

## Effects of Perfluorocarbon Associated High Frequency Oscillatory Ventilation on Hemodynamics and Gas Exchange in the Newborn Piglets with Respiratory Distress

We sought to know whether there is a further improvement in gas exchange when partial liquid ventilation (PLV) is added to high-frequency oscillatory ventilation (HFOV) in a piglet model of saline lavage-induced acute lung injury. Seven 7-9 day-old newborn piglets of mixed strain were treated with repeated saline lavage to achieve a uniform degree of acute lung injury. Then, HFOV were applied to the subject. Four animals received two consecutive doses (15 mL/kg) of perfluorodecalin at 30-min interval (PFC+HFOV group). The other three animals remained on HFOV alone (HFOV-only group). Repetitive lung lavage led to a significant acute aggravation in both gas exchange and hemodynamic parameters. Subsequent application of HFOV produced a significant rapid recovery in both gas exchange and hemodynamic parameters to near baseline levels. During and after perfluorodecalin dosing, there were no significant changes in gas exchange or hemodynamic parameters over time in both groups, and no significant differences in gas exchange or hemodynamic parameters between groups. We concluded that the addition of 30 mL/kg of perfluorodecalin to HFOV showed no detrimental effect on hemodynamics, but did not produce a significant improvement in gas exchange over a three-hour period.

**Key Words :** *Liquid Ventilation; Fluorocarbons; Ventilations, High-Frequency*

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## INTRODUCTION

Although mechanical ventilation has remarkably improved the outcome of premature infants, its detrimental effect, lung injury from barotrauma and volutrauma has brought about a problem of chronic lung disease of prematurity. Even if surfactant therapy can reduce lung injury from mechanical ventilation, it has failed in some cases due to its uneven distribution, delayed action, and inactivation. Recently, newer mechanical ventilation modes and strategies aimed at reducing barotrauma and volutrauma have been introduced, but the risk of lung injury from mechanical ventilation still remains.

Several studies suggest newer technologies, such as partial liquid ventilation (PLV) and high-frequency oscillatory ventilation (HFOV) that can reduce the severity of lung injury in experimental and clinical settings (1-9). HFOV has been known to be effective rescue modality in patients with a significant impairment of gas exchange (10-12). In a prospective, randomized study of pediatric patients with respiratory failure, HFOV was associated with a significant decrease in the incidence of chronic lung disease in those patients who ultimately survived (13). PLV evenly reduces surface tension of alveoli and enhances

alveolar recruitment, and improves gas exchange and pulmonary function with minimizing lung injury (14-17). Combination of these two ventilatory strategies may have theoretical advantages of further improvement of alveolar recruitments and resultant enhanced gas exchange in severe respiratory failure with atelectasis-prone lung.

We accomplished this pilot study to evaluate whether the combination of PLV by perfluorocarbon with HFOV can show additive effects on the improvement of gas exchange without detrimental effects on hemodynamic parameters in newborn piglets with saline lavage-induced severe respiratory failure.

## MATERIALS AND METHODS

### Animal Preparations and Surgical Procedures

The institutional Animal Care and Use Committee of the Samsung Biomedical Research Center, Seoul, Korea approved this investigation.

Studies were performed on seven, 7-9 day-old newborn piglets of mixed strain (Yorkshire, conventional breed, purchased

