of studies on animal models and humans demonstrate that HFOV can support gas exchange with much smaller V_T and provides more effective lung recruitment than can be achieved with conventional ventilation. However, available evidence does not support that HFOV reduces pulmonary inflammation in adult ARDS. Moreover, at present, evidence is lacking that HFOV improves survival in adults with ARDS. The promise of HFOV as a lung-protective ventilation strategy remains attractive, but additional clinical trials are needed to determine whether this approach is superior to lung-protective ventilation using conventional mechanical ventilation.

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Discussion

Fessler: Now that the debate is over, it's difficult for me to rebut, because I agree with almost everything Dean said. I share a great deal of equipoise about HFOV, and I share all the concerns Dean elucidated. Hypothetically, HFOV is very attractive because it seems to take what we know about lung-protective ventilation to the next level. But the data, particularly the human data, is either absent or, in the case of the Papazian study,[1] quite worrisome. I think we need a large definitive trial that uses everything that we've learned about the right way to ventilate people conventionally and with HFOV and pit them in a head-to-head comparison.

1. Papazian L, Gainnier M, Marin V, Donati S, Arnal JM, Demory D, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. Crit Care Med 2005;33(10):2162–2171.

Deem: Hank, I have a question about the Luecke study[1] that measured lung recruitment with computed tomography. You said that HFOV recruits more lung for the same mean airway pressure. I didn't see the mean airway pressure from the conventionally ventilated patients in that study. Was it reported? Was it really 28 cm H_2O?

1. Luecke T, Herrmann P, Kraincuk P, Pelosi P. Computed tomography scan assessment of lung volume and recruitment during high-frequency oscillatory ventilation (abstract). Crit Care Med 2005;33(3 Supp):S155–S162.

Fessler: No, it was not reported in that study, which is just in abstract form currently. That summary statement was based on the animal data and which groups had comparable mean airway pressure.

Deem: So we really don't have data in humans to support that statement?

Fessler: That's correct.

Deem: It would be very unusual to ventilate a patient with conventional ventilation at a mean airway pressure of 28 cm H_2O, at least in my practice.

Fessler: That's frequently true, and the way that we've been taught to use high-frequency oscillation is to start at a mean airway pressure higher than the patient has on conventional ventilation. So, inevitably, you're going to increase the mean airway pressure, at least when you start ventilating with HFOV.

Kacmarek: Although I am *not* an advocate of high frequency, I think Dean's conclusion was a little unfair. I think if you look carefully at the data, there is equivalence between conventional ventilation and high-frequency ventilation.[1–6] I don't think there is evidence either from neonates or adults that one is better than the other, but clearly there is no evidence that one is more *harmful* than the other. And even though no randomized controlled trials show a benefit or lack of benefit, there is clearly enough data in case series and in randomized trials in neonates that we should not dismiss high frequency as an acceptable way of managing patients in the ICU [intensive care unit]. HFOV is not an approach *I* would choose, but it's also clearly not an approach we can put in the "ICU adventurism" category.

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Hess: What troubles me is that even a very pro-HFOV group, such as the Toronto group, found, in their retrospective series, a high pneumothorax rate (22%).[1] And a quarter of the patients who they were trying to rescue with the oscillator had HFOV discontinued because of difficulties with oxygenation, ventilation, or hemodynamics. That seems like a long run for a short slide.

1. Mehta S, Granton J, MacDonald RJ, Bowman D, Matte-Martyn A, Bachman T, et al. High-frequency oscillatory ventilation in adults: the Toronto experience. Chest 2004; 126(2):518–527.

Kacmarek: But that is not true in the Derdak study.[1]

1. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, et al; Multicenter Oscillatory Ventilation For Acute Respiratory Distress Syndrome Trial (MOAT) Study Investigators. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized controlled trial. Am J Respir Crit Care Med 2002;166(6):801–808.

Hess: Correct.

Kacmarek: In the Papazian study,[1] what was the pneumothorax rate, and how did they ventilate patients conventionally? Did they do a good job?

1. Papazian L, Gainnier M, Marin V, Donati S, Arnal JM, Demory D, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. Crit Care Med 2005;33(10):2162–2171.

Hess: They used a V_T of 6 mL/kg predicted body weight.

Kacmarek: Yes, but how much PEEP and what plateau pressure did they use? That finding of a high pneumothorax rate doesn't go across all of the data on HFOV.

Hess: Point well made. They used PEEP 2 cm H_2O above the lower inflection point (on average 12 ± 4 cm H_2O). Plateau pressure was kept at less then 35 cm H_2O (25–26 cm H_2O on average).

Rubin: In support of what Bob said about neonates, the neonates on high-frequency oscillation tend to be some of the sickest. We have a very difficult time using lung-protective strategies, particularly low V_T, in the smallest children because of their size, the problems with tubing compliance, and the leak around the tube. It may be that HFOV is one of the best opportunities for using some of the ultimate low-V_T lung-protection strategies with patients who we know are surfactant deficient and have injured lungs and other troubles. And that may help to explain some of the differences we've seen between the adult and neonatal studies.

Steinberg: I'd like to speak in defense of Dean's interpretation of HFOV as "ICU adventurism," because, though I agree that there's a fair bit of equipoise and some data suggest it can be done, I think that it would be the wrong message to say that HFOV is a reasonable way of managing moderately sick ARDS patients. The complexity of HFOV care is part of what weighs into that.

