

Review

Bench-to-bedside review: High-frequency oscillatory ventilation in adults with acute respiratory distress syndrome

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Abstract

Mechanical ventilation is the cornerstone of therapy for patients with acute respiratory distress syndrome (ARDS). Paradoxically, mechanical ventilation can exacerbate lung damage – a phenomenon known as ventilator-induced lung injury. While new ventilation strategies have reduced the mortality rate in patients with ARDS, this mortality rate still remains high. High-frequency oscillatory ventilation (HFOV) is an unconventional form of ventilation that may improve oxygenation in patients with ARDS, while limiting further lung injury associated with high ventilatory pressures and volumes delivered during conventional ventilation. HFOV has been used for almost two decades in the neonatal population, but there is more limited experience with HFOV in the adult population. In adults, the majority of the published literature is in the form of small observational studies in which HFOV was used as 'rescue' therapy for patients with very severe ARDS who were failing conventional ventilation. Two prospective randomized controlled trials, however, while showing no mortality benefit, have suggested that HFOV, compared with conventional ventilation, is a safe and effective ventilation strategy for adults with ARDS. Several studies suggest that HFOV may improve outcomes if used early in the course of ARDS, or if used in certain populations. This review will summarize the evidence supporting the use of HFOV in adults with ARDS.

Introduction

Mechanical ventilation remains the cornerstone of therapy for patients with acute respiratory distress syndrome (ARDS) and acute lung injury. Paradoxically, mechanical ventilation has the potential to cause further lung injury in patients with ARDS and acute lung injury – a phenomenon known as ventilator-induced lung injury, which occurs when alveolar overdistension due to high ventilator pressures or volumes disrupts the alveolar epithelial membrane (volutrauma) [1]. Lung injury can also occur in the setting of repeated opening and closing of alveoli due to inadequate end-expiratory

alveolar recruitment, which can disrupt both the alveolar epithelial and capillary endothelial membranes (atelectrauma). These mechanical insults lead to the release of inflammatory cytokines that further exacerbate lung injury and may contribute to the development of multiple organ failure [1-3].

Lung-protective conventional ventilation (CV) strategies are structured to limit alveolar overdistension, with the use of small tidal volumes and low end-inspiratory pressures, and to avoid repeated end-expiratory alveolar collapse with adequate positive end-expiratory pressure. Such a strategy was evaluated in the ARDS Network trial, and was associated with a 9% absolute reduction in mortality compared with a strategy that employed a higher tidal volume [4]. Notwithstanding, mortality in the low tidal volume group remained high at 31%, spurring investigators to develop alternative lung-protective mechanical ventilation strategies that could further reduce mortality in patients with ARDS.

High-frequency oscillatory ventilation – potential benefits and mechanisms

High-frequency oscillatory ventilation (HFOV) theoretically satisfies all of the goals of a lung-protective strategy, and offers several potential advantages over CV. Utilizing a piston pump, HFOV achieves gas exchange by delivering very small tidal volumes at frequencies ranging from 3 to 15 Hz. The potential advantages of HFOV over CV include: the delivery of smaller tidal volumes, limiting alveolar overdistension; the application of a higher mean airway pressure (mPaw) than that in CV, promoting more alveolar recruitment; and the maintenance of a constant mPaw during inspiration and expiration, thus preventing end-expiratory alveolar collapse.

APACHE = Acute Physiologic and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; CV = conventional ventilation; FiO₂ = fraction of inspired oxygen; HFOV = high-frequency oscillatory ventilation; IL = interleukin; mPaw = mean airway pressure; OI = oxygenation index; PaO₂ = partial pressure of arterial oxygen; PAOP = pulmonary artery occlusion pressure; RM = recruitment manoeuvre; TNF = tumour necrosis factor.

The principles of oxygenation during HFOV are similar to those during CV, and oxygenation is dependent on an optimal lung volume recruitment strategy (mPaw) and the consequent reduction of intrapulmonary shunting of blood. Ventilation is inversely related to the respiratory frequency and is directly related to the excursion of the diaphragm, the latter expressed as the pressure amplitude of oscillation. By maintaining a continuous distending pressure, HFOV facilitates CO₂ elimination mainly by accelerating the molecular diffusion processes. Gas transport and CO₂ elimination during HFOV, however, also result from several other mechanisms, including bulk convection, pendelluft, Taylor dispersion, and cardiogenic mixing [5].

During HFOV a piston pump oscillates at frequencies between 180 and 1800 breaths/min. As the ventilator itself is a closed system and does not provide fresh gas, a bias flow of gas at 5–60 l/min is used across the tubing connecting the oscillator to the patient. The amount of bias flow, together with a resistance valve in the circuit, is used to control the mPaw within the circuit. HFOV is unique, compared with other modes of high-frequency ventilation, because the return stroke of the piston during expiration creates a vacuum, leading to active expiration of gas. Humidification in HFOV is easily achieved by passing the bias flow of gas through a humidifier.

