Liquid ventilation in the preterm neonate

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Introductory article

Partial liquid ventilation with perfluorocarbon in premature infants with severe respiratory distress syndrome

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Background. The intratracheal administration of a perfluorocarbon liquid during continuous positive-pressure ventilation (partial liquid ventilation) improves lung function in animals with surfactant deficiency. Whether partial liquid ventilation is effective in the treatment of infants with severe respiratory distress syndrome is not known. Methods. We studied the efficacy of partial liquid ventilation with perfluorocarbon in 13 premature infants with severe respiratory distress syndrome in whom conventional treatment, including surfactant therapy, had failed. Partial liquid ventilation was initiated by instilling perfluorocarbon during conventional mechanical ventilation to a volume approximating the functional residual capacity. Infants were considered to have completed the study if they received partial liquid ventilation for at least 24 hours. Results. Ten infants received partial liquid ventilation for 24 to 76 hours. In the other three infants, partial liquid ventilation was discontinued within four hours in favor of high-frequency ventilation, which was not permitted by the protocol, and the data from these infants were excluded from the analysis. Within one hour after the instillation of perfluorocarbon, the arterial oxygen tension increased by 138 percent and the dynamic compliance increased by 61 percent; the mean (±SD) oxygenation index was reduced from 49 ± 60 to 17 ± 16. Chest radiographs showed symmetric filling, with patchy clearing during the return from partial liquid to gas ventilation. There were no adverse events clearly attributable to partial liquid ventilation. Infants were weaned from partial liquid to gas ventilation without complications. Eight infants survived to 36 weeks' corrected gestational age.

Conclusions. Partial liquid ventilation leads to clinical improvement and survival in some infants with severe respiratory distress syndrome who are not predicted to survive.

Surfactant replacement therapy, improvements in ventilatory strategies, and the widespread use of antenatal steroids have had an enormous impact on neonatal respiratory disease. The majority of babies with respiratory failure are now expected to respond to conventional time cycled, pressure limited ventilation with surfactant replacement therapy, and to survive. However, as survival is not always assured, several alternative treatment modalities aimed at treating respiratory failure in sick babies, either as a primary treatment or rescue therapy, have been developed over recent years. The introductory article by Leach and colleagues describes the newest of these treatments - partial liquid ventilation (PLV) with perfluorocarbons. It is worthwhile briefly considering the current status of some of the other treatments in order to identify the possible role for PLV in the newborn and to understand the importance of critical evaluation of new technologies in neonatal intensive care.

Extracorporeal membrane oxygenation (ECMO)

ECMO employs a membrane oxygenator to effect gas exchange in an extracorporeal circulation and has been used successfully as an adjunct to ventilatory support in infants with reversible respiratory failure. The initial enthusiasm for ECMO led to its widespread use, particularly in North America, without any convincing evidence from large randomised controlled trials of its benefit over conventional treatments. However, a large multicentre randomised controlled trial of the use of ECMO for severe respiratory failure in term and near term neonates has recently been performed in the UK\(^1\) in which the mortality in the group treated with conventional therapy was approximately 60% and ECMO halved the chance of death (RR with ECMO = 0.55 (95% CI 0.39 to 0.77)). The success of ECMO in this study was different with different diagnoses. A much better improvement in survival was seen in babies with meconium aspiration...
syndrome than in those with congenital diaphragmatic hernia.

ECMO can only be applied to larger infants because of technical considerations, not least the difficulty in establishing adequate vascular access in smaller babies. It is not used routinely in preterm infants below 34 weeks gestation because of concern that the associated haemodynamic disturbance and the need for anti-coagulation may increase the risk of major intracranial haemorrhage.

The success of ECMO in managing severe respiratory failure in term and near term babies has thus been very impressive and any new treatments for such babies would need to be evaluated by comparison with ECMO. However, ECMO is not available for the treatment of small preterm babies with severe respiratory failure and other treatment modalities need to be evaluated.

High frequency oscillatory ventilation (HFOV)

This mode of ventilation relies on maximal recruitment of respiratory units to improve oxygenation by the use of a high mean airway pressure. The generation of rapid small tidal volumes using oscillation with active inspiration and active expiration improves elimination of CO₂. It has been suggested that the small changes in lung volume which occur during HFOV may decrease the risk of air leaks and bronchopulmonary dysplasia (BPD). This treatment is widely used as a rescue therapy in babies who do not respond to conventional ventilation. It has also been adopted by some neonotologists as the primary mode of respiratory support for babies with respiratory failure.

Several randomised controlled trials in neonates have shown short term improvements in gas exchange with HFOV compared with conventional mechanical ventilation. However, the long term benefits from this mode of ventilation have unfortunately been less impressive to date.

