Liquid Ventilation: Current Status
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OBJECTIVES
After reading this article, the reader should be able to:

1. List the potential medical applications of liquid-assisted ventilation (LAV).
2. Describe the properties of perfluorochemical liquids that are important for their use in liquid ventilation.
3. Describe the potential benefits of LAV in respiratory distress syndrome, congenital diaphragmatic hernia, acute respiratory distress syndrome, and aspiration syndromes.
4. Delineate specific nonrespiratory applications of LAV.

Introduction
With the advent of modern technology and the evolution of intensive care units, the ability to treat respiratory problems has improved remarkably. This accomplishment is particularly remarkable with respect to the 40,000 preterm infants born each year of whom thousands have severe respiratory problems. Fortunately, the number of smaller and more immature infants who are treated, survive respiratory distress, and recover uneventfully is increasing. However, the overall success of treating neonatal respiratory distress remains limited by the inherent problems of surfactant deficiency and structural immaturity of the lung. Consequently, infants delivered preterm who have respiratory insufficiency experience diminished lung distensibility that results in progressive atelectasis and respiratory failure requiring mechanical ventilation. Currently, many of these infants improve over time when their ventilation is supported mechanically and surfactant is introduced into their lungs. However, as many as 37% of these severely impaired infants are left with bronchopulmonary dysplasia related to damage of pulmonary tissues and structures from conventional mechanical ventilation (CMV).

Of equal importance, acute respiratory distress syndrome (ARDS) due to trauma, aspiration, or infection strikes more than 100,000 adults in the United States annually. Despite aggressive therapeutic procedures, 60% to 70% of these patients die, and as in infants, many suffer complications associated with CMV. Although structural damage in adults or immaturity in infants cannot be altered acutely, current advances, such as exogenous surfactant replacement therapy to reduce alveolar interfacial surface tension and subsequent inflation pressures, have allowed clinical improvement in gas exchange and decreases in ventilatory requirements, barotrauma, and mortality. Therefore, it appears that the complications associated with respiratory distress can be lessened in proportion to the therapeutic reduction of interfacial surface tension and ventilatory requirements. The concept of maximally reducing surface tension has been explored through liquid ventilation (LV) techniques with perfluorochemical (PFC) liquids.

In addition to respiratory support, other possible medical applications for liquid-assisted ventilation (LAV) are being investigated. Liquid in the lung can remove debris caused by cystic fibrosis, alveolar proteinosis, or aspiration syndromes. In addition, with the aid of liquid in the lungs, pharmacologic agents can be administered with greater effectiveness in lung diseases involving infection and cancer. For example, therapeutic treatment of lung cancer with drugs can have devastating effects on other tissues in the body. By using LV as a carrier for the drug, adverse side effects can be minimized because the agent is administered directly to the surface of the lung. Furthermore, recent studies have shown that it is possible to enhance high-resolution computed tomography (HRCT) images of the respiratory system by administering PFC to the lungs. Finally, as depicted in the underwater science-fiction novel and film, The Abyss, liquid breathing has the potential to allow humans to survive in unusual environments such as in great deeps, in space, and under great acceleration.

The biomedical application of LAV has been explored in animal models for more than 3 decades. More recently, clinical investigational trials have shown that it is possible to maintain gas exchange in critically ill neonates, children, and adults using LV. This review dis-

ABBREVIATIONS
ARDS: acute respiratory distress syndrome
CDH: congenital diaphragmatic hernia
CMV: conventional mechanical ventilation
ECMO: extracorporeal membrane oxygenation
ECLS: extracorporeal life support
FRC: functional residual capacity
GV: gas ventilation
HFOV: high-frequency oscillatory ventilation
HRCT: high-resolution computed tomography
I:E: inspiratory-to-expiratory time
IL: interleukin
LAV: liquid-assisted ventilation
LPS: lipopolysaccharide
LV: liquid ventilation
NMR: nuclear magnetic resonance
NO: nitric oxide
PFC: perfluorochemical
PLV: partial liquid ventilation
RDS: respiratory distress syndrome
TLV: total liquid ventilation
TNF: tumor necrosis factor