In some animal models, the use of HFOV is associated with less evidence of lung injury, as demonstrated by reduced lung expression of inflammatory cytokines – including IL-1 β , IL-6, IL-8, IL-10, transforming growth factor and adhesion molecules, as well as messenger RNA for TNF – compared with CV [6-8]. These cytokine reductions were noted despite the application of similar mPaw during HFOV and CV. One study in neonates demonstrated cytokine reductions during HFOV [9], while two other human studies have shown negative results [10,11]. Animal models also demonstrate reduced pathological injury with HFOV, with less hyaline membrane formation, less alveolar leukocyte infiltration and less airway epithelial damage compared with CV [12-14]. In a rabbit model, HFOV was associated with a reduction in TNF levels, leukocyte infiltration and pathological changes even when compared with a CV strategy that emphasized low tidal volume and high positive end-expiratory pressure [15]. In contrast, the use of HFOV in premature neonates did not reduce concentrations of albumin, IL-8 and leukotriene B₄, when compared with high-rate, low-pressure CV [16].

The applied mPaw during HFOV is usually higher than that applied during CV [17,18]. Theoretically, a higher sustained mPaw increases alveolar recruitment, which improves ventilation–perfusion matching and oxygenation. This was demonstrated in a study using electrical impedance tomography, in which HFOV resulted in a homogeneous lung volume distribution compared with nonuniform lung inflation during the inflation limb of a pressure–volume curve

manoeuvre [19]. The high mPaw applied during HFOV is not associated with high peak airway pressures, as the pressure oscillations produced by the piston are significantly attenuated distally, resulting in low-amplitude alveolar pressure oscillations around the mPaw. The use of HFOV therefore allows the application of a higher overall mPaw without abandoning a ‘lung-protective’ strategy.

The active expiratory phase is a unique feature of HFOV, and may be important for alveolar ventilation. At typical HFOV settings, bulk flow appears to play a minor role in ventilation, given that the tidal volume at typical ventilator settings is approximately 2 ml/kg [20], which is lower than anatomical dead space. Bulk flow, however, probably occurs at lower frequencies and higher pressure amplitudes, which result in tidal volumes closer to the CV range [21]. Other proposed mechanisms of ventilation during HFOV include asymmetric velocity profiles, pendelluft, cardiogenic mixing, laminar flow with Taylor dispersion, collateral ventilation and molecular diffusion [5,22].

Clinical trials

A large number of randomized controlled trials in the neonatal literature have failed to show a mortality benefit associated with the use of HFOV. The number of trials evaluating HFOV in adults is more modest, with only two randomized controlled trials [23,24] and a handful of case series. Most of the studies have used HFOV as ‘rescue’ therapy for patients with severe ARDS who are failing CV. Table 1 presents a summary of these trials. None of these trials have shown a reduction in mortality with the use of HFOV.

In the first published observational study, Fort and colleagues reported their experience with HFOV in 17 patients with ARDS due to sepsis or pneumonia [17]. The severity of illness was high, with a mean Acute Physiologic and Chronic Health Evaluation (APACHE) II score of 23.3 and an oxygenation index (OI) – $(Paw \times FiO_2 \times 100) / PaO_2$ – of 48.6. Patients had significant improvements in the FiO₂ and OI over the 48-hour study duration, and the 30-day mortality rate was 53%. Of note, nonsurvivors had a higher baseline OI and had been ventilated conventionally for more days prior to HFOV than survivors.

Four subsequent observational studies were similar in a number of important details [18,25-27]. In these studies, the number of patients was small, ranging from 16 to 42, and most patients had ARDS secondary to sepsis or pneumonia. In all cases, HFOV was used as rescue therapy for patients with severe ARDS who remained hypoxaemic during CV. In all four of these studies the initiation of HFOV was associated with significant improvements in oxygenation within 24 hours. Mortality rates in these studies were high, but the patients were very ill (mean APACHE II score >21, PaO₂/FiO₂ = 73–98 mmHg), and the majority of deaths occurred due to multiorgan failure. As in the study by Fort and colleagues

Table 1**Studies evaluating the use of high-frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome**