There are no published randomised controlled trials of the use of HFOV as a rescue therapy in preterm neonates. The only published trial in term and near term infants found that the proportion of babies who responded to HFOV was not significantly different from those treated with conventional ventilation. This study also failed to demonstrate a significant difference in mortality or the need for ECMO.

There are five published randomised controlled trials, involving some 822 subjects, comparing the use of HFOV against conventional ventilation as a primary mode of respiratory support in preterm babies. None of these trials has found an improvement in survival with HFOV use.

The effect of HFOV on development of BPD or air leaks is less clear. Two studies found no difference in the rate of BPD, and a third did not report the incidence of BPD but found no difference in the need for ventilatory support at 30 days. A further study demonstrated a decrease in the incidence of BPD (defined as oxygen dependency and an abnormal chest radiograph at 36 weeks post-conceptional age) with HFOV, but no reduction in the need for supplemental oxygen at hospital discharge or in age at hospital discharge. The fifth study by Gerstmann et al also found less BPD (defined as a lower “chronic lung disease score” at 30 days) in those babies treated with HFOV, and fewer of the babies receiving HFOV required supplemental oxygen at hospital discharge, although the mode of ventilation used did not predict independently the need for home oxygen therapy in a multiple logistic regression analysis.

Inhaled nitric oxide (NO)

Nitric oxide is an endogenous vasodilator which is produced by vascular endothelium and induces relaxation of underlying smooth muscle cells. Inhaled NO is rapidly inactivated by binding to haemoglobin and therefore has vasodilator effects specific to the pulmonary circulation (unlike other pulmonary vasodilators). Pulmonary hypertension is a common feature in infants with respiratory failure. Inhaled NO may improve oxygenation in these infants through either a reversal of extrapulmonary shunting or a redistribution of pulmonary blood flow and enhanced ventilation-perfusion matching.

It has recently been shown that NO can reduce the need for ECMO in term neonates with severe respiratory failure. In a randomised controlled trial in preterm neonates at high risk for developing BPD, NO has been shown to cause a short term reduction in the oxygenation index and the pulmonary artery pressure. However, our own (unpublished) observations in this population have shown that these effects were not sustained and did not reduce mortality or the incidence of BPD. Further multicentre clinical trials of the use of NO in sick neonates are in progress.

Liquid ventilation

There are three theoretical advantages to ventilating the lung with liquid rather than gas. Firstly, removal of the air/fluid interface within the alveoli results in a reduction of surface tension and an associated increase in compliance; secondly, lung volume may be recruited by inflation of atelectatic alveoli; and thirdly, the continuous alveolar lavage provided by liquid ventilation may be of benefit by reducing the alveolar load of inflammatory mediators.

Several groups have explored liquid ventilation in animal models using different liquids. Although saline was the first liquid to be studied, the poor solubility of respiratory gases in saline made it unsatisfactory for use. Successful liquid ventilation has been achieved using oxygenated oils. None of the oils used were suitable for long term ventilation because of their direct toxic effects on the lungs. The perfluorocarbons (PFCs) are biologically inert, clear, colourless liquids which have a higher density than the tissues and are immiscible with body fluids. They are able to dissolve large amounts of respiratory gases. These physical properties make them a potentially suitable treatment modality.
Theoretical advantages of liquid ventilation with perfluorocarbons

- Reduction of surface tension with improvement in pulmonary compliance
- Reduction of interstitial edema
- Continuous alveolar lavage
- High respiratory gas solubility
- Biologically inert

Suitable medium for use in liquid ventilation (see box). Perfluorocarbon - the PFC used in the paper by Leach et al. - is an eight carbon chain in which all of the available binding sites are occupied by fluoride apart from one terminal position which is occupied by bromide, making the compound radio-opaque. It is impossible to determine whether PLV contributed to the improvement in survival. The patients in these studies had numerous other clinical problems, but these were felt to be of less importance than underlying severe illness rather than a consequence of the PLV. Again, lack of control data makes it impossible to assess properly the role of PLV in the development of these problems. Small pleural leaks of perfluorocarbon occurred in a few patients who had developed pneumothorax, but these appeared to cause no major clinical problems and resolved spontaneously.

The paper by Leach et al. is a description of the use of PLV in a group of 13 neonates with severe respiratory failure. Eight of the 10 babies treated using the study protocol survived; the two babies were too small to have undergone ECMO. There are no other reports of liquid ventilation in humans in peer reviewed journals, although some data have been shown in abstract form and clinical trials are currently underway in North America.