from Paju farm, Paju, Kyungki-Do, Korea). Surgical preparation of neonatal piglets was initiated by sedation with ketamine (20 mg/kg, IM) and xylazine (2 mg/kg, IM), followed by thiopental anesthesia (5 mg/kg, IV). After local injection with lidocaine (1%) a tracheostomy was performed, and the piglet was paralyzed with pancuronium (0.1 mg/kg, IV) followed by hourly intravenous injections. Sedation was maintained with hourly doses of thiopental. The paralyzed piglet was placed on a mechanical ventilator (Sechrist Infant Ventilator, IV-100V) to attain an arterial O<sub>2</sub> tension of 80–100 mmHg and an arterial CO<sub>2</sub> tension of 35–45 mmHg. The right femoral artery was cannulated for arterial blood gas sampling and systemic arterial blood pressure monitoring. An infusion of 0.9% saline containing 1U of heparin/mL was provided at a rate of 1–2 mL/hr through the arterial catheter that were attached to a blood pressure transducer (Hewlett Packard Model M1276A). A Hewlett Packard neonatal monitoring system (M1276A) continuously monitored electrocardiogram, oxygen saturation, and system arterial and pulmonary arterial pressure. Animals were maintained supine with the head of the bed elevated at 20 degrees upward throughout the study. Constant body temperature was maintained at between 38–39°C by using a warmed operating table and servo-controlled overhead heater.

### Perfluorodecalin

Perfluorodecalin, a kind of PFC, is insoluble in water and is too stable in room temperature to react when exposed to air or water. The density of perfluorodecalin is 1.95 g/mL at 25°C, kinematic viscosity is 2.90 centistoks at 25°C, boiling point is 142°C, vapor pressure is 14 mmHg at 37°C, surface tension is 15 dyne/cm at 25°C, oxygen solubility is 49 mL gas/100 mL liquid at 25°C, and 140 mL gas/100 mL liquid.

### Experimental Protocols

After a period of stabilization at about 30 min after anesthetic and surgical procedures, the ventilator settings were adjusted as follows: FiO<sub>2</sub> 1.0, rate 25/min, PIP 30 cmH<sub>2</sub>O, PEEP 4 cmH<sub>2</sub>O, and iT 0.7 sec. The newly adjusted settings were maintained for 10 min. At this point, baseline measurements of arterial blood gases, hemodynamic parameters were done. Thereafter, induction of acute lung injury was done by repetitive lung lavage with warm saline. A dose of 30 mL/kg of 37°C saline was instilled into trachea and was removed repeatedly 4–6 times until an arterial O<sub>2</sub> tension of 60 mmHg was reached at a ventilator setting of FiO<sub>2</sub> 1.0, Fr 25/min, PIP 30 cmH<sub>2</sub>O, PEEP 4 cmH<sub>2</sub>O, and iT 0.7 sec. Lavage baseline point (lavage), when stabilization was reached, was appointed as about 30 min after lung lavage. Measurement of arterial blood gases and hemodynamic parameters were done again at this lavage baseline point. Then the newborn piglets were randomly divided into two groups: HFOV only group (n=3)

and PLV with perfluorocarbon plus HFOV group (PFC+HFOV group, n=4). HFOV (SensorMedics 3100A, SensorMedics Critical Care, Yorba Linda, CA, U.S.A.) was applied to the newborn piglets in HFOV only group at a setting of FiO<sub>2</sub> 1.0, iT 33%, MAP 15 cmH<sub>2</sub>O, delta P 35–40 cmH<sub>2</sub>O, and Fr 15 Hz. Newborn piglets in PFC+HFOV group received both perfluorodecalin and HFOV. Thirty min after HFOV was applied, two consecutive doses of 37°C, 15 mL/kg of perfluorodecalin were administered slowly at a 30-min interval through the side-port of an adapter that connects ventilator circuit with endotracheal tube for 5 min. During the 5 min for administration of perfluorodecalin, HFOV was replaced with conventional ventilation at the same settings as baseline. And then HFOV was applied at an altered setting, FiO<sub>2</sub> 1.0, iT 50%, MAP 15 cmH<sub>2</sub>O, delta P 35–40 cmH<sub>2</sub>O, and Fr 10 Hz. Prolonged iT and decreasing frequency were necessary to obtain adequate chest vibration of piglets, which was testified in our previous pilot study. All newborn piglets in each group were maintained for three hours and were monitored for arterial blood gases, hemodynamic parameters, and oxygenation index at 30 min after the beginning of HFOV (HFOV), at 30 min after each perfluorocarbon dosing (30'/PFC1, 60'/PFC2), and at 180 min after the first perfluorocarbon dosing (180').