| Author, year | Study design | <i>n</i> | Baseline characteristics | Mean CV prior to HFOV (days) | Mortality | Death due to respiratory failure (%) | Selected complications |
|-------------------------------------|-----------------------------|----------|---|------------------------------|------------------------------------|--------------------------------------|--|
| Fort and colleagues, 1997 [17] | Prospective, observational | 17 | Mean age 38, APACHE II score 23, PaO ₂ /FiO ₂ ratio 69, OI 49 | 5.1 | 30-day mortality 53% | 33 | 3 (17.6%) HFOV patients withdrawn for hypotension |
| Claridge and colleagues, 1999 [30] | Prospective, observational | 5 | Trauma patients; mean age 37, APACHE II score 28, PaO ₂ /FiO ₂ ratio 52 | 1.4 | 20% | 0 | None reported |
| Mehta and colleagues, 2001 [18] | Prospective, observational | 24 | Mean age 48, APACHE II score 22, PaO ₂ /FiO ₂ ratio 99, OI 32 | 5.7 | 30-day mortality 66% | 6 | 2 patients (8.3%) had pneumothorax |
| Derdak and colleagues, 2002 [23] | Randomized controlled trial | 148 | Mean age 50, APACHE II score 22, PaO ₂ /FiO ₂ ratio 112, OI 25 | 2.8 | 30-day mortality: HFOV 37%, CV 52% | 16 in both arms | Similar in both groups |
| Andersen and colleagues, 2002 [25] | Retrospective | 16 | Mean age 38, SAPS II score 40, PaO ₂ /FiO ₂ ratio 92, OI 28 | 7.2 | 3-month mortality 31% | Not reported | 1 (6.3%) patient had pneumothorax |
| David and colleagues, 2003 [26] | Prospective, observational | 42 | Median age 49, APACHE II score 28, PaO ₂ /FiO ₂ ratio 94, OI 23 | 3.0 | 30-day mortality 43% | 33 | 1 (2.4%) patient had pneumothorax |
| Cartotto and colleagues, 2004 [29] | Retrospective | 25 | Burn patients; mean age 44, APACHE II score 17 | 4.8 | Inhospital mortality 32% | 4 | 3 (12%) patients had severe hypercapnea |
| Mehta and colleagues, 2004 [28] | Retrospective | 156 | Median age 48, APACHE II score 24, PaO ₂ /FiO ₂ ratio 91, OI 31 | 5.6 | 30-day mortality 62% | Not reported | 34 (21.8%) patients had pneumothorax |
| Bollen and colleagues, 2005 [24] | Randomized controlled trial | 61 | Mean age 81, APACHE II score 21, HFOV 37 patients, CV 24 patients, OI 22 | 2.1 | HFOV 43%, CV 33% | 0 in both arms | HFOV: 4 (10.8%) patients had hypotension, 1 (2.7%) patient had air leak; CV: 1 (4.2%) patient had hypotension, 1 (4.2%) patient had air leak |
| Ferguson and colleagues, 2005 [42] | Prospective | 25 | Mean age 50, APACHE II score 24, PaO ₂ /FiO ₂ ratio 121, OI 23 | 0.5 | 44% in intensive care unit | Not assessed | 5 (25%) patients had barotrauma |
| Pachl and colleagues, 2006 [20] | Prospective, observational | 30 | Mean age 55, SOFA score 9.6, PaO ₂ /FiO ₂ ratio 121, OI 26 | 7.7 | 46.7% | Not reported | Not reported |
| Finkelman and colleagues, 2006 [27] | Retrospective | 14 | Mean age 56, APACHE II score 35, PaO ₂ /FiO ₂ ratio 73, OI 35 | 1.7 | 30-day mortality 57% | Not reported | 1 patient had HFOV discontinued for haemodynamic instability |

APACHE, Acute Physiology and Chronic Health Evaluation; CV, conventional ventilation; OI, oxygenation index (FiO₂ × mean airway pressure × 100 / PaO₂); HFOV, high-frequency oscillatory ventilation; SAPS, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment.

[17], Mehta and colleagues [18] also observed that nonsurvivors were ventilated conventionally for a longer duration prior to HFOV than survivors, suggesting that early application of HFOV may be advantageous.

In one study of 42 patients with ARDS, David and colleagues observed a higher mortality rate in patients who failed to improve their oxygenation in response to HFOV (change in

PaO₂/FiO₂ <50), compared with patients who responded [26]. Furthermore, the mortality rate in patients ventilated conventionally for ≥3 days prior to HFOV was 64%, compared with 20% mortality in patients ventilated conventionally for <3 days.

The largest observational study was published by Mehta and colleagues, who reported their experience with 156 patients

with severe ARDS at three academic hospitals [28]. HFOV was used as rescue therapy for patients failing CV, and the severity of illness and mortality rates were quite high (mean APACHE II score = 24, OI = 31, mortality = 61.7%). The authors reported a high rate of pneumothoraces (22%), and 26% of patients had HFOV discontinued because of difficulties with oxygenation, ventilation or haemodynamics. Predictors of poor outcome on multivariable analysis were older age, higher APACHE II score, lower pH and a greater number of CV days prior to HFOV. The most significant post-treatment predictor of mortality was the OI at 24 hours.

Two studies evaluated HFOV in very specific patient populations. Cartotto and colleagues reported significant improvements in oxygenation within 1 hour of initiating HFOV in 25 patients admitted to a specialized burn unit [29]. In trauma patients, Claridge and colleagues reported a significant and persistent improvement in oxygenation within 2 hours of initiation of HFOV [30].

Only two prospective, randomized controlled trials have compared HFOV with CV in adults, involving a total of 209 patients. The first trial enrolled 148 patients to evaluate the safety and efficacy of HFOV compared with CV [23]. They observed an early but nonsustained improvement in the PaO₂/FiO₂ ratio in the HFOV group compared with the control group, with similar complication rates in both groups. Although the trial was not powered to detect a mortality difference, there was a nonsignificant trend towards reduced 30-day mortality (37% versus 52%, $P=0.102$) in the HFOV group, which persisted at 90 days. This study has been criticized because the CV group received a higher tidal volume (8 ml/kg measured body weight, 10.6 ml/kg predicted body weight) and peak airway pressures (38 ± 9 cmH₂O at 48 hours) than are currently considered the standard of care following the publication of the ARDS Network trial results [4]. This trial, however, was designed prior to the publication of the ARDS Network trial.

