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Review Article

Liquid Ventilation

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Abstract

Mammals have lungs to breathe air and they have no gills to breath liquids. When the surface tension at the air-liquid interface of the lung increases, as in acute lung injury, scientists started to think about filling the lung with fluid instead of air to reduce the surface tension and facilitate ventilation. Liquid ventilation (LV) is a technique of mechanical ventilation in which the lungs are insufflated with an oxygenated perfluorochemical liquid rather than an oxygen-containing gas mixture. The use of perfluorochemicals, rather than nitrogen, as the inert carrier of oxygen and carbon dioxide offers a number of theoretical advantages for the treatment of acute lung injury. In addition, there are non-respiratory applications with expanding potential including pulmonary drug delivery and radiographic imaging. The potential for multiple clinical applications for liquid-assisted ventilation will be clarified and optimized in future.

Keywords: Liquid ventilation, perfluorochemicals, perfluorocarbon, respiratory distress, surfactant.

Introduction

Liquid-assisted ventilation, as an alternative ventilation strategy for respiratory distress, is progressing from theory and basic science research to clinical application.[1] The potential use of liquid ventilation (LV) has been investigated since 1962 when Kylstra evaluated the ability to sustain gas exchange in mice spontaneously breathing saline oxygenated at 6 atmospheres.[2] Clark subsequently demonstrated that spontaneously breathing mice could survive when submerged in perfluorocarbons (PFCs) under normobaric conditions.[3] The first trial of liquid ventilation in preterm neonates in 1989 showed the feasibility and potential of liquid ventilation in humans.[4] Relatively few agents have the properties of carrying O_2 and CO_2– essentially only silicone oils and perfluorocarbons (PFCs). Silicone oils found to be toxic, and hence only PFCs remained for possible use.[5] PFCs were synthesized during the development of the atomic bomb (the Manhattan Project) where they were given the code name 'Joe's stuff.'[3] Over the last 40 years, liquid ventilation has been studied in various animal models: normal, premature and with lung injury.[1-3,5]

Two primary techniques for liquid-assisted ventilation have emerged; total liquid ventilation and partial liquid ventilation.[1] While total liquid ventilation remains as an experimental technique, partial liquid ventilation could be readily applied, but its implementation in clinical practice awaits results from ongoing and future clinical trials that may define its effectiveness.[6]

The PFC liquids used to support pulmonary gas exchange are a type of synthetic liquid fluorinated hydrocarbon (hydrocarbons with the hydrogen replaced by fluorine, and for perflubron where a bromine atom is added as well) with high solubility for oxygen and carbon dioxide.[3] These are chemically and biologically inert, clear and odorless, have low surface tension, and undergo no metabolism in kidneys or liver. The oxygen carrying capacity can be more than three times that of blood (35-70 ml gas/dl at 25 °C) and that of CO_2 is approximately four times greater than that for oxygen (122-255 ml/dl).[1] They can be stored at room temperature and function as high efficiency heat exchanger.[7,8] Most PFCs have a surface tension of 12-18 dyne/cm[1.62]. Although nearly twice as dense as water, most PFCs have a similar kinematic viscosity to water.[9] In general, because PFC liquids are more dense and viscous than gas, with slower spreading and higher diffusion coefficients, assisted mechanical ventilation techniques are required to support pulmonary gas exchange when the lung is totally or partially filled with this medium.[7] Non-medical uses of PFC include the cosmetic industry for their water retention properties, as cooling agents and as insulators. In medical applications, besides use as a respiratory medium, PFCs are being evaluated as contrast agents for computerized tomography and magnetic resonance imaging, as sensitizing agents during radiotherapy and as possible intravenous oxygen-carrying agents.[9,10]

The ideal PFC for liquid ventilation should have: (i) a high solubility for oxygen and carbon dioxide to maintain gas exchange, (ii) a greater density than body fluids so that it descends to the dependent regions of the lungs and re-opens the areas of atelectasis, (iii) a low surface tension to work like surfactant and improve lung compliance,[5] (iv) property of being inert and not metabolized and eliminated intact by evaporation during exhalation or transpiration through the skin,[11] (v) sufficient volatility to allow elimination in an acceptable time.[5] All studies reporting uptake during using liquid ventilation have detected very low levels of PFC in the blood and tissues. The most current studies report PFC levels of less than 5.8 mcg/ml of blood. In tissue, the lowest levels were found in the

