Management of meconium aspiration syndrome with High-frequency oscillatory ventilation

Asma Bouziri, Asma Hamdi, Ammar Khaldi, Sarra Belhadj, Khaled Mnif, Nejla Ben Jaballah

Pediatric Intensive Care Unit- Children's Hospital. Tunis. Tunisia
Tunis El Manar University

N. Mathlouthi, B. Ben Ayed, M. Dhouib, K. Chaabene, K. Trabelsi, H. Amouri, M. Guermazi

Prise en charge de l'inhalation méconiale par la ventilation par oscillation à haute fréquence

LA TUNISIE MEDICALE - 2011 ; Vol 89 (n°07/08) : 632 - 637

N. Mathlouthi, B. Ben Ayed, M. Dhouib, K. Chaabene, K. Trabelsi, H. Amouri, M. Guermazi

Management of meconium aspiration syndrome with High-frequency oscillatory ventilation

LA TUNISIE MEDICALE - 2011 ; Vol 89 (n°07/08) : 632 - 637

RÉSUMÉ

Prérequis : la ventilation par oscillation à haute fréquence (VOHF) a été préconisée pour améliorer l'inflation des poumons tout en réduisant, potentiellement, le risque de barotraumatismes. Il y a peu de données, dans la littérature, sur l'utilisation précoce de la VOHF chez des nouveau-nés à terme hypoxémiques.

But : Evaluer l'efficacité de la VOHF, utilisée comme mode de ventilation initial, chez des nouveau-nés présentant une inhalation méconiale sévère (IM).

Méthodes: Dans un service de réanimation pédiatrique niveau III, 17 nouveau-nés à terme atteints d'IM sévère ont été ventilés d'emblée en mode OHF et évalués prospectivement. Les paramètres de ventilation, les gaz du sang, l'index d'oxygénation (IO) et la différence alvéolo-artérielle d'oxygène (D (A-a) O2) ont été enregistrés durant la VOHF et comparés à des intervalles de temps multiples.

Résultats: les objectifs de ventilation ont été facilement atteints avec la VOHF. L'initiation de la VOHF a causé une diminution significative de la FiO2, atteinte précocement au bout d'une heure (de 0.93 ± 0.11 à 0.78 ± 0.25; P=0.031) et l'amélioration a été soutenue pendant toute la période de l'essai (1-32 heures). Il y avait également une diminution significative de la D (A-a) O2 et de l'IO, respectivement, à 4 heures (de 562.5 ± 71.7 à 355.4 ± 206 mm Hg; p=0.03) et 8 heures (de 23.3 ± 17 à 14.6 ± 16.3; p=0.04), qui était soutenue jusqu'à 16 et 40 heures après le début de la VOHF. Trois nouveau-nés (17.6%) ont développé un pneumothorax sous VOHF. Un patient est resté oxygénodépendant jusqu'à l'âge de 28 jours. Aucune autre complication associée à la VOHF n'a été détectée. Seize nouveaux nés (94 %) ont été sevrés, avec succès, de la VOHF et 15 (88 %) ont survécu.

Conclusion : L'utilisation de la VOHF, comme mode initial de ventilation, chez des nouveau-nés atteints d'IM sévère est une stratégie efficace.

Mots-clés

Ventilation à haute fréquence ; ventilation Mécanique ; inhalation méconiale ; nouveau-né; insuffisance respiratoire

SUMMARY

Background: High-frequency oscillatory ventilation (HFOV) has been advocated for use to improve lung inflation while potentially decreasing lung injury. There were few data on the early use of HFOV in hypoxemic term neonates.

Aim: To evaluate the effectiveness of HFOV, used as the initial mode of ventilation, in neonates with severe meconium aspiration syndrome (MAS).

Methods: In a tertiary care paediatric intensive care unit, 17 term neonates with severe MAS were managed with HFOV, used as the initial mode of ventilation, and prospectively evaluated. Ventilator settings, blood gases, oxygenation index (OI) and alveolar-arterial oxygen difference (P(A-a)O2) were prospectively recorded during HFOV treatment and compared at the multiple time intervals.

