Liquid ventilation innovations in ventilatory management

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The goal of mechanical ventilation is to maintain adequate gas exchange by opening and stabilizing alveolar units with minimal detriment to the pulmonary and circulatory systems. The optimal ventilatory strategy may be difficult to achieve, especially in patients with respiratory failure.

Total liquid ventilation is a process whereby a liquid perfluorocarbon (PFC) replaces both the functional residual capacity and the tidal volume within the lung. Gas exchange is accomplished by mechanically assisted inspiration and expiration of tidal volumes of the liquid using a liquid ventilator. The PFC liquid is then oxygenated and purged of carbon dioxide by a membrane lung. Perfluorocarbons are excellent media for gas exchange due to their extraordinary gas solubility and diffusibility of oxygen and carbon dioxide.

Partial liquid ventilation (PLV) is a modified method of the total liquid ventilation technique. In PLV, a functional residual capacity of PFC liquid is maintained in the lung, and the patient is ventilated with a conventional gas mechanical ventilator. Studies of the acute respiratory distress syndrome in animal models and in human series have demonstrated encouraging results using PLV and PFC. The high density, low surface tension, and other qualities of PFC in the setting of PLV may offer a highly innovative approach that can be directed toward the management of patients in respiratory failure.

Key words: Mechanical ventilation, partial liquid ventilation, perflubron, perfluorochemical, respiratory distress syndrome.

Introduction

Respiratory distress syndromes occur in patients of all ages, representing a final common pathway of inadequate gas exchange due to factors such as infection, traumatic shock, severe burns, aspiration of toxic substances, and conditions associated with premature birth. We are seeing more of these critically ill patients in the operating room and the intensive care unit. Conventional management of patients with acute ventilatory impairment is supportive and aimed at providing adequate oxygen and carbon dioxide exchange without imposing further burden upon the lungs or cardiovascular system. Despite considerable strides in understanding the pathophysiology and course of acute respiratory distress syndrome (ARDS), mortality rates remain high. A recent investigation spanning 3 years in adults and children with ARDS demonstrated a 40% mortality rate due to respiratory failure. Respiratory support methods, such as positive pressure ventilation, extracorporeal membrane oxygenation, new regimens of surfactant replacement therapy, high-frequency ventilation, and inhaled nitric oxide, are associated with a host of untoward effects. These include inflammation and infection of the airways, mechanical injury to the lungs, and hemodynamic instability. Table I
outlines the contemporary ventilatory management approaches to patients with respiratory disease.

Another concept in ventilatory management of patients with acute respiratory failure has emerged during the past three decades and involves a liquid vehicle for transport of oxygen and carbon dioxide to and from the lungs. A prerequisite for this unconventional method of ventilatory management calls for the instillation of an organic liquid into the lungs. These organic liquids, perfluorocarbons (PFCs) or perfluorochemicals, trace their origins back to 1966 with the pioneering efforts of Clark and Gollan and their classic laboratory investigations demonstrating the ability to achieve adequate gas exchange within the lung by using an organic liquid.\(^2\) Figure 1 depicts one artist's early perceptions of this concept. This report details the advances and promising uses of total liquid and partial liquid ventilation in patients with substantial respiratory pathophysiology.

**Early studies in liquid ventilation**

The concept of sustaining gas exchange and homeostasis with a liquid originated with Kylstra, a physiologist at the State University of New York in Buffalo, and colleagues who studied survival time in mice submerged in various liquid mediums. They discovered that mice breathing a balanced salt solution saturated with oxygen at a pressure of 8 atm could survive for up to 18 hours. These mice were able to extract sufficient oxygen from the saline solution, but due to the poor solubility of carbon dioxide in the saline solution, its elimination was insufficient, and hypercarbia ultimately resulted. Kylstra et al also noted difficulties with cycling a fluid medium into and out of small airways, requiring slower respiratory rates in order to allow time for the diffusion of the respiratory gases.\(^3\)

