High-frequency oscillatory ventilation — rescue treatment for infants with severe respiratory failure

Johan Smith, Clarissa H Pieper, Gert F Kirsten, David Maree, Jeanette van Zyl, Marie-Louise Pretorius

Objective. To assess the efficacy of high-frequency oscillatory ventilation (HFOV) as a rescue mode of therapy in newborn infants with severe respiratory failure poorly responsive or unresponsive to conventional ventilation and supportive management.

Design. Prospective, descriptive clinical study.

Setting. Tertiary care neonatal intensive care unit.

Patients and methods. All infants with radiographic evidence of diffuse bilateral lung disease and failure to maintain adequate blood gas values while receiving conventional support were offered HFOV.

Intervention. HFOV, utilising a high-pressure/volume strategy.

Outcome variables. Improvement in arterial/alveolar oxygen tension ratio (a/APO$_2$) of the infants subsequent to their transferral to HFOV; survival rate; and outcome of infants weighing more than 2 000 g who met criteria for extracorporeal membrane oxygenation (ECMO). Identifying the infants who met ECMO entry criteria allowed the success of HFOV to be compared with that of ECMO, the 'standard' treatment for infants considered unventilatable. Neonatal complications such as bronchopulmonary dysplasia, intraventricular haemorrhage and air leaks were documented.

Results. Conventional support failed in 34 consecutive infants; they were transferred to HFOV at a mean postnatal age of 30 hours. Their respiratory diagnoses included respiratory distress syndrome (RDS) (N = 19), neonatal 'adult respiratory distress syndrome' (ARDS) (N = 3) and meconium aspiration syndrome (MAS) (N = 12). Owing to similarities in the underlying pathophysiology, RDS and ARDS were grouped together for the purposes of analysis.

After starting HFOV the a/APO$_2$ had significantly improved ($P < 0.05$) by 6 hours in the RDS group and by 12 hours in the infants with MAS. This improvement was sustained throughout the first 48 hours of HFOV. Twenty-six (76%) of the infants ultimately survived. Among those who met the criteria for ECMO (N = 13), the survival rate was 92%. Air leaks occurred on HFOV in 6 infants, 3 each in the MAS and RDS groups. Bronchopulmonary dysplasia was diagnosed in 6 (40%) of the 15 RDS infants and in 2 (18%) of the 11 infants with MAS. Eight infants died, 3 following nosocomial sepsis (*Pseudomonas* sp.), 3 due to extensive air leaks, 1 due to irreversible shock (unproven sepsis), and 1 due to ARDS.

At a median age of 13.5 months the neurological development of 11 (5%) of 17 infants was normal; in 3 (18%) it was suspect and in 3 abnormal.

Conclusions. The study demonstrates that a high-pressure/volume approach to HFOV is an effective mode of rescue ventilation for infants who present with severe respiratory failure caused by a variety of lung conditions during the neonatal period.

Mortality and respiratory morbidity from respiratory distress syndrome (RDS) and meconium aspiration syndrome (MAS) in neonates remain relatively high, despite the availability of assisted ventilation and surfactant replacement therapy.[1-5] According to a report by the South African Department of Health, RDS was responsible for 10% of deaths in the age group 0 - 4 years during 1992.[5] Adhikari and Gouws[3] showed that the incidence of meconium aspiration varies from 4 to 11/1 000 between institutions in South Africa. The mortality rate among infants with MAS who required intensive care and conventional ventilation was 36%.

High-frequency oscillatory ventilation (HFOV) has previously been shown to improve survival rates in some infants with RDS, MAS, neonatal 'adult respiratory distress syndrome' (ARDS), lung hypoplasia syndromes and air leaks, who failed to respond to conventional ventilation (CV) and supportive management.[6-8] Infants with congenital diaphragmatic hernia and certain categories of MAS, however, do not always respond favourably to ventilation with high-frequency oscillators.[6,9] There is therefore a need to define the most appropriate indication(s) for HFOV, especially in units with restricted physical resources and a limited number of high-frequency oscillators.

The aim of this study was to assess the efficacy of HFOV as rescue treatment for infants with diffuse lung disease who suffered from severe respiratory failure and in whom conventional mechanical ventilation and supportive management failed.

