

## Review

**Clinical review: High-frequency oscillatory ventilation in adults – a review of the literature and practical applications**Frank V Ritacca<sup>1</sup> and Thomas E Stewart<sup>2,3</sup><sup>1</sup>Clinical Fellow, Division of Respiriology and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada<sup>2</sup>Associate Professor, Division of Respiriology and Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada<sup>3</sup>Director, Critical Care Unit, Mount Sinai Hospital and University Health Network, University of Toronto, Toronto, Ontario, Canada

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**Abstract**

It has recently been shown that strategies aimed at preventing ventilator-induced lung injury, such as ventilating with low tidal volumes, can reduce mortality in patients with acute respiratory distress syndrome (ARDS). High-frequency oscillatory ventilation (HFOV) seems ideally suited as a lung-protective strategy for these patients. HFOV provides both active inspiration and expiration at frequencies generally between 3 and 10 Hz in adults. The amount of gas that enters and exits the lung with each oscillation is frequently below the anatomic dead space. Despite this, gas exchange occurs and potential adverse effects of conventional ventilation, such as overdistension and the repetitive opening and closing of collapsed lung units, are arguably mitigated. Although many investigators have studied the merits of HFOV in neonates and in pediatric populations, evidence for its use in adults with ARDS is limited. A recent multicenter, randomized, controlled trial has shown that HFOV, when used early in ARDS, is at least equivalent to conventional ventilation and may have beneficial effects on mortality. The present article reviews the principles and practical aspects of HFOV, and the current evidence for its application in adults with ARDS.

**Keywords** acute lung injury, acute respiratory distress syndrome, high-frequency oscillatory ventilation, mechanical ventilation, ventilator-induced lung injury

**Introduction**

The development of the positive pressure mechanical ventilator in the 1950s marked a significant achievement in the care of patients with respiratory failure, and was a cornerstone in the establishment of the discipline of critical care medicine. Since then, we have learned that although mechanical ventilation is often life saving, it can also be injurious, especially in patients suffering from acute respiratory distress syndrome (ARDS) [1]. ARDS can also result in refractory hypoxemia, which can often stimulate attempting nonconventional ventilation strategies such as using nitric oxide, recruitment maneuvers, or prone positioning. High-frequency oscillatory ventilation (HFOV) has emerged as one such rescue strategy for adults with ARDS. Moreover, given that it appears to

injure the lung less than conventional modes of ventilation, it may also be ideally suited to use early in ARDS.

HFOV fits within the spectrum of the other high-frequency ventilation modes whose common underlying concept is the delivery of breaths at high frequencies and low tidal volumes ( $V_t$ ), which are often below the anatomic dead space. The high-frequency modes are generally divided into those in which the expiratory phase is passive and those in which expiration is active. High-frequency jet ventilation and high-frequency positive pressure ventilation are examples of devices employing passive expiration.

High-frequency positive pressure ventilation was first developed in the 1960s and typically uses a flow generator that is

$\Delta P$  = oscillatory pressure amplitude; ARDS = acute respiratory distress syndrome;  $FiO_2$  = fractional inspired concentration of oxygen; HFOV = high-frequency oscillatory ventilation;  $PaO_2$  = pressure of arterial oxygen;  $P_{aw}$  = mean airway pressure; PEEP = positive end-expiratory pressure;  $V_t$  = tidal volume.

time cycled and achieves flow rates of 175–250 l/min. The respiratory rate is usually 60–100 breaths/min and achieves  $V_t$  values of 3–4 ml/kg. Although theoretically attractive, this mode seems to offer little advantage over conventional ventilation in patients with lung injury and, as such, application is limited. In high-frequency jet ventilation, gas is delivered through a small cannula under high pressures (70–350 kPa) and, combined with entrainment of humidified gas by the Venturi effect, adequate tidal volumes are achieved. Although high-frequency jet ventilation is sometimes used in patients with bronchopleural fistulae, most centers limit their use to rescue situations. For more detailed reviews of these modes of ventilation, the reader is referred to a few of the many reviews on these topics [2,3].

