REVIEW ARTICLES

LIQUID VENTILATION

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ABSTRACT

Concept of liquid breathing in humans was first presented in front of the world in the form of a fiction movie "The Abyss". However, this fiction is fast becoming a reality. Since the first description of acute respiratory distress syndrome (ARDS) in 1967, the search has been on to get a novel approach of mechanical ventilation for these patients. Protective lung strategies have been devised to serve the same purpose. In the meantime, scientists have been busy in developing an ideal liquid which could dissolve maximum amount of oxygen and carbon di-oxide, has minimum metabolism in the body, protect lungs against ventilator-associated injury and can be used as a vehicle to administer drugs in the lungs. Perflubron has emerged as a liquid which could provide a solution to most of above requirements. Liquid ventilation with perflubron has been used by many centres for treatment of ARDS in adults and hyaline membrane disease in premature neonates, with encouraging results. This article discusses the review of available literature on the subject.

Keywords: Liquid ventilation, perflubron

INTRODUCTION

We all breathed liquid for nine months, Bud, the body will remember" is the dialogue occurred in a scene of 20th Century Fox science fiction film "The Abyss" when one of the characters was trying to encourage his friend to breath liquid. This film was directed by the "Titanic" fame director James Cameron and was released in 1989. The film is a story of a group of people working on an undersea rig. Different characters are seen discussing the technique, equipment, mechanism and advantages of "breathing" liquid while under water. The main advantage of breathing liquid under water described in the film is relief from "the Bends" (Bubbling out of nitrogen from the tissues if one returns to lower pressures too quickly. However, this fiction is fast becoming a reality for intensive care providers with many more benefits. In addition to what was described in the movie.

History

Probably, the idea of liquid breathing has been there since 1920s [1], when researchers attempting to ameliorate the effects of war gas poisoning found that the lungs could tolerate lavage with large quantities of saline solution. This idea gained some footings when in 1962 when Dr. J. Kylstra, a physiologist at the state university of New York at Buffalo, realized that salt solutions could be saturated with oxygen at high pressures. Working in a US Navy compression chamber, Klystra performed an experiment to see if mice would be able to move saline solution in and out of their lungs. He and his colleagues ventilated the animals with saline mixed oxygen at 6 atmospheres [2] and were able to keep them alive for 18 hours. Animals finally died due to gradual increase in carbon dioxide because it could not be removed rapidly enough [3].

Subsequent use of oxygenated silicone oils met with some success, but these liquids were subsequently found toxic. Next step in liquid breathing came when Dr. Leland Clark presented his experiment of "liquid breathing mouse" in 1966 [4] recognizable with their famous "liquid breathing mouse photograph" (Fig. 1). Dr. Clark realized that oxygen and carbon di-oxide were soluble in fluorocarbon liquid and so this liquid may be able to support respiration [4]. Dr. Clark and Gollan were able to demonstrate that spontaneously breathing mice could survive when submerged in perflurocarbon (PFC) at normal atmospheric pressure [4]. It was proposed as a

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means of improving gas exchange in infants with acute respiratory failure in 1970. But, the first clinical trial of PFC ventilation in neonates could be performed in 1989. Dr. J. S. Greenspan is the physician who performed this trial at department of paediatrics, Jefferson Medical College, Philladelphia, USA. Three very sick premature neonates (gestational age 28, 24, and 23 weeks) were ventilated with perfluorocarbons (PFCs) using a liquid ventilator [5]. This study demonstrated improvement in lung compliance as well as, drastic improvement in lung physiology [5].

Further clinical trials were not done for next few years, probably, due to non availability of liquid ventilator system and a pharmaceutical grade PFC. The real breakthrough occurred in 1991, when it was discovered that liquid ventilation could be performed in normal pigs without the use of "liquid ventilator". Sustained, highly efficient gas exchange could be achieved by simply filling the lungs with PFCs [6] to a prescribed level and then connecting the animal to a conventional ventilator. This new technique was named partial liquid ventilation (PLV) or perfluorocarbon associated gas exchange (PAGE) [7]. Initial experience with partial liquid ventilation (PLV) in adult patients suffering from acute respiratory distress syndrome (ARDS) was presented in 1996 [7].