Department of Paediatrics and Child Health and Neonatal Services, Tygerberg Hospital and University of Stellenbosch, Tygerberg, W Cape

Johan Smith, MMed (Paed)

Clarissa H Pieper, MMed (Paed), MSc

Gert F Kirsten, MD

David Maree

Jeannette van Zyl, MB ChB

Marie-Louise Pretorius, MB ChB

Patients

Consecutive infants with severe respiratory failure in whom conventional ventilatory support failed to achieve adequate oxygenation and/or who did not respond to bovine

surfactant replacement therapy (SRT) and other supportive medical management were transferred to HFOV.

All the infants had bilateral lung disease and fulfilled one or more of the following criteria at the time of initiation of the trial: (*i*) post-surfactant arterial/alveolar oxygen tension ratio (a/APO$_2$) below 0.25 ($N = 21$); (*ii*) partial carbon dioxide tension (PaCO$_2$) above 8 kPa (60 mmHg) despite ventilator positive inspiratory pressure (PIP) in excess of 27 cm H$_2$O ($N = 2$); (*iii*) pulmonary interstitial emphysema and/or pneumothoraces ($N = 2$); (*iv*) partial arterial oxygen tension (PaO$_2$) below 6.7 kPa (50 mmHg) despite a fractional inspiratory oxygen concentration (FiO$_2$) of 1.0 and PIP above 30 cm H$_2$O ($N = 7$); and (*v*) persistent pulmonary hypertension of the neonate (PPHN) associated with lung disease ($N = 11$). Infants who had congenital diaphragmatic hernia, asphyxia-related multi-organ failure with hypoxic encephalopathy, lethal congenital malformations, or 'asymmetrical' lung disease such as focal MAS, unilateral lung atelectasis or unilateral pulmonary interstitial emphysema (PIE) were prospectively excluded from the study. This was done because experience from Wilford Hall (San Antonio, Texas) with more than 400 infants has shown that infants with homogeneous lung disease respond better to HFOV than those with focal or unilateral involvement.[9]

Conventional ventilation was supplied by pressure-limited, time-cycled neonatal ventilators (Sechrist, Anaheim, Calif. or Healthdyne, Marietta, Ga.) using acceptable strategies to achieve optimal alveolar recruitment, alveolar ventilation and oxygenation.[10] Medical management included: (*i*) SRT in cases of RDS or MAS in which the a/APO$_2$ remained 0.22 or below within 6 hours of admission; (*ii*) circulatory support (optimising preload and using inotropic support); and (*iii*) alkali infusion and intravenous tolazoline therapy in cases of PPHN.[11] The infants were sedated with a continuous infusion of midazolam. Babies weighing more than 2 000 g also received pancuronium. HFOV was provided by a SensorMedics 3100A oscillator.

Upon transfer to HFOV a high mean airway pressure (MAP), high-volume strategy was followed for infants with diffuse homogeneous alveolar disease (white-out). The MAP setting on the oscillator was equal to the calculated MAP on conventional ventilation plus 2 - 4 cm H$_2$O. In cases of pulmonary air leaks a MAP equal to the MAP on CV was used. A frequency of 10 Hz was used for infants weighing less than 2 000 g and 8 - 10 Hz for those weighing over 2 000 g. The inspiratory time (Ti) was kept at 33%. Pressure amplitude was adjusted according to visible chest wall excursions, transcutaneous PaCO$_2$ and measured arterial PaCO$_2$. During HFOV the settings were constantly adjusted to maintain the PaO$_2$ PaCO$_2$ and pH within the desired range.[10] Inspired gas temperature was kept at 36°C. Once optimal lung volume was obtained, the FiO$_2$ was reduced in a stepwise fashion to below 0.30 in preference to lowering the MAP. Optimal lung volume was defined as 8 to 9 posterior rib level expansion and decreased opacification or haziness of both lung fields on the chest radiograph. With the FiO$_2$ below 0.30, MAP reduction was given equal priority in the weaning process. Oscillatory amplitude was weaned according to PaCO$_2$ levels. Once low settings on HFOV were reached or patchy atelectasis due to mucus occurred, the infants were transferred to CV for further weaning and extubation. A MAP below 8 - 10 cm H$_2$O and oscillatory amplitude equal to or below 20 - 22 cm H$_2$O in the presence

of adequate blood gas levels while receiving a FiO$_2$ of 0.35 or less were considered 'low settings'.