The other randomized controlled trial was terminated prematurely after enrolment of 61 patients with ARDS, due to poor accrual. Bollen and colleagues found an early improvement in the OI in patients treated with HFOV, but no differences in mortality or failure of therapy between the HFOV and CV groups [24]. The results of this trial are difficult to interpret because of the small number of patients, as well as the baseline differences between the HFOV and CV groups in the OI (25 versus 18) and the PaO₂ (81 mmHg versus 93 mmHg), a lack of explicit ventilation protocols and an 18% crossover rate to the alternate arm.

The relative success of HFOV depends on the control ventilation strategy with which it is compared. Future randomized trials of HFOV in adults with ARDS will require thoughtful design of the conventional control strategy, consistent with the current lung-protective standard of care. Several

animal studies [14,31,32] show comparable physiological responses from HFOV and conventional mechanical ventilation when similar strategies are used for ventilation. There may therefore be no difference in outcome if both HFOV and CV are applied with a similar open lung-protective strategy.

In summary, a small number of studies show that the use of HFOV in adult patients with ARDS is associated with improvements in oxygenation, without a significant reduction in mortality. Application of HFOV early in the course of ARDS may be associated with improved outcomes. A recent Cochrane review that included one adult trial and one paediatric trial concluded that there was not enough evidence to demonstrate a morbidity or mortality benefit of HFOV over CV [33].

Haemodynamic effects of HFOV

Theoretically, haemodynamic compromise may occur during HFOV due to the higher mPaw, the consequent higher pleural pressure and the reductions in venous return and cardiac output. In a large observational study by Mehta and colleagues, 32 patients (20.5%) had a pulmonary artery catheter in place during HFOV [28]. Patients treated with HFOV had an early and nonpersistent increase in pulmonary artery occlusion pressure (PAOP), a small persistent increase in central venous pressure and a small decrease in cardiac output compared with baseline, associated with a mPaw increase of 8 cmH₂O. These findings are very similar to three previous clinical studies in adults reporting an early rise in central venous pressure and/or PAOP [17,18,26], and two other studies reporting a reduction in cardiac output with the application of HFOV [28,34]. Two paediatric studies also found significant reductions in cardiac output measured noninvasively in infants converted from CV to HFOV [35,36].

In contrast, the randomized trial by Derdak and colleagues found no significant differences in the heart rate, mean arterial blood pressure or cardiac output between HFOV and CV groups over the initial 72 hours of treatment [23]. Pulmonary artery catheters were present in 56% (42/75) of HFOV patients and in 51% (37/73) of CV patients. The PAOP was slightly higher in the HFOV group compared with the CV group throughout the initial 72 hours ($P=0.008$), and the central venous pressure and PAOP were significantly increased at 2 hours compared with baseline values.

The clinical significance of these haemodynamic effects is not known, as none of the studies have reported fluid or vasopressor administration at the time of HFOV initiation. A recent animal study [31] compared the impact of lung recruitment (up to 30 cmH₂O) on the haemodynamics and organ blood flow during HFOV and CV. Regardless of the ventilatory approach, at comparable mPaw the blood flow to the brain, kidneys and jejunum was maintained during recruitment. Organ perfusion was maintained despite

reductions in the mean arterial blood pressure, cardiac output and stroke volume, and increases in the left ventricular end-diastolic pressure, PAOP and intracranial pressure during both HFOV and CV.

Predictors of response to HFOV

One possible explanation for the lack of mortality benefit of HFOV is that the intervention is introduced too late in the course of ARDS. Three prospective trials and one retrospective trial identified the duration of CV prior to the initiation of HFOV as an independent predictor of mortality [17,18,26,28]. In addition, a recent systematic review found that the duration of CV prior to starting HFOV differed significantly between survivors and nonsurvivors [37]. When adjusted for age and the APACHE II score, each extra day on CV prior to starting HFOV was associated with a 20% higher mortality, although this association disappeared when pH was included in the multivariate analysis. The authors concluded that prolonged CV prior to HFOV was not related to mortality.

Although HFOV has not been shown to reduce mortality in patients with ARDS, there may be certain subgroups who benefit. Although Bollen and colleagues reported no mortality difference between the HFOV-treated and CV-treated groups, a *post-hoc* multivariate analysis, which included adjustment for the APACHE II score and age, showed that patients with a higher baseline OI had a lower odds ratio for mortality when treated with HFOV compared with CV [24]. This effect achieved statistical significance for patients with an OI >30.

Pachl and colleagues compared the effects of HFOV in 30 patients with ARDS due to pulmonary causes (for example, pneumonia, lung contusion) or extrapulmonary causes (for example, sepsis, pancreatitis) [20]. With the application of a similar HFOV strategy in these two groups, patients with extrapulmonary ARDS showed significant improvements in the PaO₂/FiO₂ ratio with HFOV, whereas patients with pulmonary ARDS showed no improvement. This may be due to more recruitable lung tissue present in patients with extrapulmonary ARDS, as shown by Gattinoni and colleagues during CV [38]. The poor response of patients with pulmonary ARDS, however, may have been due to a significantly longer duration of CV prior to HFOV than that for patients with extrapulmonary ARDS (10.7 days versus 4.95 days, $P=0.017$). Indeed, patients whose PaO₂/FiO₂ ratio improved during HFOV had a shorter duration of pretreatment with CV, and a higher baseline OI than nonresponders.

