HOT OFF THE BREATH

High-frequency oscillatory ventilation and acute respiratory distress syndrome: at the crossroads?

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Acute respiratory distress syndrome (ARDS) was characterised by Ashbaugh and colleagues[1] nearly half a century ago, and yet, to the casual observer, it might appear that little progress has been made since. Clinicians are still struggling with how best to define and treat ARDS.[2 3] A major advance was the recognition that mechanical ventilation may induce further lung injury and the application of so-called lung protective ventilation (6 ml/kg ideal body weight tidal volumes and plateau pressures <30 cm H_2O) reduces mortality.[4] High-frequency oscillatory ventilation (HFOV) is an attractive mode of ventilation because it combines improved lung recruitment with small tidal volumes, often below anatomical dead space, applied at very high frequency. Thus, it theoretically provides ultra-lung protective ventilation, limiting atelectrauma (caused by cyclical alveolar opening and closing) and volutrauma (alveolar over-distension). For those not familiar with this mode of ventilation, it should be noted that, unlike conventional ventilation, increasing the frequency of HFOV reduces CO_2 elimination. HFOV has often been used as a rescue therapy for severe ARDS and refractory hypoxaemia; however, uncertainty remains over its role in early ARDS. Although there is substantial experimental data, clinical studies are limited to case series and two small trials[5 6] where controls did not receive what is now accepted as standard lung protective ventilation following the ARDSNet study.[4]

Two recently randomised clinical trials sought to establish if HFOV could reduce mortality in early ARDS.[7 8] The UK-based OSCAR study[7] randomised 795 patients to receive either HFOV or conventional ventilation. No difference was observed in 30 day mortality between groups (41.7% vs 41.1%, respectively). The larger OSCILLATE study[8] planned to recruit 1200 patients but was stopped after 548 patients on recommendation from the data monitoring committee, as in-hospital mortality was significantly higher in those assigned to HFOV (47% vs 35%). Recruitment was broadly similar in both trials, which aimed to enrol patients with early ARDS and a PaO_2/FiO_2 $\leq$200 mm Hg rather than using HFOV as a rescue therapy. From these trials, it would appear that HFOV does not improve mortality in early ARDS, and at worse, might be harmful. However, although ostensibly both trials applied a similar intervention to a similar group of patients, there were significant differences between studies and also in how this technology was applied in UK Intensive Care Units prior to publication of these studies. The major differences between studies are summarised in tables 1 and 2.

VENTILATOR SELECTION

For the past two decades, adult HFOV in Europe and North America has largely been undertaken using the SensorMedics 3100B oscillator (CareFusion). The OSCAR trial chose to use the Novalung R100 ventilator (Metran) device which, despite having been used in Japan, was relatively untried in the UK and had only been awarded a CE mark shortly before the start of the study. All 25 critical care units in the UK providing HFOV prior to the trial used the SensorMedics 3100B oscillator[7]; no explanation was given for choosing this unfamiliar equipment.

CENTRE SELECTION

Centre characteristics can be an important determinant of outcome in mechanical ventilation as intensive care units dealing with higher caseloads have better outcomes.[9] HFOV can be a complex intervention, with centres building up experience in its use over several years.[10] OSCILLATE used 39 centres, predominantly North American hospitals with previous experience of HFOV employing the 3100B oscillator. In OSCAR, only 3 centres had significant experience of HFOV, 6 had limited experience and the remaining 20 had none. No centre had used the Novalung R100 previously and a substantial effort was put into training over 2300 clinical staff. Lack of equipoise is likely to have existed in the UK centres with substantial prior HFOV experience. The inability to use HFOV as a rescue therapy in the OSCAR trial is likely to have contributed to this. In OSCILLATE, 34 patients in the control group received HFOV (31 in accordance with the trial protocol); however, neither trial specifically recorded the use of HFOV outside of the trial in the severe ARDS subgroup.

