Partial Liquid Ventilation Compared with Conventional Mechanical Ventilation in an Experimental Model of Acute Lung Injury

M. W. DAVIES*, M. J. STEWART*†, R. CHAVASSE*, W. BUTT‡
*Division of Neonatal Services, Royal Women's Hospital, Melbourne, VICTORIA
†Department of Neonatology, ‡Paediatric Intensive Care Unit,Royal Children's Hospital, Melbourne, VICTORIA

ABSTRACT

Objective: *To compare the effects of partial liquid ventilation with conventional mechanical ventilation on oxygenation and pulmonary mechanics in saline lavaged rabbits.*

Methods: *Following acute lung injury (saline-lavage), rabbits were assigned to continue conventional mechanical ventilation (n = 6) or commence partial liquid ventilation (n = 6). In both groups the inspired oxygen concentration was 100% throughout the study. The target $PaCO_2$ of 40 - 60 mmHg was accomplished by keeping the tidal volume between 7 and 10 mL/kg. During the study the peak inspiratory pressure was adjusted to maintain the target $PaCO_2$.*

Arterial blood gases were taken pre-lavage, immediately post-lavage (time = 0) and then hourly for 5 hours. Pulmonary mechanics were estimated by measuring compliance and resistance. Pulmonary function was measured pre-lavage, immediately post-lavage and at 1 and 5 hours. At 5 hours the rabbits were killed and the lungs were removed for histological examination.

Results: *Baseline PaO_2, compliance and resistance were not significantly different between groups. The partial liquid ventilation group had a higher PaO_2 and a significantly better oxygenation index one hour after commencing partial liquid ventilation and a significantly higher PaO_2 averaged over the three hours post-treatment. There were no significant differences in compliance, resistance or lung damage scores.*

Conclusions: *In this experimental model of acute lung injury, partial liquid ventilation resulted in immediate and sustained increase in PaO_2 over 3 hours without significant change in lung mechanics or histological lung damage.* (**Critical Care and Resuscitation 2001; 3: 81-85**)

Key words: Partial liquid ventilation, surfactant deficiency, disease models, animal, fluorocarbons, respiratory distress syndrome

Mortality and morbidity from respiratory disease and its treatment are common in babies, children and adults requiring intensive care. Partial liquid ventilation (PLV), also known as perfluorocarbon-associated gas exchange (PAGE) or liquid assisted ventilation, has been proposed as both a rescue therapy for refractory respiratory failure and a less injurious form of respiratory support for patients with less severe respiratory failure.[1] The technique, first described by Fuhrman et al,[2] involves filling the lung to approximately its functional residual capacity with perfluorocarbon (PFC) liquid and continuing with conventional mechanical ventilation (CMV). PFC's are a group of chemicals derived from the fluorination of hydrocarbons. They are colourless, odourless liquids that are insoluble in water (and almost insoluble in lipid) and are chemically and biologically inert. The vapour pressure of PFC's vary but most will evaporate faster than water.[3,4] Randomised clinical trials to evaluate PLV are underway or planned.

Correspondence to: Dr. M. Davies, Department of Neonatology, Royal Women's Hospital, Herston, Brisbane, Queensland 4029 (e-mail: mwdavies@ozemail.com.au)

The primary objective of this study was to investigate the effect on oxygenation of PLV versus CMV alone in an animal model of surfactant-deficient, acute lung injury. Secondary objectives included investigation of the effects of PLV on lung mechanics and lung injury, and to identify technical and clinically important aspects of this therapy that may require further study.

