Liquid ventilation

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There has been a recent explosion of interest in the use of liquid ventilation. Over time humans have lost the physiological attributes necessary for respiration in water. However, perfluorocarbons have high solubilities for oxygen and carbon dioxide, as well as a low surface tension. These characteristics allow them to be used as a medium to assist gas exchange and recruit atelectatic-dependent lung zones in respiratory distress syndrome. Current trials may prove perfluorocarbon to be a useful adjunct in lung protective strategies in respiratory distress syndrome.

Key Words: *Liquid ventilation*

La ventilation liquide

RÉSUMÉ : Récemment, il y a eu une véritable explosion d'intérêt pour l'utilisation de la ventilation liquide. Au fil des temps, les humains ont perdu les caractéristiques physiologiques indispensables à la respiration dans l'eau. Cependant les perfluocarbones possèdent de fortes solubilités pour l'oxygène et le gaz carbonique, et leur tension superficielle est faible. Ces caractéristiques font qu'ils peuvent servir de milieu à l'échange gazeux et ouvrir les territoires d'atélectasie dans les parties déclives du poumon dans le syndrome de détresse respiratoire. Les essais courants pourraient démontrer que les perfluocarbones sont un adjuvant utile dans les approches qui favorisent la protection des poumons dans le syndrome de détresse respiratoire.

Because aquatic hypoxia appears to have triggered the evolution of air breathing in vertebrates, it seems incongruous that, when humans have spent millions of years evolving from watery origins, we should be considering converting ourselves back to our liquid breathing, aquatic form, albeit for only a short period of time.

What has stimulated the current interest in liquid breathing? Initially it was an insatiable human desire to explore the ocean depths and outer space. In the former, liquid breathing would overcome the problems of nitrogen narcosis and decompression sickness, while in the latter, astronauts would be provided with unlimited protection against acceleration and deceleration forces. More recently, however, intensivists and respirologists have become increasingly aware of the deleterious side effects associated with mechanical ventilation and oxygen therapy when used in severely compromised noncompliant lungs. Ventilator-induced lung injury is now a well recognized entity, as is oxygen toxicity. To circumvent these problems, a plethora of ventilator modes and techniques have been developed. Extracorporeal membrane oxygenation (ECMO) is now commonly used to provide lung rest in neonates with severe but potentially reversible lung disease. Surfactants and nitric oxide are both being used in an attempt to improve pulmonary compliance and ventilation perfusion mismatch. Permissive hypercapnia and permissive hypoxia are now common practice to reduce further the risks of barotrauma and oxygen toxicity. Notwithstanding the above, is there some other way of providing adequate gas exchange with minimal associated morbidity and cost?

WHAT DO WE KNOW ABOUT RESPIRATION IN WATER?

First, water has a very low solubility for oxygen (2 mL/100 mL at 101 kPa) and is relatively viscous. Fish breathe by taking large quantities of water in through the mouth and forcing it over their gills. The gills offer a large

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surface area for gas exchange, with highly active, fast swimming fish having much larger gill areas than sluggish, bottom living fish. Once the water immediately adjacent to the gill has been depleted of oxygen, the water needs to be replaced. Fish have a unidirectional, low resistance system allowing water to be pumped (the goldfish) or forced (the tuna) over the gills, ensuring a continuous high rate of water flow and therefore adequate supply of oxygen. Mammals, on the other hand, have bidirectional fluid flow (they breathe air in and out) and would not be able to move sufficient quantities of the oxygen poor, high viscosity liquid through their lungs to gain adequate gas exchange. Kylstra et al (1) believed that these problems were not insurmountable, in that at high pressures the oxygen content of a fluid could be significantly increased, and in the early 1960s they demonstrated that mice could survive for hours in a hyperbaric isotonic solution with an oxygen content similar to that of air. Was there a liquid with a high oxygen and carbon dioxide solubility that did not require hyperbaric oxygenation? In the 1950s both Dow Corning and 3M had reported the high oxygen containing capabilities of fluorochemicals, a biologically inert group of solvents. In 1966 Clarke and Gollan (2) reported prolonged survival of cats and mice submerged in perfluorocarbons at atmospheric pressure. They also showed that mice could be returned to air breathing and survive for a number of weeks. Perfluorocarbons had the advantage of being slightly less viscous and having a considerably lower surface tension than saline. While spontaneous ventilation would be possible, carbon dioxide retention would become a problem over time. To facilitate spontaneous ventilation, liquid ventilators were developed (3). These were essentially the equivalent of an ECMO circuit in that each expired tidal breath had to be purged of carbon dioxide and recharged with oxygen – a system requiring bubble oxygenators and roller pumps. Also, perfluorocarbons are very expensive, making tidal liquid ventilation prohibitively costly.