Perflurocarbons, Structure and Physical Properties

Perfluorocarbons (PFC) are clear, odorless, inert fluids which are immiscible in aqueous solutions and body fluids (table-1). They have very high (25 times the plasma) oxygen solubility (53 ml/100ml) at 37 C [8], and three times the CO2 solubility (210 ml/100ml). They are high density compounds with low surface tension and ideal vapour pressure for easy removal from lungs. The high density allows perfluorocarbon liquid to displace the oedematous fluid and spread evenly through the airspaces of the lungs [9]. PFCs do not require any metabolism from liver or kidneys [1]. They are eliminated by evaporation without any significant absorption through the lungs. Structurally, they are similar to hydrocarbons with all hydrogen molecules replaced by fluorine. The carbon chains vary in length [6]. Perflurocarbons have the unique ability to lower surface tension due to their own low surface tension of 18 dynes/cm. All of these properties may enhance their potential to support injured lungs [7]. This directed the initial clinical focus on neonatal therapy in the treatment of premature lung disease and they were used as "surfactant substitutes". The most commonly used perfluorocarbon is perfluobron (perfluoro-octylbromide) (Fig. 2), a pharmaceutical grade PFC which is currently undergoing Food and Drug Administration (FDA) phase II and III clinical evaluation [10]. It is available in the market with the name of "liquivent".

As the perfluorocarbons are biochemically inert compounds, minimally absorbed; neither metabolised in the body nor eliminated through kidneys or liver, they have no clinically significant systemic effects. There are no serious or long lasting effects on lung parenchyma [7]. No adverse histologic, biochemical or toxic effects have been identified in these substances, thus making them highly attractive as medium for liquid ventilation [11].

Why PFCs why not water?

Question could arise as to why we cannot use water to carry oxygen into the lungs as compared to perfluorocarbons. The simple answer would be that perfluorocarbons have got higher solubility for oxygen and carbon-di-oxide and have lower surface tensions than water (as described above). These properties allow them to flow through extremely narrow airways, whereas water would obstruct the airway without filling them completely [10].

Anti-inflammatory Effects of PFCs

Multiple studies have shown that perfluorocarbons have got distinct anti inflammatory effects which could benefit the patients of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [12, 13]. Tumor necrosis factor alpha concentration is decreased during ventilation with perfluorocarbons [14]. However, some of the potential modulatory effects of perflubron on excessive inflammatory response that occur during ALI and ARDS may be influenced in part by the extant of PFC partitioning into the liquid bilayers of cellular membranes [15].

An influence of PFCs on proinflammatory and procoagulant features of monocytic cells present in the alveolar space, such as alveolar macrophages (AMs), may be involved [16]. An interference of perfluorohexane with the expression of the procoagulant protein TF on monocytes and AMs as well as with the release of proinflammatory cytokines has been established by certain workers [16]. These effects may contribute to the protective role of liquid ventilation with perfluorocarbons in injuries associated with local activation of inflammatory processes.

Types of Liquid Ventilation

Liquid ventilation is currently performed by one of two techniques.

- Total Liquid Ventilation (TLV).
- Partial Lung Ventilation (PLV).

Total Liquid Ventilation (TLV)

In TLV lungs are filled with perfluorocarbon 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. [7] 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 exudate may be lavaged from the airways in the setting of respiratory failure. In addition, the distribution of perfluorocarbon within the lungs may be more uniform during TLV. Main disadvantage of using total lung liquid ventilation is that this technique needs special “liquid ventilator”, which is not freely available, expansive and needs special training for its use.