HFOV is similar to other high-frequency modes in that effective oxygenation is achieved by the application of high mean airway pressure ( $P_{aw}$ ). As previously discussed, however, HFOV differs in that expiration is an active process controlled by the ventilator. Theoretically, this results in improved  $CO_2$  elimination and reduced gas trapping. The present article reviews the rationale for the use of HFOV as a ventilatory strategy in adults, reviews practical issues for intensivists using this modality, and reviews the evidence supporting its use in adult patients with ARDS.

### A need for novel modes of ventilation

Despite the fact that patients with respiratory failure often require positive pressure mechanical ventilation, it has become clear that mechanical ventilation using conventional strategies can be harmful. Gross barotrauma resulting in extraparenchymal air in the forms of pneumothorax, pneumomediastinum, or subcutaneous emphysema are obvious examples of the detrimental effects of mechanical ventilation [4]. However, more subtle microscopic damage can also occur in lungs that have been subjected to mechanical ventilation.

This damage has been termed ventilator-induced lung injury, and can mimic the histological, radiographic, and clinical changes that occur in patients with ARDS [5]. The damage is thought to result from excess airway pressures (barotrauma), from high lung volumes (volutrauma), or from the repetitive opening and closing of collapsed lung units with successive tidal breaths (atelectrauma) [6]. Evidence for this comes from numerous studies in animals, which have shown that the ventilator can induce pathologic changes in normal lungs and have shown that strategies minimizing these effects are beneficial [6–9]. In addition, we now know that lung injury itself (ventilator induced or otherwise) can propagate the proinflammatory cytokine cascade (biotrauma) and can contribute to the development of multisystem organ failure in humans with ARDS [10,11]. It is important to note that multisystem organ failure is often the cause of death in those patients that die from ARDS [12–14].

Previous ventilator strategies have focused on normalization of arterial blood gases [15]. The tidal volumes and subse-

quent airway pressures needed to achieve these goals are typically safe in normal lungs; however, it is currently felt that these levels are probably injurious in patients with lung injury, where the same volumes are delivered to a much smaller lung volume, resulting in overdistension [16]. Two large randomized, controlled trials in humans with ARDS have shown that ventilatory strategies limiting overdistension using low tidal volumes can have a mortality benefit [17,18]. One of these studies also included efforts to recruit collapsed lung units and to keep these units open [18]. The benefit of 'opening' the lung either with recruitment maneuvers, with application of higher levels of positive end-expiratory pressure (PEEP), or with high  $P_{aw}$ , such as that achieved with HFOV, is more controversial because recruitment with any of these strategies can result in overdistension of more 'normal' lung regions. Overall, the use of these techniques is supported by a large body of animal literature for the use of PEEP [19–22] and, to a lesser degree, by clinical trials [18,23,24]. There is also some suggestion that the benefit of recruitment maneuvers themselves depends on several patient-specific factors [25].

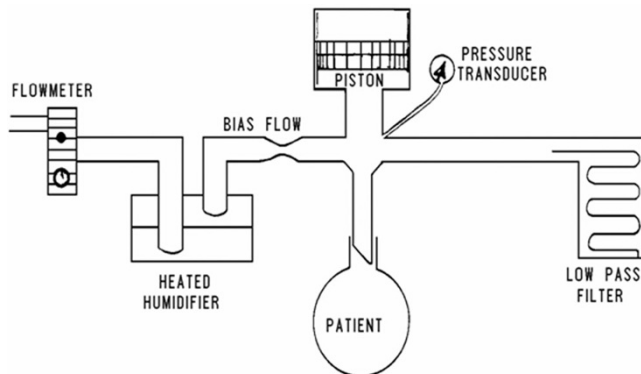
Lung protective strategies in ARDS are currently aimed at reducing plateau airway pressures and tidal volumes, and at attempting to have an open lung [26]. Based on this rationale, the high  $P_{aw}$  in conjunction with small  $V_t$  values appears to make HFOV ideally suited as a lung protective strategy.