A milestone in the use of carbon fluids for ventilation occurred in 1966 when Clark and Gollan discovered that oxygen and carbon dioxide were very soluble in fluorocarbon liquids and that these liquids could sufficiently support gas exchange.\(^2\) Using animal models, these investigators circulated oxygenated fluorocarbons to anesthetized mice via an endotracheal tube at a rate of six "liquid breaths" per minute. Animals were kept alive for up to 1 hour and survived an additional 2 weeks after resumption of gas ventilation. Ultimately, the mice succumbed to ventilatory failure. Whether injury sustained to the lungs was caused by the fluorocarbon or by the mechanical ventilation devices was not determined. As with the study by Kylstra and colleagues, problems observed by Clark and Gollan were attributed to the size of the animals' airways, which physically limited the amount of fluid that could be cycled into and out of the lungs. Consequently, carbon dioxide retention remained a problem. It was obvious that more studies were needed before liquid ventilation could be utilized in humans.
Perfluorocarbons (PFCs) are biologically and chemically inert colorless fluids. Various compounds of PFC exist. For example, 3M, St. Paul, Minnesota, manufactures a PFC FC77, with a density of 1.75 g/mL, viscosity of 0.0112 g/sec cm, surface tension of 14 dynes/cm, oxygen solubility of 48 mL/100 mL, and a vapor pressure of 75 mmHg. The Alliance Pharmaceutical Corporation (San Diego, California) manufactures “perflubron” (trade name LiquiVent), which has a slightly different physiochemistry with a higher specific gravity (density, 1.93 g/mL), a viscosity of 0.017 g/sec cm, and a surface tension of 18 dynes/cm.

Perflubron is an efficient carrier of oxygen and carbon dioxide, has low pulmonary absorption, and is eliminated by the lungs via evaporation. At 1 atm of pressure and 37°C, 53 mL of oxygen is carried in 100 mL of perflubron, an amount that is 25 times the amount that dissolves in plasma. Likewise, carbon dioxide is highly soluble in the organic liquid, with approximately 210 mL dissolved in each 100 mL of the solution. Table II compares the physical properties of perflubron to those of water.

### Table II

<table>
<thead>
<tr>
<th></th>
<th>Perflubron</th>
<th>Water</th>
</tr>
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<tbody>
<tr>
<td>Density (g/cm$^3$)</td>
<td>1.918</td>
<td>0.99336</td>
</tr>
<tr>
<td>Viscosity (g/sec cm)</td>
<td>0.017</td>
<td>0.006947</td>
</tr>
<tr>
<td>Surface tension (dynes/cm)</td>
<td>18.1</td>
<td>60</td>
</tr>
<tr>
<td>O$_2$ Solubility (mL/100 mL)</td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td>CO$_2$ Solubility (mL/100 mL)</td>
<td>210</td>
<td>55</td>
</tr>
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</table>

As an 8-carbon chain in which all potential sites are bonded to a fluorine atom except for a terminal bromine (Figure 2), perflubron is distinctively radiopaque. This has proved to be a highly desirable characteristic because it allows for radiographic-assisted monitoring of PFC distribution in the lungs. Kazerooni et al demonstrated a symmetrical opacification of the lungs in a gravity-dependent distribution during PLV in 13 adult humans. This characteristic provides clinicians the opportunity to observe pneumothoraces, pleural effusions, and atelectatic areas of the lungs not previously seen without the radiopaque fluid. Radiographic monitoring of the distribution of perflubron may be a useful tool to assess the need for redosing of PFC loss due to evaporation, lung volume changes, spillage, or other factors.

Liquid ventilation with PFC has generally been performed by one of two techniques: (1) total liquid ventilation (TLV) and (2) partial liquid ventilation (PLV). Following is a description of each technique.

### Total liquid ventilation

Total liquid ventilation utilizes a method whereby PFC is instilled and mechanically cycled through the lungs with tidal volumes consisting entirely of the liquid. Oxygen is then absorbed into the blood, while carbon dioxide diffuses into the PFC. Subsequently, this liquid is cycled out of the lung, the carbon dioxide is purged, and oxygen is infused across an extracorporeal membrane gas exchanger. A “liquid” ventilator (a cycling pump with an extracorporeal gas exchanger) is required when TLV is utilized.