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C₈F₁₇Br) compound is very stable, is biologically inert, and is not metabolized. This low molecular weight (499; C₈F₁₇Br) compound is very stable, is biologically inert, and is not metabolized. All studies reporting uptake as a function of time and dose (TLV) demonstrated and confirmed adequate for prolonged ventilation. In some cases, animals survived for hours if the liquid was oxygenated continuously, but the increased work of breathing led to fatigue. Another unique early technique used gravity-assisted ventilation with oxygenated PFC. PFC was drained from a reservoir into the lungs of intubated animals. Neither of these early methods proved adequate for prolonged ventilation. In a later attempt to improve on these techniques, the concept of demand-regulated LV was demonstrated by Shaffer and Moskowitz. This technique allowed experimental animals to control the cycling of the respirator that circulated oxygenated liquid to and from the lungs. This method established tidal volume and breathing frequency requirements and reduced the effort required of the patient. The early experiments with this type of ventilation reported effective oxygenation and better removal of carbon dioxide. This particular device was cited explicitly in the novelization of The Abyss and formed the conceptual basis for the deep diving device depicted in the movie.

Experiments with this type of ventilation established the necessary system components as well as tidal volume and breathing frequency requirements for mechanical ventilation with liquids. A system for time-cycled, pressure-limited TLV was developed, and animals of various gestational ages and lung abnormalities were maintained with adequate gas exchange for extended periods of time. This LV strategy allows for fine control of tidal volume, airway and alveolar pressure, and functional residual capacity (FRC). Functionally, the system resembles an extracorporeal membrane oxygenation (ECMO) circuit in that it has a pump to regulate flow, an oxygenator (for oxygenation of the expired fluid), a heater, and a condensing system to recapture PFC (Fig. 2). Because PFC liquids have a high heat capacity, the patient’s body temperature can be regulated easily and closely by the liquid temperature during ventilation.

Over the years, the liquid ventilator has been refined sufficiently to allow computer operation using the same control modes as gas ventilators; that is, it is time-cycled and
can be pressure- or volume-limited, have the inspiratory-to-expiratory time (I:E) ratio be changed, and have the waveform altered. Many of the same general principles used for gas ventilation are applied during LV. The ventilatory rate generally remains constant at 5 breaths/min during TLV (due to longer diffusion times of gases through liquids), and the tidal volume is used to regulate minute ventilation and, therefore, PaCO₂. With a time-cycled system, tidal volume is regulated by changing flow rates or pressure limits. Unlike gas ventilation (GV), TLV allows unique control and measurement of FRC by monitoring the change in weight as liquid is exchanged between the subject and the LV system. FRC and inspired oxygen concentration can be adjusted to optimize oxygenation. All manipulations can be made within the boundaries of set pressure, volume, and flow limits.

PARTIAL LIQUID VENTILATION (PLV)
Because initial TLV studies demonstrated residual improvements in respiratory function after a return to GV, it was suggested that the administration of PFC liquid to the lungs may function similarly to an artificial surfactant for respiratory distress syndrome (RDS) or a lavage medium for certain other types of pulmonary dysfunction. More recently, several investigators have explored tracheal instillation of PFC liquids in combination with GV in a variety of neonatal, juvenile, and adult animals as well as in preterm human infants and adults who have respiratory failure. Currently, this combined ventilation scheme with PFC liquids and GV is known as PLV and is characterized by filling and sustaining the lung with a volume of PFC liquid less than or equal to the FRC while conventional GV is maintained (Fig. 3). It has been proposed that residual PFC is oxygenated and carbon dioxide is exchanged in the lung by means of the tidal gas movement provided by GV. During PLV, the air-liquid interface in the lungs is not eliminated completely, so some of the major mechanical advantages of a liquid-liquid interface may not be appreciated. However, this technique offers specific advantages over GV for many pulmonary disorders, particularly where surfactant therapy is not an option.

