

# Oxygenation is Not Improved by Partial Liquid High Frequency Ventilation Using a High Lung Volume Strategy. An Experimental Study

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## ABSTRACT

**Objective:** To investigate the effect on oxygenation and lung damage of partial perfluorocarbon liquid high frequency oscillatory ventilation (PL-HFOV) versus high frequency oscillatory ventilation (HFOV) alone, in rabbits with acute lung injury, using high lung volume strategy HFOV.

**Methods:** Twelve adult New Zealand white rabbits were initially ventilated with HFOV after anaesthesia, sedation and paralysis. After induction of lung injury with saline lavage, all animals received a single sigh breath of 30 cmH<sub>2</sub>O for 30 seconds. They were then allocated to receive either HFOV alone (n = 6) or PL-HFOV (n = 6). Arterial blood gases were taken pre- and post-lavage and then hourly for 5 hours. The oxygenation index (OI, in cmH<sub>2</sub>O/mmHg) was calculated using the formula:  $OI = (MAP \times F_{iO_2} \times 100) / PaO_2$ . The lungs were then removed for histological examination to score lung injury.

**Results:** Two rabbits died in the PL-HFOV group and none in the HFOV group,  $p = 0.45$  (Fisher's exact test). At one hour the oxygenation index (OI) was 4.5 in the HFOV group and 6.6 in the PL-HFOV group,  $p = 0.49$  and the PaO<sub>2</sub> was 374 mmHg in the HFOV group and 311 mmHg in the PL-HFOV group,  $p = 0.39$ . Average OI over the first three hours was 3.6 in the HFOV group and 5.0 in the PL-HFOV group,  $p = 0.27$  and the PaO<sub>2</sub> was 404 mmHg in the HFOV group and 337 mmHg in the PL-HFOV group,  $p = 0.12$ . The lung histology damage score was 2.33 in the HFOV group and 2.50 in the PL-HFOV group,  $p = 0.83$ .

**Conclusions:** In this model of acute lung injury, using a high volume HFOV strategy to optimise lung recruitment, PL-HFOV did not result in any further improvement in oxygenation when compared with HFOV alone. The question of safety with PL-HFOV remains. (*Critical Care and Resuscitation* 1999; 1: 339-343)

**Key words:** Partial liquid ventilation, high-frequency ventilation, respiratory distress syndrome, disease models, animal

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Mortality and morbidity from respiratory disease and its treatment are common in infants and children 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.

High frequency oscillatory ventilation (HFOV) is an accepted rescue therapy for infants and children with severe respiratory failure refractory to conventional mechanical ventilation. It is especially effective when a high lung volume strategy, aimed at maximising alveolar recruitment, is used for infants with surfactant deficiency.<sup>1</sup>

The technique of PLV with high frequency oscillatory ventilation (PL-HFOV) involves filling the

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lung to approximately its functional residual capacity with perfluorocarbon liquid (PFC) whilst continuing HFOV. There are five published reports where PL-HFOV has been used in animal models of acute lung disease.<sup>2-6</sup> Only two of these directly compared HFOV alone with PL-HFOV,<sup>2,6</sup> with conflicting results. No study to date has investigated the effects of PL-HFOV using high lung volume strategy HFOV before starting PLV.

The primary objective of this study is to investigate the effect on oxygenation of PL-HFOV versus HFOV alone in rabbits with acute lung injury, using high lung volume strategy HFOV. A secondary objective included investigation of the effects of PL-HFOV on lung injury.

#### MATERIALS AND METHODS

Twelve adult New Zealand white rabbits were anaesthetised with halothane and had venous and arterial 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 was commenced with HFOV (SensorMedics 3100, Yorba Linda, USA). Initial ventilator settings were: mean airway pressure (MAP) 6 cmH<sub>2</sub>O, frequency 10 Hz, delta P ( $\Delta$ P) 20 cmH<sub>2</sub>O. The rabbits were ventilated with an inspired oxygen fraction (F<sub>I</sub>O<sub>2</sub>) of 1.0 throughout the study.

Acute lung injury was induced with recurrent saline lavage as used by McCulloch *et al.*<sup>7</sup> The lungs were lavaged with 30 mL/kg aliquots of warmed normal saline until the oxygen saturation (SaO<sub>2</sub>) remained less than 90% for five minutes after the previous lavage. During the lavages the MAP was increased to 9 cmH<sub>2</sub>O. At the end of the lavage procedure, a single sigh breath of 30 cmH<sub>2</sub>O was given for 30 seconds and the MAP was set at 12 cmH<sub>2</sub>O. Rabbits were then assigned to continue HFOV alone (n = 6) or PL-HFOV (n = 6).