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liver and the highest levels in the lung, followed by fat. Excluding lung and fat, tissue levels were less than 250 mg/g of tissue after 24 hours of liquid ventilation.[11]

Techniques

The first liquid ventilation with PFCs in animals was performed by a chamber above the animal (under the force of gravity), then draining the liquid into a chamber below the animal. [9] In another method, liquid ventilation was done with an extracorporeal circuit. However, the technique and the equipment required were very complex. In particular, the extracorporeal circuit had problems in development, like malfunction of the expiratory valve.[12] PFC is instilled at a rate of 1 ml/kg body weight per minute through the side port of endotracheal tube without interrupting mechanical gas ventilation, maintaining a positive end expiratory pressure of 4 cm of water. PFC is added as needed to replace liquid lost through evaporation and to maintain the liquid FRC throughout the treatment period. The rate of supplemental administration of PFC reflects a loss or gain of functional residual capacity (FRC).[13] There is a lavage effect during liquid breathing that mobilizes alveolar and bronchiolar exudates and fluid to the central airways, where they can be removed by suctioning.[14] While computer-controlled, time-cycled, pressure/volume-limited total liquid ventilators can take maximum advantage of these liquids by eliminating the whole gas phase in the distressed lung, partial liquid ventilation takes advantage of having these liquids in the lung while maintaining gas ventilation. The benefits of both partial and total techniques have been demonstrated in animal models of neonatal and adult.[1]

Total Liquid Ventilation (TLV)

The lungs are filled with PFC to a volume equivalent to the functional residual capacity (FRC), approximately 30 ml/kg and a "liquid ventilator" is used to generate tidal breathing with perfluorocarbon. Optimal CO2 clearance is achieved when ventilation is performed at a rate of 4-5 breaths/minute. Typical tidal volumes are in the 15-20 ml/kg range. One of the advantages of TLV is that exudates may be lavages from the airways in the setting of respiratory failure. In addition, the distribution of PFC within the lungs may be more uniform during TLV.[1] Practically this method was not proved to be adequate for prolonged ventilation.[15]

Partial Liquid Ventitation (PLV)

Sometimes called PAGE (PFC associated gas exchange).[14] 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. Several investigators have explored tracheal instillation of PFC liquids in combination with gas ventilation in a variety of neonatal, juvenile, and adult animals as well as in preterm human infants and adults who have respiratory failure.[11]

Perflubron will be more uniformly distributed if it is given in a rotational fashion with alternation between supine and prone position during incremental dosing. This effect is independent of the mode of ventilation. There was no relationship between improvement in oxygenation and nondependent perflubron distribution. Continuous mechanical ventilation and rotating dosing, both led to an important decrease in the oxygenation index after a 15 ml/kg dose of perflubron. This information had important effect on the development of dosing strategies and clinical trial design.[16]

Over the last 40 years, liquid ventilation has been studied in various animal models: normal, premature and with lung injury, while human studies were focusing mainly on neonates and very limited studies done on human adults.

Advantages of liquid ventilation with PFCs

In acute lung injury, liquid ventilation with PFC may improve the clinical picture by different mechanisms.

1. Improvement in oxygenation in acute lung injury

In acute lung injury, collapse is mainly in the dependent regions of the lungs.[17] Because PFCs are dense, they will gravitate to the dependent parts of the lungs.[17,18] and this will re-open collapsed regions of lung, acting as liquid Positive End Expiratory Pressure (PEEP). Ventilation/perfusion relationships may also improve.[19] Low-bias flow oscillation (LBFO) with partial liquid ventilation (PLV) is a practicable mode of ventilation in a model of acute lung injury and is associated with significant preservation of perflubron in comparison with high-frequency oscillatory ventilation-PLV. The lower evaporative losses during LBFO-PLV were associated with improved inflammatory cellular pattern.[20]

2. Improvement in lung compliance

PLV is thought to improve lung compliance by eliminating the air-liquid interface. The exact pattern of distribution of PFCs in the alveoli during PLV is not yet known. Unlike surfactant, PFC has a constant surface tension. Giving more PFC will therefore not reduce the surface tension any more but it will progressively open up atelectatic alveoli by a PEEP-like effect and improve oxygenation.[21] Some authors suggest using PFCs by vapor or aerosol and they can give same effect on lung compliance with less side effects.[22-24]

3. Anti-inflammatory effect

Studies on animals suggest that the use of PFC in liquid ventilation may reduce pulmonary inflammation and injury. 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.[11]

4. Alveolar and endobronchial lavage

There is also a lavage effect during liquid breathing that mobilises alveolar and bronchiolar exudates and debris to the trachea, where they can be removed by suctioning.[14]

Liquid ventilation in normal lungs

Studies in animals with normal lungs showed worse gas exchange with liquid ventilation compared with gas ventilation.[25]

Classification of clinical applications of liquid ventilation[11,14]

A. Classification for liquid ventilation comprises of severe respiratory failure due to; a) Hyaline membrane disease, b) Adult respiratory distress syndrome, c) Meconium aspiration syndrome, d) Pulmonary interstitial emphysema, and e) Congenital diaphragmatic hernia.