### Monitoring of Arterial Blood Gases, Hemodynamic Parameters and Oxygenation Index

Heart rate and systemic arterial pressure (SAP) were measured through neonatal monitor (Hewlett-Packard Model M1276A) by using femoral arterial catheters. Arterial blood pH, O<sub>2</sub> tension, and CO<sub>2</sub> tension were measured from arterial blood samples taken from the femoral arterial catheter. Blood gases were analyzed by using Ciba-Corning blood gas analyzer. Oxygenation index was calculated as follows:  $OI = [MAP (cmH_2O) \times FiO_2] / [7.5 \times PaO_2 (kPa)]$

### Data Analysis and Statistics

All numerical values measured were described as mean  $\pm$  standard deviation. Arterial blood gases, hemodynamic parameters, and oxygenation indices were assessed by repeated measures analysis of variance with the group as the main effect, and time as the within-subject factor for the analysis of group-by-time interaction and intragroup differences, taking the Bonferroni principles into account. Intergroup difference at each time point was evaluated by one-way analysis of variance. We used SPSS (version 10.0) and StatView (version 5.0) for these analyses. *p*-value lower than 0.05 was regarded significant.

## RESULTS

At a baseline time point, there were no significant differences

in heart rates, mean arterial blood pressures, arterial blood pH and gas tensions, and oxygenation indices between HFOV-only group and PFC+HFOV group.

Repetitive lung lavage produced a significant decrease in arterial blood pH ( $p<0.0001$ ) and  $\text{PaO}_2$  ( $p<0.0001$ ), and an increase in  $\text{PaCO}_2$  ( $p<0.0001$ ), mean arterial blood pressure ( $p<0.0001$ ) and oxygenation index ( $p<0.0001$ ) in both the HFOV-only group and PFC+HFOV group. After all, acute respiratory failure manifested by marked acidemia, hypoxemia, and hypercapnia was induced to newborn piglets in each group, but there were no significant inter-group differences in heart rates, mean arterial blood pressures, arterial blood pH and gas tensions, and oxygenation indices (Table 1).

After HFOV was applied to newborn piglets in each group, arterial blood pH ( $p=0.002$ ) and  $\text{PaO}_2$  ( $p=0.0003$ ) were signif-

icantly increased, and  $\text{PaCO}_2$  ( $p<0.0001$ ), mean arterial blood pressure ( $p<0.0001$ ) and oxygenation index ( $p=0.0002$ ) were significantly decreased in both groups of animals. There were no significant differences between the groups in heart rates, arterial blood pH and gas tensions, and oxygenation indices, except in mean arterial blood pressure at this time point. Mean arterial blood pressure of newborn piglets in PFC+HFOV group was significantly lower than that of animals in HFOV-only group ( $54.2 \pm 5.1$  vs.  $86.6 \pm 23.1$ ,  $p=0.03$ ) (Fig. 1, 2).

