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High frequency oscillation for preterm infants with severe respiratory failure

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Abstract

High frequency oscillation (HFO) as rescue treatment for preterm infants with severe respiratory failure has been assessed and prognostic factors identified. Thirty six infants with a median gestational age of 27 weeks were studied. Immediately before transfer to HFO, the infants were receiving an inspired oxygen concentration of ≥85% and/or a mean airway pressure of ≥12 cm H_2O and had a median alveolar-arterial oxygen gradient (A-aD_{O_2}) of 73·28 kPa (range 49·34–89·91). Seventeen infants subsequently died. Comparison of those 17 with the remaining 19 infants demonstrated that respiratory distress syndrome and persistent fetal circulation were associated with a significantly better outcome than pulmonary airleak. The A-aD_{O_2} after two and six hours on HFO was significantly higher in those infants who survived compared with those who died. We conclude that a diagnosis of pulmonary airleak and failure to show early improvement in respiratory status indicate a poor prognosis when HFO is used as rescue treatment.

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Despite improvements in mechanical ventilation, infants still die of severe respiratory failure.[1] To improve their outlook new techniques of respiratory support have been introduced. It is claimed that extracorporeal membrane oxygenation (ECMO) substantially increases survival, even when applied to infants with a predicted mortality of 80% or greater.[2] Unfortunately, because of increased risk of intracerebral haemorrhage,[3] ECMO is thought not to be suitable for premature infants. High frequency oscillation (HFO) can be used to support those vulnerable infants and may reduce the risk of residual chronic lung disease.[4] HFO, however, can also give rise to serious complications.[5] Therefore, it is important to use this technique only in those babies most likely to benefit from it. The aim of this study was, therefore, to assess the efficacy of HFO as rescue treatment for preterm infants with severe respiratory failure and to identify those factors that have prognostic significance.

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Patients and methods

METHODS

Premature infants with respiratory failure deemed to be unresponsive to conventional ventilation by the clinician in charge of the case were changed to HFO. To maintain blood gases within the desired range (pH 7·25–7·4, arterial oxygen tension (Pa_{O_2}) 6·67–9·33 kPa, and arterial carbon dioxide tension (Pa_{CO_2}) 5·33–8·00 kPa), when they were transferred from conventional ventilation to HFO, all infants needed an inspired oxygen concentration (F_{IO_2}) of 85% or greater and/or a mean airway pressure of at least 12 cm H_2O.

HFO was provided by a SensorMedics 3100 oscillator, fitted with adjustable controls including frequency, fractional inspiratory time, amplitude, and mean airway pressure. When changing to HFO the same (F_{IO_2}) was maintained, a frequency of 10 Hz and a fractional inspiratory time of 0·30 were used. The previously set mean airway pressure was raised by 2 cm H_2O.[6] The amplitude was increased by adjusting the displacement or power of the oscillator until visible chest wall vibration was observed. During subsequent HFO, the settings were adjusted to maintain the blood gases within the desired range (see above) and at the same time avoiding lung overdistension. Once improvement in respiratory status was seen, the F_{IO_2} was reduced in preference to lowering the mean airway pressure.

Blood gases were checked immediately before and at least two and six hours after transfer to HFO and more frequently when clinically indicated. All blood samples were taken from an indwelling arterial line that had been inserted for clinical purposes. The nursing staff recorded all ventilation and oscillation settings hourly. From the nursing records and the arterial blood gases alveolar-arterial oxygen gradients (A-aD_{O_2}) and the arterial/alveolar (a/A) ratio were calculated. The outcome of the infants was documented from the medical records.

ANALYSIS

Differences between infants who died and survived were assessed for statistical significance using either Fisher's exact test or the Wilcoxon rank sum test as appropriate.

PATIENTS

The 36 infants who were included in the study had a variety of diagnoses (table 1).