Partial Lung Ventilation (PLV)

Partial liquid ventilation was started in 1991 when it was discovered that pigs can be ventilated with liquid by using gas ventilator systems [6]. This can be claimed as a landmark discovery in liquid ventilation subject because it made the concept easily practicable in almost all clinical setups where gas ventilation is being done. This process is called partial liquid ventilation because the volume of PFC liquid instilled into the lungs does not exceed functional residual capacity. During PLV, one performs gas ventilation of the perfluorocarbon-filled lungs using a standard gas mechanical ventilator. This is a relatively simple technique which does not require use of a specialised device. The mechanisms of improved gas exchange during partial liquid ventilation in the setting of ARDS have been investigated. Cross-sectional computed tomography imaging of the lungs in patients with ARDS has demonstrated that the atelectasis and consolidation occurs predominantly in the dependent zones, while ventilation is most preserved in the nondependent regions. The high density and low surface tension of perfluorocarbon are ideal qualities to counteract this pathophysiology and studies suggest that recruitment of dependent atelectatic alveolar units does occur. Evidence also suggests that PLV causes compression of pulmonary vasculature by the dense perflurocarbons resulting in redistribution of pulmonary blood flow from dorsal to better – ventilated middle and ventral lung regions, thereby improving arterial oxygenation in situations of acute lung injury [17].

Mechanism of Certain Beneficial Effects of PLV in Patients of Acute Lung Injury (ALI) or ARDS

The pathophysiologic features of ALI and ARDS include interstitial oedema, alveolar infiltrates and diminished production of surfactant. This all leads to reduced pulmonary compliance and ventilation perfusion mismatches. Distribution of the disease is also not homogenous. Effects of the disease are more pronounced in the dependent portions leading to airway collapses in these regions. This scenario needs lung recruitment and lung protective strategies to improve the clinical condition. Several features of partial lung ventilation may facilitate these ventilatory strategies (table-2).

Improved gas exchange by diffusion: Low surface tension of PFC allows the liquid to reach gravity dependent non-ventilated alveoli. This not only serves to open them but also acts as a reservoir of oxygen and thus decreases shunt fraction and so a non functional portion of lung starts taking part in gas exchange [17].

Alveolar recruitment: Due to their high density (twice as dense as water) PFC fills the

dependent portions of the lung first hence facilitates lung recruitment [9]. The alveoli are not only recruited but are also kept open by the dense and incompressible liquid supporting the "open-lung technique" of ventilation in ARDS.

Improvement in lung compliance: As the surface tension of PFC is lower than water [7] and far lower than the accumulated fluid and surfactant of the diseased lung so it produces a definite improvement in lung compliance and gas exchange [17].

Redistribution of pulmonary blood flow: Due to high density PFC displaces blood from less ventilated lower compartments to better ventilated middle and upper compartments of the lungs and so decrease ventilation perfusion mismatch [18].

Pulmonary Lavage: This effect is maximum with total liquid ventilation where debris is easily removed during each breath [7] During PLV, because the exudative material is lighter in weight it floats over the surface of ventilatory liquid (PFC) from where it can be easily sucked out [19].

Suppression of Inflammatory Response: There could be a direct anti-inflammatory effect of perfluobron upon the diseased lung. Studies have shown decrease in release of cytokines, neutrophil chemotaxis, reduction in Interleukin 6 and 8 (IL - 6, IL-8), white cell count and protein capillary leak [20, 21].

Decreased oxidative lung damage: There are studies to suggest that partial lung ventilation definitely decreases oxidative lung damage seen in acute lung injury caused by systemic bacterial endotoxaemia [22].

Less mechanical damage as compared to conventional mechanical ventilation: The light microscopy clearly shows that conventional mechanical ventilation results in more structural damage to alveolar walls with alveolar oedema formation and haemorrhage as compared to partial liquid ventilation which is much more gentle [23].

