CHAPTER 133 ■ HIGH-FREQUENCY VENTILATION: LESSONS LEARNED AND FUTURE DIRECTIONS

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Mechanical ventilation practices continue to evolve. In particular, the ventilatory care of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) has been refocused on avoiding or minimizing further damage to the fragile, injured lung. Conventional ventilators have been used successfully to limit this ventilator-induced lung injury (VILI) (1–3), but questions remain regarding the optimal method for lung protection during mechanical ventilation. The recognition of the critical role that VILI can play in the outcome of adults with ALI/ARDS has, in part, spawned a renewed interest in alternative modes of ventilation that may be more lung protective.

High-frequency ventilation (HFV) is just such a modality. In this chapter, we briefly review the different subtypes of HFV and then concentrate on high-frequency oscillation as the mode with the most supporting data and promise. As will be seen, a great deal of experience with HFV has been accrued in the neonatal and pediatric settings. We will draw on this knowledge where relevant, but focus this chapter from the viewpoint of HFV as an emerging therapy in the adult intensive care unit (ICU).

DEFINITIONS, TERMINOLOGY, AND SUBTYPES OF HIGH-FREQUENCY VENTILATION

High-frequency ventilation is a collection of ventilatory modes, grouped together by their common property of employing high respiratory rates, all greater than 60 breaths per minute (4,5). In addition to high-frequency oscillation (HFO), other modes in this group include high-frequency jet ventilation (HFJV) and high-frequency percussive ventilation (HFPV).

High-frequency Jet Ventilation

HFJV is a mode of ventilation in which gas is delivered through a small-bore catheter into the lungs at rates of 100 to 150 breaths per minute (5,6). Delivered tidal volume is still small, but higher than just the volume exiting the jet, as the jets entrain an additional flow of gas by the Venturi effect. Exhalation is passive during HFJV, and gas trapping or dynamic hyperinflation can be an issue. In practice, a conventional ventilator is set up as a “slave” to the jet to provide positive end-expiratory pressure, along with basic monitoring and alarms.

HFJV is a very efficient mode for removing CO₂. Additionally, because of HFJV’s very high flow rates and the differing pulmonary time constants in the clinical setting of bronchopleural fistulae, this mode of ventilation is purported to have beneficial effects in the presence of this disorder; however, these benefits have not been verified during objective testing (7,8). Concerns with HFJV relate to the delivery of high pressures (10–50 pounds per square inch), unpredictable tidal volumes, and the development of dynamic hyperinflation, all of which may worsen VILI rather than minimize it. In addition, problems with adequate humidification of inspired gas and the subsequent risks of tracheobronchitis have been noted and documented.

High-frequency Percussive Ventilation

HFPV is the newest and least well studied of the HFV modes. It combines a high-frequency rate of 200 to 900 breaths per minute superimposed on a conventional pressure mode of ventilation (9). HFPV is reported to enhance the clearance of respiratory secretions and has been successfully used in this regard in patients with burns and inhalational injury (9).

High-frequency Oscillation

HFO is a mode of mechanical ventilation that delivers very small tidal volumes around a set mean airway pressure at high respiratory rates of 3 to 15 Hz (equivalent to 180–900 breaths per minute, as 1 Hz = 60 breaths per minute) (10). HFO has been widely and effectively used in neonates and children for close to 20 years (11–15), but only recently has become available in the adult ICU; previous versions of this ventilator were only capable of generating sufficient flow so as to provide adequate CO₂ elimination in patients under 35 kg. In contrast to other HFV modes, humidification is less of an issue during HFO, as a continuous bias flow of humidified gas is passed in front of an oscillating membrane (Fig. 133.1). This oscillating membrane pushes the humidified gas into the patient and also provides active expiration, a factor that likely accounts for the lack of important gas trapping that is observed when HFO is employed at adequate airway pressures (16). The elegance of HFO is that it allows for “decoupling” of oxygenation and ventilation. Alveolar ventilation, and thus carbon dioxide elimination, are dependent on the frequency and tidal volume but are relatively independent of lung volume (17). In contrast, oxygenation is proportional to mean airway pressure and lung volume (18,19).
Section XIII: Respiratory Disorders

RESISTANCE

VOLLMESSENGER

Patient

Bias Flow

Humidifier

OSILATORING MEMBRANE

2030

RATIONALE FOR THE USE OF HIGH-FREQUENCY VENTILATION IN ACUTE LUNG INJURY

Ventilator-induced Lung Injury

VILI is histologically indistinguishable from ARDS; three decades of experimental research has shown it to occur through a number of mechanisms, including (a) overdistention injury (volutrauma) (20–28), (b) collapse–reopening injury (atelectrauma) (1,2,20,29–34), and (c) oxygen toxicity (35–37). Each of these can lead, in turn, to further injury—termed biotrauma, the release of inflammatory mediators that may worsen pulmonary injury and propagate systemically to harm distant organs (1,2,31,32,38–45).