### High-frequency oscillatory ventilation

The potential of high-frequency ventilation in humans has been studied since the observation that adequate gas exchange occurred in panting dogs with tidal volumes lower than the anatomic dead space [27]. In the 1970s, groups in Germany and Canada found a system that oscillated gas into and out of an animal's lungs was effective at  $CO_2$  elimination [28,29]. Commercial products are now available for children and for adults.

These ventilators operate on the following principle (Fig. 1). A bias flow of fresh, heated, humidified gas is provided across the proximal endotracheal tube. The bias flow is typically set at 20–40 l/min, and the  $P_{aw}$  at the proximal endotracheal tube is set at a relatively high level (25–35 cmH<sub>2</sub>O). An oscillating piston pump akin to the woofer of a loudspeaker vibrates this pressurized, flowing gas at a frequency that is generally set between 3 and 10 Hz. A portion of this flow is thereby pumped into and out of the patient by the oscillating piston. The  $P_{aw}$  achieved is sensitive to the rate of bias flow but can be adjusted by varying the back pressure on the mushroom valve through which the bias flow vents into the room. The  $P_{aw}$  can thus be modified by either adjusting the bias flow rate or the back pressure.

The set power on the ventilator controls the distance that the piston pump moves and, hence, controls the  $V_t$ . The result is a visible wiggle of the patient's body, which is typically titrated to achieve acceptable  $CO_2$  elimination. The oscilla-

**Figure 1**

Schematic representing the major functioning parts of the high-frequency oscillatory ventilator. See text for a detailed explanation. Reproduced with permission from SensorMedics, Yorba Linda, California, USA [[www.viasyshealthcare.com](http://www.viasyshealthcare.com)].

tory pressure amplitude ( $\Delta P$ ) is measured in the ventilator circuit and is therefore only a surrogate of the actual pressure oscillations in the airways. These pressures are generally greatly attenuated through the endotracheal tube and larger airways so the pressure swings in the alveoli are much less. The  $P_{aw}$ , on the other hand, is believed to be similar in the ventilator circuit and the alveoli.

The operator uses the parameters of power (which results in  $\Delta P$ ) and frequency (reductions in which improve  $\text{CO}_2$  clearance) to manipulate the  $V_t$ . It seems counterintuitive that reductions in frequency would improve alveolar ventilation; however, HFOV differs from conventional ventilation in that the lung never achieves an equilibrium volume during inspiration and expiration. Lowering the frequency therefore allows more time for a larger  $V_t$  to occur. With HFOV,  $\text{CO}_2$  elimination is proportional to the  $V_t$  and the frequency, but increases in the  $V_t$  achieved by lowering the frequency are thought to more than compensate for the reduction in frequency. It is also important to note that the actual  $V_t$  received by the patient depends on a number of factors, including the size of the endotracheal tube, the airway resistance, and the compliance of the total respiratory system. Unfortunately, there are no predictable relationships between power and  $\Delta P$  with the  $V_t$  received by the patient. In addition, the  $V_t$  can change on a breath-to-breath basis, and therefore ventilator settings are used with clinical factors such as the amount of wiggle in monitoring the patient.

As with conventional ventilation, oxygenation is primarily determined by the  $P_{aw}$ , by the lung volume, and by the fractional inspired concentration of oxygen ( $\text{FiO}_2$ ). The initial settings are typically chosen to achieve a  $P_{aw}$  value roughly  $5 \text{ cmH}_2\text{O}$  greater than that achieved with conventional ventilation. Failure to adequately oxygenate the patient is frequently remedied by increasing the  $P_{aw}$  or the  $\text{FiO}_2$ . There is no evidence guiding exactly how ventilator adjustments

should be made in the hypoxemic patient on HFOV. Generally, when  $\text{FiO}_2 > 0.6$ , our approach has been to increase the  $P_{aw}$ . These increases are made slowly to give time for alveolar recruitment and to assess for cardiovascular impairment. In addition, these increases are frequently made in conjunction with a recruitment maneuver.  $P_{aw}$  values as high as  $35\text{--}45 \text{ cmH}_2\text{O}$  have been used and tolerated [30,31]. In our experience, a higher  $P_{aw}$  may result in hemodynamic impairment, especially if the intravascular volume is inadequate. Should significant derecruitment from oscillator disconnects or circuit changes occur, our experience suggests that recruitment maneuvers are also helpful in this situation. Many pediatric and adult trials using HFOV (discussed later), however, have not utilized such an approach. Once the patient improves and the  $\text{FiO}_2$  can be decreased to below  $0.6\text{--}0.4$ , the  $P_{aw}$  is generally weaned slowly, decreasing  $P_{aw}$  by  $1\text{--}2 \text{ cmH}_2\text{O}$  and assessing response.