PARTICIPANT SELECTION

Each trial broadly included similar patients; it is, however, notable that APACHE II scores were significantly higher in the OSCILLATE study (29 vs 21.8). In OSCAR, inclusion was dependent on the onset of mechanical ventilation within the previous 7 days, but up to 14 days of respiratory failure were permitted in OSCILLATE. Patients were included if the PaO_2/FiO_2 was $\leq$200 mm Hg on a PEEP of $\geq$5 cm H_2O[5] or $FIO_2 \geq 0.5$ irrespective of PEEP.[8] The OSCILLATE trial used an additional step of standardised ventilator settings for 30 min ($FIO_2 \geq 0.6$, PEEP of $\geq$10 cm H_2O and tidal volume 6 ml/kg predicted weight) to reassess if PaO_2/FiO_2 was still $\leq$200 mm Hg, but this excluded only 19 individuals.

VENTILATION PROTOCOL

Ventilation strategies in these two studies were very different for HFOV and conventional ventilation arms (table 2). OSCILLATE adopted an 'open lung' approach from the outset by using recruitment manoeuvres in both arms. Following this, the smallest tidal volumes for either HFOV or conventional ventilation were applied, aiming for a pH>7.25. The oscillation strategy was based on a round-table discussion of experts in HFOV.[11] Target oxygen saturations were 88–93% and were achieved using mean airway pressure-inspired oxygen charts, which in the conventional arm, were based on a previous trial.[12] Recruitment manoeuvres were mandated frequently with increases in mean airway pressure (HFOV arm) or PEEP (conventional arm) within defined safety parameters. Importantly, cross-over to the other arm of the study could occur as a rescue intervention in refractory hypoxaemia. In contrast, OSCAR did not mandate recruitment manoeuvres in

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Table 1 Overview of OSCILLATE and OSCAR

Intervention	OSCILLATE	OSCAR
Oscillator	SensorMedics 3100B oscillator (CareFusion)	Novalung R100 (Metran)
Distribution	Extensively used in North America and Europe	Extensively used in Japan, not used in Europe or North America
I:E ratio	Usually used with 1:2 I:E Which may lead to lower pressures in alveoli than measured on oscillator	Fixed I:E 1:1
Modes	HFOV mode only—transition to conventional ventilation requires swapping ventilators	HFOV, PCV, VCV, PSV, CPAP
Centres	39—mainly North America (35)	29 UK
	Previously used HFOV	20 no HFOV experience, 6 limited
	Enrolled if PaO_2/FiO_2 ≤200 mm Hg on a FIO_2≥0.5 irrespective of PEEP Randomised if PaO_2/FiO_2≤200 mm Hg after 30 min on standard settings (FIO_2≥0.6, PEEP of ≥10 cm H_2O and tidal volume 6 ml/kg)	Randomised if PaO_2/FiO_2≤200 mm Hg on a PEEP of ≥5 cm H_2O
Recruitment manoeuvres	Mandated in protocol	Maybe used not mandated
Cross-over to HFOV	Permitted	Not permitted
Mortality	47% HFOV vs 35% control In hospital	41.7% HFOV vs 41.1% conventional ventilation at 30 days

HFOV, high-frequency oscillatory ventilation.

either arm of the trial and allowed ventilation in the conventional limb according to local practice but encouraged lung protective ventilation and setting of PEEP and inspired oxygen according to ARDSNet.

This lack of protocolised ventilation in the control arm of the OSCAR study may explain the large disparity in mortality in conventional ventilation groups between trials (table 2), especially as patients in OSCILLATE had higher APACHE II scores. Tidal volumes were also much lower in OSCILLATE; a recent observational study of ARDS found that non-adherence to tidal volumes of <6.5 ml/kg ideal body weight increased absolute mortality by 7.8% at 2 years.[13] Failure to adhere to lung protective ventilation (30%) was also a feature of a recent UK trial comparing extracorporeal membrane oxygenation with conventional ventilation.[14] It is conceivable that had the OSCAR trial achieved tidal volumes approaching 6 ml/kg

Table 2 Delivery of ventilation in OSCILLATE and OSCAR (SD in brackets, ventilation parameters at day 1)