Information on the infants' ventilatory progress was obtained from their medical records. Infants served as their own controls. The a/APO$_2$ was determined before and after switch-over to HFOV and thereafter at 6 - 12-hourly intervals up to 48 hours of HFOV. The oxygenation index (OI) was calculated before changing to HFOV.[12] The OI is a measurement of the amount of inspired oxygen and driving pressure required to oxygenate the arterial blood. A higher OI indicates a more severe oxygenation deficit. For infants weighing over 2 000 g (> 34 weeks' gestation) the OI was used to determine the need for ECMO. An OI of 30 or above for more than 4 hours before changing to HFOV has previously been shown to carry a mortality risk of 70% or more.[13] In addition to weight, gestational age and OI, the following selection criteria were used to determine ECMO candidates: acute deterioration (either PaO$_2$ < 50 mmHg (6.7 kPa) or pH < 7.15 for 2 hours), unresponsiveness (two of the following for more than 3 hours — PaO$_2$ < 50 mmHg (6.7 kPa) on FiO$_2$ 1.0; pH < 7.27; evidence of barotrauma (interstitial emphysema, pneumothorax)). Meconium aspiration syndrome was diagnosed in infants who had bilateral patchy infiltrates or diffuse lung opacification on the chest radiography together with a history of both meconium-stained liquor and meconium aspiration at birth.

Bronchopulmonary dysplasia (BPD) was defined as dependence on oxygen beyond 28 days with a chest radiograph showing persistent changes.[14] Neonatal 'ARDS' was respiratory distress necessitating ventilation with positive end-expiratory pressure (PEEP) exceeding 5 cm H$_2$O in a near-term or term infant who had echocardiographically documented PPHN and a chest radiograph with dense, bilateral alveolar opacification.[15]

Where possible infants were followed up after discharge and their motor developmental outcome assessed according to the method of Tison.[16] Motor development was classified as normal, suspect or abnormal. Suspect development was defined as abnormal muscle tone with normal reflexes, and abnormal development as any form of cerebral palsy.

Statistical analysis was done on a personal computer using the Stratgraphics programme. Basic descriptive analysis as well as ANOVA methods and Student's *t*-test were used.

Results

Between May 1992 and November 1994, 34 infants with RDS ($N = 19$), neonatal ARDS ($N = 3$) and MAS ($N = 12$) received a trial of HFOV. Owing to similarities in their disease profiles, the infants with RDS and ARDS were grouped and analysed together. The clinical characteristics and ventilator settings with calculated indices are summarised in Tables I and II.

Three patients (9%) initially failed to respond to HFOV after 1, 6 and 31 hours respectively, and died. Their diagnoses were severe air leak, ARDS, and shock probably related to sepsis. Of the remaining 31 infants, a further 5 died during the neonatal period. Three contracted fulminating nosocomially acquired *Pseudomonas* septicaemia and 2 developed extensive air leaks. Twenty-six infants (76%) survived to discharge. Two (18%) of the 11

infants with MAS and 6 (40%) of the 15 with RDS who survived developed BPD. The outcome in the various patient groups is shown in Table III.

Table I. Clinical characteristics of the 34 infants studied (median and range)

	MAS (N = 12)	RDS (N = 22)
Birth weight (g)	3 165 (2 460 - 3 900)	1 487 (720 - 3 200)
Gestational age (wks)	40 (34 - 43)	32 (27 - 40)
Gender (M/F)	5/7	13/9
Inborn/outborn	6/6	17/5
Apgar < 6 at 5 min	6 (50%)*	5 (23%)
Surfactant before HFOV	3 (25%)	20 (91%)
Surfactant doses before HFOV	1	1 (1 - 3)
PPHN	9 (75%)	4 (18%)
Age at HFOV (h)	14 (1 - 65)	18 (3 - 216)

* P = 0.03, MAS v. RDS.