Table 1 Diagnoses of infants supported by HFO (number of infants given surfactant in parentheses)

	Died (n=17)	*Survived (n=19)*
Severe respiratory distress syndrome	3 (3)	10 (9)
Persistent fetal circulation	2 (2)	7 (5)
Pulmonary airleak	7 (7)	1 (1)
Pulmonary hypoplasia	5 (2)	1 (0)

Respiratory distress syndrome was diagnosed if the infant developed respiratory distress before 4 hours of age and had a symmetrical ground glass appearance on the chest radiograph. In addition no infectious agent had been isolated in the first 48 hours of life. Persistent fetal circulation was diagnosed in infants who were severely hypoxic, who had a right to left shunt at atrial and ductal levels due to pulmonary hypertension, but in whom a structurally normal heart was confirmed echocardiographically. Pulmonary hypoplasia was diagnosed if high peak pressures (>30 cm H_2O) were required both for resuscitation and during ventilation for at least the first week of life and this was associated with small volume lungs on the chest radiograph. In those infants who died, the diagnosis was confirmed on post-mortem examination by finding a reduced lung weight and a radial alveolar count of less than 4. Pulmonary airleak was diagnosed if the infant had pulmonary interstitial emphysema or pneumothorax.

The median gestational age of the infants was 27 weeks (range 23–36), birth weight 868 g (428–3000), and postnatal age 2·5 days (range 0·1–23). The infants were all initially ventilated using Sechrist IV ventilators and oral endotracheal tubes. Immediately before transfer to HFO the infants were receiving a median peak inspiratory pressure of 31 cm H_2O (range 19–46), mean airway pressure of 13 cm H_2O (range 8–30), and F_{IO_2} of 95% (range 60–100).

The majority of infants (table 1) had received exogenous surfactant replacement treatment in the first 48 hours of life, as their a/A ratio had been less than 0·22. At the time of transfer the infants' median a/A ratio was 0·079 (range 0·03–0·148).

This study was approved by the King's College Hospital ethics committee.

Table 2 Patient characteristics and ventilator requirements prior to transfer to HFO; figures are median (range)

	Died (n=17)	*Survived (n=19)*
Gestational age (weeks)	26 (25–31)	28 (23–36)
Birth weight (g)	804 (590–1906)	816 (428–3000)
Postnatal age (days)	3 (0·1–8)	2 (0·2–23)
Mean airway pressure (cm H_2O)	13 (11–30)	13 (9–24)
Ventilator rate (/min)	76 (40–100)	69 (45–100)
F_{IO_2} (%)	97 (71–100)	93 (60–100)

Table 3 Changes in mean airway pressure and oxygenation immediately before (0) and at 2 and 6 hours after transfer to HFO; figures are median (range)

	Died (n=17)	*Survived (n=19)*	*p Value*
Mean airway pressure (cm H_2O)			
0	13 (11–30)	13 (9–24)	
2	19 (12–38)	15 (10–23)	
6*	20 (10–32)	15 (9–24)	
a/A			
0	0·061 (0·03–0·108)	0·088 (0·03–0·148)	
2	0·089 (0·02–0·176)	0·140 (0·057–0·263)	<0·01
6*	0·090 (0·056–0·222)	0·166 (0·058–0·212)	<0·05
$A\text{-}aDo_2$ (kPa)			
0	76·74 (53·07–89·91)	69·16 (49·34–86·45)	
2	73·28 (38·84–81·26)	47·35 (23·41–82·06)	<0·01
6*	69·69 (13·03–88·84)	36·58 (21·41–83·26)	<0·05

*Two infants had died by the 6 hour recordings.

Results

Despite using HFO, 17 infants subsequently died. All died of respiratory failure, but in one case this was complicated by candida septicaemia, in six by severe air leak, and three had terminal pulmonary haemorrhage. The median duration of HFO overall was 2·7 days (range 0·08–11·1). As expected, the 17 infants who died spent significantly less time on the oscillator (median 1·0 days, range 0·08–11·1) compared with a median of 2·5 days (range 1·0–10·4) in the survivors, $p<0·01$.

During HFO, no infant developed a new intracerebral bleed, but six cases had worsening of existing bleeds and all died. Five infants who had pulmonary interstitial emphysema before starting HFO developed pneumothoraces and two infants with pulmonary hypoplasia developed both pulmonary interstitial emphysema and pneumothorax on HFO.