HFOV and adjunctive therapies

HFOV has been studied in conjunction with inhaled nitric oxide, recruitment manoeuvres (RMs) and prone positioning to further improve oxygenation. Mehta and colleagues administered inhaled nitric oxide at 5–20 ppm to patients receiving HFOV and found that 91% of patients

demonstrated at least a 20% improvement in the PaO₂/FiO₂ ratio, with an average improvement in the PaO₂/FiO₂ ratio of 37% [39]. The use of inhaled nitric oxide allowed significant reductions in FiO₂ within 8–12 hours of initiation. Mehta and colleagues postulated that alveolar recruitment during HFOV may increase the amount of the alveolar/capillary interface available for inhaled nitric oxide to act upon, potentially resulting in greater improvements in ventilation–perfusion matching than with each individual therapy.

Lung recruitment can take up to 12 hours with HFOV due to the low tidal volumes and the lack of ‘tidal recruitment’ [40,41]. The use of RMs may increase or hasten alveolar recruitment. Ferguson and colleagues evaluated the regular use of RMs in 25 adults with early ARDS [42]. They applied a series of three RMs (mPaw 40 cmH₂O for 40 s) at HFOV initiation, twice daily, and as needed for hypoxaemia. This strategy resulted in a significant and sustained improvement in oxygenation, which occurred more rapidly than reported in other HFOV studies [17,18,23]. Of note, oxygenation improvements associated with the RMs were greater during the initial days of HFOV. Only eight out of 244 (3.3%) RMs were aborted, mainly for transient hypotension.

Papazian and colleagues compared the impact of supine HFOV, prone HFOV and prone CV on 12-hour oxygenation in 39 patients with ARDS [11]. While both groups of prone patients (CV and HFOV) had similar and significant improvements in oxygenation, the supine HFOV group showed no improvement. These data are in contrast to previously published studies showing improvements in oxygenation following the initiation of HFOV [17,18,23,28]. The most probable explanation for this difference is that an insufficient airway pressure was applied during HFOV in Papazian and colleagues’ study. The average mPaw applied was only 25 cmH₂O, compared with >30 cmH₂O in previous studies [17,18,23,28]. The improvement in oxygenation in the prone HFOV group therefore probably reflects the effect of the change in position only, and not the combined effect of the two modalities. Furthermore, the 12-hour observation period may have been insufficient for maximal HFOV-induced lung recruitment, as other studies have shown that the maximal improvement in oxygenation occurs beyond 12 hours [17,23].

Strategies such as nitric oxide, prone positioning and RMs may further improve oxygenation in patients with ARDS who are being treated with HFOV, although there have been no demonstrated mortality benefits with any of these adjunctive therapies.

Predictors of mortality on HFOV

Many observational studies of HFOV have found a correlation between mortality and the APACHE II score, the OI or the duration of pretreatment with CV. In their large retrospective study, Mehta and colleagues found that independent predictors of mortality at baseline included age, the APACHE

Table 2**Initial parameters for high-frequency oscillatory ventilation**

| Parameter | Initiation settings |
|---|---|
| FiO ₂ | Same FiO ₂ that patient was receiving during conventional ventilation, adjust to SpO ₂ > 90% |
| Mean airway pressure (mPaw) | 3–5 cmH ₂ O higher than patient was receiving during conventional ventilation, titrate upward to reduce FiO ₂ below 0.6 |
| Bias flow | 40 l/min, titrate to exceed any spontaneous inspiratory efforts |
| Pressure amplitude of oscillation ('power' or ΔP) | Titrate to produce a 'wobble', or body movement, from shoulders to midhigh |
| Frequency | 5 Hz, then titrate to PaCO ₂ |
| Percentage inspiratory time | 33% |

II score, a low pH and a greater number of CV days prior to HFOV [28]. In addition, they reported that the most significant post-treatment predictor of mortality was the OI at 24 hours. This association was also observed by Derdak and colleagues, who found the 16-hour OI to be the most significant post-treatment predictor of outcome [23]. On the other hand, Bollen and colleagues found that the degree of early post-treatment improvement in OI was not associated with mortality [24].

Bollen and colleagues performed a systematic review of predictors of mortality in patients treated with HFOV [37]. In their analysis of nine trials (two randomized and seven observational), they found that survivors and nonsurvivors differed significantly in terms of age, prior time on CV, APACHE II score, pH and OI. On multivariate analysis, however, only the OI was found to be independently associated with mortality.

When and how to initiate HFOV, and challenges in management of patients on HFOV

Any patient with ARDS who remains hypoxaemic during CV can be considered for HFOV. ARDS is defined as the presence of bilateral infiltrates on chest radiograph, a PaO₂/FiO₂ ratio <200 mmHg and no clinical evidence of left ventricular failure. HFOV is not indicated for pure hypercapnic, nonhypoxaemic respiratory failure. In our intensive care unit we consider HFOV when patients require a FiO₂ >0.6 and a positive end-expiratory pressure >10 cmH₂O, or peak inspiratory pressures >35 cmH₂O. Suggested initiation settings for HFOV are presented in Table 2. Detailed management strategies for HFOV are beyond the scope of the present review, and have been summarized elsewhere [23,42,43].