Despite these drawbacks, research with tidal liquid ventilation continued unabated in animals (4-8). In 1990 Greenspan et al (9), using a relatively simple gravity assisted liquid ventilator, reported the use of liquid ventilation as rescue therapy in three preterm neonates in whom conventional ventilation (including high frequency oscillation and surfactant) had failed. They found a consistent improvement in compliance with uniform expansion of the lungs. Oxygenation improved in two of the three infants. No significant cardiovascular compromise occurred. Unfortunately, all infants died within 19 h of liquid ventilation. Of significance, the greatest observed increase in hemoglobin saturation occurred during subsequent conventional ventilation.

Observations such as these presaged the reports by Fuhrman et al (10) in 1991 of a hybrid form of liquid ventilation, where conventional mechanical ventilation was superimposed on a lung filled with perfluorocarbon. He coined the acronym PAGE (perfluorocarbon associated gas exchange) for this technique, which has the advantages of liquid ventilation without the requirement for sophisticated, complex liquid ventilators. Thirteen normal piglets had a functional residual capacity equivalent of perfluorocarbon instilled into their tracheas. This was left in situ, and conventional volume regulated ventilation was resumed above the liquid. Blood gas, respiratory and hemodynamic measurements were repeated during the experiment. They found that, using this technique, partial liquid ventilation was achieved providing excellent gas exchange with acceptable alveolar pressures and no impairment of cardiac output.

Since this initial account, a number of investigators (11-20) have reported the success of partial liquid ventilation in a variety of animal models of acute lung injury. All have shown a dramatic improvement of pulmonary compliance with a dose-dependent improvement in oxygenation. The research to date examining the effect of a perfluorocarbon filled lung on cardiac output and pulmonary vascular resistance has not demonstrated the expected decrease in cardiac filling and increase in pulmonary artery pressures (5,12, 21,22). With these encouraging results, a number of trials in humans have been undertaken. Hirschl et al (23) published a report of 19 adults, children and neonates in severe respiratory failure and on extracorporeal life support who had a period of partial liquid ventilation. Of 16 patients with sufficient data for analysis, all showed a significant decrease in alveolar-arterial gradient and increase in compliance. Perfluorocarbon administration was well tolerated, although six patients did re-accumulate pneumothoraces. Mucous plugs, which may have been related to partial liquid ventilation, formed in one patient but resolved with aggressive suctioning. Eleven patients (58%) survived with no long term sequelae associated with perfluorocarbon instillation. Other studies are not yet complete, but preliminary reports have been encouraging. A large multicentre phase II/III Food and Drug Administration-approved pediatric study is underway. Four hundred and eighty patients with acute lung injury will be included in the study, the primary end-point being ventilator-free days. Oxygenation and compliance will be secondary end-points with long term follow-up focusing on perfluorocarbon-related side effects.

Although the positive results from laboratory and clinical studies thus far are impressive, a clear understanding of how partial liquid ventilation works remains elusive. Why the dramatic improvement in lung mechanics at low doses of perfluorocarbon is not associated with similar improvements in oxygenation is baffling. It is apparent that a large gas/liquid interface is necessary for gas exchange between inspired gas and perfluorocarbon to occur. However, the gas then needs to diffuse along a concentration gradient through the liquid to reach the alveolar-capillary membrane for gas exchange to occur. The liquid needs to be a very thin layer and requires stirring to facilitate diffusion. In addition, the weight of the dense liquid in the lung must affect the distribution of pulmonary bloodflow and therefore the ventilation-perfusion relationship. This requires further study.

Notwithstanding the above unanswered questions, there is no doubt that liquid ventilation is here to stay and may soon be part of our therapeutic armamentarium in the management of certain types of lung disease.

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