Results: Target ventilation was easily achieved with HFOV. Initiation of HFOV caused a significant decrease in FIO2, achieved as early as 1 hour (from 0.93 ± 0.11 to 0.78 ± 0.25; p=0.031) and the improvement was sustained during the 1-32 hours period. There were a significant decreases in P (A-a) O2 and OI, repectively, at 4 hours (from 562.5 ± 71.7 to 355.4 ± 206 mm Hg; p=0.03) and 8 hours (from 23.3±17 to 14.6±16.3; p=0.04), that were sustained up to 16 and 40 hours . Three neonates (17.6%) developed pneumothorax on HFOV. One patient required oxygen support at 28 days. No significant others complications associated with HFOV were detected. Sixteen infants (94 %) were successfully weaned from HFOV and 15 (88%) survived to hospital discharge.

Conclusion: Use of HFOV as the initial mode of ventilation in neonates with severe MAS is an effective strategy.

Key-words

High-frequency ventilation, mechanical ventilation, meconium aspiration, newborn; respiratory insufficiency.

Meconium aspiration syndrome (MAS) is a life-threatening respiratory disorder in infants born through meconium-stained amniotic fluid and remains a major indication for extracorporeal membrane oxygenation (ECMO) in the newborn (1) Therapy for the disease remains problematic, and newer treatments such as exogenous surfactant, high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO) are being applied with increasing frequency and have reduced ECMO use (2, 3). HFOV has been advocated for use to improve lung inflation while potentially decreasing lung injury through volutrauma.There are several studies on the " rescue" use of HFOV in hypoxemic term neonates (4-7). However, the role of HFOV, for the early management of term neonates with hypoxemic respiratory failure, had less been evaluated (8). Our treatment options for neonates with severe MAS is to use HFOV as the initial mode of ventilator therapy. The objective of this study was to evaluate the effectiveness of this strategy.

METHODS

This study was performed in the pediatric and neonatal intensive care unit of children's hospital of Tunis (Tunisia). Facilities for specific neonatal care are limited in Tunisia with few neonatal intensive care units in the public health institutions and no neonatal transportation service.

All the neonates referred to us are outborn and most of them are transferred from the general paediatric wards, at a "late" stage in their disease process on spontaneous ventilation. Exogenous surfactant is not approved for term neonates in our unit and ECMO is not available in our country. As a result, our treatment options for severe MAS are to use HFOV as the initial mode of ventilator therapy. Newborns with severe MAS treated, between august 2003 and december 2007, with HFOV, as the initial mode of ventilator therapy were prospectively evaluated.

Entry criteria for HFOV treatment:

Neonates with MAS were treated with HFOV if they had the following criteria :

- acute respiratory failure, requiring mechanical ventilation, - fraction of inspired oxygen (FiO_2) of at least 0.5 and a mean airway pressure (MAP) of at least 10 cm H_2O, to maintain arterial oxygen saturation, as measured by pulse oximetry, between 90 and 95% and partial pressure of arterial oxygen (PaO_2), mesured from an arterial blood sample, between 50 to 70 mmHg,
- significant pulmonary air leak (diffuse pulmonary interstitial emphysema, pneumothorax or pneumomediastinum). The diagnosis of MAS was based on the triad of (1) the presence of meconium-stained amniotic fluid, (2) aspiration of meconium from below the vocal cords and (3) chest radiograph consistent with MAS (infiltrate, consolidation, atelectasis, hyperinflation, air leak). The patients with major congenital anomalies, intractable shock (as defined by a mean arterial pressure of > 2 SD below normal, despite inotropic support with > 20 mg/kg/minute of dopamine and dobutamine an adequate preload) or who were ventilated before admission were excluded from the study. The study protocol was approved by the institutional review board and informed consent was obtained from the parents after medical explanations.

HFOV strategy:

The high-frequency ventilator used was a piston-driven device that offers an active expiratory phase and a variable inspiration/expiration ratio (3100A, Sensor Medics, Yorba Linda, CA).

