Liquid Ventilation in an Infant With Pulmonary Alveolar Proteinosis

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Summary. Partial liquid ventilation (PLV) has been applied in various pulmonary diseases. We describe the use of partial liquid ventilation as a lavage method following normal saline (NS) lavage in an infant with pulmonary alveolar proteinosis (PAP) and severe hypoxemia. A 6 weeks old 3.4 kg former 36 weeks gestation boy on supplemental oxygen was transferred to our NICU with persistent tachypnea, dry cough, and increasing oxygen requirements. A lingular open lung biopsy revealed PAP. He developed progressive respiratory failure requiring ventilatory support, necessitating conventional NS lavage, followed by lung lavage with perflubron (LiquiVent; Alliance Pharmaceutical Corp. and Hoechst Marion Roussel) while on venovenous extracorporeal life support (ECLS). Lung lavage with NS and perflubron yielded minimal cloudy effluent. Gas exchange and pulmonary function deteriorated following NS lavage and attempts to discontinue ECLS were poorly tolerated. In contrast, tidal volume, P aO 2 , and pulmonary compliance increased after PLV, while the (A-a) D O 2 decreased to a point where ECLS was no longer required. Once perflubron was added repeatedly to the ventilator circuit to correct for evaporation over the 4 days of PLV. Cardiovascular status remained stable for several days; however, eventually he required reinitiation of ECLS and more mechanical ventilatory support with each trial off ECLS. He was maintained on high pressures and F iO 2 without any possibility to wean him from mechanical ventilation. Life support was withdrawn 1 month after admission. The survival from PAP in infants remains dismal, even with total lung NS lavage. While both NS and perflubron lavage in this patient were not effective in removing the proteinaceous alveolar debris, PLV following NS lavage was associated with an improvement in gas exchange and lung compliance.


Key words: alveolar proteinosis; partial liquid ventilation; extracorporeal life support.

INTRODUCTION

Pulmonary alveolar proteinosis is a rare disease of unknown etiology, characterized by an abundant deposition of periodic acid-Schiff-positive proteinaceous material in the alveoli. 1 It is also a well-known cause of chronic neonatal respiratory distress in which severe impairment of gas exchange and pulmonary defenses against organisms occurs. Whole lung lavage with normal saline in conjunction with extracorporeal life support has been used successfully in symptomatic neonates and children to improve oxygenation. 2 Mortality remains high and prognosis poor despite current aggressive management practices. Partial liquid ventilation has been used with success in acute lung injury models. It has never been used in a diffuse air space disease such as pulmonary alveolar proteinosis. We experimentally applied partial liquid ventilation as a last resort in the treatment of an infant in severe progressive respiratory failure with atypical pulmonary alveolar proteinosis, unresponsive to conventional therapies and we used perflubron as an alternative lavage medium to normal saline in the hope to improve gas exchange.

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CASE PRESENTATION

A 6-week-old 3.4 kg boy presented with persistent tachypnea, dry cough, and increasing oxygen requirements. Past medical history revealed a former 36-weeks gestation infant with a birth weight of 2.9 kg and RDS at birth. He was treated with surfactant and was mechanically ventilated for 1 week with subsequent supplemental nasal cannula oxygen and rapid development of radiographic changes indicative of BPD. He was discharged at 5 weeks of age on systemic steroids, diuretics, and oxygen.

He was readmitted a week later and transferred to our institution with tachypnea, dry cough, and increasing oxygen requirement. Chest X-ray (Fig. 1) and high resolution chest CT showed diffuse alveolar disease. Sweat chloride was normal. Flexible bronchoscopy revealed normal airways with scant secretions. Open lung biopsy demonstrated a significant degree of pulmonary alveolar proteinosis (Fig. 2). He developed a pneumothorax after the lung biopsy. Adequate lung reexpansion followed chest tube placement. He developed progressive respiratory failure necessitating mechanical ventilatory support. His respiratory status deteriorated despite the use of steroids, diuretics, and rhDNase (Pulmozyme®, Genentech, San Francisco, CA). Because of persistent respiratory failure and increasing ventilatory support requirements, total lung lavage with normal saline under venovenous ECLS was carried out, which yielded minimal cloudy effluent in which surfactant protein B was detected when sent to a reference laboratory. Gas exchange and pulmonary function deteriorated further following normal saline lavage.

Because attempts to discontinue ECLS were poorly tolerated, lung lavage and ventilation with perflubron was instituted experimentally to improve oxygenation and serve as an alternative lavage medium for removal of proteinaceous material. The protocol, as part of a Phase II trial of PLV in adults, children and neonates with acute parenchymal lung injury, was reviewed and approved by the Institutional Review Board. The trachea was reintubated with an experimental polyurethane perflubron-compatible endotracheal tube; baseline chest x-ray and airway examination with bronchoscopy were performed. Time-cycled, pressure-controlled ventilation on a VIP

Fig. 1. PA chest X-ray of the infant at initial presentation, demonstrating diffuse alveolar infiltration.

