Liquid lung ventilation as an alternative ventilatory support

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The concept of liquid ventilation has evolved in recent years into the concept of partial liquid ventilation. In this technique, conventional mechanical ventilation is combined with intratracheal perfluorocarbon administration. Partial liquid ventilation is a promising technique for improving gas exchange during mechanical ventilation in neonatal and acute respiratory distress syndrome. The initial data showed no adverse effects on the cardiovascular system, and histological studies demonstrated that perfluorocarbons minimize or prevent the progress of lung injury in animals. Partial liquid ventilation is currently in use in human trials, and in this review we describe the principles of the technique and recently available data of its application.

Introduction

Laplace, a French mathematician (1749–1827), was the first to draw attention to surface active forces in general, and described the relationship between force, surface tension, and radius of an air–liquid interface of a bubble:

$$P = 2\gamma/r$$

(P = pressure to stabilize a bubble; γ = surface tension at air–liquid interface; and r = radius of a bubble). Almost a century later, von Neergaard [1] applied this law to pulmonary alveoli by demonstrating that the pressures required to expand an air-filled lung were almost three times that required to distend a lung filled with fluid. In this way the surface tension effect at the air–liquid boundary was eliminated [1] (Fig. 1). From these findings, he concluded that: (1) two-thirds of the retractive forces in the lung are caused by surface tension phenomena, which act at the air–liquid interface of the alveoli; and (2) the surface tension at the air–liquid interface must be reduced by the presence of a surface active material with a low surface tension to allow normal breathing.

It was not until 1959 that von Neergaard's findings became clinically relevant, when Avery and Mead [2] published direct evidence linking absence of the surface active material to the appearance of stiff lungs in newly born premature babies with respiratory distress syndrome (RDS). This surface active material is called pulmonary surfactant, which is a complex of phospholipids and at least four specific surfactant proteins (SP-A, SP-B, SP-C, and SP-D). Pulmonary surfactant is synthesized and secreted from the alveolar type II cells and lies as a monolayer at the air–liquid interface to reduce the surface tension in the lung. In neonatal RDS and in
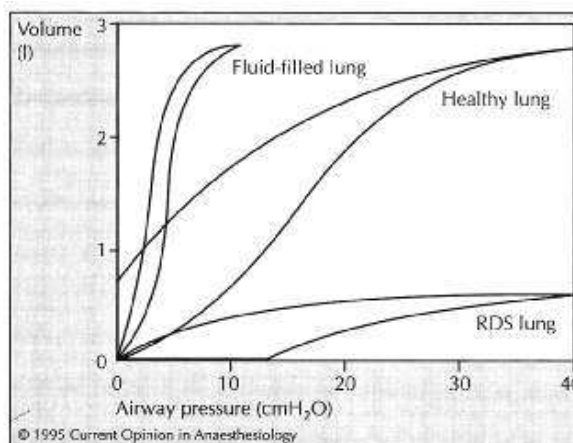

Fig. 1. Pressure–volume diagram of a normal air-filled lung and a lung with respiratory distress syndrome (RDS). Von Neergaard [1] showed in 1929 that much larger pressures were required to expand an air-filled lung than a lung filled with fluid. In RDS even higher pressures are required to expand the lung because of the high surface tension at the air–liquid interface in the alveoli, caused by a diminished surfactant system.

adults with acute RDS (ARDS), both characterized by a diminished surfactant system, there is always a limited response to conventional mechanical ventilation in improving gas exchange. Therefore, in 1976 Shaffer et al. [3] eliminated the elevated surface forces at the air–liquid interface in stiff lungs by filling them with perfluorocarbons, which are known to decrease surface tension and have the ability to dissolve high amounts of oxygen. Since then, perfluorocarbons have been investigated intensively as an alternative means of respiratory support [4].

Abbreviations

ARDS—acute respiratory distress syndrome; $PaCO_2$—arterial carbon dioxide tension; PEEP—positive end-expiratory pressure; PLV—partial liquid ventilation; RDS—respiratory distress syndrome.

This alternative respiratory support was originally performed by totally filling the lungs with perfluorocarbon using a modified ventilator that oxygenates the perfluorocarbon extracorporeally; this was called total liquid ventilation. This technology is not encouraging as it requires sophisticated equipment; thus the search began for a simpler technique of liquid ventilation to support pulmonary gas exchange.

