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S. Riphagen
D. Bohn

High Frequency oscillatory ventilation

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S. Riphagen · D. Bohn (✉)
Department of Critical Care Medicine,
Hospital for Sick Children, Toronto
Department of Anaesthesia, University of Toronto, Canada
e-mail: dbohn@sickkids.on.ca;
Tel.: + 1 (416) 813-6477;
Fax: + 1 (416) 813-7299

Mailing address: Department of Critical Care Medicine,
Hospital for Sick Children, 555 University Ave,
Toronto Ontario M5G 1X8, Canada

Introduction

Clinical experience with the use of high frequency oscillatory ventilation (HFOV) for the treatment of acute hypoxic respiratory failure (AHRF) in the term and near term infant now extends over 15 years. Its introduction was preceded by animal studies, using the lung lavage model to produce surfactant deficiency as a paradigm for the infant respiratory distress syndrome. These showed improved oxygenation and less lung damage compared with conventional ventilation when HFOV was combined with a lung recruitment manoeuvre. Replicating this benefit in humans has proved more difficult. The initial large multicentre trial (the HiFi trial) [1], completed before surfactant became available and where lung recruitment was not used, failed to better outcomes compared with conventional mechanical ventilation (CMV). More disturbingly, however, the study suggested there was an increased incidence of intraventricular haemorrhage in babies randomised to HFOV, a finding not substantiated in further studies in the post surfactant era [2–6] (see Table 1). There is now a general acceptance that HFOV is a safe and effective form of ventilation in preterm infants without there being any clear demonstrable benefit in terms of reduced mortality or decreased incidence of chronic lung disease.

Clinical experience with HFOV outside the newborn period is based largely on rescue studies. The most commonly used oscillator (SensorMedics 3100A, SensorMedics, Yorba Linda, Calif., USA) is capable of ventilating patients of up to 50 kg body weight, albeit using slower frequencies and higher peak to peak airway pressures than used in newborns. Published results of randomised clinical trials (RCTs) of term newborns and children with AHRF have been equivocal [7–11]. Using the randomised crossover design, the study by Arnold et al. [11] failed to demonstrate a reduction in mortality in a relatively small study of paediatric patients ($n = 58$). However, there were fewer crossovers from HFOV to the conventional arm than vice versa. As in many other studies of this type, they were able to show a short term physiological benefit in terms of improved oxygenation and a decreased oxygen requirement at 28 days. The equivocal result of this study may have been influenced by the prolonged period on conventional ventilation before the patients were entered into the randomised trial (80 h with CMV vs 143 h for HFOV). Certainly, the animal studies using the lung lavage model have demonstrated that the lung is not nearly as recruitable if a long intervening interval of CMV has been used and resulted in a secondary injury. This begs the question as to whether HFOV should still be considered as a rescue mode or should it be introduced earlier in the disease process when the lung is potentially recruitable before the secondary injury has occurred. Neonatal studies have also taught us that we should be more aggressive in our volume recruitment manoeuvres. Thome [12] has shown that lung recruitment on HFOV is both time- and pressure dependent in the human, surfactant-deficient lung. Most of the protocols in neonatal trials have used mean arterial pressure (MAP) levels

Table 1 High-frequency oscillatory ventilation in preterm infants

Author	Year	*n*	Patient weight	Surfactant	Volume recruitment	% mortality		% incidence of CLD	
						HFOV	CMV	HFOV	CMV
HiFi study [1]	1989	673	750–2000 g	No	No	17	18	40	41
Clark et al. [2]	1992	83	< 1751 g	No	Yes	17	12	30	65
HiFO [3]	1993	176	> 500 g	No	Yes	11	2	Not reported	
Ogawa et al. [4]	1993	92	> 750–2000 g	Yes	Yes	0	2	9	13
Gerstmann et al. [5]	1996	125	< 35 weeks' gestational age	Yes	Yes	0	3	24	44
Rettwitz-Volk et al. [6]	1998	96	> 750–1500 g	Yes	No	11	8	0	0[a]

[a] Incidence of CLD defined as $FIO_2 > 0.21$ to maintain arterial oxygen tension > 45 mmHg at 37 weeks.
Other studies use $FIO_2 > 0.21$ at 28–30 days

of 1–2 cmH_2O above that on CMV and increased them in small increments.