- **Animal investigations using TLV** In 1973, seeking a biochemically safe PFC liquid for ventilation, Tuazon et al studied TLV using Caroxin-D PFC in 32 dogs with healthy lungs. They demonstrated that:
  1. Life can be sustained for up to 1 hour when ventilated with the oxygen-enhanced perfluorocarbon.
  2. Reestablishing spontaneous ventilation with air occurs without deleterious effects.
  3. Although residual perfluorocarbon can remain in the lung for up to 1 year after liquid ventilation, it did not cause any obvious functional lung damage.

A previous study demonstrated that healthy adult dogs could be ventilated with a PFC liquid (FX-80), although upon reoxygenation to breathing gas, animals were hypoxic with labored breathing. Histological examination of the lungs 3 hours after liquid ventilation showed acute inflammation followed by a macrophagic response most promi-
...ent at 72 hours. Normal lung function returned after 10 days. In the years that followed, advancements with organic liquid and in the techniques of delivering them were refined and improved. Medical-grade perfluorochemicals were developed and made available for clinical trials. Of particular interest was the efficacy of PFC ventilation in animals with lung injury. In animal models of severe respiratory failure, ventilation with PFC improved pulmonary function and gas exchange, reduced inflammatory infiltration, increased pulmonary compliance, and significantly reduced physiological shunt. Investigators speculated that tidal volumes of the PFC provided a lavage effect with removal of pulmonary exudates, reexpanded atelectatic alveoli, and subsequently improved ventilation-perfusion matching.

**Early human trials with TLV** The first human trial and the only reported human study utilizing the TLV technique was reported in 1990 by Greenspan et al. A gravity-assisted technique of TLV was successfully used on three preterm infants in whom conventional therapy for severe respiratory distress had failed. The use of perflubron in this small, case-control study demonstrated no adverse effects; marked improvements in pulmonary compliance occurred in all three subjects. Two neonates demonstrated improvements in oxygenation. All three infants succumbed by 19 hours after treatment, but the severity of respiratory disease before initiation of liquid ventilation was thought to be the cause of their ultimate demise.

**Partial liquid ventilation**

Liquid ventilators appropriate for use in humans are not yet available. The majority of clinically based research has focused upon the idea of PLV incorporating a standard mechanical ventilator in concert with the PFC partially filling the lung (Figure 3). Partial liquid ventilation obviates the need for a cumbersome system to oxygenate and purge the liquid of carbon dioxide. Rather, it utilizes the natural diffusibility characteristics of the respiratory gases in the PFC to achieve the desired outcome. It may lessen the risk of barotrauma from a heavy, fluid-laden lung (one concern of a totally fluid filled lung) by enabling instillation of smaller amounts of liquid into the lungs. This idea was first demonstrated by Fuhrman et al using PFC instillation in conjunction with a conventional mechanical ventilator in 13 piglets with normal lungs. After instilling a volume of a particular PFC species (FC-77), an amount equal to the functional residual capacity, mechanical gas ventilation was carried out, and adequate oxygen and carbon dioxide exchange resulted. This novel approach to ventilation was originally termed “perfluorocarbon-associated gas exchange,” and most recently, PLV. From experimental evidence accumulated to date in several small and large lung animal models of ARDS, it is anticipated that lung injury due to high oxygen concentrations, airway pressures, and tidal volumes can be minimized by the instillation of PFC into acutely injured lungs of patients requiring mechanical ventilation. In animal models of severe respiratory failure, PLV with perflubron is associated with improvements in pulmonary gas exchange and pulmonary function and a reduction in pulmonary pathology.

Because of the investigational nature of the approach, a variety of dosage strategies have been investigated in PLV. Generally, small amounts of 2

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**Figure 3**
Schematic representation of partial liquid ventilation

A liquid functional residual capacity is maintained and tidal volumes of gas are delivered by a conventional mechanical ventilator.
to 10 mL/kg are initially administered via the endotracheal tube with final doses in the 19 to 40 mL/kg range. The total amount is typically equivalent to the patient's functional residual capacity (FRC). Practically, the instillation continues until a sustained meniscus of the liquid is noted in the endotracheal tube at the level of the sternum with the patient positioned supine. Additional PFC is administered to maintain desired levels as determined by chest radiograph, the presence of a visible meniscus, and improvement in gas exchange. Recently, in an adult animal model of respiratory failure, Parent and colleagues demonstrated a dose-dependent improvement in oxygenation during PLV with perflubron to an optimal dose of 40 mL/kg.