Fuhrman et al. [5] were the first to demonstrate the feasibility of applying perfluorocarbons in healthy animals without the need for a specialized liquid breathing system, and our group was the first to apply this technique in an animal model of acute respiratory failure. In this technique the lung is filled with perfluorocarbon to a volume equaling the functional residual capacity maximally, followed by conventional mechanical gas ventilation. This technique is now called partial liquid ventilation (PLV). In this review the principles of PLV and recently available data are described.

Perfluorocarbons

The physical properties that make perfluorocarbon fluids suitable for liquid ventilation are their low surface tension and their ability to dissolve high amounts of oxygen and carbon dioxide (Table 1). The total amount of oxygen solved in perfluorocarbons is about three times as much as the same amount of blood can chemically bind. Perfluorocarbons are colorless, clear and odorless liquids with a high density. They are chemically very stable, biologically inert liquids, and cannot be metabolized in biological systems because of the strong bond present between carbon and fluorine atoms. Perfluorocarbons can be derived from simple organic compounds (such as benzene) and can be produced in large quantities.

Table 1. Physical properties of some perfluorocarbon liquids.

	Perflubron	FC-77	RM-101
Density (g/ml)	1.92	1.75	1.77
Vapor pressure (mmHg at 37°C)	10.5	75	64
Surface tension (dyn/cm)	18	14	15
O_2 solubility (ml/100 ml)	53	56	52
CO_2 solubility (ml/100 ml)	210	198	160

Animal experiments with partial liquid ventilation

Fuhrman et al. [5] demonstrated that it was possible to instil perfluorocarbons (30 ml/kg) in healthy piglets during mechanical ventilation without deterioration of gas exchange. The adequate gas exchange was achieved at tidal volumes and airway pressures similar to mechanically gas-ventilated animals, suggesting that the presence

of perfluorocarbon did not alter the mechanical function of the lung during the use of this technique. After these experiments our group applied this concept to acute respiratory failure in surfactant-depleted animals. To determine the optimal dose of perfluorocarbon in acute respiratory failure, we treated lung-lavaged rabbits with five incremental doses of 3 ml/kg body weight perfluorocarbon in 15 min steps up to a total volume of 15 ml/kg body weight [6]. The animals were ventilated in a volume-controlled mode with 6 cmH2O positive end-expiratory pressure (PEEP). All animals survived the experiment conducted over a period of 80 min. Arterial oxygen tension in the perfluorocarbon-treated animals improved significantly with each subsequent dose of perfluorocarbon to values that did not significantly differ from the pre-lavage values. Arterial carbon dioxide tension ($PaCO_2$) and peak airway pressures decreased significantly after instillation of 3 ml/kg perfluorocarbon and remained stable with subsequent treatment doses. These data clearly showed that oxygenation improved dose-dependently, in contrast to lung mechanics that showed improvement after only a single, low dose of perfluorocarbon [6].

To see if these effects were longer lasting, we conducted 180-min experiments with PLV under the same experimental conditions [7]. Oxygenation was restored to an almost 'healthy' state immediately after instillation of perfluorocarbon, and remained stable. Alveolar ventilation and $PaCO_2$ could be kept at a constant level in the perfluorocarbon group. Moreover, the perfluorocarbon-treated animals showed a persistent and significant decrease in peak and mean airway pressure compared with post-lavage data, and respiratory system compliance improved. More importantly, these improvements occurred without significant changes in mean arterial pressure, heart rate, or central venous pressure. Additionally, microscopic examination of the lungs from perfluorocarbon-treated animals did not reveal any morphological abnormalities, whereas the lungs of the conventionally ventilated group showed atelectasis, hyaline membranes, and overdistension and rupture of alveoli.

On the basis of these results we were interested in investigating the effect of a longer ventilation period (360 min) on the one hand, and of incremental doses of perfluorocarbon on the other. Therefore, the effect of incremental doses of intratracheal perfluorocarbon in lung-lavaged rabbits was studied over time [8]. Oxygenation showed a time- and dose-dependency in such a way that deterioration of oxygenation was faster in those animals which received less perfluorocarbon. The relationship between the dose of perfluorocarbon administered and the time at which impairment of lung function was seen, strongly supports the suggestion that during PLV, evaporation of perfluorocarbon over time would cause the affected alveoli to collapse and, therefore, limit the efficacy of pulmonary gas exchange that would occur earlier with small doses of perfluorocarbon.