- Initial HFOV settings: initial settings of the ventilator were standardized according to the following parameters: F_iO_2 of 1; frequency of 12 Hz; inspiratory time of 0.33; bias flow of 10 L/min; MAP of 14 cm H_2O and pressure amplitude of oscillation initially adjusted to provide adequate chest wall movement.
- Management of oxygenation: we employed a strategy that consisted of incremental increases in MAP until arterial oxygen saturation was ≥ 90%, with an F_iO_2 of < 0.6. Our goal was to maintain the lowest F_iO_2 and ideal lung expansion with avoidance of lung over distension and atelectasis. We defined ideal lung inflation as expansion to 9 posterior ribs on chest radiography for infants without severe air leak and as expansion to 7 to 8 posterior ribs for infants with severe air leak. Lung inflation was determined using chest radiography, obtained within 2 hours after initiation of HFOV. Once lung inflation was improved, we reduced the F_iO_2 and then the MAP. In infants with severe air leak, we gave priority to reducing the MAP over reducing F_iO_2. Our target PaO_2, mesured from a postductal arterial blood sample, was 50 to 70 mmHg.
- Management of ventilation: modulation of $PaCO_2$ was accomplished by adjusting the pressure amplitude. Pressure amplitude of oscillation was titrated to maintain $PaCO_2$ within the target range (45 to 55 mmHg). If adequate ventilation could not be achieved with the maximum pressure amplitude of oscillation (70 cm H_2O), the oscillatory frequency was incrementally decreased by 1 Hz to a minimum of 7 Hz. The inspiratory/expiratory ratio was kept at 0.33. iNO in an initial concentration of 20 ppm was started when oxygenation did not improve after two hours of optimized HFOV, if there was echocardiographic evidence of pulmonary hypertension. Haemodynamic support with inotropes and/or fluids was given by central venous catheter to optimize arterial blood pressure. Chest tube drainage was performed if necessary. All patients were sedated with a combination of opioid and benzodiazepine. Muscle relaxants (vecuronium) could be given in combination with sedation to infants in whom there was acute deterioration of gas exchange during excessive spontaneous activity. Endotracheal suctioning was performed every two to three hours. Patients were preoxygenated and were then removed from the oscillator during endotracheal suctioning.
- Withdrawal from HFOV:

Patients were withdrawn from HFOV, to receive conventional ventilation (CV), if they had the following criteria: 1) inability to maintain an oxygen saturation of ? 90 % on an F_iO_2 of 1 for 3 hours, despite an ideal lung inflation on chest radiography 2)

inability to maintain $PaCO_2$ within the target range despite maximal pressure amplitude (70 cm H_2O) and minimum frequency (7 Hz) 3) circulatory failure at the MAP required to achieve adequate oxygenation.

- Weaning from HFOV: the weaning process was initiated once F_iO_2 was < 0.4. MAP was gradually decreased by 1 to 2 cmH_2O and the pressure amplitude of oscillation was adjusted to maintain $PaCO_2$ at the target level. Extubation was considered when patient's condition had been stable for 12 to 24 hours, while adequate oxygenation could be maintained with an FiO_2 of < 0.3 and a MAP less than 8 cmH_2O. Patients were extubated directly to a nasal continuous positive airway pressure, nasal cannula oxygen or room air.

Monitoring and data collection:

All patients were monitored with continuous arterial blood pressure measurements by indwelling catheter, continuous pulse oximetry and continuous limb lead electrocardiography. Arterial catheter was utilized for rapid arterial blood gas analysis. Clinical data, ventilator settings and arterial blood gases (PaO_2, $PaCO_2$ and arterial oxygen saturation) were prospectively recorded at 1 hour of HFOV, every 4 hours for 24 hours and then every 8 hours from hours 25 to 48 hours of HFOV. Oxygenation index (OI) (= [MAP x FiO_2 x 100]/PaO_2) and alveolar-arterial oxygen difference (P[A-a]O_2) (= [FiO_2 x (743-47) – ($PaCO_2$/0.8)] - PaO_2) were calculated at the same time intervals. MAP, frequency, pressure amplitude and FiO_2 were recorded from the visual display on the ventilator. At a minimum, chest radiographs were performed within 2 hours of HFOV and then every 12 hours and interpreted for presence or absence of lung hyperinflation and air leak by two experienced intensivists. Data on demographics and outcome parameters were also collected for each patient. We defined chronic lung disease as the requirement for supplemental oxygen at 28 days of life.