Numerous studies, performed using both small and large animals, consistently show that ventilatory high end-inspiratory stretch can cause a clinical and histologic picture similar to ARDS even in the absence of any other noxious stimulus (20–28). Patients with ARDS are at increased risk of regional lung overdistention because of the patchy nature of ARDS (46,47); the small areas of relatively normal lung (the so-called “baby lung”) receive the bulk of the tidal volume and are at particular risk of volutrauma (48,49). Repeated opening and closing of alveolar units can also cause VILI. In the injured lung, alveolar damage and absolute, or qualitative, deficiencies in alveolar surfactant lead to alveolar instability and localized lung unit collapse. Through each respiratory cycle, these unstable alveoli undergo collapse and reopening, a process that generates injurious mechanical forces and causes further lung injury. There is a substantive body of animal evidence showing that efforts to limit lung unit closing on expiration by maintaining an adequate positive end-expiratory pressure (PEEP) are relatively protective against atelectrauma (1,2,20,30–34). Here, the paradigm is one of “opening the lung and keeping it open,” thereby avoiding cyclic collapse and recruitment/derecruitment (2,50).

The major cause of death among ARDS patients is not refractory hypoxemia, as one might expect, but rather multi-organ dysfunction syndrome (MODS) (51). One hypothesis to explain the link between VILI and multiorgan failure is biotrauma (38,39)—the release of inflammatory mediators in response to injurious ventilation; these mediators may enter the systemic circulation, and hence lead to the development of MODS. Inflammatory mediators, such as interleukins, tumour necrosis factor-α, and platelet-activating factor, are released in response to VILI, oxygen-free radicals, and alveolar shearing. These mediators perpetuate the cascade of lung inflammation and worsen lung injury (31,32). Additionally, injurious ventilation has been shown to increase these inflammatory mediators in the peripheral blood of patients with ARDS (44,52). Through a variety of mechanisms, this inflammatory injury can lead to nonpulmonary organ dysfunction (41–43).

With an increased appreciation of the mechanisms of VILI, the next logical step is to employ ventilatory strategies that attempt to decrease overdistention, minimize shear injury, and limit oxygen toxicity (53–55). However, these aims may be competing; increasing PEEP may increase the risks of regional alveolar overdistention, while lowering tidal volumes can result in progressive alveolar collapse, a reduction in total lung volume, and higher oxygen requirements. The goals of mechanical ventilation in a patient at risk of VILI therefore should be to ventilate and oxygenate the patient while staying within a “safe window,” avoiding both overdistention and derecruitment—collapse—as illustrated in the volume-pressure curve of the lung shown in Figure 133.2 (56).

Impact of Limiting Ventilator-induced Lung Injury with Conventional Ventilation

In the mid-1990s, given the expanding animal data on VILI outlined above and in light of initial promising, but uncontrolled,
human studies of lung-protective ventilation (57,58), a call was made for randomized trials (53). Initial trials focused on avoiding volutrauma, comparing strategies that limited tidal volumes and inspiratory pressures with traditional strategies, both using conventional ventilation. Three smaller studies did not find mortality differences between these approaches (59-61). However, a large, methodologically rigorous, and adequately powered trial conducted by the National Institutes of Health (NIH) ARDS Network did show important differences in mortality (3). In this study, 861 patients were randomly assigned to receive a low-stretch strategy with a targeted tidal volume of 6 mL/kg predicted body weight (PBW) and a plateau pressure limit of up to 50 cm H\(_2\)O or to a higher-stretch strategy using a targeted tidal volume of 12 mL/kg PBW and a plateau pressure limit of up to 50 cm H\(_2\)O. The low-stretch strategy was associated with a mortality reduction from 40% in the control group to 31% in the experimental group (relative risk [RR] 0.78; 95% confidence interval [CI] 0.65-0.93). This trial clearly indicates that avoiding volutrauma saves lives in patients with acute lung injury. The trial has subsequently generated significant discussion regarding its mechanisms of benefit (62) and its choice of control strategy (63-66), but nevertheless, 6 mL/kg PBW has emerged as a standard for tidal volume limitation against which other strategies are compared (67,68).

Another early randomized controlled trial (RCT) published in the late 1990s demonstrated dramatic reductions in mortality using a lung-protective strategy whose goal was to limit both volutrauma and atelectrauma using low tidal volumes and higher PEEP compared with traditional ventilation (69). Amato et al. found a statistically significant reduction in 28-day mortality (11/29 [38%] vs. 17/24 [71%] deaths; RR 0.33; 95% CI 0.31-0.91) favoring patients exposed to the lung-protective strategy. In light of the subsequent positive ARDS Network trial noted above, interpretation of this trial is confounded by the use of both lower PEEP levels and higher tidal volumes and inspiratory pressures in the control group; the relative contribution of efforts to avoid cyclic collapse and reopening is unclear.