The rabbits assigned to the PL-HFOV group had perfluorocarbon liquid (FC-77, 3M Pharmaceuticals, St Paul, Minnesota, USA) instilled into the endotracheal tube (ETT) via a sideport adapter, with an initial volume of approximately 25 mL/kg instilled over 20 minutes. The PFC was not oxygenated before administration. HFOV was continued throughout the PFC instillation. PFC was given until a fluid level was seen in the ETT during a brief disconnection from the ventilator. Additional PFC was periodically instilled whilst continuing HFOV to maintain a fluid level in the ETT (as above).

In both groups the MAP was adjusted to maintain SaO<sub>2</sub>  $\geq$  90% and  $\Delta$ P adjusted to maintain normocarbida. Arterial blood gases (ABG) were taken pre-lavage, post-lavage (after the sigh breath, time = 0) and then hourly (hours 1 to 5) until 5 hours post-lavage. Oxygenation was assessed by measuring PaO<sub>2</sub> (mmHg) and calculating the oxygenation index (OI, in cmH<sub>2</sub>O/mmHg).  $OI = (MAP \times F_{I}O_2 \times 100) / PaO_2$ . At 5 hours the rabbits were killed with a barbiturate overdose and the lungs removed 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.*<sup>7</sup> 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. Thus a score of 0 indicates no lung damage while a score of 9 represents severe damage.

HFOV has previously been studied by McCulloch *et al.*<sup>7</sup> in saline-lavaged rabbits. The mean (SD) PaO<sub>2</sub> in a group of rabbits ventilated with high lung volume HFOV was 395.4 (31.5) mmHg at the end of the study period. Using this data a sample size of six would be sufficient to show a difference of 60 mmHg, a 15% difference in PaO<sub>2</sub> ( $\alpha$  0.05,  $\beta$  0.2). Data were compared using Student's *t* test.

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

Outcome data are summarised in Table 1. Comparing treatment with control groups, the rabbits were of similar weights and required a similar number of lavages to induce the desired degree of lung injury. There was no difference in oxygenation immediately post-lavage and immediately pre-treatment.

ABGs were not performed immediately post-lavage (before the sigh breath) and the degree of hypoxia induced by the saline lavage is not readily apparent. In a similar study (done contemporaneously in our laboratory) using conventional mechanical ventilation, rabbits that had lung lavage with an identical protocol had a mean partial pressure (SD) of arterial oxygen of 56 mmHg (32 mmHg) immediately post-lavage.<sup>8</sup> The severity of hypoxia is similar to that achieved by McCulloch *et al.*<sup>7</sup> in this animal model.

Two rabbits in the PL-HFOV group died prior to the 5 hour blood gas. The missing data due to these

**Table 1. Control versus treatment groups**

| Group                            | HFOV*       | PL-HFOV*    | t test<br>p value |
|----------------------------------|-------------|-------------|-------------------|
|                                  | n=6         | n=6         |                   |
| Weight (kg)                      | 2.43 (0.19) | 2.63 (0.20) | 0.10              |
| Number of lavages                | 6.5 (1.64)  | 7.8 (4.27)  | 0.51              |
| Pre-lavage OI                    | 1.82 (0.56) | 2.82 (2.94) | 0.44              |
| Pre-lavage PaO <sub>2</sub>      | 372 (69)    | 353 (147)   | 0.78              |
| 0 hour                           |             |             |                   |
| - OI                             | 4.13 (1.81) | 4.74 (1.6)  | 0.55              |
| - PaO <sub>2</sub>               | 377 (118)   | 323 (127)   | 0.47              |
| 1 hour                           |             |             |                   |
| -OI                              | 4.51 (2.73) | 6.6 (6.57)  | 0.49              |
| - PaO <sub>2</sub>               | 374 (125)   | 311 (117)   | 0.39              |
| Average hours 1, 2 & 3           |             |             |                   |
| -OI                              | 3.64 (0.96) | 5.03 (2.76) | 0.27              |
| - PaO <sub>2</sub>               | 404 (74)    | 337 (71)    | 0.12              |
| - MAP                            | 13.4 (1.2)  | 14 (0.53)   | 0.28              |
| - PaCO <sub>2</sub>              | 45.6 (77)   | 45.8 (56)   | 0.96              |
| Lung damage score – all.         | 2.33 (0.82) | 2.50 (1.64) | 0.83              |
| Lung damage score – excl. deaths | 2.33 (0.82) | 2.00 (1.41) | 0.69              |

\* Mean (SD)

PaO<sub>2</sub> = partial pressure of arterial oxygen (mmHg), PaCO<sub>2</sub> = partial pressure of arterial carbon dioxide (mmHg), OI = oxygenation index (MAP x F<sub>I</sub>O<sub>2</sub> x 100 / PaO<sub>2</sub>), MAP = Mean airway pressure (cmH<sub>2</sub>O)

premature deaths precluded data analysis of repeated measures of the partial pressure of arterial oxygen (PaO<sub>2</sub>) and oxygenation index by ANOVA as originally planned. Therefore a summary variable comprising the averaged oxygenation parameters over the first three hours post-treatment was calculated and compared between groups. No rabbit died in the HFOV group – the difference in mortality was not statistically significant ( $p = 0.45$ , Fisher's exact test). We suspected a liquid leak may have played a role in the two premature deaths, however even during the lung harvest it was unclear whether the leak was ante- or post-mortem. X-rays were not available.

