High-frequency partial liquid ventilation in respiratory distress syndrome: hemodynamics and gas exchange

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Sukumar, Minakshi, Mahesh Bommaraju, John E. Fisher, Frederick C. Morin III, Michele C. Papo, Bradley P. Fuhrman, Lynn J. Hernan, and Corinne Lowe Leach. High-frequency partial liquid ventilation in respiratory distress syndrome: hemodynamics and gas exchange. J. Appl. Physiol. 84(1): 327–334, 1998.—Partial liquid ventilation using conventional ventilatory schemes improves lung function in animal models of respiratory failure. We examined the feasibility of high-frequency partial liquid ventilation in the preterm lamb with respiratory distress syndrome and evaluated its effect on pulmonary and systemic hemodynamics. Seventeen lambs were studied in three groups: high-frequency gas ventilation (Gas group), high-frequency partial liquid ventilation (Liquid group), and high-frequency partial liquid ventilation with hypoxia-hypercarbia (Liquid-Hypoxia group). High-frequency partial liquid ventilation increased oxygenation compared with high-frequency gas ventilation over 5 h (arterial oxygen tension 253 ± 21.3 vs. 17 ± 1.8 Torr; P < 0.001). Pulmonary vascular resistance decreased 78% (P < 0.001), pulmonary blood flow increased fivefold (P < 0.001), and aortic pressure was maintained (P < 0.01) in the Liquid group, in contrast to progressive hypoxemia, hypercarbia, and shock in the Gas group. Central venous pressure did not change. The Liquid-Hypoxia group was similar to the Gas group. We conclude that high-frequency partial liquid ventilation improves gas exchange and stabilizes pulmonary and systemic hemodynamics compared with high-frequency gas ventilation. The stabilization appears to be due in large part to improvement in gas exchange.

perfluorocarbon; pulmonary vascular resistance; mechanical ventilation; respiratory failure; prematurity

PARTIAL LIQUID VENTILATION with perflubron (LiquiVent, Alliance Pharmaceutical, San Diego, CA, and Hoechst Marion Roussel, Frankfurt, Germany) is being tested in clinical trials as a new technique for the management of respiratory failure. Laboratory studies have demonstrated that gas exchange and lung mechanics improve with partial liquid ventilation using conventional ventilatory schemes compared with conventional gas ventilation in multiple models of lung disease (3, 17, 22, 31). More recently, a study of preterm infants with severe respiratory distress syndrome suggested improved lung function and survival with conventional partial liquid ventilation (16). High-frequency ventilation offers advantages over conventional ventilation (9, 10, 25); we hypothesized that these advantages might be conferred if high-frequency ventilation were used with partial liquid ventilation in the management of the sick preterm infant. Because the mechanism(s) and site(s) for gas transfer within the partially liquid-filled lung are not fully understood (7), it was not known whether high-frequency ventilation of the liquid-filled lung could achieve adequate gas exchange. We studied the effect of high-frequency partial liquid ventilation using a single-liquid functional residual capacity dosing strategy on gas exchange in preterm lambs with severe respiratory distress syndrome.

Hemodynamic stability is an important consideration with regard to central nervous system morbidity in the preterm infant (27). Stable or improved systemic and pulmonary hemodynamics have been demonstrated during conventional partial liquid ventilation in the normal lamb (18) as well as in the newborn lamb with congenital diaphragmatic hernia (31) and in an adult saline lavage model of surfactant deficiency (12). We studied pulmonary and systemic hemodynamics in preterm lambs with severe respiratory distress syndrome. We further explored the mechanism(s) for the hemodynamic response to high-frequency partial liquid ventilation compared with high-frequency gas ventilation.