Drawing on the promise of the Amato trial, three RCTs have now been completed analyzing the effects of higher versus lower levels of PEEP, while limiting tidal volumes in all study patients. Two of these—the ExPress trial by Mercat et al. and the Lung Open Ventilation Study conducted by Meade et al.—are very recently completed and not yet published; both were presented at the 2006 European Society of Intensive Care Meeting. The one fully published trial, the ALVEOLI study, was conducted by the NIH ARDS Network investigators (70) and was stopped early, which likely contributed to the large baseline imbalance in age favoring the lower PEEP group. When we consider the relative risk after adjusting for baseline imbalances in prognostic factors (including age) from this trial, along with the preliminary findings from the two recent trials, a consistent trend favoring higher PEEP begins to emerge. Therefore, while no single trial has definitively shown an incremental mortality benefit with higher PEEP and attempts to limit atelectrauma while already avoiding overdistention injury, when viewed together, these trials suggest that this benefit may well exist. They also suggest that a higher level of PEEP with or without other maneuvers to open the lung, along with limited tidal volumes and inspiratory pressures, may be considered a very reasonable comparison strategy in future ventilation trials; this approach may be superior, and there is no suggestion of harm compared with lower PEEP levels. These studies clearly demonstrated that ventilatory strategy is important in patients with ARDS, and that lung-protective strategies can minimize VILI and decrease mortality in humans with ARDS. As such, and given the proposed mechanisms of lung protection (Fig. 133.2), a strategy that minimizes overdose and allows the use of high PEEP should be the ideal mode in patients with ARDS. This is where HFO may have great clinical benefit.

**Animal Studies Comparing Conventional Ventilation to High-frequency Oscillation in Acute Lung Injury**

The very small delivered tidal volumes are the key to the lung-protective potential of HFO. Because cyclic alveolar stretch is minimal, clinicians are able to set the mean airway pressure (mPA) on HFO significantly higher than they are able to set PEEP on conventional ventilation, thereby avoiding cyclic collapse and atelectrauma—and yet they are still able to avoid very high peak inspiratory pressures and subsequent
Elimination—which is inversely proportional to
leads to improved oxygenation through
Respiratory Disorders
solid line
). HFOV, high-frequency
dashed line
2. This is important clinically in that it indicates that
if V
falls
a
Crit Care Clin.
re-
1
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2002;18:91–106.)
ies is that CO
major message from these theoretical and experimental stud-
outside the scope of this chapter; the reader is referred to a num-
velocity profiles, Pendelluft, cardiogenic mixing, and diffusion
removal during HFO is achieved through a number of alternative
(see below).
Mechanisms of Gas Transport during
High-frequency Oscillation
Tidal volumes are extremely small with HFO, often smaller
than the anatomic dead space, in the range of 1 to 2 mL/kg
(90). In addition to relying on bulk flow, adequate CO
re-
from these studies, including the following:
1. At adequate mP
,based on a safe window for lung protection, may be a
(see below).
IMPLEMENTING AND OPTIMIZING
HIGH-FREQUENCY OSCILLATION
IN ADULTS
Because of the lack of an appropriate surrogate end point that
correlates with mortality (3,100), a large multicenter trial will
be needed to definitively determine the relative effects of HFO
compared with conventional mechanical ventilation (CMV) in
terms of lung protection and mortality (101,102). Similarly,
when making decisions regarding the best methods for apply-
ing HFO, we must draw inferences from multiple alternate
sources (including animal studies, neonatal RCTs, and adult
case series), since large RCTs comparing different HFO strate-
gies are unavailable and would be, frankly, difficult to justify
ethically in the absence of demonstrable efficacy over conven-
tional ventilation.
Animal Studies
Too many animal studies have been conducted on high-
frequency ventilation to list them in this review (4). Rather, in
Table 133.2, we outline a number of these studies that are in-
formative when considering how best to employ HFO in adults
(72,103–118). Several key messages for HFO can be gleaned
from these studies, including the following:
1. At adequate mP
,based on a safe window for lung protection, may be a
2. Increasing mP
leads to improved oxygenation through lung recruitment.
3. Tidal pressure swings measured in the trachea can be in-
creased with either underrecruitment or overdistention of the
lung.
4. Recruitment maneuvers (sustained inflations) may be re-
quired to adequately recruit severely injured lungs.
Taken together, and in keeping with the current understanding
of VILI mechanisms, these studies suggest that HFO in adults
should be employed using an open-lung strategy, facilitated by
higher mean airway pressures and lung recruitment maneuvers
(36,119,120).
Neonatal Studies
The longest clinical experience and the most rigorous evalua-
tion of HFO have both been in the neonatal population (121–
130). The initial large RCT evaluating HFO in this setting
raised safety concerns, but it later became evident that here,
too, the safe and effective application of HFO requires lung
volume recruitment (121,131,132). Subsequent RCTs of HFO
with an open-lung approach have demonstrated HFO to be
safe and effective in improving oxygenation and, as indicated
by the current Cochrane systematic review, may reduce the risk
of death or chronic lung disease (15). Interpreting the neonata-
lar HFO literature is challenging due to differences in study
populations (preterm vs. term), interventions (degree of lung
recruitment targeted), the timing of HFO (immediately after
birth vs. later), and by the introduction of exogenous surfac-
tant as a standard therapy in the 1990s. In addition, it is im-
portant to realize that the baseline mortality rate in infant res-
piratory distress syndrome is an order of magnitude less than
that seen in adults with severe ARDS. All of these factors mean
that results from neonatal studies cannot be directly extrapo-
lated to adult populations. Important lessons can be learned
from the neonatal HFO literature, however, including the im-
portance of thoroughly understanding the underlying physio-
logic mechanisms of the therapy, and the recognition that a
learning curve may exist in the initiation of an HFO program
(131,132).
### Table 123.5