Ventilation during HFOV should ideally occur in the 'safe zone' of the pressure–volume curve, avoiding both end-expiratory derecruitment and inspiratory overdistension. However, clinical assessment of optimal lung recruitment during

HFOV is challenging. We currently use chest radiography and gas exchange to assess recruitment. Luecke and colleagues demonstrated in an animal model that volumes measured by computed tomography during HFOV were equal to those predicted from static pressure–volume curves [44]. Brazelton and colleagues found that respiratory-inductive plethysmography could be used to accurately determine lung volumes during HFOV in an animal model [45], and Tingay and colleagues successfully used respiratory-inductive plethysmography to guide HFOV in neonates [46]. Unfortunately, the use of respiratory-inductive plethysmography and computed tomography are not practical in most intensive care units, and the latter carries with it the risks of transportation. In clinical practice, to find the 'safe zone' during HFOV, the mPaw can be titrated up the inflation limb (to recruit) and down the deflation limb (to find the least pressure required to keep the lung open) of the static pressure–volume curve, using oxygenation as an outcome. This technique may allow a substantial reduction in the mPaw while reducing haemodynamic consequences [42,44].

Unlike neonates, adult patients generally require deep sedation and neuromuscular blockade to tolerate HFOV. By design, the 3100B ventilator (Viasys Healthcare Inc., Yorba Linda, CA, USA) has inadequate bias flow to meet the inspiratory demands of many spontaneously breathing adults with ARDS, and a recent bench study showed that spontaneous breathing during HFOV resulted in considerable imposed work of breathing in adults [47]. Many patients with ARDS therefore experience discomfort or dyspnea with spontaneous inspiration during HFOV. They may generate large negative airway pressures causing fluctuations in the circuit mPaw. These fluctuations may be sensed by the 3100B ventilator as a circuit disconnection, which causes the ventilator to shut off.

There are unique challenges in caring for patients on HFOV. The continuous noise precludes cardiac and respiratory auscultation. Continuous patient movement during HFOV means that procedures such as central venous catheter

insertion or bronchoscopy are challenging. Suctioning is associated with alveolar derecruitment, especially with circuit disconnection, so routine suctioning should be avoided. If the patient requires transportation, there must be an adequate battery transport system and a good supply of compressed air and oxygen.

One of the most important potential advantages of HFOV compared with CV relates to the delivery of small tidal volumes. The tidal volume delivered during HFOV correlates directly with the pressure amplitude, and correlates inversely with the frequency. Neonates tolerate frequencies up to 15 Hz with adequate ventilation, whereas most studies in adults have applied frequencies between 3 and 6 Hz, which may be a cause for concern. At the low rates and high-pressure amplitudes used in adults, Sedek and colleagues showed that tidal volumes approaching CV can be delivered during HFOV [21]. In adults, therefore, clinicians should strive to apply the highest frequencies possible, within the limits of acceptable ventilation and pH.

HFOV is not effective in all patients. Of 156 patients treated with HFOV, Mehta and colleagues reported that 26% had HFOV discontinued due to difficulties with oxygenation, ventilation or haemodynamics [28]. For hypotension related to the higher intrathoracic pressures, cautious intravascular volume loading may be required to maintain the venous return and cardiac output during HFOV. The potential for barotrauma is a concern, given the high mPaw applied during HFOV. The risk of pneumothorax varies in the published studies, probably relating to differences in the patient populations. While Mehta and colleagues reported an incidence of 21.8% [28], most other HFOV studies found rates below 10%, similar to non-HFOV ventilation studies in the ARDS population (Table 1). In the two randomized controlled trials comparing HFOV and CV, the rate of pneumothorax or other air leak was similar in the two groups [23,24], suggesting that the high incidence of pneumothorax in the study by Mehta and colleagues was related to the severity of disease rather than the ventilation strategy.

Conclusions and future directions

HFOV can be safely applied in adults with ARDS, and is associated with initial improvements in oxygenation and adequate ventilation, but without any mortality benefit. These conclusions, however, are based on a small number of studies, of which only two are randomized controlled trials. Future studies should compare HFOV with an open lung-protective strategy to determine whether one strategy is superior, whether earlier initiation of HFOV might improve outcomes and whether certain subgroups of patients may derive greater benefit from HFOV.

Competing interests

SM has received honoraria from Viasys for speaking at medical conferences. JD declares no competing interests.