Computed tomographic examination of nine patients undergoing PLV demonstrated a gravity-dependent distribution of perflubron in the lungs.17 The dispersion of this incompressible liquid to regions of the lung where consolidation is most severe causes bulk distention of the alveoli with preservation of FRC and increased compliance. Table III outlines proposed mechanisms by which PLV improves gas exchange.

Recent human trials of partial liquid ventilation

The publication of animal and human studies exploring the benefits of PLV continues to grow. The ideas of therapeutic approaches to respiratory management, rather than the limited supportive measures listed in Table I, are beginning to surface. Techniques of PLV in animal models of prematurity with respiratory distress syndrome and ARDS have demonstrated encouraging results. Tables IV and V outline recent animal studies and human clinical trials utilizing PLV. Promising results are prompting more investigations with clinical application to patients with respiratory compromise.

Two recent clinical trials used perflubron in adult and pediatric subjects who had significant pulmonary compromise. The following is a synopsis of those studies. It should be noted that the trials selected were not randomized and they did not have control groups for comparison.

- **Partial liquid ventilation in acute respiratory distress syndrome.** Hirschl et al applied the technique of PLV to 10 patients aged 19 to 55 years with severe ARDS who were receiving extracorporeal life support (ECLS).23 Criteria for ECLS included a physiologic shunt greater than or equal to 0.30, severe barotrauma, and/or the inability to support life-compatible blood gases using conventional approaches. The only exclusionary criterion was an active pulmonary air leak.

Baseline data were obtained during a 15-minute period when ECLS was completely discontinued. Partial liquid ventilation using perflubron was instituted between days 1 and 11 of ECLS therapy. Time-cycled pressure-controlled ventilation was utilized, which generated airway pressures in the range of 30 to 40 cm H₂O, positive end-expiratory pressure of 6 cm H₂O, breathing rates of 20 per minute, inspiratory/expiratory ratio of 1:1, and 100% inspired oxygen. Perflubron was instilled via the endotracheal tubes of the patients until a median dose of 19 mL/kg was administered, and preestablished ventilator settings and mechanical ventilation were continued. Additional perflubron was administered on a daily basis for up to 7 days of PLV therapy; additional cumulative PFC doses ranged from 15 to 62 mL/kg during the study period. Additional doses were based upon observation of the liquid level in the endotracheal tube, clinical pulmonary function, and distribution of the liquid in the lungs as determined by radiographic monitoring.

Discontinuation of perflubron administration led to a rapid transition to purely pressure-controlled gas ventilation. Upon discontinuation, the perflubron dissipated rapidly due to evaporation, although residual perflubron was clearly discernible on chest radiograph for 5 to 38 days after the last dose. This delayed evaporation is attributed to poorly ventilated areas of the lungs. One issue related to retained perflubron was that subsequent radiographic diagnosis of pulmonary infiltrates or atelectasis may be difficult.

No hemodynamic compromise associated with the use of PLV was demonstrated. Airway pressures and pulmonary vascular resistance were not increased and generally improved significantly. Physiological shunt decreased, and pulmonary

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**Table III**

Proposed mechanisms by which partial liquid ventilation improves gas exchange

- High density of perfluorocarbon (PFC) enhances sequential recruitment of alveoli.
- Liquid-liquid interface reduces surface tension of the PFC and enhances recruitment of alveoli.
- Weight of PFC favorsably redistributes pulmonary blood flow to nondependent regions.
- Liquid stabilization of lung alveoli increases functional residual capacity.
- Improved lung compliance enhances ventilation-perfusion matching.
- Stimulated production of endogenous surfactant is likely.
- Small airway exudates may be lavaged and removed.
Table IV
Recent investigations utilizing partial liquid ventilation in humans