Fig. 2. Histological findings of lingular lobe biopsy showing alveoli filled with dense, PAS-positive homogeneous material, mild hyperplasia of the alveolar epithelium, and absence of inflammation and fibrosis, diagnostic for pulmonary alveolar proteinosis. (PAS stain; original magnification 20×).
Bird ventilator was used at settings which included PIP of 25–30 cm H₂O, PEEP = 5 cm H₂O, respiratory rate = 30 breaths/min; I:E ratio = 1:1, and F₁O₂ = 1.0. Perflubron was administered via the endotracheal tube in 5 ml/kg aliquots over 5 to 15-min periods for a total of 20 ml/kg, a dose to approximate functional residual capacity (FRC). At this point, a meniscus was present within the endotracheal tube at the level of the sternum when the infant was transiently disconnected from the ventilator. Since a minimal amount of alveolar debris was removed at FRC, the lungs were lavaged with an additional 10 cc/kg of perflubron, but no additional debris was evacuated. Supplemental doses, ranging from 10 cc/kg to 20 cc/kg, were administered to maintain lung filling to FRC with perflubron (Fig. 3). The need for refilling was based on radiographic evidence of perflubron evaporation. Since we expected significant mucus plugging, frequent suctioning was performed. Surprisingly, a very small amount of plugging was evident during the treatment period.

The total lung lavage with perflubron or normal saline yielded minimal debris. No quantification of the proteinaceous material from either the saline or the perflubron lavage was obtained, given the minimal yield. Furthermore, the initial poor yield made it difficult to determine whether the amount of protein diminished on serial lavage aliquots during either conventional saline or experimental perflubron lavage.

As the perflubron evaporated, there was a corresponding increase in the need for ventilatory support suggested by decreased tidal volumes, PₐO₂, and increased F₁O₂ requirements. Similarly, with each filling there was an increase in the tidal volume and PₐO₂. The (A-a) DₐO₂ decreased, implying an improvement in cardiac output, and an increase in pulmonary compliance during partial liquid ventilation. Examples of the responses to dosing are given in Figure 4.

A pneumothorax developed post-thoracotomy and was evacuated successfully by chest tube prior to the instillation of perflubron; no extravasation of perflubron into the chest cavity was noted during partial liquid ventilation. The patient tolerated administration of perflubron without evidence of hemodynamic compromise. No complications occurred during or following the period of partial liquid ventilation. After a total of 4 days of PLV in which gas exchange was supported effectively, the infant was again placed on ECLS for pulmonary support. He was slowly weaned to ventilatory support with high airway pressures and F₁O₂. Two days later, all support was withdrawn given the overall poor response to therapy and prognosis from irreversible lung disease.

**DISCUSSION**

Pulmonary alveolar proteinosis in the newborn period remains a disease of high mortality and extremely poor prognosis. As in other acute parenchymal lung diseases, high levels of airway pressure and F₁O₂ during conventional mechanical ventilation did not improve recruitment of noncompliant lungs and were unable to overcome the abnormal alveolar surface tension inherent in this type of respiratory insufficiency. Total lung lavage with normal saline in combination with ECLS, especially in newborns and children, can successfully remove the offending debris deposited at the alveolar level. Liquid ventilation with perflubron has been used successfully in animal models of neonatal respiratory distress syndrome, ARDS, as a lavage medium in meconium aspiration syndrome, as a contrast material in imaging studies, and as a potential pharmaceutical or...
biological delivery agent.9 In addition, partial liquid ventilation has been applied in adults, children, and newborns with respiratory insufficiency.10–15 We describe a potential novel adjunct therapy, using PLV in the treatment of severe pulmonary alveolar proteinosis.

Perfluorocarbon has many advantages as a lavage medium. It has excellent oxygen and carbon dioxide carrying capacity and allows for homogeneous ventilation and improved recruitment of injured lungs.16,17 It is insoluble in all biologically known media and does not wash out surfactant in the process of ventilation.18 Partial liquid ventilation may be used to improve pulmonary function and tidal volume following whole lung saline lavage, as was demonstrated in this patient. Lavage with saline followed by perfluorocarbon may be most effective. Although it clearly improves oxygenation compared to normal saline, perfluorocarbon is limited in that its immiscibility does not allow for the proteinaceous debris to mix, making perfluorocarbon potentially less desirable for evacuation of alveolar debris.

Our patient had histologically proven pulmonary alveolar proteinosis, although his presentation was atypical. Survival was not improved. While a case report of one patient with equivocal response provides limited information, we believe that perfluorocarbon as a lavage medium in this heterogeneous disease remains a potential adjunctive therapy in the treatment of PAP because it can function both as a lavage medium and as a means for gentle oxygenation and ventilation of the injured lung following an initial normal saline bronchopulmonary lavage. Because of perfluorocarbon’s major limitation as a debris-evacuating lavage medium, further experience must be gained by evaluation of more patients with PAP in severe respiratory failure before its role in the therapy of pulmonary alveolar proteinosis can be clarified.

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REFERENCES