**ANIMAL STUDIES COMPARING VILI WITH HFO VS. CMV**

<table>
<thead>
<tr>
<th>Author</th>
<th>Animal</th>
<th>Lung injury</th>
<th>HFO</th>
<th>CMV</th>
<th>LRM at onset</th>
<th>Duration</th>
<th>HFO effects on physiology</th>
<th>HFO effects on inflammation</th>
<th>HFO effects on pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton 1983</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP, PIP 25</td>
<td>Both</td>
<td>5–20 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ IL-8 mRNA</td>
<td>↑ Hyaline membranes</td>
</tr>
<tr>
<td>Tamura 1985</td>
<td>Rabbits</td>
<td>IV starch particle</td>
<td>BAL PMN &lt; 10 mL/kg</td>
<td>PEEP 2, PIP 20</td>
<td>No</td>
<td>3 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ EVLW, ↑ protein leak</td>
<td>↑ Hyaline membranes</td>
</tr>
<tr>
<td>McCulloch 1988</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>V&lt;sub&gt;1-2&lt;/sub&gt; = 2 mL/kg</td>
<td>PEEP 5, PIP 25</td>
<td>Both</td>
<td>7 h</td>
<td>↑ P&lt;sub&gt;compliance&lt;/sub&gt;</td>
<td>↑ compliance</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Riedl 1993</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 5, PIP 25</td>
<td>Both</td>
<td>4–10 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ BAL PMN # and apoptosis</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Imai 1994</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 5, PIP 25</td>
<td>Both</td>
<td>2–4 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ BAL PMN #</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Maruhashi 1994</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 5, PIP 25</td>
<td>Both</td>
<td>4 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ BAL PMN #</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Sagawa 1994</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 5, PIP 25</td>
<td>Both</td>
<td>4 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ BAL PMN #</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Takara 1997</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 5, PIP 25</td>
<td>Both</td>
<td>1–4 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ TNF-α mRNA, ↑ PMN in BAL</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Gommers 1999</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>f&lt;sub&gt;e&lt;/sub&gt; = 10 Hz</td>
<td>PEEP 6, PIP 26</td>
<td>HFO only</td>
<td>5 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ IL-8 mRNA, ↑ BAL PMN #</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Kerr 2001</td>
<td>Rabbits</td>
<td>NNMU lavage</td>
<td>f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 4, V&lt;sub&gt;1&lt;/sub&gt; = 10 mL/kg</td>
<td>No</td>
<td>1–2 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ BAL PMN #</td>
<td>↑ Lung injury</td>
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<tr>
<td>Noda 2003</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 5, PIP 25</td>
<td>Both</td>
<td>4 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ IL-8 mRNA, ↑ BAL PMN #</td>
<td>↑ Lung injury</td>
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<tr>
<td>HFO vs. lungprotective-CMV</td>
<td></td>
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<td></td>
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<tr>
<td>Vergalet de Alde 1999</td>
<td>Rats</td>
<td>Saline lavage</td>
<td>f&lt;sub&gt;e&lt;/sub&gt; = 10 Hz</td>
<td>PEEP for PaO&lt;sub&gt;2&lt;/sub&gt;, V&lt;sub&gt;e&lt;/sub&gt; = 5 mL/kg</td>
<td>Both</td>
<td>3 h</td>
<td>Similar mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>Similar BAL protein levels</td>
<td>Similar histology</td>
</tr>
<tr>
<td>Remmersburger 2000</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP = CCP</td>
<td>Both</td>
<td>4 h</td>
<td>Similar mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>Similar MPO levels</td>
<td>Similar histology</td>
</tr>
<tr>
<td>Rotta 2001</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP = CCP</td>
<td>Both</td>
<td>4 h</td>
<td>Similar mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>Similar MPO levels</td>
<td>Similar histology</td>
</tr>
<tr>
<td>Imura 2001</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = 15, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP = CCP</td>
<td>Both</td>
<td>4 h</td>
<td>Similar mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>Similar MPO levels</td>
<td>Similar histology</td>
</tr>
<tr>
<td>Sato 2003</td>
<td>Sheep</td>
<td>Saline lavage</td>
<td>f&lt;sub&gt;e&lt;/sub&gt; = 8 Hz</td>
<td>PEEP = 35, PIP = 30</td>
<td>Both, repeated</td>
<td>6 h</td>
<td>Similar mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ IL-8 mRNA, ↑ BAL PMN #</td>
<td>↑ Lung injury</td>
</tr>
<tr>
<td>Von der Heide 2004</td>
<td>Pigs</td>
<td>Saline lavage</td>
<td>mP&lt;sub&gt;e&lt;/sub&gt; = PMC, mP&lt;sub&gt;e&lt;/sub&gt; = 18, f&lt;sub&gt;e&lt;/sub&gt; = 15 Hz</td>
<td>PEEP 4, PIP 20</td>
<td>No</td>
<td>8 h</td>
<td>↑ mP&lt;sub&gt;e&lt;/sub&gt;</td>
<td>↑ IL-8 mRNA, ↑ BAL PMN #</td>
<td>↑ Lung injury</td>
</tr>
</tbody>
</table>