References

- Frank JA, Matthay MA: **Science review: mechanisms of ventilator-induced injury.** *Crit Care* 2003, **7**:233-241.
- Slutsky AS, Tremblay LN: **Multiple system organ failure. Is mechanical ventilation a contributing factor?** *Am J Respir Crit Care Med* 1998, **157**:1721-1725.
- Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: **Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial.** *JAMA* 1999, **282**:54-61.
- The Acute Respiratory Distress Syndrome Network: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.** *N Engl J Med* 2000, **342**:1301-1308.
- Slutsky AS, Drazen JM: **Ventilation with small tidal volumes.** *N Engl J Med* 2002, **347**:630-631.
- Imai Y, Kawano T, Miyasaka K, Takata M, Imai T, Okuyama K: **Inflammatory chemical mediators during conventional ventilation and during high frequency oscillatory ventilation.** *Am J Respir Crit Care Med* 1994, **150**:1550-1554.
- Takata M, Abe J, Tanaka H, Kitano Y, Doi S, Kohsaka T, Miyasaka K: **Intraalveolar expression of tumor necrosis factor-alpha gene during conventional and high-frequency ventilation.** *Am J Respir Crit Care Med* 1997, **156**:272-279.
- von der Hardt K, Kandler MA, Fink L, Schoof E, Dotsch J, Brandenstein O, Bohle RM, Rascher W: **High frequency oscillatory ventilation suppresses inflammatory response in lung tissue and microdissected alveolar macrophages in surfactant depleted piglets.** *Pediatr Res* 2004, **55**:339-346.
- Capoluongo E, Vento G, Santonocito C, Matassa PG, Vaccarella C, Giardina B, Romagnoli C, Zuppi C, Ameglio F: **Comparison of serum levels of seven cytokines in premature newborns undergoing different ventilatory procedures: high frequency oscillatory ventilation or synchronized intermittent mandatory ventilation.** *Eur Cytokine Netw* 2005, **16**:199-205.
- Vento G, Matassa PG, Ameglio F, Capoluongo E, Zecca E, Tortorolo L, Martelli M, Romagnoli C: **HFOV in premature neonates: effects on pulmonary mechanics and epithelial lining fluid cytokines. A randomized controlled trial.** *Intensive Care Med* 2005, **31**:463-470.
- Papazian L, Gainnier M, Marin V, Donati S, Arnal JM, Demory D, Roch A, Forel JM, Bongrand P, Bregeon F, Sainty JM: **Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome.** *Crit Care Med* 2005, **33**:2162-2171.
- Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB, Bryan AC: **Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology.** *J Appl Physiol* 1983, **55**:131-138.
- McCulloch PR, Forkert PG, Froese AB: **Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits.** *Am Rev Respir Dis* 1988, **137**:1185-1192.
- Sedek KA, Takeuchi M, Suchodolski K, Vargas SO, Shimaoka M, Schnitzer JJ, Kacmarek RM: **Open-lung protective ventilation with pressure control ventilation, high-frequency oscillation, and intratracheal pulmonary ventilation results in similar gas exchange, hemodynamics, and lung mechanics.** *Anesthesiology* 2003, **99**:1102-1111.
- Imai Y, Nakagawa S, Ito Y, Kawano T, Slutsky AS, Miyasaka K: **Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation.** *J Appl Physiol* 2001, **91**:1836-1844.
- Thome U, Gotze-Speer B, Speer CP, Pohlandt F: **Comparison of pulmonary inflammatory mediators in preterm infants treated with intermittent positive pressure ventilation or high frequency oscillatory ventilation.** *Pediatr Res* 1998, **44**:330-337.
- Fort P, Farmer C, Westerman J, Johannigman J, Beninati W, Dolan S, Derdak S: **High-frequency oscillatory ventilation for adult respiratory distress syndrome - a pilot study.** *Crit Care Med* 1997, **25**:937-947.
- Mehta S, Lapinsky SE, Hallett DC, Merker D, Groll RJ, Cooper AB, MacDonald RJ, Stewart TE: **Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome.** *Crit Care Med* 2001, **29**:1360-1369.
- van Genderingen HR, van Vught AJ, Jansen JR: **Regional lung**

