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Annotation

Liquid ventilation

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Abstract: Research on using liquid ventilation to provide artificial respiration in mammals has been ongoing since the 1960s. The development of inert perfluorocarbon (PFC) liquids with high oxygen and carbon dioxide solubility has made gas exchange with liquid ventilation possible. In 1991 the technique of partial liquid ventilation was introduced where PFC are instilled into the lungs whilst continuing with conventional mechanical ventilation. Partial liquid ventilation has been shown to improve gas exchange and lung function with decreased secondary lung injury, in animal models of acute lung injury and surfactant deficiency. It has been used in uncontrolled trials in preterm neonates, and preliminary results are available from a randomized controlled trial of partial liquid ventilation in paediatric acute respiratory distress syndrome. Perfluorocarbons can also be used to deliver drugs to the lungs, to lavage inflammatory exudate and debris from the lungs, and as an intrapulmonary X-ray contrast medium. Many questions about partial liquid ventilation remain unanswered particularly with regard to the dose of PFC required, its ideal method of administration and the long-term effects. Partial liquid ventilation promises to be an exciting new therapy for infants and children with a variety of respiratory problems. The technique requires ongoing research and experimentation.

Key words: fluorocarbons; partial liquid ventilation; respiration, artificial; respiratory distress syndrome; respiratory insufficiency.

BACKGROUND

Respiration is the process by which vertebrates acquire oxygen (O_2) and rid themselves of carbon dioxide (CO_2). Mammals do this at the air/liquid interface in the lungs. Some vertebrates, from lower on the evolutionary ladder (e.g. fish), do it across a liquid/liquid interface. Thus making the concept of liquid ventilation a very ancient one.

The achievement of artificial respiration by liquid ventilation in mammals was first tried in mice in the 1960s with salt solutions under hyperbaric conditions.[1] Further experiments in the 1960s showed the successful use of fluorocarbons at atmospheric pressure for liquid ventilation in cats and mice.[2] Initial experiments with perfluorocarbons (PFC) were performed with spontaneously breathing animals immersed in PFC or with gravity assisted tidal bulk flow of PFC. These techniques were unsuccessful at removing enough CO_2.[3–5] In the 1970s and 1980s the development of time-cycled, pressure-limited mechanical ventilators allowed the development of the technique of total liquid ventilation (TLV).[6] Total liquid ventilation can be used to maintain adequate gas exchange in animals.[7] It has also been shown to improve gas exchange and lung function in animal models of respiratory distress.[8–11] In 1991, Fuhrman *et al.*[12] introduced the technique of using functional residual capacity (FRC) volumes of PFC with conventional gas ventilation – PFC associated gas exchange (PAGE). This technique has become known as partial liquid ventilation (PLV) and it is this technique which has the most promise for practical clinical application.

Perfluorocarbon liquids are a group of chemicals derived from the fluorination of organic compounds such as benzene. They are colourless, odourless liquids and are chemically and biologically inert. Perfluorocarbons are insoluble in water and almost insoluble in lipid. They are more dense than water and soft tissue, and they can dissolve more than 20 times the amount of O_2, and three times the amount of CO_2, than water. They have a low viscosity and surface tension, and most will evaporate faster than water.[13,14] The physical properties of some PFC liquids used for PLV are summarized in Table 1.

PARTIAL LIQUID VENTILATION

Animal studies

Various models of lung injury and surfactant deficiency have shown the benefits of using PLV with conventional mechanical ventilation (CMV) compared to control animals (dogs, rabbits, lambs and pigs). Many animal studies have shown improvement in oxygenation, CO_2 removal and lung compliance.[15–21] It has also been shown to be more effective than surfactant alone in a premature lamb model of respiratory distress syndrome.[19] Studies that looked at lung histology have shown significantly less damage in lungs after PLV.[16,17] The need for lower peak inspiratory pressures to achieve adequate tidal volumes has been demonstrated.[15] PLV has been shown to

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Table 1 Physical properties of some perfluorocarbons compared with saline

	Saline	FC-77	Rimar	Perflubron	APF-140
Density (g/mL)*	1.0	1.78	1.78	1.93	1.95
Kinematic viscosity (centistokes)*	1.0	0.8	0.82	1.10	2.90
Vapour pressure (mmHg)†	47	85	63	11	14
Surface tension (dynes/cm)*	72	15	15	18	15
O_2 solubility (ml/100 mL)*	3.0	50	52	53	49
CO_2 solubility (ml/100 mL)†	57	198	160	210	140

