TOTAL AND PARTIAL LIQUID VENTILATION USING PERFLUOROCARBONS

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Introduction

The possibilities of using liquid instead of air in the exchange of gases have always fascinated researchers. The first studied liquid was saline solution which appeared to be unsuitable for transporting gases in normobaria. Its capacity to dissolve oxygen is low, and its viscosity and density are high as compared with air. Moreover, the introduction of saline into the lung can remove alveolar surfactant, worsening lung mechanics. Subsequently different liquids have been studied, such as silicon and animal and mineral oils, but all of these substances have proved to be too toxic for clinical use.

The possibility to effectuate gas exchange using a liquid instead of air became reality with the discovery of the properties of perfluorocarbon (PFC) liquids when in 1963 Clark and Gollan demonstrated the possibility of survival of mice, cats and newborn puppies immersing them in oxygenated PFC. A fluorocrbon product known as FX-80, manufactured by the 3M Company was the most widely used of the available fluids. Others, such as Caroxin.D, Rimar 101 and Perflubron were also found suitable. In general, the class of fluids known as PFCs have proved most promising based on their ability to dissolve large quantities of respiratory gases, as well as their chemical and biological inertness.

In 1970 Moskowitz presented a demand-regulated ventilator that used PFC instead of gas to obtain gas exchange. This device, refined in cooperation with Shaffer et al., established the tidal volume and the respiratory rate appropriate for gas exchange in animals.

In 1991 Fuhrman et al. and Lachmann et al. presented a new method of using PFC functional residual capacity (FRC) during conventional mechanical ventilation (perfluorocarbon associated gas exchange - PAGE). In 1993, Richmond et al., also showed improvements in gas exchange and compliance with PFC liquids in an acute lung injury model using a simple PFC lavage technique. These latter techniques considerably simplified the method and contributed to wider use in clinics.

Characteristics of Perfluorocarbons

PFC are derived from common organic compounds, such as benzene, by replacing all the carbon-bound hydrogen atoms with fluorine atoms, by agitating the organic compound with cobalt trifluoride, and through the use of electrochemical fluorination techniques.

PFCs are clear, colourless and odourless, and can be stored indefinitely at room temperature. They are inert, non toxic, biocompatible and resistant to autoclaving. They are insoluble in water or in lipids and water or lipids do not dissolve in them. Their electric strengths and resistivities are high and they are denser than water and soft tissue, with low surface tension and generally low viscosities. PFCs transmit sound at lower speeds than any other liquids and they have string

affinities for gases. Oxygen, carbon dioxide and many other gases are very easily dissolved in them. Compare with water, they can dissolve as much as 20 times the amount of oxygen and more than three times as much carbon dioxide. All PFCs have a low surface tension.

PFCs spontaneously evaporate from the lung and the skin. The mechanisms for uptake, distribution and elimination in the body are not clearly defined but are correlated to lipid tissue composition, organ perfusion and ventilation-perfusion ratio in the lung. The physiochemical characteristics of the PFC, i.e. molecular structure and vapour pressure, and lung pathophysiology play an important role. Small quantities of PFC can be absorbed in the blood and distributed to the tissues with preference for lipids and fats. The PFC absorbed can remain in the tissues for long periods but does not seem to exert any toxic effects. The persistence in the body and the predilection for fatty tissue warrants further investigation, particularly with respect to the developing central nervous system of neonates and premature babies.

At present Perflubron (perfluoroctylbromide: Alliance Pharmaceutical Co.) is accepted by American FDA and is used in clinical trials in North America and Europe, for adults with acute lung injury. RIMAR 101, perfluorochemical liquid, from Miteni- Mitsubishi, Italy, has been longer and more widely studied in animals and in specific clinical situations (compassionate use cases).

There are a number of PFCs in clinical use. Properties of selected PFCs are compared with water below.