- volume during high-frequency oscillatory ventilation by electrical impedance tomography. *Crit Care Med* 2004, **32**:787-794.
20. Pacht J, Roubik K, Waldauf P, Fric M, Zabrodsky Z: **Normocapnic high-frequency oscillatory ventilation affects differently extrapulmonary and pulmonary forms of acute respiratory distress syndrome in adults.** *Physiol Res* 2006, **55**:15-24.
 21. Sedeeq KA, Takeuchi M, Suchodolski K, Kacmarek RM: **Determinants of tidal volume during high-frequency oscillation.** *Crit Care Med* 2003, **31**:227-231.
 22. Pillow JJ: **High-frequency oscillatory ventilation: mechanisms of gas exchange and lung mechanics.** *Crit Care Med* 2005, **33**: S135-S141.
 23. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, Carlin B, Lowson S, Granton J, 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**:801-808.
 24. Bollen CW, van Well GT, Sherry T, Beale RJ, Shah S, Findlay G, Monchi M, Chiche JD, Weiler N, Uiterwaal CS, van Vught AJ: **High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial.** *Crit Care* 2005, **9**: 430-439.
 25. Andersen FA, Guttormsen AB, Flaatten HK: **High frequency oscillatory ventilation in adult patients with acute respiratory distress syndrome – a retrospective study.** *Acta Anaesthesiol Scand* 2002, **46**:1082-1088.
 26. David M, Weiler N, Heinrichs W, Neumann M, Joost T, Markstaller K Eberle B: **High-frequency oscillatory ventilation in adult acute respiratory distress syndrome.** *Intensive Care Med* 2003, **29**:1656-1665.
 27. Finkelman JD, Gajic O, Farmer JC, Afessa B, Hubmayr RD: **The initial Mayo Clinic experience using high-frequency oscillatory ventilation for adult patients.** *BMC Emerg Med* 2006, **6**:2.
 28. Mehta S, Granton J, MacDonald RJ, Bowman D, Matte-Martyn A, Bachman T, Smith T, Stewart TE: **High-frequency oscillatory ventilation in adults: the Toronto experience.** *Chest* 2004, **126**: 518-527.
 29. Cartotto R, Ellis S, Gomez M, Cooper A, Smith T: **High frequency oscillatory ventilation in burn patients with the acute respiratory distress syndrome.** *Burns* 2004, **30**:453-463.
 30. Claridge JA, Hostetter RG, Lowson SM, Young JS: **High-frequency oscillatory ventilation can be effective as rescue therapy for refractory acute lung dysfunction.** *Am Surg* 1999, **65**:1092-1096.
 31. David M, Gervais HW, Karmrodt J, Depta AL, Kempiski O, Markstaller K: **Effect of a lung recruitment maneuver by high-frequency oscillatory ventilation in experimental acute lung injury on organ blood flow in pigs.** *Crit Care* 2006, **10**:R100.
 32. Rimensberger PC, Pache JC, McKerlie C, Frndova H, Cox PN: **Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation and high-frequency oscillation.** *Intensive Care Med* 2000, **26**:745-755.
 33. Wunsch H, Mapstone J: **High-frequency ventilation versus conventional ventilation for the treatment of acute lung injury and acute respiratory distress syndrome: a systematic review and Cochrane analysis.** *Anesth Analg* 2005, **100**:1765-1772.
 34. David M, von Bardeleben RS, Weiler N, Markstaller K, Scholz A, Karmrodt J, Eberle B: **Cardiac function and haemodynamics during transition to high-frequency oscillatory ventilation.** *Eur J Anaesthesiol* 2004, **21**:944-952.
 35. Laubscher B, van Melle G, Fawer CL, Sekarski N, Calame A: **Haemodynamic changes during high frequency oscillation for respiratory distress syndrome.** *Arch Dis Child Fetal Neonatal Ed* 1996, **74**:F172-F176.
 36. Simma B, Fritz M, Fink C, Hammerer I: **Conventional ventilation versus high-frequency oscillation: hemodynamic effects in newborn babies.** *Crit Care Med* 2000, **28**:227-231.
 37. Bollen CW, Uiterwaal CSPM, van Vught AJ: **Systematic review of determinants of mortality in high-frequency oscillatory ventilation in acute respiratory distress syndrome.** *Crit Care* 2006, **10**:R34.
 38. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A: **Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes?** *Am J Respir Crit Care Med* 1998, **158**:3-11.
 39. Mehta S, MacDonald R, Hallett DC, Lapinsky SE, Aubin M, Stewart TE: **Acute oxygenation response to inhaled nitric oxide when combined with high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome.** *Crit Care Med* 2003, **31**:383-389.
 40. Froese AB: **The incremental application of lung-protective high-frequency oscillatory ventilation.** *Am J Respir Crit Care Med* 2002, **166**:786-787.
 41. Froese AB: **Role of lung volume in lung injury: HFO in the atelectasis-prone lung.** *Acta Anaesthesiol Scand* 1989, **Suppl 90**:126-130.
 42. Ferguson ND, Chiche J-D, Kacmarek RM, Hallett DC, Mehta S, Findlay GP, Granton JT, Slutsky AS, Stewart TE: **Combining high-frequency oscillatory ventilation and recruitment maneuvers in adults with early acute respiratory distress syndrome: the Treatment with Oscillation and an Open Lung Strategy (TOOLS) Trial pilot study.** *Crit Care Med* 2005, **33**:479-486.
 43. Mehta S, MacDonald R: **Implementing and trouble shooting high frequency oscillatory ventilation in adults in the ICU.** *Respir Care Clin N Am* 2001, **7**:683-695.
 44. Luecke T, Meinhardt JP, Herrmann P, Weisser G, Pelosi P, Quintel M: **Setting mean airway pressure during high-frequency oscillatory ventilation according to the static pressure-volume curve in surfactant-deficient lung injury: a computed tomography study.** *Anesthesiology* 2003, **99**:1313-1322.
 45. Brazelton TB III, Watson KF, Murphy M, Al Khadra E, Thompson JE, Arnold JH: **Identification of optimal lung volume during high-frequency oscillatory ventilation using respiratory inductive plethysmography.** *Crit Care Med* 2001, **29**:2349-2359.
 46. Tingay DG, Mills JF, Morley CJ, Pellicano A, Dargaville PA: **The deflation limb of the pressure-volume relationship in infants during high-frequency ventilation.** *Am J Respir Crit Care Med* 2006, **173**:414-420.
 47. Van Heerde M, van Genderingen HR, Leenhoven T, Roubik K, Plotz FB, Markhorst DG: **Imposed work of breathing during high-frequency oscillatory ventilation: a bench study.** *Crit Care* 2006, **10**:R23-R29.