A number of techniques have been explored for LAV. Thus far, investigators have considered continuous TLV, brief periods (3 to 5 min) of TLV, rapid instillation of a bolus (30 mL/kg) of oxygenated PFC, and a slow infusion of un oxygenated PFC in doses up to 30 mL/kg over 15 minutes. The optimum PFC filling strategy and the effect of any subsequent GV scheme, including high-frequency, assist-controlled, synchronized, and spontaneous breathing strategies, are still under extensive investigation.

It has been reported that the addition of small amounts of PFC liquid (3 mL/kg) to high-frequency oscillatory ventilation (HFOV) resulted in a more rapid improvement in oxygenation for lung-injured piglets compared with HFOV alone (piston-driven). Although oxygenation improved over time in both groups with HFOV, increasing doses of PFC did not result in any significant improvement.
differences in oxygenation compared with HFOV alone. Neither values for Pco₂ and pH nor cardiovascular stability differed between groups. The combination of HFOV and small-dose PFC liquid may permit more effective oxygenation at lower mean airway pressures by facilitating alveolar expansion and decreasing intrapulmonary shunt.

Respiratory Support Applications Using LAV

RESPIRATORY DISTRESS SYNDROME (RDS)
Preterm infants characteristically have homogeneous surfactant deficiency and immature parenchyma and initially present with a purely restrictive lung disease that leads quickly to atelectasis. The use of surfactant replacement therapy and prenatal steroids has substantially improved the clinical course of these infants, but they seem to have the most to gain from LAV, particularly when applied early. Surface tension forces are reduced or eliminated, atelectasis is prevented or remedied, and the liquid environment of the developing fetal lung can be reproduced. The need for excessive ventilator pressures and inspired oxygen concentrations is diminished. Multiple animal studies over the years have demonstrated significant improvements in pulmonary mechanics, gas exchange, and histology in models of premature lung disease (Fig. 4).

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)
The newborn who has CDH faces the dilemma of pulmonary hypoplasia potentially complicated by surfactant deficiency. PFC liquids have the potential to maximize recruitment of the hypoplastic lung while minimizing the surface tension forces related to surfactant deficiency, thus allowing more efficient ventilation and minimization of barotrauma. Investigation of a lamb preparation of CDH supported with PLV, either prophylactically at birth or rescued after a period of GV, showed improved gas exchange and compliance compared with conventional GV. The group prophylactically treated with PFC liquid at delivery demonstrated improved function compared with rescue treatment.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)
Term infants, pediatric patients, and adults all can present with ARDS. Whether they are receiving or are candidates for ECMO, they often have consolidated, collapsed lungs with an aggressive inflammatory process and extremely poor compliance. Therefore, they potentially can be helped by lung recruitment and improved compliance. Multiple laboratory studies have shown the ability of LAV to improve gas exchange, mechanics, and cardiopulmonary stability in both large animal models and neonatal animal models of ARDS.

ASPIRATION SYNDROMES
Patients who have aspiration syndromes can benefit from the ability of PFC liquids to support pulmonary mechanics and gas exchange while lavaging the lung. PFC liquid has been used to ventilate lambs that have meconium aspiration. In these lambs, poor gas exchange, acidosis, and low pulmonary compliance were present during GV; during subsequent TLV, meconium was observed in the expired liquid. Improvements were noted during TLV and PLV in PaO₂, alveolar-arterial (A-a) oxygen gradient, and pulmonary compliance, and pulmonary blood flow was more uniform. Based on these findings, it was concluded that TLV improved pulmonary perfusion and ventilation-perfusion matching.

Nonrespiratory Applications

DRUG DELIVERY
Delivering drugs through the endotracheal tube is not a new concept for intensive care clinicians; management of pulmonary dysfunction often includes delivery of biologically active agents to the lung. The physiologic properties of the lung as an exchanger for biologic agents include its large surface area, thin walls, and accessibility to the entire cardiac output. Theoretically, insufflation of an agent directly to the lung presents advantages for distribution and uptake. Over the years, this concept has led not only to direct endotracheal drug delivery, but to various methods for aerosolization of drugs during ventilation. In the diseased lung supported with liquid, pulmonary blood flow is distributed more homogeneously and
ventilation/perfusion is matched more evenly. Gas exchange can be supported during pulmonary drug delivery in the liquid-filled lung, and the nonbiotransformable liquid precludes any interaction between the agent being delivered and the vehicle by which it is delivered.