Statistics:

Comparisons of MAP, F_iO_2, $PaCO_2$, OI and P [A-a] O_2 were performed at the multiple time intervals on HFOV, using the one-way Friedman rank-sum procedure, a paired nonparametric statistic, and a two-tailed Wilcoxon matched-pairs test. This allowed comparison of data between the time intervals on HFOV and the precedent time. Data are expressed as mean ± SD. Significance was defined as $p < 0.05$ for all analyses. Calculations were performed by the SPSS program (version 10.0, SPSS, Chicago, IL).

RESULTS

Patient characteristics and severity of respiratory failure (Table1):

During the study period, 42 neonates were admitted to our unit for MAS. Of those, 18 patients with moderate disease were successfully treated with CV alone and 7 were treated with HFOV, used as "rescue" intervention after failure of CV. The remaining 17 neonates were treated with HFOV, used as the initial mode of ventilator therapy, and were included in the data analysis. They had a mean gestational age of 39.5 ± 1.8 weeks and a mean birth weight of 3319 ± 255 g. Their mean postnatal age was 19.7 ± 11 hours and all were breathing spontaneously at admission with an arterial oxygen saturation of 81 ± 2.7 % on an F_iO_2 of 1. Just before initiation of HFOV (H0), average values of OI and P [A-a] O_2 were 23.3±17 and 562.5±71.7 mm Hg, respectively. Five neonates (29.4%) had hypotension (mean arterial blood pressure <45 mmHg) and needed volume expansion and inotropic support prior to HFOV. Fourteen

Table 1 : Patient characteristics and outcome on high frequency oscillatory ventilation

Case N₀ / Sex	Birth weight (g)	GA (weeks)	Postnatal age (hours)	OI 0 h	P (A-a)O2 (mmHg) 0 h	Length of HFOV (hours)	Outcome
1/M	3500	42	14	44.9	592	142	S
2/F	3550	41.1	6	25	580	48	S
3/M	2850	38	43	11.63	591	42	S
4/M	3085	37	6	16.14	594	260	S
5/M	3000	41.1	20	12	401	24	S
6/F	3000	41	10	20.2	642	96	S
7/M	3350	41.2	22	11.48	610	65	S
8/M	3500	39.2	42	18.06	529	141	S
9/M	3200	36	25	23.3	611	116	S
10/M	3600	37.1	21	63	560	163	S
11/M	3650	41	12	32	529	163	S
12/F	3600	41.2	14	12	594	70	S
13/M	3300	40	26	12	530	114	D (day 5)
14/F	3400	40.0	33	12	500	136	S
15/M	3100	38.5	20	57	642	12	D (H12)- PF
16/F	3600	37.2	12	14.06	568	65	S
17/M	3140	40	9	12	400	41	S
Mean ± SD	3319±255	39.5±1.8	19.7±11	23.3±17	562.5±71.7	103±62.4	-

neonates (82.5%) had echocardiographic evidence of pulmonary hypertension, and all patients had air leak syndrome at the time of referral, before intubation (pulmonary interstitial emphysema: 12 patients, pneumothorax: 4 patients pneumomediastinum: 1 patient).

Outcome on HFOV:

1) HFOV settings and gas exchange:

The mean values of maximal MAP and pressure amplitude of oscillation on HFOV were 16±6 cm H_2O and 47.7 ± 8.3 cmH_2O, respectively. Fourteen neonates with pulmonary hypertension received iNO. Figures 1 and 2 summarize the changes of MAP, F_iO_2, $PaCO_2$, OI and P (A-a) O_2 in the whole study population at the multiple time intervals during the first 72 hours of HFOV. In all patients, target ventilation was easily achieved with HFOV and mean $PaCO_2$ remained at the target level during all the study period. Initiation of HFOV caused a significant decrease in F_iO_2, achieved as early as 1 hour after initiating HFOV (from 0.93± 0.11 to 0.78 ± 0.25; p=0.031) and the improvement was sustained during the 1-32 hours period (p ≤ 0.04 for all comparisons).