Indications of Partial Liquid Ventilation

Although exact indications for partial liquid ventilation are yet to be defined, however, PLV can be used in respiratory distress syndrome in neonates [5, 24, 25], acute lung injury (ALI), adult respiratory distress syndrome (ARDS) [25],

Table-1: Properties of per fluorocarbons PFCs

Inert
clear
Odorless
Immiscible with body fluids
High density
Low surface tension
High oxygen solubility
High Carbon-di-oxide solubility
Ideal vapour pressure
No metabolism in the body

Table-2: Potential benefits of partial liquid ventilation with perflubron

Improvement of gas exchange
Washing out of debris
Lung recruitment
Surfactant like effect
Mitigation of barotrauma/volutrauma
Mitigation of oxygen toxicity
Reduction of inflammation
Less mechanical damage

ventilator induced lung injury (VILI), acute acid induced injury, pulmonary oedema [26], persistant pulmonary hypertension, congenital diaphragmatic hernia, meconium aspiration, and pneumonia [1] Of all the clinical situations probably the strongest indication is of the premature neonates with severe respiratory distress syndrome [25] because of its early effect of suppression of inflammatory response in surfactant depleted newborns [27].

Technique of Partial Liquid Ventilation

Routine gas ventilator is employed. Patient is intubated with an adequate size endotracheal tube. Once the gas ventilation is established perfluobron (C8F17Br1, Liquivent; Alliance Pharmaceutical, San Deigo,CA) is injected through the side port of endotracheal tube. Initial dose is 12 – 16 ml/kg. Lungs are ventilated with time cycled pressure-controlled mode of ventilation at a respiratory rate of 12 – 20 breath per minute depending upon the size and requirement of patient (28). A positive end expiratory pressure of 5 – 10 cm of H2O may be added [28, 29]. Chest radiographs should be done daily. Due to volatility, liquid is reduced and to keep the lungs adequately filled it should be replaced on regular basis. According to one of the protocols [28] decision of re-dosing should be based on following parameters: [1] amount of remaining perfluobron visualized in lateral chest X-ray is decreased from previous X-rays and residual fluid is only remaining in dependent portions, [2] the presence of a perfluorocarbon meniscus on examination of the endotracheal tube

during transient ventilator disconnect,[3] sustained lung recovery.

Clinical Findings and Nursing Care during PLV

Routine nursing care of the patient remains the same as on a conventional gas ventilator. Special attention to lung sounds and adequacy of therapy by assessment of arterial blood gasses is imperative. Breath sounds of the patient are not heard during TLV, fine rales or coarse rhonchi may be auscultated during PLV [1]. Attention is given to the positioning of neonates. Suctioning only when indicated. Heart sounds will much more distinct because sound waves transmission is increased in liquids [11].

Radiographic Appearance during PLV

Radiologic appearance of patients' X-rays depend upon the dose administered. A loading dose of 10 ml/kg followed by repeated filling to carinal level can lead to inhomheonous radiograpjic filling and transient deterioration of oxygenation during first 24 -48 hours [30]. X-ray appearance becomes more symmetrically opaque after 24 to 48 hours as fluid is distributed more evenly (Fig: 3).

Fig-2. Chest radiographs of a 36 years old woman who developed ARDS after pancreatitis. She was supported with PLV for a period of 7 days. She was extubated on 10th day and was discharged from the hospital 13 days later. Top left: baseline radiograph demonstrating bilateral parenchymal infiltrates. Bottom left: radiograph obtained 2.5 h after initiating treatment with perflubron. Note the homogeneous, symmetrical airspace filling. Right: radiograph obtained 48 h after initiating treatment. Note the additional airspace filling with perflubron.

(Adapted from: Schuster DP, Lange NR, Tutuncu A, et al: Clinical correlation with changing radiologic appearance during partial lung ventilation. Chest 2001; 119:1503-1509).