METHODS

Animal Preparation

Seventeen preterm lambs with a gestational age of 125–128 days (term 145 days) were delivered by cesarean section. Time-dated, mixed-breed pregnant ewes were placed in the supine position after anesthesia was induced with thiamylal sodium. An 8.0-mm-outner-diameter endotracheal tube was placed under direct laryngoscopy, and anesthesia of the ewe and fetus was maintained with 2.5% halothane. A hysterotomy was performed, and the fetus was partially exteriorized. A 4.0-mm-outner-diameter endotracheal tube and carotid and jugular catheters were placed as described previously (15). Through a left thoracotomy incision, an ultrasonic flow probe (Transonic Systems, Ithaca, NY) was placed around the left main pulmonary artery, and left atrial and pulmonary arterial catheters were placed. At delivery, each animal was weighed, dried, and connected to a high-frequency oscillatory ventilator (model 3100A, Sensormedics, Loma Linda, CA). Initial ventilator settings included a fraction of inspired oxygen of 1.0, mean airway pressure of 15 cmH2O, amplitude of 50 cmH2O, frequency of 10 Hz, and an inspiratory time of 33%. The amplitude and frequency were adjusted in an effort to maintain arterial carbon dioxide tension (Paco2) within normal range. Anesthesia was maintained with intravenous ketamine (5 mg/kg body wt), supplemented as needed for movement. Animals were not paralyzed. Temperature and hemodynamic stability and fluid and electrolyte homeostasis were maintained as described previously (15). This study was
Experimental Design

Before they were delivered, the animals were prospectively assigned before delivery to one of two groups. One group received high-frequency gas ventilation (Gas group; n = 6) for the duration of the study. In this group, amplitude and frequency were adjusted to optimize arterial blood-gas values within preset support limits (inspired oxygen fraction 1.0, amplitude 50 cmH2O, frequency 8 Hz). A second group was switched to high-frequency partial liquid ventilation (Liquid group; n = 6) at 30 min of life. A third group was studied in which animals were switched to high-frequency partial liquid ventilation at 30 min of life and received supplemental inspired carbon dioxide and decreased concentrations of inspired oxygen to produce levels of hypoxemia and hypercarbia similar to the Gas group (Liquid-Hypoxia group; n = 5).

High-frequency partial liquid ventilation technique. High-frequency partial liquid ventilation was initiated by instilling a single dose of perflubron at a rate of ~1 ml·kg body wt·min−1 through the side port of the endotracheal tube. This was accomplished either during hand-bagged ventilation with 20–25 breaths/min or during high-frequency ventilation, with the table inclined to elevate the head of the lamb 30° to gravity assist the perflubron instillation. Filling was complete when a column of perflubron consistently welled up in the endotracheal tube during momentary disconnect, prone positioning, and zero end-expiratory pressure. The volume of perflubron required to produce this meniscus represented the animal’s liquid functional residual capacity. Mean airway pressure remained fixed at 15 cmH2O, and the frequency and amplitude were adjusted as with high-frequency gas ventilation to optimize arterial blood-gas values. After filling was completed, animals were maintained in the prone position. Perflubron was not supplemented to replace evaporative loss.

Measurements. Serial PaCO2, and arterial oxygen tension (PaO2) were measured by a Radiometer automated blood-gas analyzer (model ABL 2, Radiometer America, Westlake, OH). Pulmonary arterial, aortic, left atrial, and central venous pressures and left pulmonary arterial blood flow were monitored continuously on a recorder (model 2800S, Gould Electronics, Cleveland, OH). Left pulmonary vascular resistance was calculated as the quotient of the difference between pulmonary arterial and left atrial pressures divided by left pulmonary arterial flow. In two animals from the Liquid group, chest radiographic studies were performed at 1, 3, and 5 h.

Histopathology. The lungs from one lamb in the Gas group and one lamb in the Liquid group underwent histological analysis. Postmortem, the lungs were removed, inflated with air at 30 cmH2O static pressure via the endotracheal tube, and immediately fixed by Formalin immersion. Samples were taken from matched lung sections, stained with hematoxylin and eosin, and examined with light microscopy.

Data Analysis

Data were analyzed by a two-way analysis of variance with repeated measures, with a Bonferroni-Dunn post hoc correction.