MATERIALS AND METHODS

Twelve adult New Zealand white rabbits were anaesthetised with halothane and had venous (ear vein) and arterial (cut-down femoral artery) lines inserted. They were intubated, and then sedated and paralysed using continuous infusions of morphine and thiopentone, and intermittent boluses of pancuronium. Normal saline was continuously infused at 3 mL/kg/hr. Electrocardiogram, oxygen saturation and blood pressure were continuously monitored. Mechanical ventilation with CMV was commenced (Bear Cub, Bear Medical Systems Inc.) immediately after intubation. Initial ventilator settings were: peak inspiratory pressure (PIP) 8 - 10 cmH_2O, positive end expiratory pressure (PEEP) 3 cmH_2O, respiratory rate 30 breaths per minute, inspiratory time 1.0 second. The target $PaCO_2$ was 40 - 60 mmHg which was accomplished by keeping the tidal volume between 7 and 10 mL/kg. The tidal volume was measured by a VenTrak respiratory mechanics monitor with a neonatal flow sensor (Novametrix Medical Systems Inc. Wallingford, Connecticut, USA) placed between the endotracheal tube (ETT) and ventilator circuit manifold. The rabbits were ventilated with an inspired oxygen fraction (F_IO_2) of 1.0 throughout the study.

Surfactant-deficient acute lung injury was induced with recurrent saline lavage as described by McCulloch *et al*.[5] The lungs were lavaged with 30 mL/kg aliquots of warmed normal saline until the oxygen saturation (SaO_2) remained less than 90% for five minutes after the previous lavage. During the lavages the PIP was increased to 20 cmH_2O and the PEEP was increased to 5 cmH_2O.

Following the lavage, rabbits were assigned to continue CMV (n = 6) or commence PLV (n = 6). The rabbits assigned to receive PLV had perfluorocarbon liquid (FC-77, 3M Pharmaceuticals, St Paul, Minnesota, USA) instilled into the ETT via a side-port adaptor on the ETT manifold. An initial volume of approximately 25 mL/kg was instilled over 20 minutes. PFC was given until a fluid level was seen in the ETT during a brief disconnection from the ventilator. Additional PFC was periodically instilled to maintain a fluid level in the ETT during brief disconnection from the ventilator.

In both groups the PIP was adjusted to maintain the target $PaCO_2$. Arterial blood gases were taken pre-lavage, immediately post-lavage (time = 0) and then hourly (hours 1 to 5) for 5 hours post-lavage. Pulmonary compliance and resistance were measured (VenTrak, Novametrix Medical Systems Inc., Wallingford, USA) pre-lavage, immediately post-lavage and at 1 and 5 hours.

At 5 hr the rabbits were killed with a barbiturate overdose and the lungs filled with formalin at a pressure of 30 cm of formalin. The lungs were removed in total and kept in formalin until prepared for histological examination. Histological sections from dependent and non-dependent areas of the lung were scored according to a system similar to that used by McCulloch *et al*.[5] We assessed alveolar inflammation, the degree of hyaline membrane formation and the severity of bronchial epithelial damage. Sections were scored as 0, 1, 2 or 3 for each parameter corresponding to no, mild, moderate or severe changes. A score of "0" indicates no lung damage while a score of "9" represents severe damage.

Data from conventionally mechanically ventilated, saline-lavaged rabbits used by McCulloch *et* al,[5] showed a mean PaO_2 of 68.2 mmHg with a standard deviation of 6.32 (calculated from the quoted standard error). Therefore, a sample size of six in each group would be sufficient to show a difference of 11 mmHg in PaO_2 - a 15% difference ($\alpha = 0.05$, $1 - \beta = 0.8$).

This study was approved by the Royal Children's Hospital Animal Ethics Committee, and complies with the Australian Code of Practice for the care and use of animals for scientific purposes.

RESULTS

Table 1 summarises the major outcome data. One rabbit in the control group was excluded from analysis because of a protocol violation (lavage prematurely stopped leading to inadequate hypoxia).