Figure 1 : Changes in F_iO_2 and MAP during the initial 72 hours of HFOV are demonstrated in the whole study population. HFOV was instituted at hour 0, which represents the values of these parameters just before initiation of HFOV. Since hour 4, there are only 16 data points (one patient was protocol failure and was withdrawn from HFOV). Values are expressed as mean. * p<0.01, Wilcoxon matched-pairs test between the time intervals and the precedent time.

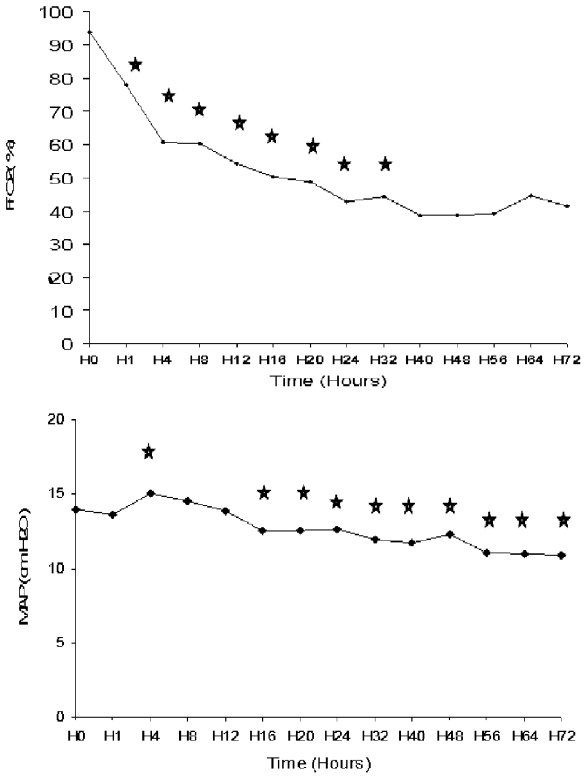
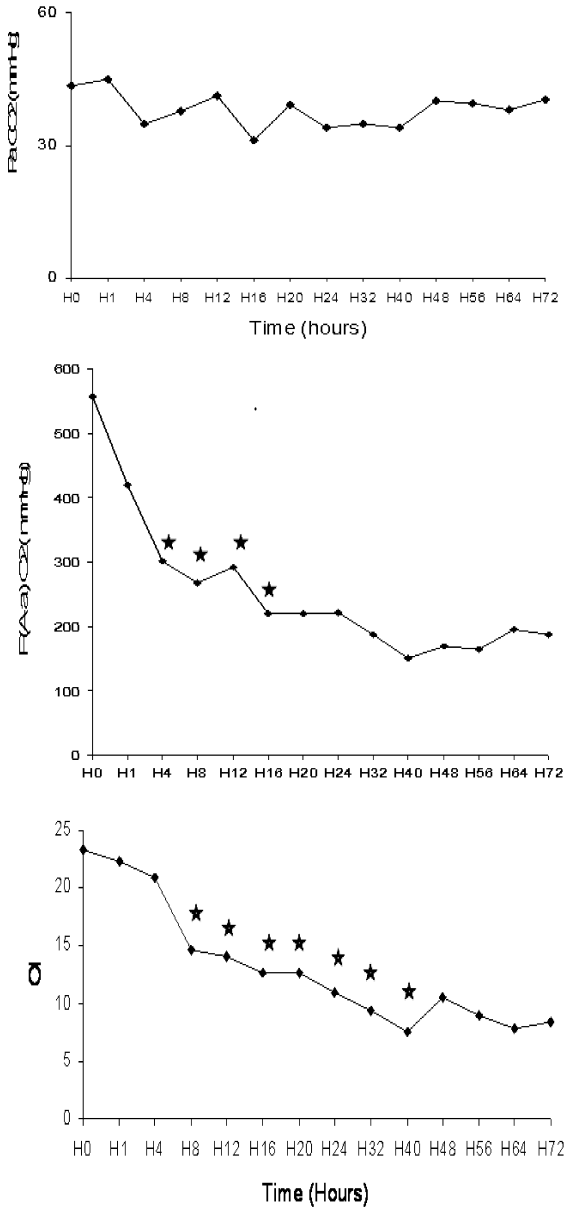


Figure 2 : Changes in PaCO2, P(A-a)O2 and OI during the initial 72 hours HFOV are demonstrated in the whole study population. HFOV was instituted at hour 0, which represents the values of these parameters just before initiation of HFOV. Since hour 4, there are only 16 data points (one patient was protocol failure and was withdrawn from HFOV). Values are expressed as mean. *p≤0.01, Wilcoxon matched-pairs test between the time intervals and the precedent time.