RESULTS

Mean gestational age for all animals was 126.3 ± 0.2 days with a mean weight of 2.6 ± 0.07 kg and did not vary among groups. The initial volume of perfluoron instilled was 19 ± 0.5 ml/kg and did not differ between the two groups receiving high-frequency partial liquid ventilation. This liquid functional residual capacity was established over a period of 14–18 min (15.3 ± 0.5 min). Chest radiographs (Fig. 1) showed progressive decrease in perflubron radiopacities after a single perflubron functional residual capacity dose, with persistence of perflubron at 5 h. High-frequency partial liquid ventilation increased oxygenation within 30 min of initiation to 341 ± 28 Torr (P < 0.001) from a baseline PaO2 value of 19 ± 2.2 Torr during high-frequency gas ventilation (Liquid group; Fig. 2). This improvement was sustained throughout the study for this group. As designed, the gas exchange in the Liquid-Hypoxia group was similar to that in the Gas group while ventilator settings were matched to those used in the Liquid group (range 50 cmH2O baseline during high-frequency gas ventilation to 36 ± 8 cmH2O during high-frequency partial liquid ventilation at 5 h).

Left pulmonary arterial flow increased with high-frequency partial liquid ventilation from a baseline value of 50 ± 34 ml·kg−1·min−1 during high-frequency gas ventilation to 76 ± 5.3 ml·kg−1·min−1 (P < 0.01), and this increase was sustained (Fig. 3). In contrast, left pulmonary arterial flow progressively decreased with high-frequency gas ventilation (78 ± 15.5 to 9.3 ± 2 ml·kg−1·min−1; P < 0.001). Pulmonary vascular resistance was four- to sixfold lower in the Liquid group, compared with the Gas group (P < 0.001). In the Liquid-Hypoxia group, pulmonary vascular resistance and blood flow values were similar to those in the Gas group. The aortic pressure decreased over time in the Gas group from 51 ± 2.8 to 24 ± 4.1 mmHg (P < 0.01; Fig. 4); the pulmonary arterial pressure was increased to that of aortic pressure. In contrast, in the Liquid group, the aortic pressure was maintained, whereas the pulmonary arterial pressure decreased (P = 0.001). The pulmonary arterial-aortic pressure differences were marked in the Liquid group, compared with the Gas group in which these were insignificant (Fig. 5). The animals in the Liquid-Hypoxia group responded similarly to those in the Gas group and showed pulmonary arterial pressures equal to aortic pressures. The central venous pressures were within normal limits and were similar for both the Gas and Liquid groups (Gas group range: 3.5 ± 0.6 mmHg at 0.5 h to 4.2 ± 0.7 mmHg at 5 h; Liquid group range: 3.7 ± 0.3 mmHg at...
Fig. 1. Serial chest radiographs in 1 lamb during single-dose high-frequency partial liquid ventilation at 0.5 (A), 3 (B), and 5 h (C) after initial dose of perflubron.
The lung histology sections (Fig. 6) show diffuse low alveolar volume with increased alveolar red blood cells, proteinaceous alveolar exudate, and disruption of the basement membrane after 5 h of high-frequency gas ventilation. In contrast, the lung receiving single-dose high-frequency partial liquid ventilation showed increased alveolar air space, preservation of alveolar morphometry with intact basement membrane, and little evidence of hemorrhage or exudate.

**DISCUSSION**

We have shown that high-frequency partial liquid ventilation improves gas exchange compared with high-frequency gas ventilation in the preterm lamb with severe respiratory distress syndrome. The $\text{PaO}_2$ was increased sevenfold during high-frequency partial liquid ventilation compared with high-frequency gas ventilation at the same mean airway pressure. The $\text{PaCO}_2$ was maintained within normal range during high-frequency partial liquid ventilation compared with the marked hypercarbia during high-frequency gas ventilation. This normocarbia was achieved despite the use of lower amplitude. Although, in general, the comparison of lung function data obtained during high-frequency and conventional ventilation is limited because of the uncertainty of lung volume conditions, the improved gas exchange at reduced driving pressures seen with high-frequency partial liquid ventilation is similar to that achieved with conventional partial liquid ventilation in this model (15).