Continuous non-skewed data were compared with Student's t test. Animals in the groups were of similar weight and required a similar number of lavages. Baseline oxygenation, $PaCO_2$, compliance and resistance were not different between groups. Both groups achieved severe hypoxia following the lavages, with similar $PaCO_2$ values. Two rabbits in the control group and 1 in the treatment group died. Missing data due to premature death of some rabbits precluded data analysis with repeated measures analysis of variance (ANOVA) as originally planned. Therefore, as a summary variable, PaO_2, $PaCO_2$ and oxygenation index (OI) were averaged over the first three hours post-treatment and then were compared between groups.

The PLV group had a significantly better oxygenat-

ion index one hour after commencing PLV and had significantly higher PaO_2 averaged over the first three hours post-treatment. Figures 1 and 2 display a comparison of overall oxygenation changes between the two groups.

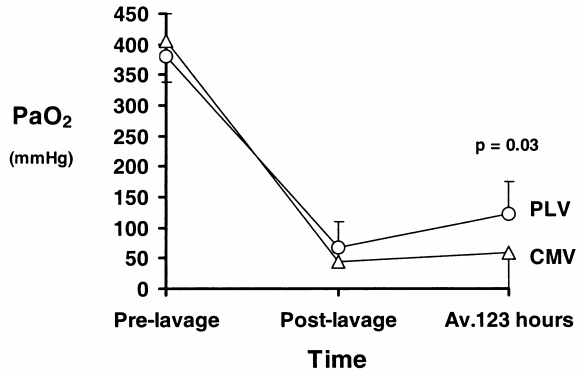

Figure 1. Pre lavage, post lavage and average partial pressures of arterial oxygen (PaO_2) values (mean ± SD) at 1,2 and 3 hr in the control (CMV = conventional mechanical ventilation) groups and treatment (PLV = partial liquid ventilation) groups.

Post-treatment there were trends towards lower $PaCO_2$ values in the PLV group but these differences were not statistically significant. There were no significant differences in compliance and resistance between groups, although there was a trend towards improvement in both these measurements in the PLV group. There was no significant difference in lung damage scores (Includes all animals, including those that died before 5 hr). During PLV the average rate of PFC top-up, after the initial dose of PFC, was 7.2 mL/kg/hr.

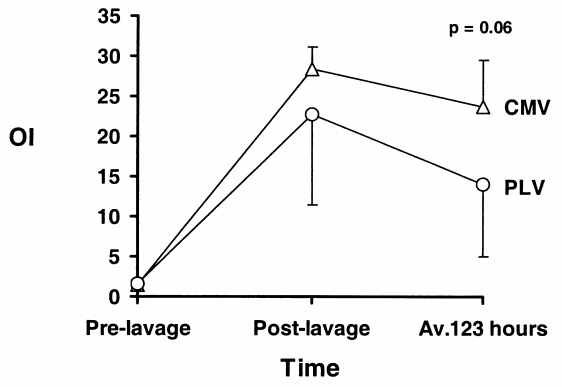

Figure 2. Pre lavage, post lavage and average oxygenation index (OI) values (mean ± SD) at 1,2 and 3 hr in control (CMV = conventional mechanical ventilation) groups and treatment (PLV = partial liquid ventilation) groups.

Table 1. Control versus treatment groups

Group		CMV* n=5		PLV* n=6		t test p value
Weight (kg)		2.85	(0.68)	2.62	(0.44)	0.60
Number of lavages		9	(7.0)	6.5	(2.51)	0.43
Pre-lavage OI		1.45	(0.19)	1.67	(0.36)	0.25
Pre-lavage PaO_2 (mmHg)		405.2	(67.2)	380.5	(70.0)	0.57
Pre-lavage $PaCO_2$ (mmHg)		45.7	(14.2)	49.7	(15.3)	0.65
0 hour	- OI	28.4	(2.72)	22.7	(11.3)	0.30
	- PaO_2	44.0	(5.96)	66.8	(42.2)	0.26
	- $PaCO_2$	53.2	(23.4)	55.7	(16.2)	0.83
	- Compliance (mL/cmH_2O)	1.56	(0.84)	1.7	(0.45)	0.73
	- Resistance (cmH_2O.L/sec)	157.3	(78.9)	135.4	(16.7)	0.56
1 hour	- OI	21.9	(4.30)	11.2	(7.72)	0.02
	- PaO_2	57.6	(12.0)	148.8	(93.7)	0.06
	- $PaCO_2$	49.5	(10.1)	39.8	(8.4)	0.10
	- Compliance (mL/cmH_2O)	1.58	(1.15)	2.28	(0.21)	0.17
	- Resistance (cmH_2O.L/sec)	146.5	(49.3)	96.4	(17.0)	0.06
Average hours 1, 2 &3	-OI	23.7	(5.87)	13.8	(8.95)	0.06
	- PaO_2	58.9	(10.8)	123.2	(53.4)	0.03
	- $PaCO_2$	49.6	(8.1)	42.5	(12.4)	0.28
Lung histology damage score		4.4	(1.82)	5.50	(0.55)	0.19