Several studies using LAV in preterm lambs that had RDS, healthy and lung-injured term lambs, and healthy rabbits have demonstrated the feasibility of using LV techniques to deliver aqueous and lipid-soluble pharmacologic agents to the lung, including vasoactive agents, antibiotics, anesthetics, and vectors for gene transfer. Because aqueous solutions are not readily soluble in PFC liquids, the success of this approach for homogenous distribution and physiologic impact has relied primarily on bulk flow and turbulent mixing during TLV. A newly developed nanocrystal technology affords the opportunity to increase the relative solubility of agents by suspension in a PFC liquid (Fig. 5). This approach has been shown to yield therapeutic serum levels and higher and more homogeneous pulmonary concentrations of gentamicin in healthy and lung-injured neonatal animals than intravenous delivery when delivered either within the initial dose of PFC or sometime during PLV. In addition to the previously mentioned biologic agents, halothane has been delivered in PFC liquid and was found to induce anesthesia effectively in experimental animals while supporting cardiopulmonary function.

Inspired gases also lend themselves well to this type of drug administration. Recent studies have demonstrated physiologic responses to inspired nitric oxide (NO) during PLV. The ability to deliver NO during PLV probably is related to recruitment of lung volume, distribution of NO in the gas-ventilated regions of the lung, and the solubility and diffusion of this gas in the PFC.

Results of these studies suggest that PFC-assisted ventilation may be a useful adjunct in delivering other therapeutic agents, such as bronchodilators, exogenous surfactant, antibiotics, steroids, chemotherapeutics, mucolytics, antioxidants, and gene therapy products, directly to the lung while protecting nontargeted organs from iatrogenic pharmacologic effects. This approach appears to have vast potential for a therapeutic role in the management of a variety of respiratory problems, including surfactant deficiency, consolidation, exudative processes, malignancy, persistent or acquired pulmonary hypertension, pneumonia, and airway reactivity.

**FIGURE 5.** A computer-generated molecular model of a PFC/gentamicin nanocrystal suspension. The white molecules represent gentamicin and the red molecules represent the PFC perfluorobron.

**FIGURE 6.** Conventional chest radiograph of a patient receiving ECMO with perflubron in the lungs. Perflubron is distributed uniformly in the lungs and imparts high radiopacity.
LUNGENAUSBAU UND WACHSTUM DES HYPOPLASTISCHEN LUNGS

This same PFC liquid, perflubron, has been shown to decrease cytokine production (tumor necrosis factor [TNF] alpha, interleukin [IL] 1, IL 6, IL 8) and chemotaxis of activated human alveolar or circulating macrophages. One study of human circulating macrophages indicated that perflubron had little or no effect on leukotriene, chemotaxis, or superoxide anion release following activation by LPS, TNF-alpha, and -formyl-Met Leu-Phe stimulation. In addition, basal concentrations of TNA-alpha, IL 1, and IL 6 from unstimulated alveolar macrophages were not altered by perflubron.

Data from humans treated with intratracheal PFC is emerging from ongoing adult clinical trials with PLV. The oxidant-generating capacity of neutrophils obtained from bronchoalveolar lavage of PFC-treated humans who had ARDS was similar to that of peripheral blood neutrophils. In another study of adult humans who had ARDS and were treated with either CMV or PLV, the white blood cell count, neutrophils, protein, IL 1, and IL 6 in the bronchoalveolar lavage were higher with CMV than PLV; IL 8 concentrations did not differ between CMV and PLV, and IL 10 levels were lower with PLV.