B. Future applications (experiments done on animals) for liquid ventilation include; pulmonary contusion, Inhalation syndrome, cystic fibrosis, pulmonary alveolar proteinosis, drug delivery, radiographic imaging, temperature control, cellular effect, growth of the hypoplastic lung, lung protection during cardiopulmonary bypass, lung protection during organ donation, and cancer therapy.

Human neonatal applications

Complications of prematurity are still common despite advances in peri-natal care of preterm infants.[6] The use of surfactant replacement therapy and prenatal steroids has substantially improved the clinical course of some preterm infants, but not all of them respond.[11] If new conventional ventilatory interventions fail, ECMO is the only alternative method, but is a complex, invasive and costly technique and difficult to apply to small infants. PFC liquid ventilation is started as a new promising technique to solve ventilation problems associated with prematurity.[6]

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 and a gravity-assisted approach was used. The infants tolerated the procedure and showed improvement in several physiologic parameters, including lung compliance and gas exchange. Improvement was sustained after liquid ventilation was discontinued, but the infants eventually deteriorated. All of the infants in these studies ultimately died from their underlying respiratory disease.[26,27]

Leach et al. 1996, reported a multi-centric study on 13 premature infants with gestational age ranging from 24 to 34 weeks (mean 28 weeks), birth weight ranging from 640-2000 grams (mean 1055g), with severe respiratory distress syndrome on whom conventional treatment including multiple surfactant therapy had failed. PLV was initiated for about 76 hours. Within one hour after instillation of PFC, the arterial oxygen tension increased by 138% and oxygenation index reduced. The dynamic compliance improved during the first hour by more than 60%. It was concluded that clinical improvement and survival occurred in some infants who were not predicted to survive.[15] The newborn who had CDH (Congenital diaphragmatic hernia) 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.[11] 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 for up to 6 days with daily dosing. Improvement was noticed in gas exchange and pulmonary compliance.[28] In a similar study, Greenspan and co-workers treated six term infants who had respiratory failure and were failing to improve while receiving ECLS. They concluded that the PLV technique appeared to be safe, improved lung function, and recruited lung volume in these infants.[29] The response of the sick term infant to PLV is slower than what typically is observed in the preterm infant who has Respiratory distress syndrome (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.[11] Results from other studies suggest that PLV may be safe and efficacious in the treatment of paediatric acute respiratory distress.[3,28,30,31]

Now there is a hypothesis which states that immersion of extremely preterm infants in PFC liquid will allow optimal percutaneous gas exchange to occur across the skin. Adding some lung gas exchange with less injurious liquid ventilation (spontaneous or mechanical), the combination of skin and lung gas exchange will provide sufficient gas exchange to support life.[32]

Human adult applications

Hirschl and colleagues treated 10 adults who had ARDS and reported a decrease in the physiologic shunt and an increase in pulmonary compliance; 50% of the patients survived in their study. Based on their clinical experiences, they concluded that PLV may be associated with observed improvements in gas exchange and pulmonary compliance.[33]

Bartlett and others presented randomized, controlled trial of PLV in 65 adult patients who had acute hypoxemic respiratory failure. Forty patients received PLV 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.[34]

In another larger trial, 311 patients were randomly assigned to receive low dose PLV (lungs filled to the carina in the supine position), or high dose PLV (lungs filled to 5 cm caudal to the incisors in the supine position). There was no difference in mortality among the groups; however, patients who received PLV had fewer ventilator-free days and more adverse events including pneumothorax, hypoxic episodes, and hypotensive episodes.[35]

Non-respiratory Applications

This aspect was tested mainly in animals and it represents the future hope of liquid ventilation. Latest research initiatives have suggested the use of PFC for brain cooling, drug delivery, gene transfer or as a contrast agent for ultrasonography of the lung.[26,36]

