HIGH FREQUENCY OSCILLATION

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It is more than 15 years since high frequency oscillatory ventilation (HFOV) was first described as a technique of ventilation [1]. In the intervening period it has passed through a phase of being a physiological curiosity, where it could be demonstrated that normal gas exchange could be maintained using tidal volumes much smaller than deadspace at rates much greater than what was then considered appropriate for mechanical ventilation. As it was shown to work very effectively in normal lungs, the next logical step was to see if the system was a viable alternative ventilation strategy in the severely diseased lung. This led to HFOV being first used, principally as a rescue operation in neonates with respiratory failure in whom conventional ventilation techniques had failed. Several studies have shown that when changing from conventional mechanical ventilation (CMV) to HFOV in these infants, \( P_{aCO_2} \) tensions may be reduced rapidly from the previously increased values using lower airway pressures, although it has been difficult to show any dramatic improvement in \( P_{aO_2} \) [2, 3].

Although HFOV has achieved some acceptance as an alternative ventilation technique in the management of newborn respiratory failure, there are still substantial gaps in our understanding of exactly how the system works, despite a considerable amount of research. In a recent review on high frequency ventilation, Froese and Bryan [4] pointed to the increasing number of publications on the subject, many repetitious, frequently with contradictory results; this has led to considerable confusion as to what role, if any, HFOV has as a mode of ventilation in clinical practice. All the original HFOV studies performed on animals with normal lungs were of short duration and the technology, in terms of ventilator design and circuitry, was relatively simple. If HFOV is to represent a genuine advance in respiratory management, it needs to be tested on more challenging models of lung disease.

There is no rationale for considering HFOV as just “another ventilator” which happens to operate at faster rates and lower airway pressures than CMV, without a clear understanding of the situations in which these features may be a considerable advantage in patient management.

There are four indications for which a clear case can be made for considering the use of HFOV in preference to CMV:

1. to minimize the effects on cardiovascular function by reducing airway pressures;
2. to improve operating conditions in some procedures on the airway and lung;
3. to achieve more effective elimination of carbon dioxide in situations in which this may be particularly important, for example persistent pulmonary hypertension of the newborn (PPHN);
4. to minimize the effect of secondary or therapy-induced lung injury in situations of diffuse parenchymal lung disease with hypoxia, such as the infant (IRDS) or adult (ARDS) respiratory distress syndromes.

It is in this last situation of acute lung injury that the best case can be made for an alternative ventilation strategy, for we have been slow to realize that, in this particular instance, the therapy is very much part of the disease. The conventional ventilator cycle produces not only a convective flow of gas to sweep carbon dioxide out of the lung, but it has to produce a pressure within the lung in excess of alveolar “opening pressure” in order to achieve oxygen exchange. In the low compliant, atelectatic lung, such as occurs with acute lung injury, airway pressure during the expiratory phase of the ventilatory cycle decreases below closing pressure, unless high positive end expiratory pressures (PEEP) are used. If high PEEP is omitted, the constant opening and closing of terminal airway units under high pressure result in further injury to the already damaged lung [5]. HFOV offers a different technique for
dealing with this type of lung disease. In the first instance, high volume cycling is not necessary to eliminate carbon dioxide, as numerous studies attest to the excellent control of $P_{a\text{CO}_2}$. Increasing airway pressure by adjusting fresh gas flow may be used as a device to increase MAP to greater than alveolar opening pressure and maintain that lung volume, at which the small airway pressure variations around the mean are less injurious to the lung by avoiding the continual cycle of inflation and collapse of terminal lung units.

If there is a role for HFOV as an alternative to CMV, it must be shown to be demonstrably superior in terms of being less injurious to the lung in diseases such as IRDS and ARDS. In the past there has been a tendency to consider these two as entirely different diseases, not only in terms of causation, which seems inherently obvious, but also as being characterized by different pathological changes. Although hyaline membrane formation occurs in both IRDS and ARDS, the other hallmarks of acute lung injury, such as oedema and neutrophil sequestration within the lungs, were considered previously to occur only in ARDS. However, we now realize that these are present also in IRDS. Merritt and colleagues [6] have observed large numbers of polymorphonuclear leucocytes (PMN) in the tracheal aspirate of infants with severe IRDS who progress to develop bronchopulmonary dysplasia, in addition to increased concentrations of elastase and proteinase. Jefferies, Coates and O’Brodovich [7] have shown that premature infants with IRDS develop a true permeability oedema, such as occurs in ARDS. Therefore, the lung has a limited repertoire of responses to injury, regardless of age. It is interesting to observe that, with surfactant replacement therapy now well established as treatment for IRDS, the first clinical trials of artificial surfactant therapy in ARDS are now being started.