Table II. Ventilator settings and calculated indices 1 - 3 hours before transferring the infants to HFOV (median and range)

	MAS (N = 12)	RDS (N = 22)
FiO_2	1.0 (0.6 - 1.0)	1.0 (0.4 - 1.0)
PIP (cm H_2O)	30 (25 - 50)	30 (15 - 47)
MAP (cm H_2O)	12.7 (7 - 22.5)	12.6 (5 - 20)
PaO_2 (kPa)	6.2 (2.7 - 8.8)	8.9 (3.9 - 25.7)
$PaCO_2$ (kPa)	4.7 (3 - 5.3)	6.1 (3.8 - 10)
OI	28 (10 - 65)	14 (4.5 - 65)

Table III. Outcome of patient groups

	MAS (N = 12)	RDS (N = 22)
Air leaks	3 (25%)	5 (23%)*
IVH (all grades)	0	3 (14%)
Atelectasis on HFOV	2 (18%)	2 (13%)
HFOV duration (h) (mean (SD))	85 (29)	95 (42)
BPD day 28	2 (18%)	6 (40%)
Survival	11 (92%)	15 (68%)

* Two infants had air leak(s) before HFOV.

Twenty of the 22 infants with RDS (91%) received and failed to respond to at least one dose of bovine surfactant. Their mean a/APO_2 ratio did not improve from pre-SRT levels to the pre-HFOV level (0.09 v. 0.12; P = NS). The 3 infants with MAS who received SRT also experienced no improvement in a/APO_2 ratio before switch-over to HFOV.

By 6 hours, infants with RDS were more likely to have responded to HFOV in terms of the a/APO_2 ratio than were neonates with MAS for the same oscillator settings (MAP 18 cm H_2O). Although both groups had a sustained improvement over the first 48 hours, the MAS infants had a lower response rate overall (P = NS) (Fig. 1). The median duration of HFOV was 95 hours and 85 hours in the RDS and MAS infants, respectively.

Thirteen infants met ECMO criteria. All of them had an OI of 30 or above for 4 hours. In addition, 2 infants had pneumothorax with pulmonary interstitial emphysema and 7
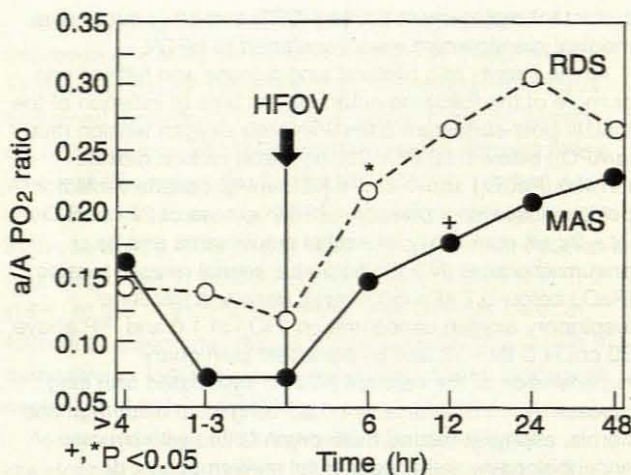

Fig. 1. Mean a/APO_2 for each treatment group over the first 48 hours after initiating HFOV. Analysis of variance for repeated measures indicated significant intragroup differences in a/APO_2 between 0 and 6 hours (P < 0.05) and 0 and 12 hours after HFOV, for RDS and MAS, respectively. No intergroup differences were noted.

experienced acute deterioration in respiratory status. Twelve (92.3%) of them responded favourably to HFOV and survived.

Air leaks developed during HFOV in 25% of the infants with MAS compared with 13.6% of those with RDS (P = NS). Intraventricular haemorrhage (IVH) occurred in 3 (14%) of the infants with RDS (Table III). Omitting those infants who weighed more than 2 000 g increased the incidence of IVH to 21%.

Five infants developed post-extubation stridor, 2 multiple suboccipital subcutaneous abscesses and 1 laryngeal ulceration. One of the infants who developed stridor required a tracheostomy for subglottic stenosis. Atelectasis during HFOV occurred more frequently in the right upper lobe (3 of 4 infants) and was the main reason for switch-over to CV during weaning (in 15% of the cohort).

Autopsies were performed on 5 of the 8 infants who died. Major findings included necrotising tracheobronchitis (N = 1), diffuse alveolar damage with air leaks (N = 2), bronchopneumonia (N = 1) and pulmonary haemorrhage (N = 1).