As per protocol design, the MAP significantly increased 4 hours after the initiation of HFOV to achieve volume recruitment (p<0.01). By 16 hours of HFOV and as the patient's oxygenation requirements improved, a significant decrease in MAP was observed (from 15±5.9 cm H_2O to 12.5±5.3 cm H_2O;

p= 0.004) and persisted for all the study period (p<0.01 for all comparisons). There were a significant decreases in $P(A\text{-}a)O_2$ and OI at 4 hours (from 562.5±71,7 to 355.4 ±206 mm Hg; p=0.03) and 8 hours (from 23.3±17 to 14.6±16.3; p=0.04), that were sustained up to 16 (p <0,03 for all comparisons) and 40 hours, respectively (p < 0,04 for all comparisons).

2) Weaning from HFOV / HFOV failure:

Sixteen infants (94 %) were successfully weaned from HFOV to a nasal continuous positive airway pressure, nasal cannula oxygen or room air. Of these 15 (88%) survived to hospital discharge. The remaining patient later developed nosocomial bloodstream infection and died at 5 days following admission. Length of HFOV, supplemental oxygenation and intensive care unit hospitalisation in the survivors were 4.3±2.6 days, 6.8±5.6 days and 9.2±6.1 days, respectively. One patient, with $P(A\text{-}a)O_2$ and OI, at the institution of HFOV, at 642 mm Hg and 22, repectively, was withdrawn from HFOV due to oxygenation failure and cardiac impairment. This patient died as a consequence of respiratory and circulatory failure at 12 hours following admission, 8 hours after withdrawing from HFOV.

Complications:

Three neonates (17.6%) developed pneumothorax on HFOV. HFOV did not cause worsening barotrauma in the remaining 14 patients. Nine patients (53%) developed episodes of moderate hypotension during institution of HFOV. These episodes responded rapidly to volume expansion (mean volume: 20 ml/kg). Head ultrasounds were performed in 11 neonates but could not be obtained prior the initiation of HFOV. Cerebral oedema was seen in the patient who was treatment failure. Only one patient (5.9%) required oxygen support at 28 days. There was no other complication attributable to HFOV.

DISCUSSION

The uncontrolled design of our study creates major limitations and precludes firm conclusions about the potential benefits of HFOV, used as the initial mode of ventilator therapy, in neonates with severe MAS. Although the results of this study do not prove that HFOV will improve outcome in these patients, they indicate that HFOV is safe and effective in achieving adequate oxygenation, in a rapid and sustained fashion.

A number of reports now demonstrate that HFOV can maintain gas exchange in hypoxemic term neonates under circumstances in which conventional approaches have been judged inadequate (4-7). To date, however, there are only one report of HFOV used as the primary means of ventilation in the management of uncomplicated respiratory failure in term and near term infants (8). This randomized controlled comparison of HFOV and conventional ventilation in 119 patients with moderate to severe respiratory failure did not show an advantage of HFOV over CV in term of neonatal death or pulmonary air leak. The small sample size of the study and the moderate rather than severe nature of respiratory failure ($P(A\text{-}a)O_2$ 251±131mmHg in the CV group and 250± 136 mmHg in the HFOV group) might blunt the benefits of HFOV.