	Water	Rimar 101*	Perflubron**	FC77***
Boiling point (°C)	100	101	143	97
Density at 25°C (g/ml)	1.00	1.77	1.93	1.75
Kinematic Viscosity (centistokes at 25°C)	1.00	0.82	1.10	0.66
Vapor pressure (mm Hg at 37°C)	47	64	11	75
Surface tension	72	15	18	14
O_2 solubility at 37°C (ml gas/ 100 ml liquid)	3	52	53	56
CO_2 solubility at 37°C (ml gas / 100 ml liquid)	57	160	210	198

* Rimar 101 from Mitsubishi, Milano, Italy
** Perfluoroctylbromide (Perflubron) from Alliance Pharm, Corporation, San Diego, California, USA.
*** FC77 from 3M Corporation, St. Paul, Minnesota, USA.

The development of applications of liquid ventilation

The first use of oxygenated PFC was for total body immersion but subsequently it was used in bronchoalveolar lavage in order to maintain gas exchange during the manoeuvre and remove foreign material from the lungs. A significant advance in the application of liquid ventilation was the introduction and elimination of liquid from the lung by gravity, by lying the subject in a suitable position.

The design of the demand-regulated ventilator by Moskowitz in 1970 and its subsequent simplification by Shaffer (Mechanically Assisted Ventilator) has led to more widespread clinical use of PFCs. The techiques allowed the functions of the experimental animal to control the cycling of the respirator that circulated oxygenated liquid to and from the lungs. That method established tidal-volume and breathing frequency requirements and at the same time reduced breathing effort by providing mechanical assistance.

A combined ventilation method, liquid ventilation/gas ventilation, has been described by Lachmann et al. as partial liquid ventilation (PLV) or perfluorocarbon-associated gas exchange (PAGE) by Fuhrman et al. and is carried out by filling and maintaining the lung with functional residual capacity of PFC while conventional gas ventilation is performed. In this technique of using liquid as a respiratory medium, it has been proposed that the residual lung liquid is oxygenated and carbon dioxide is exchanged in the lung by means of gas movement provided by the conventional gas ventilator.

Physiological processes
CO_2 elimination
The low CO_2 diffusion coefficient and increased viscosity and density of PFCS slow alveolar diffusion and expiratory flow rates, thus impeding CO_2 elimination. Carbon dioxide elimination is linked to the persistence of the PFC in the lung and dead space. Whilst PFC readily absorbs CO_2, it does not allow its rapid diffusion. PFC is highly viscous and dense and thus a very low frequency ventilatory rate is necessary during TLV. Unsuitable ventilatory rate can lead to an accumulation of CO_2 and in turn respiratory acidosis. At low frequencies CO_2 clearance is reduced because of inadequate alveolar ventilation and at high frequencies CO_2 clearance is reduced because of inadequate diffusion time. Adjustments of tidal volume during steady state ventilation can be made to keep $PaCO_2$ values within the normal physiological range, provided the frequency is low enough. During TLV, the most effective alveolar ventilation and CO_2 elimination occurs at frequencies of 3-5 breaths per minute in animals, whilst in humans the most effective rate appears to be 4-5 breaths per minute.

Adequate oxygenation
Liquid ventilation apperas to be very effective in improving oxygenation. During TLV, adequate oxygenation is achieved by manipulations of the FiO_2 of the inspired liquid and by maintaining an adequate functional residual capacity (FRC) by altering inspiratory and expiratory volumes and PEEP level.

Pulmonary perfusion
Unlike the gas-filled lung, in which alveolar pressures are uniform and vascular pressures are subject to a hydrostatic gradient, the liquid-filled lung has transmural gradients that are relatively balanced. This result in uniformly distended pulmonary blood vessels and evenly distributed blood flow, thus improving ventilation-perfusion matching. The haemodynamic disturbances during PLV

are less evident than during TLV. These changes can be overcome by increasing the perfusion pressure by colloid administration.