Seventeen (65%) of 26 survivors were seen at follow-up. Neuromotor development was assessed at the median corrected postnatal age of 13.5 months (range 3 - 26 months). Development was considered normal in 11 children (65%), as suspect in 3 (18%), and as abnormal in 3 (1 spastic quadriplegia, 2 spastic diplegia). One child had severe bilateral sensorineural deafness. Two of the children who were categorised as developmentally abnormal had had severe birth asphyxia and a birth weight below 1 600 g.

Discussion

This study confirms the efficacy of HFOV in infants with severe bilateral diffuse lung disease who failed to improve with conventional mechanical ventilation. The overall survival rate of 76.5% and normal neurodevelopmental outcome of

65% are encouraging and suggest that HFOV should be considered as an essential step in a staged approach to rescue infants who fail to respond to conventional mechanical ventilation and supportive management.

Extraordinary treatment modalities such as HFOV have been shown to benefit a large number of infants suffering from a variety of neonatal respiratory conditions.[6,7,8,17-19] The goal of introducing HFOV in the treatment of severe lung disease is to improve oxygenation/gas exchange at lower risk of barotrauma and therefore lung morbidity and mortality.[7,19] Conflicting results of studies investigating HFOV can be attributed to different devices utilised, different oscillation and MAP strategies, and the heterogeneity of underlying lung conditions of infants enrolled. Homogeneous, diffuse alveolar opacification (RDS or group B streptococcal pneumonia) or non-homogeneous lung involvement, either unilateral or patchy (MAS, air leaks), results in varying response rates to HFO.[6,9,18,19] Management strategies for HFO under these diverse circumstances therefore have to differ. Diffuse, homogeneous lung disease on chest radiography was the presenting problem in the majority of infants with RDS and MAS in our study. Pathophysiologically this represents damaged, atelectatic lungs which have to be re-expanded and then maintained above their closing pressure.[20] Since there is inconsistency in the recommendations regarding the initial levels of MAP to be employed on switch-over from CV to HFOV, we chose the high-pressure/volume strategy. Our approach was influenced by the disappointing results of the HIFI study,[17] which showed no advantage of HFOV over CV in the management of RDS when similar MAPs were used (a low-pressure/volume approach),[20,21] and the favourable results of studies in which high priority was given to achieve early alveolar re-expansion by volume recruitment manoeuvres.[7,20-23] Increasing MAP on transfer from CV to HFOV resulted in significantly improved oxygenation (improved a/APO$_2$ ratios) in both the RDS (after 6 hours) and the MAS (after 12 hours) infants in the present study, confirming the effectiveness of this approach. The slightly poorer improvement in a/APO$_2$ ratios observed in the MAS infants could be attributed to underlying PPHN, blunting the magnitude of the oxygenation response. The lastmentioned finding supports the strategy that once adequate lung volume has been achieved, other treatment modalities such as nitric oxide should be considered to further decrease pulmonary shunting and thereby improve oxygenation.

In contrast to a previous report, we did not observe uniformly poor response of infants with MAS to HFOV.[6] Our success rate (92% survival) with HFOV in this group of patients may have been influenced by the prospective selection of infants with a more uniform appearance of MAS on chest radiography. Although we empirically increased the MAP by 2 - 4 cm H$_2$O upon transferring infants from CV to HFOV (in the absence of air leaks), the volume optimisation strategy proposed by Chan et al.[24] provides a more realistic approach to identification of the initial optimal MAP in infants with RDS (stiff lungs). By increasing MAP in a stepwise manner from 0 cm H$_2$O to + 2 cm H$_2$O, and then to + 5 cm H$_2$O, they were able to determine the optimal oxygenation response within 40 minutes.

From the results of our own study and those of others it appears that HFOV is effective, even after lung injury is established.[17,19,25] As we have mentioned, there are categories of infants with established disease who respond more poorly to HFOV than others.[6,18,19] Specific conditions include air leaks,[18] pulmonary hypoplasia syndromes,[17,18] and subgroups of MAS with airway disease (gas trapping).[17] Recently Paranka et al.[17] showed that the presence of congenital diaphragmatic hernia with lung hypoplasia (CDH/LH) or an a/APO$_2$ ratio below 0.05 among non-CDH/LH patients at the onset of HFOV and subsequent lack of improvement after 6 hours of HFOV (a/APO$_2$ ≤ 0.08) were independently predictive of failure to respond to HFOV. Overall, in the present study the a/APO$_2$ was a very poor predictor of responsiveness to HFOV in babies of 34 weeks' gestational age or more. An initial a/APO$_2$ of less than 0.05 and a subsequent ratio of 0.08 predicted poor responsiveness with a sensitivity of 10% and specificity of 0%, and a sensitivity of 46% and specificity of 0% at the onset of oscillation and after 6 hours, respectively.