HFO, high-frequency oscillation; CMV, conventional mechanical ventilation; LRM, lung recruitment manoeuvre; mP<sub>e</sub>, mean airway pressure; f<sub>e</sub>, frequency; PEEP, positive end-expiratory pressure; P<sub>IP</sub>, peak inspiratory pressure on CMV; EVLW, extravascular lung water; V<sub>e</sub>, tidal volume; EELV, end-expiratory lung volume; PMN, polymorphonuclear cells; PAF, platelet-activating factor; TXB<sub>2</sub>, thromboxane B<sub>2</sub>; BAL, bronchoalveolar lavage; T<sub>NF</sub>, tumor necrosis factor; NNMU, N-nitroso-N-methylurethane; CCP, critical closing pressure (i.e., pressure on deflation limb of volume-pressure curve corresponding to 50% of total lung capacity); MPO, myeloperoxidase; PMC, point of maximal curvature (on the deflation limb of the volume-pressure curve); IL, interleukin; gene ex, gene expression; exog surf., exogenous surfactant. Study selection criteria: Population: Animal models (excluding preterm animals) of acute lung injury; intervention: HFO vs. conventional ventilation, no additional cointerventions; outcome: any marker(s) of lung injury (not gas exchange alone); therefore, no crossover studies.

VILI, ventilator-induced lung injury; HFO, high-frequency oscillation; CMV, conventional mechanical ventilation; LRM, lung recruitment manoeuvre; mP<sub>e</sub>, mean airway pressure; f<sub>e</sub>, frequency; PEEP, positive end-expiratory pressure; P<sub>IP</sub>, peak inspiratory pressure on CMV; EVLW, extravascular lung water; V<sub>e</sub>, tidal volume; EELV, end-expiratory lung volume; PMN, polymorphonuclear cells; PAF, platelet-activating factor; TXB<sub>2</sub>, thromboxane B<sub>2</sub>; BAL, bronchoalveolar lavage; T<sub>NF</sub>, tumor necrosis factor; NNMU, N-nitroso-N-methylurethane; CCP, critical closing pressure (i.e., pressure on deflation limb of volume-pressure curve corresponding to 50% of total lung capacity); MPO, myeloperoxidase; PMC, point of maximal curvature (on the deflation limb of the volume-pressure curve); IL, interleukin; gene ex, gene expression; exog surf., exogenous surfactant. Study selection criteria: Population: Animal models (excluding preterm animals) of acute lung injury; intervention: HFO vs. conventional ventilation, no additional cointerventions; outcome: any marker(s) of lung injury (not gas exchange alone); therefore, no crossover studies.
Uncontrolled Adult Studies

The studies reporting the clinical experience with HFO in adults, which are summarized in Table 133.3 (133–143), are also informative for optimizing an HFO protocol. Almost all of them studied HFO as rescue therapy for patients with extremely severe disease who were “failing” conventional ventilation. Despite being limited by their uncontrolled nature and by selection bias, consistent messages that arise from these rescue series include:

1. HFO is usually effective in improving oxygenation.
2. HFO appears safe, with no obvious increased rates of complications.
3. Both baseline oxygenation index and duration of CMV prior to HFO are associated with increased mortality.

Our prospective, multicentered study from our group is unique in that it tested an explicit protocol for applying HFO early in the course of ARDS, incorporating lung recruitment maneuvers (RMs) and a descending titration of mean airway pressure to optimize lung volumes for gas exchange and lung protection (140). RMs—sustained inflation maneuvers with 30 to 40 cm H2O pressures for 30 to 40 seconds—have been found to be safe in adults on CMV, but studies have shown mixed results in terms of efficacy and duration of their oxygenation effects (144–152). Because of the small tidal volumes generated with HFO, there is very little tidal recruitment of the lung, creating a more compelling rationale for RMs during HFO compared with CMV (19,50,102,153,154). The main finding from a physiologic standpoint in our study was that the combination of HFO and RMs was well tolerated and resulted in rapid and sustained lung recruitment (140). Furthermore, the explicit HFO protocol appeared feasible; adherence was excellent, and the method for weaning HFO and transitioning to CMV appeared practical and safe.