Animal studies of HFOV in acute lung injury

In order to establish if HFOV is less injurious to the lung in situations such as these, several groups of investigators have attempted to produce a valid animal model of acute lung injury and then to assess the effects of ventilation on the damaged lung. The Toronto group has used the surfactant-depleted lung produced by repeated lavage, a technique described first by Lachmann, Robertson and Vogel [8]. They have shown conclusively that, by both blood-gas and pathological criteria, HFOV causes less damage to the

![Fig. 1. $P_{a\text{O}_2} v. time$ in a lung lavage model treated with HFOV (four survivors; one death) and CMV (five deaths). PL = Lung lavage; SI = sustained inflation or sigh manoeuvre. Note the improved $P_{a\text{O}_2}$ and survival in the HFOV-treated group compared with CMV. † Time of death and last $P_{a\text{O}_2}$ before death. (Reproduced, with permission, from [9].)
injured lung than CMV at matched mean airway pressures, using what they have termed their “open lung strategy” [9]. When they subjected the animals to lavage and rendered the lungs surfactant-depleted and poorly compliant, they were unable initially to demonstrate any difference between the modes of ventilation, until they used a sustained inflation or “sigh” manoeuvre of 1.5 kPa for 15 s. Following this, they produced excellent oxygenation in the HFOV group animals while in the CMV group the animals remained hypoxic and died from pressure related complications (fig. 1). Postmortem histology of the lungs in this study also showed some striking differences: those treated with CMV had changes consistent with severe lung damage as seen in ARDS (hyaline membrane formation, PMN infiltration and oedema formation), while the lung histology in the HFOV group was normal (fig. 2). This study led to an appreciation that, in the presence of the diffusely atelectatic lung, both modes of ventilation were equally injurious unless the lung was subjected to a pressure greater than opening pressure by a sustained inflation, and maintained at that volume. In the case of HFOV this was achieved readily by a 15-s inflation while, with CMV, the lung rapidly became atelectatic again after such a manoeuvre, despite the use of PEEP.

Fig. 2. Uninflated lung sections from CVB-treated animals (top) and HFOV-treated animals (bottom). Note the marked hyaline membrane formation (arrows) and PMN sequestration in the CMV group compared with the normal appearance of the lung in the HFOV-treated animals. (Reproduced, with permission, from [9].)

Fig. 3. \( F_{\text{IO}_2} \), mean airway pressure and \( a:\text{A} \) oxygen ratio in the premature baboon model of IRDS treated with HFOV (△) and CMV (○). The HFOV-treated animals had lower \( F_{\text{IO}_2} \) requirements, lower airway pressures and higher \( a:\text{A} \) oxygen ratios than the CMV-treated group. Higher \( a:\text{A} \) ratio indicates better oxygenation on lower \( F_{\text{IO}_2} \). (Reproduced, with permission, from [10].)
The group from San Antonio, Texas has chosen to use another model of lung injury analogous to IRDS [10, 11]. Their model was the premature baboon, which shows all the characteristics of IRDS, with severe hyaline membrane formation in the lung. They compared the outcome in baboons treated with HFOV with those treated with CMV and showed that mortality was clearly greater in CMV-treated animals, which typically showed the effects of severe pulmonary barotrauma at postmortem. In contrast, the HFOV-treated animals survived much longer with better gas exchange, required smaller FiO₂ and airway pressures, and had little evidence of pulmonary barotrauma at postmortem (fig. 3). Furthermore, when they performed pressure-volume curves on the excised lungs at postmortem there was a striking difference between the two groups: the curve in the CMV group was almost flat with little or no change in volume with incremental increases in distending pressure, while the curve in the HFOV-treated animals showed a relatively normal configuration (fig. 4).

Clinical studies of HFOV in acute lung injury

At the same time as these animal studies were being performed, reports of the use of HFOV in infants with IRDS were appearing in the literature which suggested that effective gas exchange could be maintained at lower mean airway pressures than used on CMV. However, in all these studies, the change to HFOV had been made only after CMV had been used for a substantial period and failed; all these infants had substantial degrees of underlying barotrauma. It was not clear if the early introduction of HFOV in neonates with IRDS requiring ventilation would decrease the frequency of ventilation and oxygen induced chronic lung injury. In order to answer these questions, the National Institutes of Health sponsored a multicentre randomized trial in North America comparing HFOV with CMV in infants of 750–2000 g birthweight requiring positive pressure ventilation in the treatment of ventilatory failure in the first 24 h of life and who had been treated with CMV for less than 12 h. All premature infants in the 750–1250 g group were eligible for study, while in the 1250–2000 g infants the ratio PaO₂ (mm Hg)/FiO₂ had to be < 100 with a mean airway pressure (MAP) 0.9 kPa. Eleven major neonatal centres in North America participated and 673 preterm infants were studied. The major end point of the study was the frequency of bronchopulmonary dysplasia (BPD). There was a crossover category in which infants could be changed from one mode of ventilation to another after randomization, which was defined as a treatment failure. The crossover criteria were:
FIG. 5. Frequency of intraventricular haemorrhage (IVH) and bronchopulmonary dysplasia (BPD) in the multicentre HFOV trial comparing the frequency from all centres (NIH, 673 infants) with that from an outborn and inborn centre which contributed approximately equal numbers of patients to the trial (inborn 59, outborn 56). This difference was not statistically significant. ■ = HFOV; □ = CMV.