* 25°C; †37°C.

decrease intrapulmonary shunting.[22] In all animal studies haemodynamic stability of PLV animals has been demonstrated to be equal to control animals.[15–22] Partial liquid ventilation has been shown to have increased improvement on oxygenation when combined with nitric oxide in pulmonary hypertension in piglets.[22]

Whilst most of these studies have demonstrated benefits of PLV over only a few hours, two studies have demonstrated the feasibility of longer periods of PLV. Neonatal piglets with normal lungs ventilated for 24 h had stable ventilation and similar blood gases compared with controls and no haemodynamic deterioration was noted in either group.[23] A recent study in newborn piglets with surfactant deficiency demonstrated improvement in oxygenation and lung histology with up to 20 h PLV.[16]

The technique has also been used with high frequency ventilation (HFV). Animal studies investigating the effects of PLV with HFV have shown the technique provides good gas exchange.[16,24–27] Only two of the studies directly compared a HFV-PLV group with a HFV alone control group.[16,24] Baden *et al.*[24] showed that the addition of PLV to HFV gave an immediate improvement in oxygenation but this was no different to the HFV alone group after 2 h. They used a maximal alveolar recruitment strategy during the treatment phase with 15 s, 30 cmH_2O sigh breaths every 60 min in both groups. Sukumar *et al.*[27] showed improved gas exchange and pulmonary blood flow with HFV-PLV. A mean airway pressure of 15 cmH_2O was maintained throughout without the addition of sigh breaths. Smith *et al.*,[26] comparing various methods of HFV-PLV, showed that those forms of HFV which allow volume recruiting manoeuvres, such as the addition of intermittent conventional breaths, gave superior gas exchange. It seems that, with the use of strategies aimed at maximal alveolar recruitment, HFV-PLV may not confer any additional benefit over HFV alone.

Most of the PFC instilled into the lungs evaporates into the expired air.[14] Since PFC is insoluble in water, all the PFC in blood or tissue is dissolved in lipid. Small amounts of PFC are detected in the blood of liquid-ventilated animals.[28] Uptake of PFC by other tissues is dependent on its blood flow and fat content, with highest levels (apart from the lungs) found in fat, brain and intestine.[28] Probably minuscule amounts are transpired through the skin. There is also an uptake of PFC by macrophages in the lung, liver and spleen.[14] Perfluorocarbon has been detected in the tissues of beagle dogs 3 years after 1 hour of total liquid ventilation.[29]

Human studies

There have been several published reports of the use of PLV in human neonates.[30–36] All these studies have been uncontrolled. The most significant study reported by Leach *et al.*,[34] who reported the use of PLV in 13 premature infants (gestational age mean 28, range 24–33 weeks) with severe respiratory distress syndrome – all were failing conventional therapy. Ten infants had 24–72 h of PLV and had demonstrated improvement in oxygenation and lung compliance. Six out of 10 survived to 36 weeks corrected age. The PLV was said to be well tolerated without any haemodynamic disturbance.

Pranikoff *et al.*[32] reported the use of PLV in newborn infants with congenital diaphragmatic hernia. Partial liquid ventilation was used in four infants, all of whom were on extracorporeal life support at the time. The authors noted improvement in oxygenation and total lung compliance with haemodynamic stability and no respiratory deterioration or other acute adverse effects.

Fuhrman *et al.*[37] have reported results from a prematurely halted clinical trial in paediatric acute respiratory distress syndrome (ARDS). The trial protocol underwent a number of amendments during the trial, resulting in three different sets of inclusion criteria. The final group, with liberalized entry criteria, had an unexpected decrease in mortality in the control group and the trial was stopped to allow full data analysis to determine the safety of PLV in this patient group. One hundred and eighty-two patients were enrolled (< 20% of target enrolment) with overall mortality of 24/91 (26%) in the PLV group and 18/91 (20%) in the conventional mechanical ventilation group. The authors concluded that PLV with LiquiVent® (Alliance Pharmaceutical Corp., San Diego, CA, USA) was safe; however, it was underpowered to detect real differences in mortality and ventilator free days between the groups.