Practical aspects of use

In the study by Leach et al. infants received PLV with perfluorocarbon and conventional time cycled, pressure limited ventilation. The mean amount of perfluorocarbon instilled was 15 ml/kg over a mean period of 25 minutes. Additional perfluorocarbon was given to replace evaporative losses to maintain a meniscus in the endotracheal tube. While perfluorocarbon was being instilled, ventilator settings were altered to maintain reasonably constant tidal volume. If liquid ventilation became more widespread, experimental lung injury. It is likely that this is due to a reduction in barotrauma or in the intra-alveolar concentration of inflammatory mediators by continuous alveolar lavage. However, it has been suggested that PFCs may have a direct effect on the inflammatory process. Clearly, if PFCs are shown to exert a direct anti-inflammatory effect, they cannot be considered as biologically inert and studies of the long term biological effects will be necessary.

Liquid ventilation in infants was first described in 1990 by Greenspan et al. who reported its use in three moribund neonates. Each of the subjects had two short cycles of TLV (3-5 minutes) separated by 15 minutes of conventional gas ventilation. Two of the three babies had an increase in PaO2 after liquid ventilation and all showed an increase in lung compliance. In a later report by the same group a further three babies were studied and similar findings were reported. All six babies subsequently died as predicted prior to their recruitment.

The group in Ann Arbor, Michigan have published a series of papers documenting their experience of the use of PLV in humans. This work describes PLV with daily dosing of perfluorocarbon for up to seven days in neonatal, paediatric, and adult patients, all of whom were concurrently receiving ECMO for their severe respiratory failure. They reported an increase in pulmonary compliance in all groups over a three to four day period of treatment and an increase in indices of oxygenation in all groups over the same time. Short term improvements in these parameters were also found in the group of babies with congenital diaphragmatic hernia shortly after each dose of perfluorocarbon. All of these patients were also receiving numerous other therapeutic interventions. The lack of control data from these studies makes it impossible to determine to what extent PLV was responsible for any of the observed improvements in the physiological parameters. Five of the 10 adults, all six of the children, and two of the four neonates survived their illness. The lack of control data also makes it impossible to determine whether PLV contributed to an improvement in survival. The patients in these studies had numerous other clinical problems, but these were felt to be of less importance than underlying severe illness rather than a consequence of the PLV. Again, lack of control data makes it impossible to assess properly the role of PLV in the development of these problems. Small pleural leaks of perfluorocarbon occurred in a few patients who had developed pneumothorax, but these appeared to cause no major clinical problems and resolved spontaneously.

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Table 1 Predictive value of various parameters of airway exudate. Clearly, the incidence and effect of this acute complication will need to be monitored if liquid ventilation is increasingly used.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk criteria threshold</th>
<th>Predicted mortality</th>
</tr>
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<tbody>
<tr>
<td>A−aP lO2</td>
<td>&gt;600 mm Hg for 4 hours</td>
<td>90%</td>
</tr>
<tr>
<td>Short</td>
<td>&gt;600 mm Hg for 4 hours</td>
<td>80%</td>
</tr>
<tr>
<td>Krummel</td>
<td>&gt;600 mm Hg for 4 hours</td>
<td>94%</td>
</tr>
<tr>
<td>Beck</td>
<td>&gt;600 mm Hg for 4 hours</td>
<td>70%</td>
</tr>
<tr>
<td>Kirkpatrick</td>
<td>&gt;600 mm Hg for 6 hours</td>
<td>100%</td>
</tr>
<tr>
<td>a/A ratio</td>
<td>Arterial to alveolar oxygen tension difference; a/A ratio of arterial to alveolar oxygen tension.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Surfactant failure in preterm infants

<table>
<thead>
<tr>
<th>Study</th>
<th>Surfactant</th>
<th>Definition</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujiiwa</td>
<td>TA Surfactant</td>
<td>Increase in aA by &gt;0.2 and decrease in MAP by &gt;2 mm Hg until 129 hours after surfactant</td>
<td>22%</td>
<td>35%</td>
</tr>
<tr>
<td>Chomon</td>
<td>TA Surfactant</td>
<td>aA &lt;0.3 at 24 hours of age</td>
<td>45%</td>
<td>38%</td>
</tr>
<tr>
<td>Collaborative European Multicentre Study Group</td>
<td>Curosurf</td>
<td>aA &lt;0.3 at 24 hours after surfactant</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td>Segeret</td>
<td>Surfactant</td>
<td>Decrease in FIO2 by &gt;50% within 6 hours of surfactant</td>
<td>53%</td>
<td>44%</td>
</tr>
<tr>
<td>Hamwi</td>
<td>Eosurf</td>
<td>Decrease in O2 by &gt;25% within 6 hours of surfactant</td>
<td>50%</td>
<td>22%</td>
</tr>
<tr>
<td>Kunit</td>
<td>Curosurf</td>
<td>Increase in aA by 0.112 one hour after surfactant</td>
<td>50%</td>
<td>45%</td>
</tr>
</tbody>
</table>

A−aP lO2 = alveolar-arterial oxygen tension difference; a/A ratio = ratio of arterial to alveolar oxygen tension; MAP = maximum arterial pressure; FIO2 = fractional inspired oxygen.