Our ventilation strategy was designed to avoid ventilator-induced lung injury and occurence of intractable respiratory failure. The rationale for this strategy is the potential of HFOV to maintain adequate gas exchange without imposing the large pressure swings and tidal volumes associated with ventilator-induced lung injury and to augment the response to iNO by improving lung inflation. Numerous experimental studies have demonstrated that HFOV diminishes the amount of ventilator lung injury and may be more effective when used early in the course of respiratory failure(9-16). In experimental MAS, many data indicate that HFOV may be superior to CV for treatment of respiratory failure and results in superior oxygenation and less ventilator-induced lung injury (17-21). In a piglet model of MAS, the histologic changes on CV were significantly worse than those on various types of HFOV.(17) Moreover, studies have also shown that HFOV augments the response to iNO in persistent pulmonary hypertension of the newborn associated with MAS or diffuse parenchymal lung disease (22-23). The obstructive nature of MAS and suboptimal lung inflation prevents iNO from reaching many alveoli and diffusing to the vasculature to cause dilatation and may compromise the efficacy of iNO.

Our strategy resulted in a high survival rate (88 %) despite the severity of our patients, based on indices of gas exchange, and the fact that exogenous surfactant and ECMO were not used. Even in tertiary neonatal centers of the developed world, where these therapies are available, at least 3 -6.5% of infants with MAS die (24-26). MAS remains the major indication for ECMO in the newborn and infants with hypoxemic respiratory failure because of MAS have a potential for increased survival with ECMO (1). There is a significant disturbance of the pulmonary surfactant system in MAS and inhibition of surfactant function in the alveolar space is an important element of the pathophysiology of the disease. Surfactant therapy, as standard bolus therapy (27, 28) or in association with therapeutic lung lavage (29) in ventilated infants with MAS has been found to improve oxygenation in most studies.

We also found HFOV is a safe mode of ventilation in neonates with severe MAS. HFOV did not cause worsening volutrauma in most neonates. Nevertheless, 17.6 % of our patients developed pneumothorax during HFOV. Some air-trapping may have contributed to the substantial incidence of pneumothorax and perhaps use of lower frequencies would have been more appropriate in these infants with obstructive pulmonary disease. In a piglet model of MAS, early institution of HFOV at 15 Hz seems to exacerbate air trapping when compared with both CV and HFOV at lower rates (18).

CONCLUSION

In neonates with severe MAS, HFOV, used as the initial mode of ventilator therapy, is safe and effective in achieving adequate oxygenation. However, the results of this study do not prove that HFOV will improve outcome in these neonates and randomized controlled trials are needed to identify its benefits over conventional modes of mechanical ventilation.