The recognition that ventilator associated lung injury may have a significant impact on the outcome from AHRF has led to the adoption of a reduced tidal volume ventilation strategy together with lung recruitment manoeuvres. While the concept is physiologically appealing, maintaining lung volumes above the critical opening pressure is not without difficulty and hazard when using CVM. This has led adult intensivists to explore the use of HFOV, a mode of ventilation previously considered to be only applicable to infants or older children. HFOV fulfils all the ideals of a non-injurious mode of ventilation, i.e. small tidal volumes combined with maintenance of a high lung volume. The adult experience with HFOV is confined to a single rescue study by Fort et al. [13], where patients were switched from CMV to HFOV because of worsening hypoxaemia. This study showed a physiological improvement in terms of a fall in the oxygenation index. The rescue nature of this study is highlighted by the fact that peak inspiratory pressures of up to 54 cmH_2O on CVM were used before the switch to HFOV.

Rettwitz-Volk W, Veldman A et al. (1998) A prospective, randomized, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. J Pediatrics 132: 249–252

This prospective, randomised trial enrolled preterm babies ($n = 96$) from three centres in Germany within the first 2 h of life to be ventilated either by CMV or by HFOV using a device (Stephan 3000) not used in the previously reported randomised clinical trials. The primary end point was survival. All patients received surfactant. No definitive lung recruitment strategy nor intermittent volume recruitment manoeuvres were used. The investigators opted for a reduction in MAP rather than fractional inspired oxygen (FIO_2) as their key objective. The mortality in the HFOV arm was 11 % compared to 8 % in the CMV arm. This trial found no differences in the incidence of barotrauma, air leaks or serious intracranial pathology. The incidence of chronic lung disease (CLD), as evidenced by an FIO2 requirement of > 0.21 at 37 weeks' post conceptual age, was zero in both arms of the study.They concluded that HFOV was as safe as CMV in surfactant treated preterm neonates when comparable airway pressures were used.

Gerstmann DR, Minton SD et al. (1996) The Provo Multicenter Early High-Frequency Oscillatory Ventilation Trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 98: 1044–1057

One hundred and twenty five preterm infants from three tertiary neonatal intensive care centres, two in the United States and one in Belgium, were randomised prospectively to either HFOV or CMV after surfactant administration to determine whether the early use of HFOV using a lung recruitment strategy would reduce the incidence of CLD at 28 days. Their objective was to recruit patients within 2 h of birth in order to mitigate any secondary ventilator induced injury. Adequate lung recruitment was defined clinically by the ability to wean oxygen to below FIO_2 0.3 and radiologically (diaphragms at the level of the 8th or 9th rib posteriorly). Their study was driven by the animal model findings which suggested that with an aggressive early open lung strategy, HFOV was associated with a reduction in acute lung injury and preservation of surfactant. The results from this study suggest that there is no difference between the two forms of ventilation in terms of serious intraventricular haemorrhage (IVH) or air leaks. However, the HFOV group had a lower incidence of CLD (24 vs 44 %), less surfactant usage, lower incidence of hearing abnormalities and lower hospital cost compared to the CMV group.

Ogawa Y, Miyasaka K, Kawano T et al. (1996) A multicentre randomised trial of high frequency oscillatory ventilation as compared with conventional ventilation in preterm infants with respiratory failure. Early Hum Dev 32: 1–10

This Japanese RCT compared HFOV with CMV using the same entry criteria as the HiFi study (infants 750–2000 g birthweight). All patients received surfactant replacement therapy. The end points were survival and the incidence of CLD and of IVH. Survival was the same as in the Provo study [5], but the astonishing finding was that, with either mode, the figures for the incidence of CLD were lower than in any other published study (9 and 13%), so low in fact that it would take huge numbers to show a statistical difference between the two modes of ventilation. The was no difference in the incidence of IVH, which was much lower than in the HiFi study. This paper has been largely ignored perhaps because the results are so good with either mode that they are rather embarrassing for occidental neonatal medicine.

Clark RH, Dykes FD et al. (1996) Intraventricular hemorrhage and high–frequency ventilation: a meta-analysis of prospective clinical trials. Pediatrics 98: 1058–1061

This meta-analysis was undertaken primarily to determine whether there was an increased risk of IVH associated with the use of high frequency ventilation in preterm neonates based on the published literature. The group analysed nine trials (5 HFOV and 4 high frequency jet ventilation) including the HiFi study [1]. This was by far the largest and tended to dominate the analysis. For this reason results were analysed with and without the HiFi data. When the HiFi study was excluded, there was no difference in the incidence of IVH or periventricular leucomalacia in either of the treatment groups. The authors pointed out that meta-analysis does not carry the same weight as a carefully conducted prospective clinical trial and that the variation in the clinical outcomes between the various studies is probably related to factors other than mode of ventilation or the type of surfactant used.