Might it have a beneficial effect in the short term?

The paper describes a number of short term outcome measures in infants who have received liquid ventilation including changes in arterial oxygen and carbon dioxide tensions (PaO2 and PacO2), dynamic compliance, ventilatory requirements, and oxygenation index.

One concern of the authors of this paper is that three infants who had refractory hypercapnia and received high frequency ventilation were withdrawn from PLV because of recurrent hypercapnia. These infants do not appear to have been included in the analysis of short term outcome measures although it is arguable that these three infants were the most severely ill of the group. Despite this, two of them survived, which casts some doubt on the severity of risk of infants entered into the study.

Might it have a benefit in the long term?

The main question with any new experimental treatment must be whether the incidence of significant long term outcome measures is altered by the use of such a treatment. Death, chronic lung disease, and neurodevelopmental outcome are arguably the main long term outcome measures which are important in neonatal medicine.

Some early clinical trials of other therapies in newborn infants with severe respiratory failure have selected infants with a poor prognosis for “rescue” treatment.34–36
LEARNING POINTS

- Partial liquid ventilation with perfluorocarbons can be used to provide ventilatory support in preterm infants.
- It is associated with short term improvements in pulmonary compliance and gas exchange.
- The use of historical controls in the assessment of new therapeutic strategies may be misleading because of a constantly changing clinical environment.
- The use of partial liquid ventilation in the treatment of neonatal respiratory failure must be evaluated in the context of a randomised controlled trial in a high risk population.

Prognosis was assessed using data from retrospective studies. Parameters of oxygenation and/or respiratory support identify a "high risk" group in whom the mortality was expected to exceed 80-90%, 21-23 Although various such attempts to quantify disease severity in term and preterm infants have been made (tables 1 and 2), there is still little consensus regarding the criteria which are the most reliable predictors of eventual outcome. Few methods of assessing disease severity have been validated prospectively. 445 Nevertheless, clinical studies using such criteria to predict mortality have often reported improved survival in treated infants and, generally, the authors have concluded that their results provide evidence that a particular intervention is effective. This has led to criticism of the use of historical controls in this way. 446

In uncontrolled studies one of the difficulties in assessing the effectiveness of any intervention is the uncertainty in predicting the likely outcome if the infants had been managed conventionally. Advances in "conventional" neonatal management have resulted in a constantly changing environment in which the efficacy of any new treatment needs to be evaluated. Any assessment of disease severity developed in one population at a given time cannot therefore necessarily be reliably applied to a different population at a different time.

The paper by Leach et al suggests that the infants treated with PLV were at "high risk of morbidity or death on the basis of the lack of a sustained response to surfactant therapy." A number of studies have demonstrated an association between an infant's initial response to surfactant and eventual outcome. 447-449 The reported incidence of "surfactant failure" in these studies of preterm infants varies from 22% to 60% (table 2). The variation probably reflects inconsistencies in definition, surfactants used, and ventilatory management, but differences in infant populations are also likely to have been important. The value of any prognostic index therefore needs to be questioned until its usefulness has been validated prospectively, preferably in a separate population.

In the study of Leach et al an assessment of risk based on the authors' own population would have been preferable in order to be more certain that they were dealing with a high risk group. The proportion of survivors in infants receiving liquid ventilation was 54-62%, depending on whether one includes infants withdrawn from the study and whether one classifies the infant who died of severe lung disease at five months as a "survivor." This survival rate is similar to that in our own unit for a group of infants with similar baseline oxygenation indices who were treated with conventional ventilation; our observations have shown that the predicted survival of a preterm infant with an oxygenation index of >30 is approximately 65%. This again highlights how vital it is to calculate risk with conventional treatment in one's own population, at least when comparing the result of an experimental treatment using historical controls.

The data presented in the paper by Leach et al do not suggest that PLV has had a statistically significant impact on survival or morbidity in those surviving to discharge. This is not surprising in view of the small number of cases and the high risk of death in all infants with severe respiratory distress syndrome. Furthermore, the data presented support the view that PLV in this context does not necessarily improve gas exchange, pulmonary compliance, and lung injury during total and partial liquid ventilation in the acute respiratory distress syndrome. Clin Care Med 1996; 24:1028-104.


21 Leach CL, Holm B, Morris F. Partial liquid ventilation in premature