HFOV	OSCILLATE	OSCAR
Initial mean airway pressure settings	Mean airway pressure 30 cm H_2O	5 cm H_2O above plateau pressure at randomisation
Target	SaO_2 88–93% pH 7.25–35	PaO_2 8–10 kPa pH >7.25
I:E ratio	1:2	1:1
pH adjustment	Primarily by adjusting frequency	Primarily by adjusting cycle volume
Oxygenation adjustment	According to mean airway/FIO2 chart and recruitment manoeuvres	Adjusting mean airway pressure, then FIO_2
Recruitment manoeuvres	Initiation of HFOV FIO2>0.6 or persistent desaturation Up to 4 mandated (in 24 h), then at clinician discretion	Not in algorithm
Mean airway pressure	31 (2.6)	26.9 (6.2)
Frequency	5.5 (1)	7.8 (1.8)
APACHE II	29 (8)	21.8 (6)
Mortality	40% <28 days 47% in hospital	41.1% at 30 days
Conventional Ventilation	OSCILLATE	OSCAR
	6 ml/kg ideal body weight Plateau pressure <35 cm H_2O Pressure control Recruitment manoeuvre at randomisation and prior to increases in PEEP PEEP/FIO_2 set according to chart and target SaO_2 of 88–93%	Encouraged to use 6–8 ml/kg ideal body weight PEEP and FIO_2 according to ARDSNet strategy
	Strictly protocolised	Local practice
Tidal volume	6.1 (1.3)	8.3 (2.9)
PEEP	18 (3.2)	11.4 (3.6)
Plateau	32 (5.7)	30.9 (11)
APACHE II	29 (7)	21.7 (6.1)
Mortality	29% <28 days 35% in hospital	41.1% at 30 days

ARDS, acute respiratory distress syndrome; HFOV, high-frequency oscillatory ventilation.

ideal body weight, the two arms would not have demonstrated equivalently. In OSCILLATE, more patients in the intervention group required vasoactive drugs and required them for a longer duration, possibly due to the high inflation pressures and frequent recruitment manoeuvres associated with the protocol and perhaps a less aggressive recruitment strategy would have mitigated this.

CONCLUSION

These two studies[7 8] reinforce the importance of conventional lung protective ventilation in managing patients in ARDS. They also beg the question of why HFOV was not shown to be beneficial when one considers this mode of ventilation might be considered an optimal protective strategy. Data suggest that tidal volumes lower than 6 ml/kg (such as those that can be achieved with HFOV) are advantageous.[15 16] However, measuring tidal volume during HFOV is not a feature of standard oscillators and larger tidal volumes than anticipated may be delivered.[17] In addition to reducing frequency and increasing amplitude, larger endotracheal tube (ETT) size may be an important variable in increasing tidal volumes delivered to patients.[17] The OSCAR trial recommended that the ETT tube was changed for one with a larger diameter. Importantly, the OSCILLATE protocol aimed for a maximal amplitude and adjusted pH with as high a frequency as possible over the range 3–12 Hz. However, on day 1, frequency was 5.5 Hz (SD 0·97), and it is possible that delivered tidal volumes were larger than the study hoped to achieve.

Ventilator settings for HFOV have largely developed by trial and error and although one of the two trials[8] used a protocol based on expert opinion;[11] this has not been validated in other studies. HFOV is a complex intervention[10] that requires experience and expertise. High inflation pressures and frequent recruitment manoeuvres may have led to increased haemodynamic compromise. When HFOV is initiated, there may be significant effects on preload, afterload, pulmonary vascular resistance, ventricular function and cardiac output.[18] Avoidance of overdistension of lung, judicious use of fluids, sedatives and vasoactive drugs are all important aspects of patient management acquired through experience of using HFOV.

Which way at the crossroads for HFOV? The results of OSCAR and OSCILLATE will be a disappointment for proponents of HFOV; however, it is too early to abandon this therapy from the armamentarium of ARDS strategies. Future studies should focus on selection of patients likely to benefit from this intervention and on careful titration of mean airway pressures probably without sustained high inflation pressure recruitment manoeuvres.[19 20] Novel techniques of measuring recruitment such as electrical impedance tomography, ultrasound, bedside CT scanning, transpulmonary pressure, or inflammatory cytokines may have a role to play in optimising recruitment and tidal volumes while minimising adverse effects on cardiac function.

Contributors All authors contributed equally to the manuscript.

Competing interests MW was involved in recruitment of patients to OSCAR and was a local investigator for OSCILLATE, although the study was terminated before any patients were recruited. MW has been loaned an electrical impedance tomography device for research purposes by CareFusion. MW has also provided clinician feedback on ventilator interfaces to CareFusion. AGS and MAG have no conflicts of interest to declare.

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