PFC liquids also appear to affect neutrophil-epithelial cell interactions. When neutrophils and epithelial cells were exposed simultaneously to PFC, adhesion and target cell injury following stimulation were reduced. Prior exposure to PFC with subsequent washing and stimulation did not alter neutrophil release of proinflammatory stimuli or adhesion to epithelial cells. More importantly, because the presence of perflubron does not cause direct suppression of the neutrophil response system, it would be expected that perflubron would not impede the ability of neutrophils to respond to an inflammatory challenge during acute lung injury.

In summary, it appears that the presence of PFC may provide a mechanical barrier or direct cytoprotective effect to reduce lung injury by attenuating leukocyte infiltration and the effects of local or circulating proinflammatory mediators on lung structures.

**TEMPERATURE CONTROL**

PFC liquids have very high heat capacity relative to respiratory gases. The pulmonary vasculature vasoconstricts less in response to hypothermia than does the skin vasculature. In addition, because the lung surface area is large (35 times that of the body surface area), the entire cardiac output essentially comes in contact with the pulmonary surface, and because the epithelial barrier is thin, the lung is an excellent heat exchanger. As a result of these anatomic and physiologic factors, much more effective warming/cooling can occur via the pulmonary administration of heat/cold (especially through breathing a heated/cooled liquid) than by warming/cooling the skin. Hence, there is a potential benefit to using LV techniques to provide hyper- and hypothermia. These heat exchange principles employing LV techniques have been demonstrated experimentally in both newborn and adult animals. Temperatures of inspired liquid must be controlled carefully in the normothermic patient. It is noteworthy that the adjunctive support of this media may help to maintain temperature control in the thermally unstable neonate.

**Clinical Studies**

**NEONATAL**

The first human trials of PFC liquid breathing were conducted in Philadelphia, Pennsylvania in 1989 and were initiated in near-death infants who had severe respiratory failure. TLV was administered in two 3- to 5-minute cycles separated by 15 minutes of GV. A gravity-assisted approach was used, and tidal volumes of liquid were given to a liquid-filled lung for two sequential 5-minute cycles. The infants tolerated the procedure and showed improvement in several physiologic parameters, including lung compliance and gas exchange. Improvement was sustained after LV was discontinued, but the infants eventually deteriorated. Hence, although the protocol used a form of TLV, the benefit of GV was sustained after administration of PFC liquid to the immature injured lung. All of the infants in these studies ultimately died from their underlying respiratory disease, but TLV was shown to support gas exchange and allow residual improvement in pulmonary function following return to GV. Further clinical trials were limited by the need for a medically approved liquid ventilator and medical-grade breathing fluid. Subsequent human protocols have used a PLV approach to LV.

Over the past 6 years, several PLV studies using sterile perflubron (LiquiVent™) have been completed or are ongoing in humans. Leach and collaborators reported on 13 preterm infants who had severe RDS in whom conventional treatment had failed. The infants were treated with PLV for up to 96 hours by protocol (maximal time on PLV for any infant was 76 h). Their lungs were filled with LiquiVent™ to approximately 20 mL/kg, and supplemental doses generally were administered hourly. The study was not randomized or blinded. The arterial oxygen tension increased by 138%, the dynamic compliance increased by 61%, and the oxygenation index was reduced from a mean of 49 to 17 within 1 hour of initiation of PLV. It was concluded that clinical improvement and survival occurred in some infants who were not predicted to survive.

Pranikoff and associates reported results for four patients who had CDH and were being managed for up to 5 days on extracorporeal life support (ECLS). PLV was performed in a phase I/II trial for up to 6 days with daily dosing. This technique appeared to be safe and possibly was associated with improvement in gas exchange and pulmonary compliance. In a similar study, Greenspan and coworkers treated six term infants who had respiratory failure and were failing to improve while receiving ECLS. They administered PLV with hourly dosing of LiquiVent™ for up to 96 hours. They concluded that the technique appeared to be safe, improved lung function, and recruited lung volume in these infants.