As already described, one of the theoretical advantages of HFOV over other high-frequency modes is the decoupling of oxygenation and  $\text{CO}_2$  elimination. Ventilation is determined by changes in power (a surrogate for  $V_t$ ) and in frequency. Simply increasing the power will often result in improved ventilation. Once this is maximized, the frequency can be reduced. One must, however, keep in mind that these steps may lead to larger tidal volumes (as already mentioned) and to larger pressure swings at the alveoli, and as a result may lead to the potential to negatively impact on lung protection [30–32]. Finally, deflation of the endotracheal tube cuff may help eliminate  $\text{CO}_2$  by allowing the front of fresh gas to be advanced to the distal end of the endotracheal tube, allowing a slight reduction of the anatomic dead space, which may be significant in situations when the  $V_t$  is small. However, this may sacrifice the ability to maintain a high  $P_{aw}$ .

### Potential disadvantages of HFOV

Patients on HFOV often require heavy sedation and/or neuromuscular blockade, which may be problematic, especially in view of evidence supporting a benefit to daily waking of sedated mechanically ventilated patients [33]. Such an approach is often not possible in patients requiring HFOV. Suctioning patients on HFOV can be achieved using a closed inline system that does not require the patient to be disconnected from the oscillator. The extent to which this prevents derecruitment is not clear. In addition, a higher  $P_{aw}$  may explain the reductions in cardiac preload that are occasionally seen with HFOV. Consequently, fluid balance needs to be carefully monitored as hypoxemia can, at times, be exacerbated by relative hypovolemia. Transportation out of the intensive care unit on the oscillator is currently not possible. Procedures like bronchoscopy may also lead to loss of  $P_{aw}$ . Other potential disadvantages include loss of the ability to auscultate the lung, the heart, and the abdomen, and difficulty in recognizing pneumothorax, right mainstem bronchus intubation, and endotracheal tube dislodgement (in these situations, patient wiggle will decrease and  $\Delta P$  will increase).

Patients are switched back to conventional mechanical ventilation when they are able to tolerate a lower  $P_{aw}$  (currently 20–24 cmH<sub>2</sub>O). However, the ideal timing is unknown and further work is required. Unlike in neonates, we know of no experience with transitioning adults directly to extubation from HFOV. The modest bias flow rates, which for the most part are insufficient to allow spontaneous respiratory efforts, are probably the primary reason that this has not occurred.

### Evidence for use of HFOV in adults

The use of HFOV has been extensively studied in the neonatal and pediatric populations. A number of studies did not show any significant benefit of HFOV over conventional ventilation in preventing chronic lung disease [34–37]. Two further studies have recently been released regarding HFOV in neonates, and are two of the largest to date in this field. Johnson and colleagues randomized 800 infants to HFOV versus conventional ventilation, and found no significant difference in mortality rates, chronic lung disease, or adverse events in the two groups [38]. In contrast, the study by Courtney and colleagues, which randomized a similar number of infants, found a significant benefit of HFOV over conventional ventilation in terms of earlier extubation and survival without oxygen therapy [39]. This study differed in that the infants were very high risk (600–1200 g at birth) and the ventilation protocols were more tightly controlled, suggesting that HFOV might be most useful if used in a uniform way in a well-defined population [40]. In contrast to the number of studies in neonates, where HFOV appears to have found a permanent home, evidence for HFOV in adults with lung injury is limited.