The poor predictive power observed highlights the influence of patient selection, time elapsed before initiation of HFOV, size of study populations and dependence of variables on physician-directed changes to the ventilator. Subjecting certain categories of critically ill infants to a too-short trial of HFOV (i.e. ≤ 6 hours) to evaluate their response might not be adequate. Before deciding to withdraw HFOV, attention has to be focused on the underlying lung and cardiac physiology. Meconium aspiration syndrome with bilateral patchy or diffuse opacification and associated PPHN might necessitate a more lengthy trial of HFOV before withdrawal is considered. Concern has been raised regarding the relationship of a high-MAP, high-volume approach and raised intracranial pressure and an increased risk of intracranial haemorrhage in premature infants.[17,21,26] There is evidence to support the view that HFOV induces changes in intracranial compliance through affecting cerebral blood volume and interstitial fluid volume as a consequence of impaired venous return.[27] Walker et al.[28] demonstrated in newborn lambs that intracranial compliance and cerebral perfusion pressure at normal and elevated airway pressure were similar during HFOV and CV. They concluded that HFOV did not seem to be mechanically disruptive to the newborn cerebral circulation. The 21% incidence of IVH among infants with RDS in the present study was similar to that of comparable historical controls in our unit,[29] corroborating the findings of Walker et al.[28]

Necrotising tracheobronchitis (NTB) has been reported as a complication related to mechanical ventilation in infants with RDS.[30] Although the exact causation is not known, raising the mean airway pressure above 20 cm H$_2$O in anaesthetised adult rabbits undergoing HFOV resulted in a significant drop in bronchial mucosal blood flow in the presence of a constant cardiac output.[31] The present study documented NTB in 1 of 5 patients on whom autopsy was performed. This patient was our index case and was switched from CV to HFO at the postnatal age of 37 hours. The potential contributory role of CV to the occurrence of NTB in this case could therefore not be determined.

Several First-World countries now have a number of neonatal units with both HFOV and ECMO available as the final forms of intervention in near-term or term infants with severe respiratory failure. It remains controversial whether ECMO facilities should be available in developing

countries.[11] HFOV, however, appears to be relatively free of significant morbidity compared with ECMO, and should therefore be considered as part of a staged intervention strategy in the attempt to rescue severely ill infants with RDS, neonatal ARDS and certain categories of MAS.