References

1. Flamant C, Nolent P, Hallalel F, Lardeux C, Chevalier Jy, Renolleau S. Evolution of extracorporeal membrane oxygenation (ECMO) in neonatal acute respiratory failure, fifteen years of experience]. Arch Pediatr 2004; 11: 308-14.
2. Roy Bj, Rycus P, Conrad Sa, Clark RH. The changing demographics of neonatal extracorporeal membrane oxygenation patients reported to the Extracorporeal Life Support Organization (ELSO) Registry. Pediatrics 2000; 106: 1334-8.
3. Somme S, Liu DC. News trends in extracorporeal membrane oxygenation in newborn pulmonary diseases. Artif Organs 2001; 25: 633-7.
4. Carter Jm, Gerstmann Dr, Clark RH. High frequency oscillation and extracorporeal membrane oxygenation for the treatment of acute neonatal respiratory failure. Pediatrics 1990; 85: 159-64.
5. Clark Rh, Yoder Ba, Sell MS. Prospective, randomized comparison of high-frequency oscillation and conventional ventilation in candidates for extracorporeal membrane oxygenation. J Pediatr 1994; 124: 447-54.
6. Kohlet D, Perlman M, Kirpalani H. High frequency oscillation in the rescue of infants with persistent pulmonary hypertension. Crit. Care Med 1988; 16: 510-16.
7. Varnholt V, Lasch P, Suske G, Kachel W, Brands W. High-frequency oscillatory ventilation and extracorporeal membrane oxygenation in severe persistent pulmonary hypertension of the newborn. Eur J Pediatr 1992;151: 769-74.
8. Rojas Ma, Lozano Jm, Rojas MX, et al. Randomized, multicenter trial of conventional ventilation versus high-frequency oscillatory ventilation for the early management of respiratory failure in term or near-term infants in Colombia. J Perinatol 2005; 25: 720-4.
9. Hamilton Pp, Onayemi A, Smyth JA, et al. Comparison of conventional and high frequency ventilation: oxygenation and lung pathology. J Appl Physiol 1983; 55: 131-8.
10. De Lemos Ra, Coalson Jj, Gertsmann DR, et al. Ventilatory management of infant baboons with hyaline membrane disease: the use of high frequency ventilation. Pediatr Res 1987; 21: 594_602.
11. De Lemos Ra, Coalson Jj, De Lemos 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.
12. Imai Y, Kawano T, Miyasaka K, Takata M, Imai T, Okuyama K. Inflammatory chemical mediators during conventional ventilation. Am J Respir Crit Care Med 1994; 150: 1550-4.
13. 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; 137:1185-92.
14. Meredith Ks, De Lemos Ra, Coalson JJ, et al. Role of lung injury in the pathogenesis of hyaline membrane disease. J Appl Physiol 1989; 66:2150 - 8.
15. Delemos Ra, Coalson Jj, Meredith Ks, Gerstmann Dr, Null Dm Jr. A comparison of ventilation strategies fot the use of high-frequency oscillatory ventilation in the treatment of hyaline membrane disease. Acta Anaesthesiol Scand 1989; 90 (Suppl) : 102-7.
16. Jackson Cj, Truog We, Standaert TA, et al. Reduction in lung injury after combined surfactant and high-frequency ventilation. Am J Respir Crit Care Med 1994; 150: 534-9.
17. Wiswell Te, Foster Nh, Slayter Mv, Hachey WE. Management of a piglet model of the meconium aspiration syndrome with high-frequency or conventional ventilation. Am J Dis Child 1992; 146:1287-93.
18. Hachey We, Eyal Fg, Curtet- Eyal Nl, Kellum FE. High-frequency oscillatory ventilation versus conventional ventilation in a piglet model of early meconium aspiration. Crit. Care ed 1998; 26: 556-61.
19. Huang Qw, Sun B, Gao F, et al. Effects of inhaled nitric oxide and high-frequency ventilation in rabbits with meconium aspiration. Biol Neonate 1999; 76:374-82.
20. Vankaam Ah, Haitsma Jj, De Jaegere A, Van Aalderen Wm, Kok Jh, Lachmann B. Open lung ventilation improves gas exchange and attenuates secondary lung injury in a piglet model of meconium aspiration. Crit Care Med 2004; 32:443-9.
21. Calkovska A, Sun B, Curstedt T, Renheim G, Robertson B. Combined effects of high-frequency ventilation and surfactant treatment in experimental meconium aspiration syndrome. Acta Anaesthesiol. Scand 1999; 43: 135-45.
22. Kinsella Jp, Trug We, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 1997; 131(1 Pt 1):55-62.
23. Kinsella Jp, Abman SH. Inhaled nitric oxide and high frequency oscillatory ventilation in persistent pulmonary hypertension of the newborn. Eur. J. Pediatr. 1998; 157 Suppl1: S28-30.
24. Wiswell TE. Advances in the treatment of the meconium aspiration syndrome. Acta. Paediatr 2001; 436 Suppl:28-30.
25. Dargaville Pa, Copnell B, Australian and New Zealand Neonatal Network. The epidemiology of meconium aspiration syndrome: incidence, risk factors, therapies, and outcome. Pediatrics 2006; 117: 1712-21.
26. Nolent P, Hallalel F, Chevalier Jy, Flamant C, Renolleau S. Meconium aspiration syndrome requiring mechanical ventilation: incidence and respiratory management in France (2000-2001). Arch. Pediatr 2004; 11: 417-22.
27. findlay Rd, Taeusch Hw, Walther FJ. Surfactant replacement therapy for meconium aspiration syndrome. Pediatrics1996; 97:48-52.
28. Lotze A, Mitchell Br, Bulas Di, Zola Em, Shalwitz Ra, Gunkel JH. Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. Survanta in Term Infants Study Group. J Pediatr 1998; 132: 40-7.
29. Wiswell Te, Knight Gr, Finner NN, et al. A multicenter, randomized, controlled trial comparing Surfaxin (Lucinactant) lavage with standard care for treatment of meconium aspiration syndrome. Pediatrics 2002; 109:1081-7.