* CMV = conventional mechanical ventilation (mean ± SD), PLV = partial liquid ventilation (mean ± SD)
PaO_2 = partial pressure of arterial oxygen (mmHg), $PaCO_2$ = partial pressure of arterial carbon dioxide (mmHg), OI = oxygenation index (MAP x F_IO_2 x 100 / PaO_2).

DISCUSSION

Respiratory mortality and morbidity continue to be major problems in intensive care patients. Secondary lung damage in patients treated with CMV can lead to prolonged dependence on oxygen therapy and mechanical ventilation, increasing the length of stay in the intensive care unit and duration of hospital admission. Partial liquid ventilation (i.e. filling the lung to approximately its functional residual capacity with PFC and continuing with conventional mechanical ventilation)[2] has been used in an attempt to decrease the complications and mortality associated with respiratory failure.

During gas ventilation, nitrogen is the inert carrier of O_2 and CO_2. In liquid ventilation, PFC liquids act as the inert carrier, having a higher oxygen carrying capacity and solubility for CO_2,[3,4] (compared with water, dissolving more than 20 times the amount of O_2 and three times as much CO_2). PFCs have a low viscosity (facilitating their movement into small peripheral airways) and a low surface tension.[3] When they are 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 to decrease mechanical trauma. PFCs do not disturb natural surfactant production[6] and do not increase surfactant removal from the lungs.[7,8]

As PFCs have a high density when compared with water and soft tissue,[3] they mechanically recruit collapsed alveoli. This occurs preferentially in the dependent portions of the lung improving ventilation/ perfusion matching and decreasing intra-pulmonary shunting with re-distribution of pulmonary blood flow from dependent to non-dependent areas.[9] Less dense exudate and debris may also be lavaged from peripheral airways and float to the top of the PFC to allow their removal by suction.[9,10]

Various models of lung injury and surfactant deficiency have shown the benefits of using PLV compared with CMV in control animals. Many animal studies have documented improvement in oxygenation, carbon dioxide removal and lung compliance.[10-15] PFCs have also been shown to be more effective than surfactant alone in a premature lamb model of respiratory distress syndrome.[14] Studies that looked at lung histology have shown significantly less damage in lungs after PLV.[10,12] In all animal studies haemodynamic stability of PLV animals has been demonstrated.[10-16] and an improvement on oxygenation when PLV is combined with nitric oxide in pulmonary hypertension in piglets has also been demonstrated.[16]

This study supports previous work that has shown improved oxygenation with PLV used to treat severe respiratory failure in similar models of parenchymal lung disease. Whilst there was a trend towards improved compliance in the group that received PLV, the lack of a statistically significant difference may have been due to inadequate sample size. We found no statistically significant difference in histological lung damage between groups. However, the overall lung damage scores were low which may reflect the use of an adult rabbit lung which is more resistant to histological damage.