$P_{aCO_2} > 8.6 \text{kPa and } P_{aO_2} < 6.0 \text{kPa with } F_{IO_2} = 1.0$ and MAP of at least $1.5 \text{kPa; } P_{aO_2} < 4.6 \text{kPa with } F_{IO_2} = 1.0$ and MAP at least $1.5 \text{kPa}; P_{aCO_2} > 10 \text{kPa}$. The results of the study have been published recently and, as far as the exponents of HFOV are concerned, are apparently disappointing [12]. There was no difference in BPD in the two groups according to the established criteria of the requirement for supplementary oxygen and abnormal chest x-ray findings persisting to the 28th day. What was more disturbing was the finding that there was reported to be a statistically increased incidence of intraventricular haemorrhage (IVH) in the HFOV-treated group.

It is difficult to reconcile these disappointing results in terms of BPD with the clear superiority of HFOV demonstrated in the two animal models of lung injury mentioned previously. It is even more difficult to understand the higher frequency of IVH associated with the use of HFOV in the multicentre trial. There has been some criticism of the design of the trial, particularly centred on the inexperience of many of the centres in the use of the new technology, and this may help to explain the similar frequency of air leak with BPD, but it needs more careful scrutiny of the data to discover the reason for the greater incidence of IVH.

At the outset, it is difficult to reconcile the wide discrepancy between the frequency of IVH reported by different centres, which varied from 4 to 48%. Further scrutiny of the data from the trial provides the answer. A comparison was made of the results from two different neonatal centres which contributed similar numbers to the multicentre study; one dealt exclusively with outborn babies and the other only with inborns. These data showed that the incidence of IVH with HFOV was much greater than CMV in the outborn unit, while this was reversed in the inborn (fig. 5). Furthermore, this very high rate of IVH (48%) in the outborn unit was the major factor in the total IVH rate reaching statistical significance in the study as a whole. When comparing mortality, the incidence of BPD and air leaks, the results from the outborn centre were also clearly worse compared with the inborn centre (fig. 5). The obvious explanation may seem to be that outborn babies are sicker and have been subjected to longer periods of CMV before the change to HFOV, which may have induced lung damage before they entered the study. If this were true, the incidence of BPD and air leak should have differed also between the outborn and inborn centres in those babies treated with CMV—which it did not. The real explanation lies in the frequency of crossovers from HFOV to CMV. In the outborn centre, 44% of babies were crossed from HFOV, compared with 3% in the inborn. Most of these crossovers came under a clause of "physician discretion", which was not part of the original procedure, but which some centres began applying during the trial. This perhaps demonstrates a lack of belief in the efficacy of HFOV, but unfortunately unbalances the study and makes it difficult to interpret the data. However, the results of this trial will be sufficient to cast a shadow over HFOV in the management of IRDS, particularly as physicians are likely to focus on the IVH data. It is worth emphasizing
that the results from the inborn centre show a lower incidence of IVH in infants treated with HFOV.

CONCLUSION

Is HFOV still a credible alternative ventilation technique, or is it merely a “flash in the pan”, relegated to be a mere physiological curiosity? Will the further development of HFOV be stunted by some of the interesting developments in surfactant replacement therapy, both in ARDS and in IRDS [13]? Is neonatal Extracorporeal Membrane Oxygenation (ECMO) [14], which is becoming increasingly in vogue in North America, a more appropriate alternative ventilation technique for management of neonatal respiratory failure? The animal models of the use of HFOV in acute lung injury show clearly and unequivocally that it is less injurious to the low compliant, diffusely atelectatic lung than CMV, so why do the results of the HIFI trial suggest that this cannot be duplicated in the clinical situation? Clearly it will not work unless introduced early before barotrauma damages the lung. The “open lung” strategy is also clearly important in the successful use of HFOV, a policy that was not pursued in the multicentre study. The importance of this approach has been emphasized in a recent study [15] in the animal lung lavage model, which showed HFOV at a high lung volume (HFO-A/Hi) produced superior gas exchange and less barotrauma compared with both HFOV at low lung volume or CMV (fig. 6). In addition, hysteresis and compliance were better in the HFO-A/Hi based on analysis of the pressure-volume curve of the lung. It is interesting to note also that, despite the rather negative results of the multicentre study, human studies in progress in Japan [K. Miyasaka, personal communication] and France [16] suggest that the early use of HFOV, together with the use of sustained inflation or sigh manoeuvre, has led to better oxygenation and a successful reduction in the number of premature infants with BPD (fig. 7). Apart from effects on oxygenation in the diffusely atelectatic low compliant lung, HFOV still remains the least traumatic and most efficient method of controlling $P_{aCO_2}$. This has been used to great effect in the management of various forms of PPHN [17, 18] in which we have been able to
reduce $P_{aCO_2}$ rapidly, increase $pH$ and reverse ductal shunting by changing from CMV to HFOV, using low mean airway pressures and inflicting little damage on the lung.

Whatever place HFOV may eventually have in the management of these forms of severe respiratory failure, there is no doubt that the use of the technique has resulted in increased understanding of the mechanisms of lung injury and how the lung may be damaged further by conventional ventilator therapy.

REFERENCES