Pulmonary and systemic hemodynamics also improved with high-frequency partial liquid ventilation. Several mechanisms may contribute to the improved pulmonary vascular resistance and pulmonary blood flow with high-frequency partial liquid ventilation. While pulmonary vascular resistance normally falls precipitously during the first day of birth (5), persistent pulmonary hypertension with right to left shunting has been observed in preterm neonates with respiratory distress syndrome (28). Acidosis is associated with persistent pulmonary hypertension of the newborn and the failure of normal transition of circulation from the...
fetus to the newborn (1). Clinically, persistent pulmonary hypertension of the newborn (5) is highly predictive of early pulmonary death. In this study, the improved PaO₂, P a CO₂, and pH during high-frequency partial liquid ventilation were clearly associated with reduction in pulmonary vascular resistance. When respiratory acidosis and hypoxemia were superimposed with high-frequency partial liquid ventilation (Liquid-Hypoxia group), the improvement in pulmonary vascular resistance was markedly attenuated, and the increase in pulmonary blood flow was nullified. This suggests that the improved gas exchange is a major contributing mechanism to the improved hemodynamics during high-frequency partial liquid ventilation. In contrast, exogenous surfactant, as an alternate approach to surface tension reduction, has not clearly affected pulmonary arterial pressure and ductal shunting in neonates with severe respiratory distress syndrome despite improvement in gas exchange (28). Other factors improving pulmonary hemodynamics during high-frequency partial liquid ventilation may include redistribution of pulmonary blood flow as previously described in the perfluorocarbon-filled lung (19) associated with changes in alveolar and airway surface tension and the higher density of the perfluorocarbon (1.972 mg/ml) compared with blood. With use of a zonal perfusion model (29, 30), changes in alveolar vascular relationships may result in recruitment of lung segments with improved ventilation-perfusion matching and in this way may alter pulmonary hemodynamics. Decreased pulmonary perfusion and cardiac output (19, 20), which can be offset by fluids and pressors (2), have been described in the perfluorocarbon-filled normal lung with total liquid ventilation. However, the volume of perfluorocarbon liquid used in this technique of partial liquid ventilation (liquid functional residual capacity 19 ± 0.3 ml/kg) is less than that used for total liquid ventilation (liquid functional residual capacity 30 ml/kg plus liquid tidal volumes 15–20 ml/kg) and may have less impact on vascular compartment transmural pressure. The baseline elevation in pulmonary vascular resistance in this model of respiratory distress syndrome also may account for the difference in response.

Major fluctuations in both arterial and venous pressure are thought to be involved in the pathogenesis of central nervous system injury and intraventricular hemorrhage (27). Stable systemic hemodynamics have been described during high-frequency gas ventilation (13) compared with conventional gas ventilation. In this model of severe respiratory distress syndrome, however, systemic arterial pressure progressively fell with high-frequency gas ventilation, although central

Fig. 4. Aortic pressure and pulmonary arterial pressure during high-frequency gas ventilation (baseline at 0.5 h) for 3 groups: Gas group (A), high-frequency partial liquid ventilation (Liquid group; B), and high-frequency partial liquid ventilation with hypoxia (Liquid-Hypoxia group; C). Values are means ± SE. **P < 0.001.

Fig. 5. Pulmonary arterial aortic pressure difference during high-frequency gas ventilation (baseline at 0.5 h) for 3 groups: Gas group, high-frequency partial liquid ventilation (Liquid group), and high-frequency partial liquid ventilation with hypoxia (Liquid-Hypoxia group). Values are means ± SE. *P < 0.01, **P < 0.001, Liquid vs. Gas groups. †P < 0.01, ‡P < 0.001, Liquid vs. Liquid-Hypoxia groups.
venous pressure remained stable. The fixed maximum mean airway pressure of 15 cmH₂O in this study, despite deterioration in gas exchange, may account for this difference. In contrast, during high-frequency partial liquid ventilation at these same mean airway pressures, arterial and venous pressures both were stable. The augmented stability of venous and arterial blood pressures suggests possible protection from intraventricular hemorrhage.