Bhuta T, Henderson-Smart DJ (1997) Elective high-frequency oscillatory ventilation versus conventional ventilation in preterm infants with pulmonary dysfunction: systematic review and meta-analyses. Pediatrics 100: E6

Eight randomised trials were identified but only four published trials met inclusion criteria for the meta-analysis. These were systematically reviewed to determine whether HFOV was beneficial when compared to CMV with respect to a number of respiratory and neurological outcomes, as well as mortality. The results are dominated by the HiFi trial, the largest of the four. This trial did not use a high volume lung strategy nor surfactant, and the results published from this trial have not been generalisable to other trials. The studies done subsequent to the HiFi study have shown decreases in measures of CLD, including reduction in days on supplemental oxygen and oxygen at discharge without significant increase in neurological morbidity. One trial showed a decrease in hospitalisation costs for those children who were oscillated. Long-term pulmonary function and neurological outcomes have not been reported in preterm infants who were oscillated using the high lung volume strategy.

Discussion

These studies could be used to help clarify two of the fundamental issues regarding the use of HFOV in lung disease of prematurity. These are: (1) Does HFOV with a lung recruitment strategy decrease the mortality and incidence of CLD in an era of surfactant replacement therapy? (2) Is HFOV associated with an increased risk of the development of IVH in the premature infant? In attempting to answer the first question, the studies by **Gerstmann et al.** [5] and **Rettwitz-Volk et al.** [6] seem to be contradictory in that the former was positive and the latter was negative. Careful scrutiny of these two studies reveals important differences in the study design. The first was a very early intervention trial with a clearly defined lung recruitment strategy and showed improved outcomes with HFOV in terms of reduction in significant short term pulmonary morbidity and reduction in hospitalisation costs. **Rettwitz-Volk et al.'s** study did not place the same emphasis on lung recruitment and, in addition, the mortality in both arms of the study paralleled that of the HiFi trial published 10 years ago, before surfactant was used clinically. The significance of this observation is that surfactant replacement therapy has made a major impact on the mortality from neonatal lung disease, and all the HFOV randomised trials comparing HFOV with CMV published since its introduction into clinical medicine have shown mortality rates of 1 to 2% in both study arms except for this. In addition, there must be concern about overinterpreting the findings of any study that reports a mortality that is between 5 and 10 times that of previous studies, that uses an oscillator of a different design to that widely used in clinical practice, and where lung recruitment was not part of the methodology.

Scrutiny of the data from the published RCTs comparing HFOV and CMV in the newborn also provides an interesting insight into the impact that surfactant has made on the incidence of CLD in premature infants. A meta-analysis of the published RCTs of the surfactant replacement therapy alone clearly demonstrates that

while introduction of this therapy has reduced the mortality in this disease it has not affected the incidence of CLD [16]. The studies listed in Table 1 tend to confirm this, as the mortality is lower in the trials done since surfactant became available while the incidence of CLD is unaffected. There are two noteworthy exceptions. The incidence of CLD in both arms of the **Ogawa et al.** study was amazingly low, a reflection perhaps on better hands-on management by Japanese neonatologists, and the reduction in the incidence of CLD in the HFOV arm of the **Gerstmann et al.** study. Despite, this it is still well short of the 9 and 13 % reported by **Ogawa et al.**. Using the meta-analysis tool, which can be somewhat of a blunt instrument when trying to evaluate outcomes from clinical trials, one could conclude, based on the paper by **Bhuta and Henderson-Smart [15]**, that the case for HFOV being superior to conventional ventilation for lung disease of prematurity is proven.

The second issue is that of the association of HFOV with IVH, which is one that has been around since the original HiFi study. The meta-analysis by **Clark et al.** [14], which includes both HFOV and HFJV, would suggest that this association is heavily biased by the findings of the original HiFi study, but has not been borne out in subsequent randomised trials. However, there is still an ongoing concern that the remarkable efficiency for CO_2 elimination associated with HFOV can lead to hypocarbia, cerebral ischaemia and the setup for IVH in premature infants. Physicians working in neonatal intensive care should be very aware of this association and be vigilant about not letting their patients become hypocarbic.

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