In the same study [8] we adressed the issue on how much perfluorocarbons can be applied in PLV without causing adverse effects on peak inspiratory pressure. It was shown that at doses of perfluorocarbon exceeding 25 ml/kg, gas ventilation with constant tidal volume resulted in higher peak airway pressures than during convenventional gas ventilation. This effect was attributed to tissue elasticity becoming the predominant component of alveolar retractive forces [6–8].

The above-mentioned studies were conducted in rabbits with a small thoracic diameter. Because perfluorocarbon has a high specific gravity, we hypothesized that it could lead to haemodynamic compression in which it might block pulmonary capillary perfusion in the lower parts of the lung of an adult person with a large thoracic diameter. The dose-related effect of perfluorocarbon administration on haemodynamics and gas exchange was, therefore, investigated in lung-lavaged pigs with a thoracic diameter of 24 cm and a body weight of 50 kg [9]. It was found that increasing doses of perfluorocarbon have no deleterious effect on any haemodynamic parameter. After administering 5 ml/kg perfluorocarbon, mean pulmonary artery pressure decreased and was unaffected by further perfluorocarbon administration. This can be explained by the effect of abolishment of hypoxic pulmonary vasoconstriction on mean pulmonary artery pressure, which may be the main cause of pulmonary hypertension.

The beneficial effects of PLV were shown not to be solely related to the broncheo–alveolar lavage model, but were also confirmed in other clinically more relevant animal models of respiratory insufficiency: an oleic acid model [10], a gastric aspiration model [11••], a premature lamb model [12], and near-term baboons [13]. Curtis *et al.* [10] conducted PLV in dogs in whom respiratory failure was induced by oleic acid injury. They confirmed that with increasing doses of perfluorocarbon below a volume equal to the functional residual capacity, oxygenation improved dose-dependently, and there was an increase in static compliance with no impairment in carbon dioxide elimination. Adverse haemodynamic consequences were not found to be associated with PLV. However, when compared with controls, perfluorocarbon could not lessen lung injury, in terms of lung histology, when given before or after oleic acid injury.

Recently, Nesti *et al.* [11••] conducted PLV in a piglet model of gastric aspiration at volume-controlled ventilation and compared the results with a control group. Perfluorocarbon was instilled 1 h after acid instillation. Oxygenation with perfluorocarbon improved and became significantly better from 2.5 to 6 h after injury, whereas $PaCO_2$ did not differ from the control group. Peak inspiratory pressure during fixed volume ventilation did not differ significantly between groups, but static end-inspiratory pressure and compliance were consistently improved after 3 h in the PLV group. Moreover, there was no histological evidence for ARDS in the perfluorocarbon-treated group, as opposed to the

control group. The improvements were found during the second inflammatory phase and not during the initial phase of injury. These data suggest that PLV with perfluorocarbon might prevent ARDS after aspiration if instituted in the period before the acute inflammatory process is manifest [11••].

A common problem in RDS is the high lung vascular permeability in the setting of respiratory failure. Recent preliminary results from the study by Colton *et al.* [14] showed that the increased lung vascular permeability to ^{125}I-bovine serum albumin in rats, in which lung injury was induced by cobra venom factor, could be almost prevented when the lungs were filled with perfluorocarbon before lung injury was induced. Their study [14] supports a protective effect of perfluorocarbon in the setting of lung injury.

PLV was also shown to be beneficial in animal models of neonatal RDS. Leach *et al.* [12] reported PLV (30 ml/kg perfluorocarbon) in pre-term lambs. Arterial oxygen tension increased fourfold and was sustained for 1 h. $PaCO_2$ progressively decreased and dynamic compliance improved threefold within 15 min. Sekins *et al.* [13] were able to apply PLV in three near-term baboons for 4–5 days; two baboons were born with normal lung function and the third developed respiratory distress before PLV. The authors managed to reconvert the animals from PLV to mechanical gas breathing on day 5 without complications arising.