Several limitations exist with this model. The control animals that received high-frequency gas ventilation required higher amplitudes compared with the animals treated with high-frequency partial liquid ventilation. The adverse hemodynamic findings of increased pulmonary vascular resistance and decreased aortic pressure seen in the control group could be attributed to lung overdistension with higher amplitudes (13) compared with the Liquid group. However, with high-frequency oscillatory ventilation, the amplitude is markedly attenuated through the tracheobronchial tree (8), and the difference in amplitude at the alveolar level between groups is likely negligible. Furthermore, the mean airway pressure used in the Liquid and Gas groups was the same, and, when hydrostatic pressures of perfluorocarbon are added, the extravascular compartmental pressures would be predicted as higher during high-frequency partial liquid ventilation. It could be argued, rather, that lung overdistension could have occurred in the Liquid group because of the alteration in surface tension and reduced elastic recoil, with an acute increase in compliance (15), in addition to the hydrostatic gradient secondary to the high density of perfluoron. That overdistension indeed occurs during partial liquid ventilation is supported by clinical radiographic findings of hyperinflation in infants treated with conventional partial liquid ventilation (14).

The single dose of perfluorocarbon resulted in an improvement in gas exchange and hemodynamics, which was sustained throughout the 5-h study. Chest radiographs show persistence of perfluorocarbon in air spaces, and the amount appears to diminish with time. Although not directly measured, this loss of perfluorocarbon occurs by evaporation (6). Perfluorocarbon supplementation in previous studies suggests that evaporation occurs at a rate of 2–4 ml·kg⁻¹·h⁻¹; however, evaporation of perfluorocarbon is influenced by multiple conditions, including surface area, minute ventilation, liquid volume, compartment distribution, and segmental alveolar ventilation. Al-

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Fig. 6. Hematoxylin and eosin-stained lung sections from preterm lambs with respiratory distress syndrome treated for 5 h with high-frequency gas ventilation [A (original magnification ×20) and B (original magnification ×100)] and high-frequency partial liquid ventilation [C (original magnification ×20) and D (original magnification ×100)].
though a dose-dependent effect of perflubron on oxygenation has been described in several models (11, 26), the effect of the decreasing perflubron lung volume on the interpretation of these results is uncertain. In this study, the progressive decrease in radiodensity suggests that sustained improvement in gas exchange to some degree may be independent of, or nonlinearly related to, the volume of perflubron in the lung. An additional mechanism involving quantitative increase in the alveolar surfactant pool as that which occurs in normal animals over 5 h of partial liquid ventilation (23) also may be a factor in the continued improvement in gas exchange and mechanics in the Liquid group. The lung histologies support the comparative physiological findings of gas exchange and hemodynamics.

High-frequency oscillatory ventilation has been used effectively in ventilatory management of severe respiratory distress syndrome and can support adequate gas exchange with excursion pressures lower than those employed with conventional mechanical ventilation (4, 24). Partial liquid ventilation also improves lung compliance and enables ventilatory support at lower peak and mean airway pressures when used with conventional tidal volumes. However, the supra-dead space tidal volume excursions may still contribute to injury in a premature or diseased lung (21). Combining the two modalities of high-frequency and partial liquid ventilation may offer advantage in the treatment of respiratory distress syndrome over the use of either alone.

We conclude that high-frequency partial liquid ventilation improves gas exchange and reverses acidosis in preterm lambs with severe respiratory distress syndrome. Pulmonary vascular resistance is decreased with improved pulmonary blood flow, and this change is due, at least in part, to the improved gas exchange. Systemic hemodynamics are stabilized with high-frequency partial liquid ventilation. High-frequency partial liquid ventilation may offer a safe and effective approach to the management of preterm infants with respiratory distress syndrome.

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