At present, there are two methods of administration of PFCs: Total Liquid Ventilation (TLV) and Partial Liquid Ventilation (PLV) or Perfluorocarbon Associated Gas Exchange (PAGE).

Total Liquid Ventilation (TLV)
TLV is a ventilatory technique employing PFCs instead of gas to obtain gas exchange. It requires complex equipment (pump, membrane oxygenator, CO_2 removal, etc.) and is applied after a short period of partial liquid ventilation. The lungs are gradually filled with warmed oxygenated PFC. A volume of 30 ml/kg of PFC is introduced and further quantities are administered until the lung has been completely filled. As soon as the air has been completely expelled, the patient is connected to a ventilator (similar to a dialysis pump). Tidal volume is subsequently set at 15-20 ml/kg of PFC. Respiratory rate is regulated to 4-5 breaths per minute. The maximum inspiratory peak pressure is 30 cm H_2O but a pressure of between 15 and 20 cmH_2O is usually sufficient. The negative pressure required during the expiratory phase ranges from ⁻15 to ⁻30 cm H_2O. At the end of the treatment conventional artificial ventilation can be continued until the PFC has evaporated from the lung.

Partial Liquid Ventilation (PLV)
PLV is a ventilatory technique employing PFCs to fill the functional residual capacity (FRC) of the lungs whilst gas tidal volumes are delivered by a conventional volume-regulated ventilator. A volume of 30 ml/kg of PFC is introduced in order to partially or fully replace the functional residual capacity. A further 10 ml/kg of PFC is added every hour to replace redistribution or evaporative losses.

Indications for liquid ventilation and results of the first clinical trial on ARDS

It has been supposed that liquid ventilation eliminates the air-liquid interface and reduces surface tension. For this reason it has been tested in Respiratory Distress Syndrome (RDS) in premature babies and Acute Respiratory Distress Syndrome (ARDS) in children and adults.

Preliminary clinical trials on newborns and children were interrupted due to incorrect protocol of treatment and disappointing initial results. A clinical trial conducted in the United States and Europe, involving 56 Centres, on 311 adult patients affected by ARDS from different origins was disappointing on the beneficial effects of PLV versus conventional ventilation. Two different dosages of PFC were tested. Mortality was higher in patients treated with PLV. Moreover, severe hypoxemia developed in presence of inhomogeneous lung pathology due to the compression of pathologic areas and normal areated lung units. The incidence of pneumothorax was higher and return to conventional ventilation was more difficult than previously supposed. However, the PFC used was demonstrated to be safe.

Even though the results on ARDS were disappointing, other fields of research remain open and are being thoroughly investigated. For example, it may be probably useful in meconium aspiration and inhalation syndromes where it facilitates the removal of the meconium or other material present in the lung, supports gas exchanges and eliminates dishomogeneous lung ventilation. Should the afore-mentioned be confirmed, future applications could be in the treatment of cystic fibrosis and proteinosis. In both cases PFC could remove the material present in the lungs, improve gas exchange, reduce the tendency to atelectasis and prevent the loss of surface activity.

Liquid ventilation is also investigated for the study of the lung structure, in radiology, for topical administration of drugs e.g. antibiotics and chemotherapics, heating pulmonary lobi to increase

haematic flow in the treatment of lung cancer and as a ventilatory support for unusual types of treatment.

Several problems remain to be solved:
- the safety of liquid ventilation over prolonged periods of time and return to conventional gas ventilation;
- the haemodynamic effects in the presence of pulmonary hypertension;
- the significant degree of lactic acidosis and the increase in hypoxemia in inhomogeneous lung pathology;
- the uptake and metabolism of PFC with regard to damage from long term persistence in the tissues.

Liquid ventilation in its various possible applications is a fascinating and stimulating area requiring further study. In order to avoid disappointment following the initial enthusiasm, widespread clinical trials must confirm its applicability and positive results in humans.

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