We found that the animals tolerated dosing with PFC without serious disturbance to arterial oxygen saturation (SaO_2). Generally, the initial dose of PFC could be instilled over 15 - 20 minutes. Top-up doses of PFC were required every 30 minutes as FC-77 has a high vapour pressure leading to the need for frequent re-dosing. We did not pre-oxygenate the PFC prior to administration and no effort was made to change the animals posture during initial dosing. It is not known if these factors affect acute changes in oxygenation. Safety aspects of PFC involving distribution and excretion/accumulation of PFC were not addressed in this short term study. Further studies are necessary to refine these aspects of PLV and are of prime importance when applying this technique to humans.

In conclusion, PLV with conventional ventilation is a readily applicable technique of assisted ventilation. Compared with CMV, PLV resulted in an immediate and sustained improvement in oxygenation in this model of surfactant-deficient acute lung injury.

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REFERENCES

1. Wolfson MR, Greenspan JS, Shaffer TH. Liquid assisted ventilation: an alternative respiratory modality. Pediatr Pulmonol 1998;26:42-63.
2. Fuhrman BP, Paczan PR, DeFrancisis M. Perfluorocarbon-associated gas exchange. Crit Care Med 1991;19:712-722.
3. Shaffer TH, Wolfson MR, Clark LC Jr. Liquid ventilation. Pediatr Pulmonol 1992;14:102-109.

4. Degraeuwe PL, Vos GD, Blanco CE. Perfluorochemical liquid ventilation: from the animal laboratory to the intensive care unit. Int J Artif Organs 1995;18: 674-683.
5. McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. Am Rev Respir Dis 1988;137:1185-1192.
6. Cleary GM, Antunes MJ, Wu D, et al. Disaturated phosphatidylcholine and surfactant protein B levels in healthy and meconium injured lungs after partial liquid ventilation. Pediatr Res 1997;41:249A.
7. Modell JH, Gollan F. Giammona ST, Parker D. Effects of fluorocarbon liquid on surface tension of pulmonary surfactant. Chest 1970;57:263-265.
8. Rufer R. Surfactant and alveolar surface forces after breathing of a fluorinated liquid. Fed Proc 1970;29:1813-1815.
9. Kelly KP. Partial liquid ventilation-turning back a PAGE on evolution [editorial]. Brit J Anaesth 1997;78:1-2.
10. Foust R 3rd, Tran NN, Cox C, et al. Liquid assisted ventilation: an alternative ventilatory strategy for acute meconium aspiration injury. Pediatr Pulmonol 1996;21:316-322.
11. Tutuncu AS, Faithfull NS, Lachmann B. Comparison of ventilatory support with intratracheal perfluorocarbon administration and conventional mechanical ventilation in animals with acute respiratory failure. Amer Rev Resp Dis 1993;148:785-792.
12. Smith KM, Mrozek ID, Simonton SC, et al. Prolonged partial liquid ventilation using conventional and high-frequency ventilatory techniques: Gas exchange and lung pathology in an animal model of respiratory distress syndrome. Crit Care Med 1997;25:1888-1897.
13. Leach CL, Fuhrman BP, Morin FC 3rd, Rath MG. Perfluorocarbon-associated gas exchange (partial liquid ventilation) in respiratory distress syndrome: a prospective, randomised, controlled study. Crit Care Med 1993;21:1270-1278.
14. Leach CL, Holm B. Morin FC 3rd, et al. Partial liquid ventilation in premature lambs with respiratory distress syndrome: efficacy and compatibility with exogenous surfactant. J Pediatr 1995;126: 412-420.
15. Curtis SE, Peek JT. Effects of progressive intratracheal administration of perflubron during conventional gas ventilation in anesthetized dogs with oleic acid lung injury. Adv Exper Med Biol 1994;345:51-58.
16. Zobel G. Urlesberger B. Dacar D, Rödl S. Reiterer F. Frichs I. Partial liquid ventilation combined with inhaled nitric oxide in acute respiratory failure with pulmonary hypertension in piglets. Pediatr Res 1997;41:172-177.