PFC liquids are useful contrast media. Because they are inert, non-biotransformable, and of varying radiopacity, support gas exchange and can be vaporized from the lung, they provide useful diagnostic imaging. Radiographic studies of the perflubron-filled lungs of animals and humans who had congenital diaphragmatic hernia (CDH) have proven informative to show the degree of pulmonary hypoplasia.[11]

Growing evidence from several laboratories suggests that intratracheal administration of PFC liquids may reduce pulmonary inflammation and injury.[11,37]

Virtual bronchoscopy is a relatively new technique that adds post-processing software to the three-dimensional presentations of helical computed tomography and can allow four-dimensional imaging of the inside of hollow viscera. Use of the PFC liquid perflubron as a bronchographic contrast agent has enhanced markedly the navigation of substantially more distal airways as small as 0.8 mm.[11]

Delivery of drugs to the lungs by PFCs appears promising. The high solubility of oxygen and carbon dioxide, low surface tension, and their ability to enter collapsed lung regions may permit better drug distribution in the diseased lung. PFCs have been studied for delivering antibiotics, anaesthetics and vasoactive substances.[38-40]

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.[24] As a result of these anatomic and physiologic factors and because of the fact that PFC liquids have a higher heat capacity than conventional gas mixtures, PFC liquids can be used to warm the lungs and increase core body temperature or cool the lungs and decrease core body temperature, as required by clinical circumstances.[41,42]

Another hope of liquid ventilation in neonates is lung protection during cardiopulmonary bypass which has been tested in animals. Anti-inflammatory effects, avoidance of alveolar collapse, oxygen-carrying capacity, and surfactant-like properties may protect the lung before and during cardiopulmonary bypass.[43]

The use of liquid ventilation in cancer therapy is also investigated. Liquid ventilation may assist the antineoplastic effects of radiotherapy and chemotherapy in the lung by inducing localized hyperthermia or hyperoxia of the lung surface.[9]

Finally, because perfluorochemicals have direct anti-inflammatory effect and alveolar stabilizing effect, they have been tried as potential useful tools for donor organ preservation prior to lung transplantation.[44,45]

Adverse effects

1. Pneumothorax - Pneumothorax is one of the reported complications in liquid ventilation.[35,46,47] Verbrugge and Lachmann proposed a number of reasons for this. If insufficient PEEP is applied (from gas or liquid) at end-expiration to support the non-PFC-filled alveoli, these alveoli will collapse and shear forces could cause pneumothorax.[47] So even during PLV, using conventional PEEP increases oxygenation and may avoid shear stress in non-dependent lung regions.[47,48]

2. Circulatory impairment - Hemodynamic instability was reported in TLV, where there was an uninterrupted column of PFC within the lungs and the tracheobronchial tree (reduced venous return). This is not the case with PLV as the column consists of liquid and gas (more compressible).[49]

3. Lactic acidosis - Although the circulation is maintained during liquid ventilation, a metabolic acidosis has been reported, the reason behind this is still not clear.[50]

4. Blocking of the endotracheal tube - Endotracheal tube blocking was reported in many cases due to mucous plugging, impairing gas exchange and requiring frequent suctioning and bronchoscopy. This may be due to the exudates in the peripheral airways and alveoli which have been displaced into the central airways and then removed by suction.[46]

5. Carbon dioxide elimination - In TLV, the problem of ineffective clearance of carbon dioxide was reported, but in PLV this problem was less prominent. This is mainly due to the high viscosity of PFC compared with gas and a small carbon dioxide diffusion coefficient. This can be reduced by appropriate setting of the ventilator.[48,51]

6. Toxicity - Slow clearance from the body was reported in some studies about PFC metabolism. Even after intravenous administration, elimination is mainly via the lung and little if any metabolism takes place. PFC particles are taken up by the reticulo-endothelial system. Although these substances appear to be innocuous and chemically inert, traces have been found three years later after a one hour exposure to liquid ventilation.[52,53] However, agents that might be retained in the body for long time should be used with caution, even if they appear to do no harm.[53]

7. Interference with radiographic imaging - PFCs, particularly those containing bromide or iodide ions, are radio-opaque. This

can interfere with subsequent radiography and obscure some structures, which may persist for some weeks.[12,54]

Future

This subject needs more researches as this field can represent the start of new era of clinical use of liquids rather than air to ventilate the lung. So, future efforts may involve studying the effects of various doses of perflubron and finding more clinical applications for perfluorocarbons in general. The possibility of finding new substances that can perform same job with more efficacy and less side effects should be looked for.

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