There were no significant differences in post-treatment oxygenation, MAP or PaCO<sub>2</sub>. There were no significant differences in histological lung damage scores, even if those animals that died prematurely were excluded. During PL-HFOV, the average rate of top-up after the initial dose of PFC was 5.2 mL/kg/hr of PFC. There were no significant disturbances in heart rate, oxygen saturation or blood pressure during PFC dosing in any of the PL-HFOV group animals.

## DISCUSSION

The aim of assisted ventilation in patients with respiratory failure is to maintain gas exchange with minimal physiological disturbance and secondary lung damage. In the majority of patients in intensive care, gas exchange can be maintained with conventional ventilation or high frequency oscillatory ventilation (with or without inhaled nitric oxide). There remains a small proportion of patients, whose lung disease is so

severe that gas exchange is inadequate with these techniques, who warrant the use of various rescue therapies such as PLV.

The problem of secondary lung damage is seen, to some degree, in most ventilated patients. Both HFOV and PLV have been proposed as a means of providing gas exchange whilst minimising lung injury.<sup>1,9</sup> Combining the two techniques may provide gas exchange with minimal lung injury.

Saline lavage induction of surfactant deficiency is a well established animal model of acute lung injury. It produces immediate adverse effects on lung mechanics and oxygenation, and significant small airway and alveolar damage is seen on histology.<sup>7,10</sup> All previous animal studies investigating the effects of PLV with HFOV have shown the technique provides good gas exchange.<sup>2-6</sup> However only two of the studies directly compared a PL-HFOV group with a HFOV alone control group.<sup>2,6</sup> Baden *et al*<sup>2</sup> showed that the addition of PLV to HFOV gave an immediate improvement in oxygenation that was not sustained after two hours. They used a maximal alveolar recruitment strategy during the treatment phase (not prior to starting treatment) with 15 second, 30 cmH<sub>2</sub>O sigh breaths every 60 minutes in both groups. Sukumar *et al*<sup>6</sup> showed improved gas exchange and pulmonary blood flow with PL-HFOV. A MAP of 15 cmH<sub>2</sub>O was maintained throughout without the addition of sigh breaths. Smith *et al*<sup>5</sup> comparing various methods of PL-HFOV, showed that those forms of HFOV which allow volume recruiting manoeuvres, such as the addition of

intermittent conventional breaths, gave superior gas exchange.

Our experimental study is the first to investigate the effects of PL-HFOV using a high lung volume strategy (i.e. a 30 second 30 cmH<sub>2</sub>O sigh breath), prior to commencing PLV. We have shown that when using this strategy the addition of PLV to HFOV provides no benefit in terms of oxygenation, CO<sub>2</sub> removal or decreased lung injury. These results are consistent with the findings of Baden *et al*<sup>2</sup> and Smith *et al*<sup>5</sup> which suggest that PL-HFOV may not provide any additional benefit over HFOV alone when using high lung volume strategy HFOV.

It remains to be shown whether there is any benefit from obtaining alveolar recruitment in patients on HFOV using PFC versus sigh breaths or similar manoeuvres. When PL-HFOV is used its benefits may be maximised by using lung recruitment strategies such as sigh breaths or added low rate conventional ventilation – this remains unstudied.

Although this study confirms that gas exchange can be readily maintained with PL-HFOV, safety remains a major concern. In our study the instillation of PFC down the ETT did not require any additional manoeuvres, such as short periods of intermittent breaths, and there was minimal reflux of liquid up the ETT during the instillation of PFC. We found that the animals tolerated dosing with PFC without serious disturbance to SaO<sub>2</sub> or haemodynamics. We did not pre-oxygenate the PFC prior to administration in this study. It is not known if this affects acute changes in oxygenation. No effort was made to change the animals posture during initial dosing. This would mean significant handling in practice although it could be achieved if shown to be of benefit.

The ability to detect the liquid equivalent of pneumothorax - a fluorothorax - is an important issue. We suspected a liquid leak played a role in the premature death of two of the animals; however, even during the lung harvest it was unclear whether the leak was ante- or post-mortem. Fluorothorax should not present any difficulty in diagnosis if x-rays (unavailable in this study) can be done – a combined air-liquid leak should produce a fluid level on lateral chest x-ray. Radiopaque perfluorocarbon would make AP chest x-rays of supine subjects difficult to interpret. The mortality in the PL-HFOV group (although not statistically significant) is of concern and future research should focus on the safety aspects of the technique.

In this model of acute lung injury, using a high volume HFOV strategy to optimise lung recruitment, PL-HFOV did not result in any further improvement in oxygenation when compared with HFOV alone. Nor was

there any benefit in reducing histological lung injury. The question of safety with PL-HFOV remains.

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