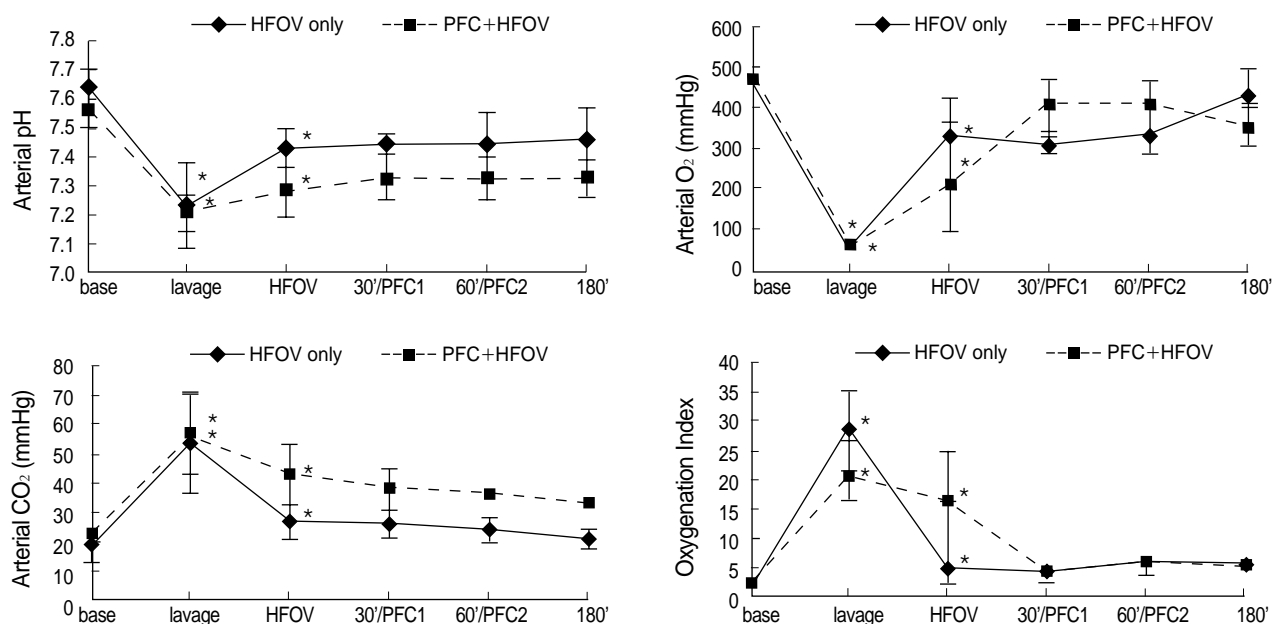
## Gas Exchange

Newborn piglets in HFOV-only group which were given only HFOV did not produce further significant alterations in arterial blood pH and gas tensions, and in oxygenation indices to the end point of experiment, since they altogether showed marked improvements in their gas exchange as soon as HFOV was applied. The gas exchange of the animals in PFC+HFOV group which were given both perfluorodecalin and HFOV showed gradual improvements as two consecutive doses of perfluorodecalin were administered, but the changes were not significant as the results from HFOV-only group were not. The fact that there were no significant differences in gas exchange pattern over time between the groups indicated that PFC did not produce an additive effect on gas exchange of the injured lung when added to HFOV. From the first perfluorodecalin dosing to the end point of experiment (Fig. 1), there were no significant differences in arterial pH, gas tensions, and oxygenation indices between the groups.

**Table 1.** Hemodynamic parameters and arterial blood gases before and after lung lavage in two groups of newborn piglets

	HFOV-only group (n=3)		PFC+HFOV group (n=4)	
	Baseline	After lavage	Baseline	After lavage
Heart rate (/min)	169 $\pm$ 21	215 $\pm$ 34	183 $\pm$ 37	196 $\pm$ 77
Arterial blood pressure (mmHg)	86 $\pm$ 9	115 $\pm$ 16*	66 $\pm$ 11	103 $\pm$ 14*
Arterial blood pH	7.64 $\pm$ 0.06	7.23 $\pm$ 0.14*	7.57 $\pm$ 0.06	7.20 $\pm$ 0.06*
$\text{PaO}_2$ (mmHg)	474.1 $\pm$ 61.4	32.9 $\pm$ 8.9*	483.3 $\pm$ 38.7	38.7 $\pm$ 10.9*
$\text{PaCO}_2$ (mmHg)	19.4 $\pm$ 6.2	53.8 $\pm$ 17.6*	21.6 $\pm$ 3.6	56.7 $\pm$ 13.9*
Oxygenation index	1.6 $\pm$ 0.1	28.3 $\pm$ 7.3*	1.6 $\pm$ 0.2	21.4 $\pm$ 4.9*

HFOV, High-frequency oscillatory ventilation; PFC, Perfluorocarbon; \*,  $p<0.05$  compared to baseline value.