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Study design</th>
<th>Subjects</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirschcl  et al (1995)</td>
<td>Noncontrolled human clinical trial</td>
<td>Adults; N = 10 Neonates; N = 5 Children; N = 4</td>
<td>Evaluated patients with severe respiratory failure who were receiving ECLS; instituted PLV in combination with ECLS. Discontinued ECLS for baseline data, then resumed ECLS in conjunction with PLV.</td>
<td>Decreased alveolar-arterial oxygen gradient $P = .002$ Increased pulmonary compliance; $P = .002$ Complications: a. 6 reaccumulated pneumothoraces b. 3 pneumothoraces c. 1 mucous plug</td>
</tr>
<tr>
<td>Gauger et al (1996)</td>
<td>Noncontrolled phase I/II experimental with pretest/postest design</td>
<td>Children ages 8 weeks to 5.5 years; N = 6</td>
<td>Pediatric patients receiving ECLS underwent PLV with perflubron in conjunction with ECLS for 3 to 7 days. (Baseline data were obtained during discontinuation of ECLS therapy for 10 minutes.)</td>
<td>$\text{PaO}_2$ values improved from baseline measures with the initiation of PLV; $P = .021$ Increased pulmonary compliance; $P = .01$ Decreased pulmonary shunt with PLV; $P = .059$ Pneumothoraces occurred in 2 subjects.</td>
</tr>
<tr>
<td>Meaney et al (1997)</td>
<td>Prospective design</td>
<td>Adults and children ages 3 months to 75 years; N = 9</td>
<td>Described the computed tomographic appearance of perflubron-filled lungs during PLV with perflubron.</td>
<td>Gravity-dependent distribution of perflubron was observed in 4 patients; patchy distribution was observed in 4 patients; and homogenous distribution of perflubron was observed in 1 patient.</td>
</tr>
</tbody>
</table>

ECLS—Extracorporeal life support
PLV —Partial liquid ventilation

Compliance improved. It must be noted, however, that all values were compared with baseline data obtained during the 15-minute discontinuation of ECLS therapy.

Pneumothoraces developed in five patients during PLV, and a serious mucous plug developed in one patient. This patient population had a predicted 10% to 20% survival rate without ECLS and a 50% to 60% survival rate with ECLS. Six of the 10 patients were successfully weaned from the ECLS, and 5 patients survived to be discharged. The study demonstrated the ability to safely use PLV in concert with ECLS therapy in adults with severe ARDS.

- Partial liquid ventilation in premature infants.

Ten premature infants with severe respiratory distress syndrome, which did not respond to conventional therapy, underwent PLV. Partial liquid ventilation was initiated by instilling perflubron via their endotracheal tubes to a volume approximating the FRC during positive-pressure gas ventilation. Chest radiographs demonstrated uniform filling of the lungs with uncomplicated weaning from PLV back to purely gas ventilation.

Both gaseous exchange and overall lung function improved in the infants during the PLV. Prior to the start of the PLV, the infants had all been receiving 100% inspired oxygen and demonstrated a mean arterial oxygen tension of 60 mmHg, which increased to 143 mmHg within 1 hour of starting combined liquid-positive pressure gas ventilation. Furthermore, carbon dioxide normalized within 4 hours, and the dynamic compliance increased by more than 60% from the baseline value. Mean airway pressures decreased in spite of an increase in tidal volumes that the therapy permitted.

Overall, 13 infants were enrolled in the trial, with 10 receiving PLV for 24 to 76 hours. Three infants were eliminated from the study because they required high-frequency ventilation. No adverse complications were caused by the partial liquid ventilation. Weaning from partial liquid back to
conventional gas ventilation took place without systemic toxicity or other adverse effects. One question that must be addressed specifically in the neonatal population is: At what point is discontinuation of PLV safe?

Eight of the patients survived to 36 weeks' gestational age. Of the infants who died during the study, three died of acute lung disease, one died of bronchopulmonary dysplasia, and two of complications of prematurity unrelated to the respiratory system. The causes of death of these six infants appeared to be unrelated to the liquid ventilation.