Partial liquid ventilation technique

Perfluorocarbon is instilled into the endotracheal tube (ETT), usually through the side-port of the ETT manifold, whilst gas ventilation (CMV or HFV) continues. The initial volume of PFC used will be equal to the patient's estimated FRC. This volume of PFC is given over 10–20 min until a fluid level is seen in the ETT when the ventilator is disconnected (that is when positive end expiratory pressure (PEEP) = 0). Repeated doses of PFC are given at regular intervals to maintain a fluid level in the ETT at a PEEP of zero. Repeated doses of PFC are needed because the FRC will increase as the liquid recruits more collapsed alveoli and to replace evaporative losses. Cessation of PLV is merely achieved by ceasing top ups of PFC. The process is identical when used with HFV.

Nursing care of the patient on PLV will generally be similar to that for any ventilated critically ill patient.[38] Optimum techniques for instillation of PFC may require multiple re-positioning of the patient in the early stages of initiating PLV. Regular or continuous topping up of PFC down the ETT (especially to replace any PFC removed with suction) will be required. Lavaged exudate, which is less dense than PFC, will float to the top of the air/liquid interface and may block large airways and the ETT – therefore close attention to airway management and suctioning will be required.

How partial liquid ventilation works

The characteristics of PFC determine the effects of PLV. During gas ventilation nitrogen is the inert carrier of O_2 and CO_2. In

liquid ventilation, nitrogen is replaced by PFC. It has a high oxygen carrying capacity and solubility for CO_2,[13,36] and the PFC is oxygenated and CO_2 removed by means of tidal gas movement provided by the gas ventilator. This appears to be true in either conventional or high frequency ventilation. The low viscosity facilitates movement of PFC in small peripheral airways.

PFC have a low surface tension.[13] When it is instilled into the lung, the air/liquid alveolar interface (which in the surfactant deficient lung has a high surface tension) is abolished thereby lowering surface tension, increasing compliance and increasing alveolar recruitment. This allows lower ventilator pressures to be used and thus decreasing baro-and volu-trauma. Perfluorocarbons do not disturb natural surfactant[39] production nor do they wash it out of the lungs.[40,41]

Perflurocarbons have a high density compared to water and soft tissue,[13] and will mechanically recruit collapsed alveoli. This will happen preferentially in the dependant portions of the lung therefore improving ventilation/perfusion matching and decreasing intrapulmonary shunting.[42] Less dense exudate and debris may be lavaged from peripheral airways and float to the top of the PFC to allow removal by suction.[17,42]

Other uses of perfluorocarbons in the lung

Drug delivery to the pulmonary circulation has been demonstrated with TLV in neonatal lambs (with acetylcholine, adrenaline and priscoline).[43] The potential for delivery of drugs to the pulmonary vasculature with PLV enhances the prospect of treating patients with pulmonary hypertension. This has already been demonstrated in animal models using PLV with nitric oxide,[22] but the use of other pulmonary vasodilators may be possible. Partial liquid ventilation may also be used to deliver bronchodilators, exogenous surfactant, antibiotics, antioxidants, steroids and chemotherapeutic agents.

Lung washout with PFC can not only remove exudate and debris (such as meconium) from the lungs but may also play a role in washing out inflammatory mediators which have been implicated in secondary lung damage.[42] Warming or cooling of PFC used for PLV can facilitate temperature manipulation and control.[38] Perflurocarbons are radiopaque and have minimal physiologic effects when instilled into the lungs and therefore have the potential for use as a X-ray contrast medium.[33,34,37] Because PFC can eliminate the air/liquid interface in the lung, it may facilitate ultrasound examination of the lungs.

THE FUTURE

Perflubron (LiquiVent®) is the only medical grade PFC licensed for use in America. It is the PFC used in almost all the clinical trials of PLV to date. Randomized controlled trials (RCT) will obviously be needed for the use of perflubron in various respiratory problems in infants and children. Whilst further phase three clinical trials are currently being planned, ongoing fine tuning of the techniques of PLVin the animal lab are necessary so that RCT are performed properly before widespread use of the technique in intensive care. We should acknowledge the lesson of the HIFI trial[45] and its misleading results.[45]

Many questions about PLV remain unanswered. What is the ideal dose of PFC? Is continuous PLV required or will intermittent bolus doses of PFC (acute alveolar recruitment) provide sufficient benefit? Does the instillation of PFC into the lungs have any effect on the cerebral circulation (especially in the immature brain)? What are the long-term effects of perflubron after the cessation of PLV? Does the PFC need to be oxygenated prior to use?

Liquid ventilation, especially PLV, promises to be an exciting new therapy for infants and children with a variety of respiratory problems. The biggest challenge will be to conduct clinical trials comparing conventional techniques with the best possible method of PLV. Determining the best possible method of using PLV requires ongoing research and experimentation.

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