HFOV has until recently mostly been investigated as a rescue therapy for patients with ARDS who are failing conventional mechanical ventilation, because of difficulty in achieving either adequate ventilation or oxygenation within safe ventilator parameters. Two case series with a total of 41 ARDS patients provided encouraging results suggesting that HFOV may be beneficial in these patients [30,31]. Mehta and colleagues studied 24 patients with severe ARDS (lung injury score =  $3.4 \pm 0.6$  [41], pressure of arterial oxygen [ $PaO_2$ ]/ $FiO_2$  ratio =  $98.8 \pm 39.0$ ) failing conventional ventilation (determined by ongoing hypoxemia or high plateau pressures), and showed that HFOV could achieve an improvement in the  $PaO_2$ / $FiO_2$  ratio within 8 hours [31]. Fort and colleagues studied 17 patients also with severe ARDS (lung injury score =  $3.81 \pm 0.23$ ,  $PaO_2$ / $FiO_2$  ratio =  $68.6 \pm 21.6$ ) deemed to be failing conventional ventilation, and found similar improvements in oxygenation [30]. Both studies suggested that mortality was improved in patients who had fewer pre-oscillator ventilator days. Although refractory hypoxemia can be problematic in managing patients with ARDS, multiple organ failure (possibly exacerbated by biotrauma) is often the cause of the patient's death [12–14]. It is therefore reasonable to assume that any ventilation strategy, if it is to be effective at achieving a mortality benefit, must be applied early in the course of illness and/or before biotrauma begins.

A prospective, multicenter, randomized study has recently been published. The Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial investigators randomized 150 patients with ARDS to HFOV (starting frequency = 5 Hz,  $P_{aw}$  = 5 cmH<sub>2</sub>O greater than that on conventional ventilation) or to conventional ventilation using pressure control, with aims of achieving a  $V_t$  of 6–10 cm<sup>3</sup>/kg actual body weight [42]. The patients in this study were ventilated conventionally for an average of 2–4 days prior to randomization. The primary outcome measure was survival without need for mechanical ventilation at 30 days. There was no significant difference between groups in the primary outcome measure. However, there was a nonsignificant trend towards a lower mortality at 30 days with HFOV versus conventional ventilation (37% versus 52%,  $P=0.102$ ). This trial was only powered to detect equivalency, and therefore interpreting trends in the data should be done with caution. In addition, there was a significant improvement in the  $PaO_2$ / $FiO_2$  ratio ( $P=0.008$ ) with HFOV for the first 24 hours, but this effect did not persist. Similar to the previous uncontrolled studies, the use of HFOV appeared to be safe, with no increased rates of barotrauma or hemodynamic instability. It should be noted that the control arm of this study may not be considered the gold standard of ventilation in ARDS today, and volume recruitment maneuvers, which may be important [43], were not incorporated into either arm of this study or any of the previous pilot studies of HFOV in adults [30,31]. Despite this, the results are very encouraging and point to the need for further investigation.

There are several unanswered questions regarding HFOV in adults. These include the ideal timing of the intervention, the proper use of adjuncts like volume recruitment maneuvers, prone position, or nitric oxide, the ideal timing of discontinuation, the proper methods to manipulate the various indices such as  $P_{aw}$ ,  $\Delta P$ , and frequency, and the effects on long-term outcomes such as lung function.

### Conclusion

It is becoming increasingly clear that conventional mechanical ventilation can lead to lung injury through overdistension, high pressures, and recurrent opening and closing of collapsed alveoli, all possibly mediated through the release of proinflammatory mediators. HFOV seems ideally suited as a lung protective strategy because of its theoretical ability to minimize many of these potential adverse effects. Although many studies of HFOV in neonates and in pediatric populations have been performed and have shown it to be a safe alternative to conventional ventilation, studies in adults with ARDS are few in number, and it is unclear whether HFOV truly offers benefit over the current best conventional strategies. In addition, many of the theoretical benefits of HFOV are unproven, and the lung volumes achieved while using high mean airway pressures and various frequencies are unknown. Despite advances in mechanical ventilation, mortality for ARDS remains high. Measures that potentially reduce mortality or intensive care unit

length of stay deserve further investigation. HFOV may represent advancement in care of these patients, although the optimal strategy of use in adults remains unknown.

## Competing interests

None declared.

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