Clinical trials with partial liquid ventilation

After these positive results in animal experiments, PLV is currently being used in human trials in neonates and adults with RDS. Leach *et al.* [15] reported a pilot safety and efficacy study in seven premature newborns with RDS who failed to respond to conventional therapy and exogeneous surfactant treatment. All patients showed improved arterial oxygen tension, and five out of seven patients showed improved $PaCO_2$ and lung compliance. In two infants who became hypercapnic, high-frequency ventilation was resumed. No serious adverse effects were found to be associated with PLV, and three of the patients survived [15]. Hirschl *et al.* [16] conducted PLV in nine adult patients with acute respiratory failure on extracorporeal life support. They found a decreased mean pulmonary shunt fraction and an increased compliance. Six patients were successfully weaned from extracorporeal life support, and five survived to be discharged without showing evidence of adverse effects. Pneumothorax, possibly related to PLV, was observed in one patient.

Mechanisms of partial liquid ventilation in the lung

The hypothetical mechanism of PLV is explained in Figure 2. Figure 2(a) shows the atelectatic RDS lung; after a small dose of perfluorocarbon (3 ml/kg), a thin film of perfluorocarbon with a low surface

tension is formed at the air–liquid interface, because of evaporation of perfluorocarbon [Fig. 2(b)], and covers the lung units of the whole lung. This film causes the increased surface tension in the diseased lung to be reduced to a low and constant value, which in turn leads to improved compliance (which does not further improve with additional doses of perfluorocarbon). The dose-dependent improvement in oxygenation may be caused by the filling of the most dependent alveoli with perfluorocarbon: the more the perfluorocarbons applied, the more the collapsed atelectatic alveoli can be opened by the non-compressible, high-density perfluorocarbon, and prevented from end-expiratory collapse [Fig. 2(b) versus 2(c)] thus eliminating intrapulmonary shunt. This mechanism was supported recently by computed tomographic scans from Quintel *et al.* [17] who showed that during PLV, perfluorocarbon distributed predominantly to the lower lung regions, whereas gas distributed to the upper lung regions. Moreover, in the basal liquid-filled areas, the low-surface-tension perfluorocarbon allows formation of air bubbles with the superimposed tidal gas volumes, and gas diffusion from perfluorocarbon to alveolar vessels contributes to effective gas exchange.

Surfactant normally present in the lung has the unique property of lowering surface tension at the air–liquid interface in parallel with the decrease in alveolar radius, thus keeping the ratio of γ/R constant and guaranteeing expiratory alveolar stability at low pressures. Perfluoro-carbons do not have this property, and when the alveoli are not fully filled with perfluorocarbon (in contrast to total liquid ventilation), end-expiratory collapse can occur in these alveoli during exhalation if the applied PEEP is not high enough to prevent end-expiratory collapse. In addition to preventing non-fluid-filled alveoli from end-expiratory collapse, a certain amount of PEEP is also necessary to prevent the bulk movement of the fluid being present in the alveoli when instituting the next inspiration. This fluid movement would lead to high peak pressures during PLV [6]. PEEP prevents this

movement by pressing the fluid distally, keeping it in the alveoli.

Limitations and possible adverse effects of partial liquid ventilation

All the animal studies discussed in this review were performed at an inspired oxygen fraction of 1.0. However, because of possible direct toxic effects of high inspiratory oxygen concentrations to the lung, it should also be possible for PLV to provide acceptable gas exchange at lower inspiratory oxygen concentrations. Hernan *et al.* [18•] recently addressed this issue in healthy piglets. They recorded gas exchange, lung mechanics, and haemodynamics at different inspired oxygen fraction during continuous positive-pressure breathing followed by the same measurements during PLV. They found arterial desaturation at an inspired oxygen fraction below 0.5 during PLV. These results show that when applying PLV, inspired oxygen concentrations of 50% or higher are necessary to achieve full arterial saturation [18•].

When perfluorcarbons are allowed to evaporate from the lungs after PLV, pulmonary function must remain normal. Salman *et al.* [19••] studied gas exchange and lung mechanics for 24 h during PLV in healthy piglets in which perfluorocarbon was not replaced in the last 22 h, and compared the results with those of a group ventilated for 24 h with PLV in which evaporative losses were replaced. They demonstrated that despite the normal preservation of lung histology at 24 h after perfluorocarbon administration, an adequate level of oxygenation could only be maintained at the cost of an increase in the level of PEEP in the group in which perfluorocarbon was allowed to evaporate. This study demonstrates that atelectasis does occur during return to conventional positive pressure breathing after PLV [19••].