Tidal volume during HFO has always been assumed to be very low, but it is not routinely measured with currently available oscillators. Tidal volume is known to be inversely related to frequency due to a decreasing inspiratory time with increasing frequency (17), and in adults, typical frequencies have been significantly lower than those used in neonates (3–6 vs. 12–15 Hz) (132,139). Sedeek et al. explored this issue in a lung-injured sheep model, measuring tidal volumes of up to 4 mL/kg at high-pressure amplitudes and low frequencies (Table 133.2) (118). These tidal volume measurements may be overestimated because of technical reasons (135), but they do highlight the importance of efforts to minimize delivered tidal volumes with adult HFO, and they have spurred further investigation. Tidal volumes on HFO measured in adults using a very accurate device (156) were small—1.1 to 2.5 mL/kg—and strongly...
### TABLE 133.2

**ANIMAL STUDIES INFORMING OPTIMAL HFO IMPLEMENTATION**

<table>
<thead>
<tr>
<th>Author</th>
<th>Animal</th>
<th>Lung injury</th>
<th>Intervention</th>
<th>Design</th>
<th>Outcomes</th>
<th>Main findings</th>
<th>Comment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohn 1980</td>
<td>Dogs</td>
<td>None</td>
<td>HFO at various frequencies</td>
<td>Single cohort</td>
<td>Gas exchange and airway pressures, Occlusion pressures</td>
<td>First description of HFO showing safety and efficacy</td>
<td>HFO capable of supporting adequate gas exchange</td>
<td>Gas trapping not an issue with HFO despite high frequencies</td>
</tr>
<tr>
<td>Bryan 1986</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>HFO at various mP_{AW}</td>
<td>Single cohort</td>
<td>Occlusion pressures</td>
<td>Gas trapping with HFO only seen at extremely low mP_{AW}</td>
<td>Gas trapping not an issue with HFO despite high frequencies</td>
<td>Gas trapping not an issue with HFO despite high frequencies</td>
</tr>
<tr>
<td>Bancalari 1987</td>
<td>Rabbits</td>
<td>Meconium aspiration</td>
<td>HFO (mP_{AW} = 11–22, f = 10–15 Hz) vs. HFJV</td>
<td>Crossover</td>
<td>Gas exchange, lung volumes (plethys.)</td>
<td>No significant gas trapping with HFO; yes with HFJV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Courtney 1992</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>HFO at various I:E ratios (constant mP_{AW}, P and f)</td>
<td>Single cohort</td>
<td>Gas exchange and hemodynamics</td>
<td>Varying I:E ratios had no significant effect on PaO_{2}, PaCO_{2}, RR or CO</td>
<td>Oxygenation response is a reasonable surrogate for recruitment</td>
<td></td>
</tr>
<tr>
<td>Pillow 1999</td>
<td>Rabbits</td>
<td>None</td>
<td>HFO at various I:E ratios</td>
<td>Single cohort</td>
<td>Airway–alveolar pressure difference</td>
<td>P_{R_{ALV}} was lower than mP_{AW} at I:E ratios below 1:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boynton 1991</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>HFO at various mP_{AW}</td>
<td>Single cohort</td>
<td>Gas exchange, lung volumes (plethys.)</td>
<td>↑ mP_{AW} leads to ↑ O_{2} through ↑ lung volume; hysteresis present</td>
<td>Oxygenation response is a reasonable surrogate for recruitment</td>
<td></td>
</tr>
<tr>
<td>Goddon 2001</td>
<td>Sheep</td>
<td>Saline lavage</td>
<td>HFO at various mP_{AW}</td>
<td>Single cohort</td>
<td>Gas exchange and mechanics</td>
<td>Best O_{2} was at mP_{AW} of P_{FLEX} + 6 also equal to PMC on deflation</td>
<td>Oxygenation response is a reasonable surrogate for recruitment</td>
<td></td>
</tr>
<tr>
<td>van Genderingen 2002 (ICM)</td>
<td>Pigs</td>
<td>Oleic acid infusion</td>
<td>HFO vs. CMV titrated to PaO_{2}</td>
<td>RCT</td>
<td>Airway pressures and shunt fraction</td>
<td>↑ mP_{AW} needed with HFO to match PaO_{2} on CMV</td>
<td>Oxygenation response is a reasonable surrogate for recruitment</td>
<td>High mP_{AW} needed for lung opening on HFO—may be reduced subsequently</td>
</tr>
<tr>
<td>Dombrowski 2002</td>
<td>Pigs</td>
<td>None</td>
<td>HFO at various mP_{AW}</td>
<td>Single cohort</td>
<td>Gas exchange and mechanics</td>
<td>Increasing mP_{AW} mirrored volume on deflation limb of pressure-volume curve; no hysteresis on HFO</td>
<td>Oxygenation response is a reasonable surrogate for recruitment</td>
<td>Lung opening may occur on HFO without RMs</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Author</th>
<th>Animal</th>
<th>Lung injury</th>
<th>Intervention</th>
<th>Design</th>
<th>Outcomes</th>
<th>Main findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathoracic tidal pressure swings and lung recruitment during HFO</td>
<td>Sakai 1999</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>HFO at various mP&lt;sub&gt;AW&lt;/sub&gt; and V&lt;sub&gt;T&lt;/sub&gt;</td>
<td>Single cohort</td>
<td>Pressure swings in airway and pleura</td>
<td>At low mP&lt;sub&gt;AW&lt;/sub&gt; pressure swings are increased; decreased after an RM. OPR is increased when the lung is overdistended or unrecruited.</td>
</tr>
<tr>
<td>van Genderingen 2002</td>
<td>Pigs</td>
<td>Saline lavage</td>
<td>HFO at various mP&lt;sub&gt;AW&lt;/sub&gt;</td>
<td>Single cohort</td>
<td>Oscillatory pressure ratio (OPR&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Underrecruited lungs lead to higher pressure swings on HFO.</td>
<td></td>
</tr>
<tr>
<td>Recruitment maneuver effects with HFO</td>
<td>Byford 1988</td>
<td>Rabbits</td>
<td>Saline lavage + CMV</td>
<td>HFO + RMs with oscillator on and off</td>
<td>Crossover</td>
<td>Gas exchange, lung volumes (plethys.)</td>
<td>RMs with oscillator on yielded ↑ recruitment at ↓ pressures. RMs with oscillator not paused may be more effective.</td>
</tr>
<tr>
<td></td>
<td>Sznajder 1988</td>
<td>Dogs</td>
<td>Oleic acid</td>
<td>HFO w. high tidal volume</td>
<td>Crossover</td>
<td>Gas exchange, lung volumes (plethys.)</td>
<td>Full lung recruitment on HFO only achieved after a RM to TLC. RMs improve gas exchange and compliance on HFO.</td>
</tr>
<tr>
<td></td>
<td>Walsh 1988</td>
<td>Rabbits</td>
<td>Saline lavage</td>
<td>HFO + various RMs</td>
<td>Single cohort</td>
<td>Gas exchange and mechanics</td>
<td>RMs improve gas exchange on HFO.</td>
</tr>
<tr>
<td></td>
<td>Suzuki 1992</td>
<td>Rabbits</td>
<td>Saline lavage + CMV</td>
<td>HFO ± RMs</td>
<td>Single cohort</td>
<td>Lung volume and gas exchange</td>
<td>HFO with our RMs was uniformly fatal; HFO + RMs improved gas exchange.</td>
</tr>
<tr>
<td></td>
<td>Delivered tidal volumes with “adult settings” on HFO</td>
<td>Sedec 2003</td>
<td>Sheep</td>
<td>Saline lavage</td>
<td>HFO at various ∆P and f</td>
<td>Single cohort</td>
<td>Delivered tidal volumes</td>
</tr>
</tbody>
</table>