These initial studies of PLV in neonates are encouraging and sus-
gest the feasibility of this technique in the neonate who has severe RDS and ARDS. The response of the sick term infant to PLV frequently is more gradual than typically is observed in the preterm infant who has RDS. The preterm infant often experiences improvement in lung compliance and gas exchange within hours of PLV initiation, most likely due to reductions in surface tension and volume recruitment. Improving lung function in the term infant often requires debris removal, which occurs gradually over several days.

**PEDIATRIC**

Three studies have evaluated PLV in children, and none has used a control group. Gauger et al reported on six pediatrics patients who had ARDS requiring ECLS. Children were treated with daily dosing of LiquiVent™ PLV for 3 to 7 days. Some improvement in gas exchange and pulmonary compliance occurred over time, and all patients survived. Similarly, Hirschl and coworkers treated seven pediatric patients who had ARDS requiring ECLS. They found an improvement in gas exchange and pulmonary compliance without adverse events related to the drug or technique when administering PLV for 1 to 7 days. Finally, Toro-Figueroa et al treated 10 children up to 17 years of age who had ARDS with PLV for up to 96 hours. Nine of the patients who tolerated initial dosing experiencing improvement in gas exchange. However, lung function did not improve. Results of these studies suggest that PLV may be safe and efficacious in the treatment of pediatric ARDS.

**ADULT**

To date, there have been two phase I/II PLV studies with LiquiVent™ reported in adults. Hirschl and colleagues treated 10 adults who had ARDS and were receiving ECLS with daily dosing of PLV for up to 7 days. The authors reported a decrease in the physiologic shunt and an increase in pulmonary compliance; 50% of the patients survived. Based on their clinical experiences, they concluded that PLV appeared safe in this patient population and may be associated with observed improvements in gas exchange and pulmonary compliance. In another study, Bartlett and others presented a phase II randomized, controlled trial of PLV in 65 adult patients who had acute hypoxemic respiratory failure. Forty patients received LiquiVent™ for 5 days, and 25 patients served as controls. Ventilator-free days and mortality did not differ between the groups, but there was a statistically significant improvement in ventilator-free days in subjects treated with PLV who were younger than 55 years of age. The authors concluded that PLV can be accomplished with safety in this population and suggested that larger trials be initiated with special consideration to age stratification.

As of this writing, a 480-patient, phase III, PLV adult trial with LiquiVent™ is ongoing in North America and Europe. It is designed to distinguish the effectiveness of PLV over CMV in a clearly defined ARDS population. Although the use of other PFCs for clinical trials is emerging, it is noteworthy that PLV studies with LiquiVent™ in the neonatal and pediatric population are currently on hold awaiting the results of this pivotal adult trial. Results of initial phase I/II trials have demonstrated the potential safety and efficacy of this therapy, particularly in younger populations of sick patients, but a full understanding of the utility of PLV awaits the results of ongoing studies.

**Conclusion**

The use of PFC liquids as an alternative respiratory medium originally was based on mechanical and biophysical mechanisms to support pulmonary gas exchange and function. Over the years, the pulmonary application of PFC liquids has evolved to include their use as a vehicle to deliver agents directly to the lung, as a substance to facilitate lung growth, as a bronchopulmonary contrast agent, and as a potential cytotoxic protective medium to attenuate inflammatory processes. However, the primary application of LV techniques remains the potential to treat lung disease with less risk of barotrauma and to provide a means for complementing existing forms of respiratory management such as surfactant therapy, ECMO, HFOV, and inhaled NO. To date, nearly 500 patients in hospitals across North America and Europe have been enrolled in various clinical trials of PLV, and preliminary results are encouraging.

The future availability of additional biomedical-grade PFC liquids with varying physicochemical characteristics will enable further tailoring of LAV techniques for individual applications. With continued efforts toward establishing the efficacy and safety of the biologic interaction of PFC fluids, LAV undoubtedly will assume an integral role in clinical medicine. Continued laboratory and clinical research should define further the applications and limitations of this alternative therapeutic approach to respiratory management.

**SUGGESTED READING**


Liquid Ventilation


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