One could speculate that this atelectasis can be attributed to an interaction of perfluorocarbons with the pul-
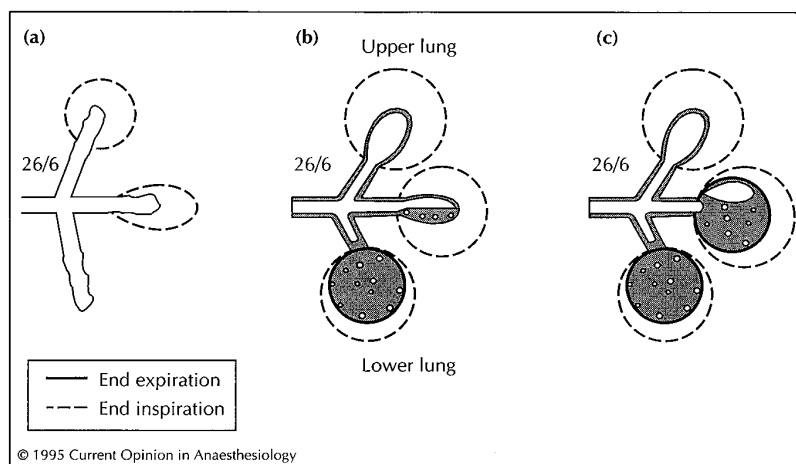

Fig. 2. The lining of the air–liquid barrier in the alveoli and the dose-dependent improvement in oxygenation. (a) the atelectatic respiratory distress sydrome lung; (b) the partially perfluorocarbon-filled lung; and (c) the effect of instilling additional perfluorocarbon. (See text for details.)

monary surfactant system. This was confirmed by a study [20] in which we investigated clearance of the radioactive tracer ^{99m}Tc-diethyl triamine pentaacetic acid in healthy rabbits after 3 h of PLV. Clearance of the tracer was found to be increased, compared with rabbits treated with mechanical ventilation only, using the same ventilatory parameters. Increased clearance of the tracer was previously shown [21] to be a sensitive indicator of changes in the lung surfactant system. It was found that clearance of the tracer increased after PLV [20]. We speculate that the increased surface tension at the alveolar–air interface in the expiratory phase in the perfluorocarbon-treated animals might have contributed the the increased clearance rate of the radioactive tracer. These data indicate an interaction of perfluorocarbons with the pulmonary surfactant system.

To investigate whether this interaction with the pulmonary surfactant system is a long-lasting effect, we exposed healthy rabbits to 3 h of PLV with 12 ml/kg body weight perfluorocarbon [22]. After 7 days the rabbits were anesthetized again and gas exchange and respiratory parameters were measured, including peak and mean airway pressures; none of the measured parameters showed a change. This indicates that the changes in the pulmomary surfactant system after PLV can be overcome in healthy rabbits [22]. The exact mechanism and effect of perfluorocarbon on the pulmonary surfactant system remains to be elucidated.

When administered into the lung, systemic absorption and distribution of perfluorocarbon to other tissues have been demonstrated [23–25]. Measurements in expired gases have indicated a rapid elimination of perfluorocarbon through the lung and possibly, to a lesser extent, via transpiration through the skin [26]. Much of the research on side effects has concentrated on intravenously administered perfluorocarbons which are phagocytosed by the macrophages of the reticuloendothelial system; these side effects are also shown when perfluorocarbon is administered intratracheally [13]. Phagocytosis leads to characteristic predictable and reversible biological effects that are a consequence of a normal host-defense mechanism [27]. Although these effects are reversible and do not seem to pose an acute toxicological risk at clinically relevant doses, studies on the long-term effects of perfluorocarbon administration are required.

Conclusion

When compared with total liquid ventilation, the technique of PLV has certain advantages, which include the lower priming volumes and use of conventional gas ventilators without the need for extra technical requirements. Perfluorocarbon is readily available and there are no problems with distribution of this material in the lung. However, no clinical data are available on the long-term outcome after its use in humans, and its effects on the pulmonary surfactant system are not yet fully elucidated. Clinical studies have been started, but

data have to be evaluated first before perfluorocarbon can be applied as a routine therapy in neonatal RDS and ARDS.

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