<sup>a</sup>Oscillatory pressure ratio is the ratio of pressure swings at the proximal and distal end of the endotracheal tube during HFO.

HFO, high-frequency oscillation; mP<sub>AW</sub>, mean airway pressure; f, frequency; HFJV, high-frequency jet ventilation; plethys., plethysmography; I:E, inspiratory:expiratory; BP, blood pressure; CO, cardiac output; PA<sub>ALV</sub>, alveolar pressure; P<sub>FLEX</sub>, pressure at the lower inflexion point of the static volume–pressure curve; OI, oxygen index; RCT, randomized controlled trial; PMC, point of maximal curvature on the deflation limb of the static volume-pressure curve; CMV, conventional mechanical ventilation; V<sub>T</sub>, tidal volume; RM, recruitment maneuver.
### TABLE 13.3.3

**UNCONTROLLED STUDIES**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Population</th>
<th>Baseline severity of illness</th>
<th>Design</th>
<th>Complications</th>
<th>Main findings</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fort 1997</td>
<td>17</td>
<td>ARDS</td>
<td>OI = 49</td>
<td>Prospective</td>
<td>Barotrauma 6%</td>
<td>Improved oxygenation;</td>
<td>Baseline OI and duration of CMV associated with ↑ mortality</td>
</tr>
<tr>
<td>Clarke 1999</td>
<td>5</td>
<td>ARDS, trauma</td>
<td>P/F = 52</td>
<td>Not reported</td>
<td>ETT obstruction 6%</td>
<td>mortality 33%;</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>Mehta 1997</td>
<td>24</td>
<td>ARDS</td>
<td>APACHE II = 28</td>
<td>Prospective</td>
<td>Barotrauma 8%</td>
<td>Improved oxygenation;</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>Andersen 2002</td>
<td>16</td>
<td>ARDS</td>
<td>OI = 2.8</td>
<td>Retrospective</td>
<td>ETT obstruction 4%</td>
<td>mortality 67%;</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>David 2003</td>
<td>42</td>
<td>ARDS</td>
<td>APACHE II = 27</td>
<td>Prospective</td>
<td>Barotrauma 2%</td>
<td>Improved oxygenation;</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>Cartotto 2004</td>
<td>25</td>
<td>ARDS, burns</td>
<td>OI = 2.7</td>
<td>Retrospective</td>
<td>Barotrauma 0%</td>
<td>Improved oxygenation;</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>Mehta 2004</td>
<td>156</td>
<td>ARDS</td>
<td>APACHE II = 16</td>
<td>Retrospective</td>
<td>Barotrauma 21%</td>
<td>Improved oxygenation;</td>
<td>Baseline OI and duration of CMV associated with ↑ mortality</td>
</tr>
<tr>
<td>Pachl 2006</td>
<td>30</td>
<td>ARDS</td>
<td>APACHE II = 24</td>
<td>Prospective</td>
<td>Not reported</td>
<td>Not reported</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>Finkelman 2006</td>
<td>14</td>
<td>ARDS</td>
<td>OI = 3.5</td>
<td>Retrospective</td>
<td>Barotrauma 0%</td>
<td>Improved oxygenation;</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>Weiler 2006</td>
<td>5</td>
<td>ARDS</td>
<td>APACHE II = 28</td>
<td>Retrospective</td>
<td>Barotrauma 0%</td>
<td>Improved oxygenation;</td>
<td>HFO appears safe and improves O₂ in rescue setting</td>
</tr>
<tr>
<td>Ferguson 2003</td>
<td>23</td>
<td>Early ARDS</td>
<td>OI = 2.3</td>
<td>Prospective,</td>
<td>Barotrauma 8%–20%</td>
<td>Rapidly improved oxygenation;</td>
<td>Pilot study of an explicit protocol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>APACHE II = 24</td>
<td>consecutive,</td>
<td></td>
<td>mortality 44%; excellent protocol adherence</td>
<td>including conversion criteria to CMV</td>
</tr>
</tbody>
</table>