Elimination of PFCs

Perfluorocarbons are eliminated by evaporation through lungs. Elimination occurs at a rate of 13.6 +/- 4.5 ml/hour initially and decreases gradually during first 48 hours after last dose administration [28].

Fig 1: Famous Liquid breathing mouse photograph by Dr. Leland Clark

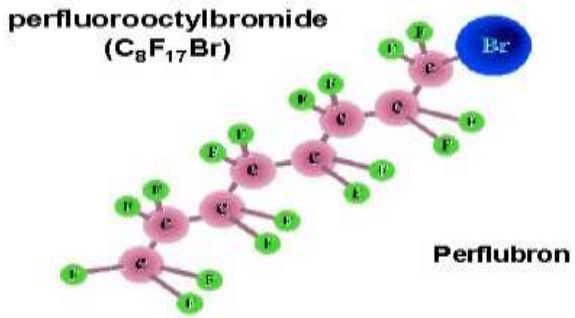

Fig 2: Structural formula of perfluro-octyl bromide (perflubron). Molecular weight = 499. Alliance Pharmaceutical Corp has launched this liquid with the name of "Liqui Vent" also available with the name of "Fluro Vent"

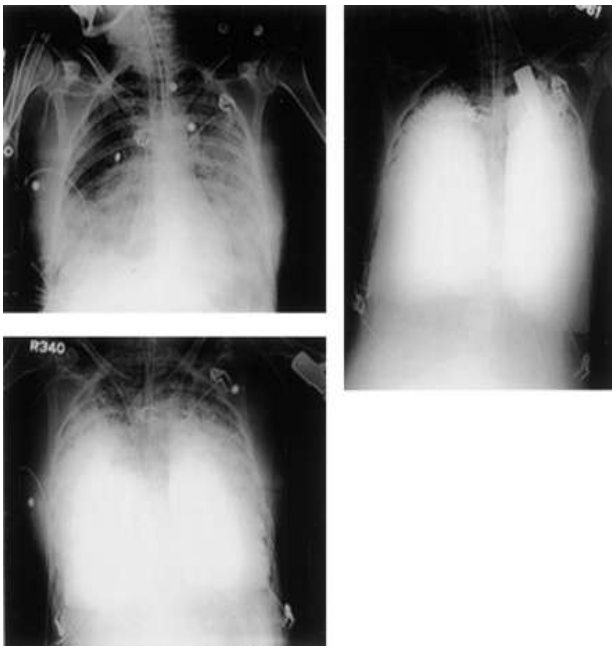

Fig 3: Chest radiographs of a 36 years old woman who developed ARDS after pancreatitis

Spontaneous Breathing and PLV

Although not tested in humans but studies are being done where animals are made to breath spontaneously after tracheal infiltration of PFCs. It has been concluded that spontaneous breathing is not only possible but also gives better haemodynamic status as compared to mechanical ventilation (31,32).

Use of PLV as Drug Delivery Vehicle

Perfluorocarbon liquids can be novel agents to deliver drugs into the diseased lungs because the maximum concentration of drug would reach at the site where it has to act and would give minimum systemic effects. PFCs due to their excellent physical properties (discussed above) have the ability to reach almost every portion of the diseased lung which aerosols can not and only a few drugs can be given through aerosols. Therapeutically useful concentrations of a large variety of drugs e.g. bronchodilators, exogenous surfactants, antibiotics, antioxidants, steroids, chemotherapeutic agents can be delivered directly into the lungs thereby protecting non targeted organs from pharmaceutical side effects [11]. PFCs could be particularly useful in delivering short lived agents such as adenosine, adenosine triphosphate and nitric oxide [11].

CONCLUSION

Review of literature very clearly indicates that liquid ventilation is a new, upcoming, and effective ventilatory strategy for management of problem cases which are difficult to manage with conventional ventilation. Partial liquid ventilation is an excellent new addition in the armamentarium of respiratory therapists and it is here to stay. Use of this technique as drug delivery vehicle will be an added advantage.

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