A significantly greater proportion of infants who had severe respiratory distress syndrome as the primary diagnosis survived than did infants with pulmonary air leak ($p<0·02$) or with pulmonary hypoplasia ($p<0·05$). The outcome of the infants with persistent fetal circulation was also better than the infants with pulmonary air leak ($p<0·03$) (table 1). Overall there was no significant difference in surfactant usage between infants who died or survived (table 1). The birth weight, gestation or postnatal age did not differ significantly between the two groups (table 2). Ventilator rate tended to be higher before transfer to HFO and the inspired oxygen concentration was significantly greater ($p<0·05$) in the group who died.

In the 36 infants overall there was a significant progressive improvement in the $A\text{-}aDo_2$ over the first six hours on HFO. Before HFO, the median $A\text{-}aDo_2$ was 73·28 kPa (range 49·34–89·91), after two hours on HFO 55·66 kPa (range 23·41–82·06), $p<0·01$, and after six hours on HFO, 46·82 kPa (range 13·03–88·84), $p<0·01$. Although there was no significant difference in the median $A\text{-}aDo_2$ before transfer to HFO, at two and six hours the median $A\text{-}aDo_2$ was significantly lower in the infants who subsequently survived compared with those who died, $p<0·01$ and $p<0·05$ respectively (table 3).

Discussion

The overall survival of 19 of 36 (53%) of our patients is most encouraging. Many of our infants, before HFO, had an $A\text{-}aDo_2$ which, in term infants, has been an indication of an 80% mortality.[7] Blum-Hoffman *et al* reported a survival rate (47%) similar to ourselves,[8] but their patients were more mature than those of the present series. These results do suggest that HFO has a role as rescue treatment for premature infants with severe respiratory failure.

There has been concern that HFO may be associated with increased intracerebral haemorrhage.[5] In the present study no infant experienced a new intracerebral bleed during oscillation and in less than 20% of our patients extensions to existing haemorrhages occurred.

As all our patients were very immature and critically ill before starting HFO, more instances of cerebral haemorrhage might have been expected.

Animal studies have suggested that HFO can be efficacious in hyaline membrane disease even after lung injury has been established.[9] The present results confirm that finding, given the high survival rate of our critically ill infants who had severe respiratory distress syndrome. In addition respiratory distress syndrome was associated with a better outcome than the other diagnosis in the babies who were included in our trial.

We did not find HFO to be helpful in infants with pulmonary hypoplasia or established airleak. The majority of those patients died. Although the numbers are small, our findings are supported by the equally poor results in the series reported by Blum-Hoffman *et al* in more mature infants who had these diagnoses.[8] In both the present and this earlier study[8] the airleak frequently worsened.

In survivors we noted an early and significant improvement in oxygenation, similar to that reported in premature baboons with established lung injury treated with HFO.[9] Unfortunately, in the baboons, despite the acute improvement in blood gases, at 24 hours there was no significant difference in the chest radiograph appearance of animals treated using conventional ventilation compared with the group on HFO. It was thus postulated that, although HFO might interrupt the progression of lung injury, it did not reverse it.[9] Even with such a limited effect of HFO in our group of preterm infants it was compatible with a higher than expected survival rate of critically ill patients.

Although many of the patients improved, as indicated by an increase in the a/A ratio and A-aDo_2 this was not accompanied by a reduction in mean airway pressure level. This, however, was due to our policy of reducing the inspired oxygen concentration before altering the pressure level[6] and reflects a concern for the damaging effects of high inspired oxygen concentrations.[10]

During HFO, oxygenation is determined by mean airway pressure and it is usually necessary to achieve a critical mean airway pressure level before any effect is seen.[6] On transfer to HFO, following our usual protocol,[6] the mean airway pressure was increased by at least 2 cm H_2O in all the patients; in the survivors this was associated with a significant improvement in oxygenation at six hours. In the group who did not survive, the mean airway pressure level over the first six hours was increased by a median of 7 cm H_2O without, however, a corresponding improvement in oxygenation. This presumably reflected the severity of their lung disease and not the inadequacy of treatment.[6]

Our results demonstrate that it was not possible to identify before HFO those infants who would benefit from HFO from either the mean airway pressure level, the a/A ratio, or A-aDo_2 (table 3). An early (within six hours) improvement in oxygenation, however, was associated with survival, as has been also noted by Blum-Hoffman *et al* in more mature patients.[8] Our data, therefore, suggest that critically ill infants need only be committed to a very short trial of HFO from which it would be possible to predict the likelihood of long term benefit.

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