HFO, high-frequency oscillation; ARDS, acute respiratory distress syndrome; OI, oxygen index; ETT, endotracheal tube; CMV, conventional mechanical ventilation.
influenced by frequency (90). Cumulatively, these data are reassuring in that HFO in adults can be set to deliver very small tidal volumes, but at the same time they highlight the potential importance of targeting the lowest tidal volume possible (153). This could be achieved by increasing frequency as high as tolerated while avoiding severe respiratory acidosis, a strategy that has been proposed as physiologically sensible (157) and recently shown to be feasible in most patients (158).

**Randomized Controlled Trials of High-frequency Oscillation in Adults**

To date, only two RCTs have compared HFO with CMV in adults (101,159). Both of these trials were planned and started prior to the completion of the first ARDS Network study that showed benefit from strict control of tidal volumes (3). Neither RCT demonstrated safety concerns (the primary outcome); rates of barotrauma and other complications were similar between groups in both studies. The larger of the two RCTs shows an impressive trend toward a mortality benefit with HFO (RR 0.72; 95% CI 0.50–1.04) despite more than 10% of the control group crossing over to HFO (101). The second trial, which began accrual at the same time, was stopped because of slow enrollment. In fact, the enrollment rates per center per month were identical in both studies; the latter study simply highlights the need for extensive multicenter collaboration for a successful HFO RCT. Mortality results from the smaller study are less encouraging, but these are significantly confounded by large baseline differences favoring the control group, and by an almost 20% crossover rate. Nevertheless, pooled results from these trials still suggest a potentially important survival benefit with HFO (RR 0.899, 95% CI 0.51–1.58; random effects model); inferences from these RCTs are limited, however, by their methodology, small sample sizes, and, importantly, by use of now dated, potentially injurious conventional ventilation strategies.

**FUTURE DIRECTIONS**

A research focus on the ventilatory care of ARDS patients has, to date, paid significantly greater dividends than the disappointing results of pharmacotherapy testing (146). Following the completion of the three conventional ventilation RCTs comparing a “lung open” approach with a lower PEEP approach, we believe that the study of HFO represents the next logical step in this evolution of ventilation strategies. We ground this belief in:

1. A strong physiologic rationale and database of animal studies (147).
2. Experience from the neonatal and pediatric arenas (150).
3. An expanding clinical experience with adult HFO (151).
4. Promising results from small nondefinitive RCTs (152).

Despite the very strong physiologic rationale and the encouraging clinical data to date, there are potential detrimental consequences of HFO. First, the physiologic benefit of HFO is likely derived from recruitment of the lung with higher mean airway pressures, while still not overdistending alveoli because of the very small tidal volumes. Hence, patients with mild disease and minimal collapsed or consolidated lung may not be good candidates for HFO (151). Second, the high mean airway pressures may negatively impact hemodynamics. Third, because the bias flow rate is insufficient to meet the inspiratory flow demands of adults in respiratory distress, all adults on HFO must have their respiratory efforts suppressed with intravenous sedation. This means that the majority of adults will be heavily sedated, and many may need transient neuromuscular blockade. Due to these concerns, and to target a population in need of recruitment, we believe that future studies should enroll patients with severe ARDS who are likely to have significant lung collapse and who frequently require significant amounts of sedation, with or without paralysis, on conventional ventilators.

In summary, we believe that HFO—and other forms of high-frequency ventilation—should currently be reserved for “rescue therapy” in patients who are failing conventional ventilation. We do not believe that HFO can be recommended for routine use in adults with ARDS at the current time because:

- There are potential detrimental physiologic and clinical consequences as described above.
- This would represent premature dissemination of a complex technology without rigorous evaluation of its risks, benefits, and indications.

A definitive RCT to establish the impact of HFO versus best current conventional ventilation on mortality is needed.

**References**

Chapter 133: High-frequency Ventilation: Lessons Learned and Future Directions


2040  

Section XIII: Respiratory Disorders

High-frequency Ventilation: Lessons Learned and Future Directions