But HFOV can be adventurism if a pulmonologist says, "I think HFOV is better and I'm just going to do that for routinely managing patients *outside* of a clinical trial." I think at this point, since no data show that HFOV is better, and because HFOV is very complex and potentially harmful if done incorrectly, I think it *is* a bit of adventurism. That said, I share the equipoise and think that HFOV should be studied in a research trial.

In addition, rescue therapy is a slightly different issue. When you get to that stage in a patient's care, the sicker the patient, the higher the risk, the more you can tolerate some adventurism. It doesn't make it less adventuristic, it just means you can tolerate or accept it more readily when you understand the processes of your decision making.

MacIntyre: I'm attracted to the idea of HFOV, but I share the equipoise voiced here, and it certainly does need to be studied. In designing such a trial, would you reserve HFOV for those who have "failed" or cannot be given lung protection with conventional approaches? Would you include a patient if you can't get the plateau pressure below 30–35 cm H_2O or the F_{IO_2} below 0.5 or 0.6, or would you open it up to more typical patients?

Hess: You could do either. They are separate questions: there's the question of *that* patient population, and then there is also the question of whether, with "garden variety" ARDS, you could improve the PEEP and lower the V_T, and if that would improve outcome. They are both important to study.

Fessler: I agree that they are separate questions. In the current environment, with the current state of knowledge, I think I can only justify using HFOV in patients who by some definition have failed conventional mechanical ventilation. I'm much more interested in studying it as a form of early intervention, a lung-protective ventilation, rather than some sort of oxygenation rescue ventilation. I think that is the more important study, if early interventions to prevent ventilator-associated lung injury are going to make the difference between life and death. The more important study is on HFOV's broad application in patients as soon as they meet the criteria for ARDS.

Branson: In the Derdak study,[1] the control group was really an "uncontrolled" group. Because, while the mean V_T was 8 cm H_2O, it could go as high as 12 or 14 cm H_2O, and they could use pressure-controlled inverse-ratio ventilation, and there was not a lot of control in that group.

I was surprised that neither of you talked about the work of breathing if you don't paralyze the patients during high-frequency oscillation. The first time I saw the high-frequency oscillator it was made by Southwest Texas Research in San Antonio, and that was about 18 years ago. Except for the color, it looks almost exactly the same today.

It's time for somebody to come up with a high-frequency ventilator that's smaller, cheaper, more efficient, and more easily combined with conventional ventilation. I'm sure technology is available to do that, but it's probably not being done because there's no competing manufacturer, so why should they change their current product?

1. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, et al; Multicenter Oscillatory Ventilation For Acute Respiratory Distress Syndrome Trial (MOAT) Study Investigators. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized controlled trial. Am J Respir Crit Care Med 2002;166(6):801–808.

Hess: I didn't directly address the issue of work of breathing, because I don't know that it's been reported. This concern may explain why the majority of patients in most case series have been paralyzed.

Fessler: Currently, I'm not sure that most physicians paralyze most patients, but clearly this ventilator cannot support spontaneous effort from the patient. So at the minimum they have to be so heavily sedated that they

don't make much spontaneous effort, and that's a worrisome aspect of HFOV. Even if it is more lung-protective, patients may still end up spending more time on the ventilator, waiting for sedatives or paralytics to wear off, and they may suffer more complications during that period.

Kacmarek: I feel myself defending a technique that I would never recommend. Based on the data, all the comments that you've made are true about adults, but they are not true for pediatric and neonatal patients. They do not have the work of breathing problems, they do not have to be paralyzed, and HFOV is not a difficult technique with pediatric patients. In fact, it's a lot easier than conventional ventilation.

HFOV has many fewer controls, which are simple and not interrelated, as they are with conventional ventilation. You have one mode to deal with, not 35 different modes, so I'm not sure I agree that HFOV necessarily involves greater complexity. You can do at least as much harm with conventional mechanical ventilation approaches as you can with HFOV. So I'm not sure those things should be considered in this discussion.

Cheifetz: A couple of comments from the pediatric world. In the field of pediatric acute lung injury, the last randomized multicenter study of HFOV versus conventional ventilation was published in 1994.[1] So the pediatric world is caught without adequate data. In terms of neuromuscular blockade and sedation, about 33% of our HFOV pediatric patients are paralyzed and heavily sedated, while the other 67% are moderately sedated. So this aspect of the debate is less important in pediatrics, though it still applies. As expected, the larger children and adolescents generally represent the problem when it comes to requiring neuromuscular blockade.

1. Arnold JH, Hanson JH, Toro-Figuero LO, Gutierrez J, Berens RJ, Anglin DL. Prospective randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. Crit Care Med 1994;22(10):1530–1539.

Kacmarek: My point was that in patients who are paralyzed because of work of breathing issues, if you left them on conventional ventilation most likely you'd have done the same because of the severity of illness at the time.

Cheifetz: I completely agree.

Rubin: We must remember that pediatric patients are very different from neonates. I think most of the children in the ICU with acute lung injury have far more in common with adults with acute lung injury than with neonates with surfactant-deficiency disease.