### Combined therapies

New therapeutic approaches combining PLV with other modalities have recently been investigated. Two recent studies evaluated PLV in conjunction with nitric oxide in piglet models of acute lung injury resulting in improvement of both arterial oxygenation and pulmonary hemodynamics.\(^2\) In a recent study utilizing acute lung-injured piglets, Baden et al demonstrated more rapid improvement in oxygenation when perflubron was instilled into the lungs in conjunction with high-frequency oscillatory ventilation compared with

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### Table V

**Investigations utilizing partial liquid ventilation in animals**

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Study design</th>
<th>Subjects</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leach et al (1993)(^{11})</td>
<td>Prospective, randomized controlled study</td>
<td>Premature sheep; N = 11</td>
<td>CMV compared with PLV perflubron in doses of 30 mL/kg.</td>
<td>Mean PaO(_2) increased in PLV animals, mean PaCO(_2) decreased in PLV animals; dynamic compliance increased during PLV.</td>
</tr>
<tr>
<td>Sekins et al (1994)(^{20})</td>
<td>Pilot trial study</td>
<td>Near term baboons; N = 11</td>
<td>Intratracheal perflubron instilled, and subjects were sustained on PLV for 96 to 120 hours.</td>
<td>Subjects tolerated 4 days of PLV followed by 1 day of CMV without complications. No significant changes were demonstrated in the lungs.</td>
</tr>
<tr>
<td>Hirschl et al (1995)(^{13})</td>
<td>Prospective, randomized controlled design</td>
<td>Lung injured sheep; N = 11</td>
<td>CMV compared with PLV with perflubron in an animal model of acute respiratory failure.</td>
<td>Decreased physiologic shunt in PLV subjects; P &lt; .005. Increased pulmonary compliance; P &lt; .005. Evidence of parenchymal injury was diminished in the PLV group.</td>
</tr>
<tr>
<td>Overbeck et al (1996)(^{21})</td>
<td>Prospective, randomized controlled design</td>
<td>Adult sheep with induced lung injury; N = 10</td>
<td>CMV compared with PLV with sequential dosing of perflubron of 10 to 50 mL/kg.</td>
<td>SaO(_2) increased in the PLV group; P = .001. PLV group showed improved pulmonary shunting; P = .004. No measured differences in pulmonary compliance were observed between groups.</td>
</tr>
<tr>
<td>Nesti et al (1994)(^{22})</td>
<td>Prospective, randomized, blinded controlled design</td>
<td>Piglet model of gastric aspiration-induced ARDS</td>
<td>CMV compared with PLV with perflubron for a period of 6 hours.</td>
<td>Oxygenation was improved in the PLV group after 2.5 hours following injury; P &lt; .05. Histologic evidence for ARDS in the PLV group was lacking 6 hours after the initial insult.</td>
</tr>
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ARDS — Acute respiratory distress syndrome  
CMV — Controlled mechanical ventilation  
PLV — Partial liquid ventilation
high-frequency oscillatory ventilation alone. Studies utilizing innovatively combined therapies are promising and set the stage for future investigation.

Summary

Liquid ventilation is based on the fundamental principles of a fluid filled lung and the physiological properties of perfluorocarbons. Total liquid ventilation requires a special apparatus to deliver and remove tidal volumes of the PFC liquid and to extracorporeally oxygenate and remove carbon dioxide. Currently, there are no liquid ventilators for humans.

Perfluorocarbon-associated gas exchange uses a conventional ventilator and combines aspects of both liquid ventilation and continuous positive-pressure gas breathing into an approach known as PLV. The high density and low surface tension of PFCs are useful qualities to help counteract the derangements seen in ARDS. Clinical trials with neonates, children, and adults are ongoing. Since the safety of PLV and improvement in gas exchange is beginning to be established, the United States Food and Drug Administration has given the product “fast track” status due to its lifesaving potential.

The clinical trials described in this article are highly encouraging in patients moribund from severe pulmonary disease in whom conventional therapy has failed. In both adults and premature infants, PLV improved gas exchange, increased pulmonary compliance, and was not associated with deleterious effects.

This innovative approach to pulmonary management could one day improve the survival rates in patients with respiratory failure stemming from a variety of causes. However, to date, human studies utilizing liquid ventilation with PFCs lack strong experimental design. Though the clinical utility of PFCs and liquid ventilation are promising, more research utilizing controlled designs in various human populations is needed.

REFERENCES


AUTHORS

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