REFERENCES

1. Davies VA, Rothberg AD, Ballot DE. The introduction of surfactant therapy in South Africa. *S Afr Med J* 1995; **85:** 637-640.
2. Ballot DE, Rothberg AD, Davies VA. The selection of infants for surfactant replacement therapy under conditions of limited financial resources. *S Afr Med J* 1995; **85:** 640-643.
3. Adhikari M, Gouws E. Meconium aspiration in South Africa. *S Afr Med J* 1995; **85:** 891-893.
4. Smith J, Kling S, Gie RP, Van Zyl J, Kirsten GF, Nel ED, Schneider JW. Bronchopulmonary dysplasia in infants with respiratory distress syndrome in a developing country: a prospective single centre-based study. *Eur J Paediatr* 1996; **155:** 672-677.
5. Mortality 0 - 4 years of age. In: Seele R, ed. *Health Trends in South Africa.* Pretoria: Department of Health, 1994.
6. Carter JM, Gerstmann DR, Clark RH, *et al.* High-frequency oscillatory ventilation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. *Pediatrics* 1990; **85:** 159-164.
7. Clark RH, Gertsmann DR, Null DM, Delemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. *Pediatrics* 1992; **89:** 5-12.
8. Kohelet D, Perlman M, Kirpalani H, Hanna G, Koren G. High-frequency oscillation in the rescue of infants with persistent pulmonary hypertension. *Crit Care Med* 1988; **16:** 510-516.
9. Clark RH, Null DM. High frequency oscillatory ventilation: clinical management strategies. *Cardio Pulmonary Review: Current Applications and Economics.* Yorba Linda, Calif.: Sensor Medics Corporation, 1991.
10. Report of a Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians. Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. *Arch Dis Child* 1992; **67:** 1221-1227.
11. Smith J, Kirsten GF. Persistent pulmonary hypertension of the neonate in a developing country — does extracorporeal membrane oxygenation have a role to play? *S Afr Med J* 1993; **83:** 742-745.
12. Horbar JD. A calculator program for determining indices of neonatal respiratory distress syndrome severity. *Am J Perinatol* 1987; **4:** 20-23.
13. Engle WA, Peters EA, Gunn SK, West KW, Langefeld C, Hui SI. Mortality prediction and interval until death in near-term and term neonates with respiratory failure. *J Perinatol* 1993; **13:** 368-375.
14. O'Brodovich HM, Mellins RB. Bronchopulmonary dysplasia: unresolved neonatal acute lung injury. In: Cherniack RM, ed. *Lung Disease: State of the Art.* Vol. 86. New York: American Lung Association, 1984; 85-100.
15. Pfenniger J, Gerber A, Tschäppeler H, *et al.* Adult respiratory distress syndrome in children. *J Pediatr* 1982; **101:** 352-357.
16. Tison A. A method for neurological evaluation within the first year of life. *Pediatrics* 1976; **7:** 1-50.
17. Paranka MS, Clark RH, Yoder BA, Null DM. Predictors of failure of high-frequency oscillatory ventilation in term infants with severe respiratory failure. *Pediatrics* 1995; **95:** 400-404.
18. Chan V, Greenough A, Gamsu HR. High frequency oscillation for preterm infants with severe respiratory failure. *Arch Dis Child* 1994; **70:** F44-F46.
19. Vierzig A, Gunther M, Kribs A, Roth B. Clinical experiences with high-frequency oscillatory ventilation in newborns with severe respiratory distress syndrome. *Crit Care Med* 1994; **22:** 583-587.
20. Bryan AC, Froese AB. Reflections on the HIFI trial. *Pediatrics* 1991; **87:** 565-567.
21. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med* 1989; **320:** 88-93.
22. Clark RH, Gerstmann DR, Null DM jun, Delemos RA. High-frequency oscillatory ventilation reduces the incidence of severe chronic lung disease in respiratory distress syndrome. *Am Rev Respir Dis* 1990; **141:** A686.
23. McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. *Am Rev Respir Dis* 1988; **137:** 1185-1192.
24. Chan V, Greenough A, Giffin F. Disease severity and optimum mean airway pressure level on transfer to high frequency oscillation. *Pediatr Pulmonol* 1994; **17:** 178-182.
25. Delemos RA, Coalson JJ, Delemos JA, King RJ, Clark RH, Gertsmann DR. Rescue ventilation with high frequency oscillation in premature baboons with hyaline membrane disease. *Pediatr Pulmonol* 1992; **12:** 29-36.
26. Bohanon KS, Gerstmann DR, Meredith KS, Null DM, Delemos RA. Intraventricular haemorrhage (IVH) in severely ill premature infants treated with high frequency oscillatory ventilation (HFOV). *Pediatr Pulmonol* 1987; **3:** 376A.
27. Bell RE, Coalson JJ, Ackerman NB jun, *et al.* A nonpulmonary complication of high-frequency oscillation. *Crit Care Med* 1986; **14:** 207-210.
28. Walker AM, Brodecky VA, de Preu ND, Ritchie BC. High frequency oscillatory ventilation compared with conventional mechanical ventilation in newborn lambs: Effects of increasing airway pressure on intracranial pressures. *Pediatr Pulmonol* 1992; **12:** 11-16.
29. Kirsten GF, Van Zyl JI, Le Grange M, Ancker E, Van Zyl F. The outcome at 12 months of very-low-birth-weight infants ventilated at Tygerberg Hospital. *S Afr Med J* 1995; **85:** 649-654.
30. Joshi VV, Mandavia MB, Stern L *et al.* Acute lesions induced by endotracheal intubation. *Am J Dis Child* 1972; **124:** 646-649.
31. Mizuno K, Itabashi K, Okuyama K. Effect of mean airway pressure on bronchial mucosal blood flow in rabbits with oleic acid-induced injury. *Acta Paediatr Jpn* 1992; **34:** 668-673.