**Fig. 1.** Plots representing gas exchange: Top left, arterial blood pH; top right,  $\text{PaO}_2$ ; bottom left,  $\text{PaCO}_2$ ; bottom right, oxygenation index at baseline (base), after lavage (lavage), after the application of high-frequency oscillatory ventilation (HFOV), 30 min after each of two consecutive doses of 15 mL/kg of perfluorodecalin at a 30-min interval (30'/PFC1, 60'/PFC2), and 180 min after the initiation of perfluorodecalin administration (180'). HFOV, High-frequency oscillatory ventilation; PFC, Perfluorocarbon; \*,  $p<0.05$  compared to previous level within the group.

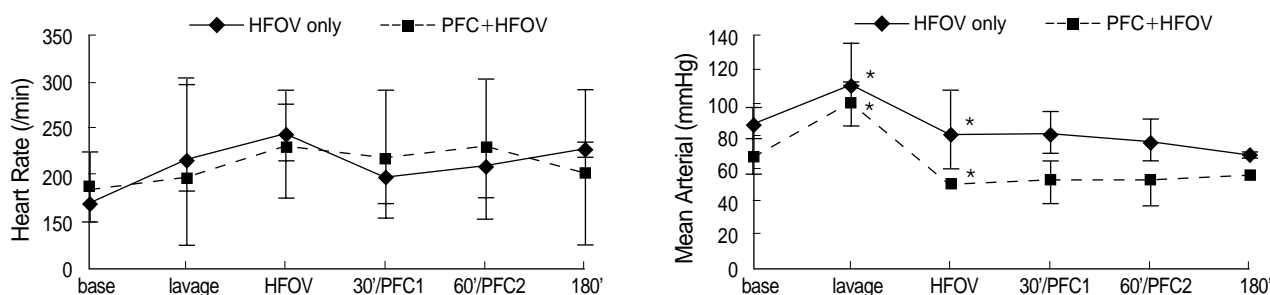


Fig. 2. Plots representing hemodynamic parameters: Left, heart rate; right, arterial blood pressure at baseline (base), after lavage (lavage), after the application of high-frequency oscillatory ventilation (HFOV), 30 min after each of two consecutive doses of 15 mL/kg of perfluorodecalin at a 30-min interval (30'/PFC1, 60'/PFC2), and 180 min after the initiation of perfluorodecalin administration (180'). HFOV, High-frequency oscillatory ventilation; PFC, Perfluorocarbon; \*,  $p < 0.05$  compared to previous level within the group.

## Hemodynamic Parameters

Heart rates showed no significant changes over time in both groups of animals and no intergroup differences throughout the experiment as well. Mean arterial blood pressure did not show a significant alteration since the first perfluorodecalin dosing. In the intergroup comparison, mean arterial pressure of newborn piglets in PFC+HFOV group was significantly lower ( $57.7 \pm 11.6$  vs.  $87.0 \pm 9.8$ ,  $p = 0.01$ ) than that of animals in HFOV-only group just after the first perfluorodecalin dosing, but thereafter, there were no more intergroup differences to the end point of experiment. The results showed that the addition of PFC to HFOV in the rescue treatment of injured lung did not bring out a significant hemodynamic impairment (Fig. 2).

## DISCUSSION

Our results showed no significant alteration in hemodynamic parameters by the administration of perfluorocarbon. Our results illustrate that the combination of PLV and HFOV was well tolerated in terms of hemodynamics. However, we did not demonstrate a significant improvement in gas exchange when perfluorocarbon was added to HFOV.

There have been several investigations that demonstrated the additive effect of the combination of HFOV and perfluorocarbon administration on gas exchange (7, 18–20). Baden et al. (7) reported in their piglet model of saline lavage-induced acute lung injury that low-dose (3 mL/kg) perflubron significantly increased arterial oxygen tension, compared with animals treated with HFOV alone, although additional doses of perflubron beyond the original dose of 3 mL/kg failed to demonstrate significant improvements in oxygenation. They supposed that oxygenation is maximized with only small doses of perflubron in a HFOV setting, and that the increased doses of perflubron are not necessary to further recruit alveoli. However, the absence of attempts to optimize lung volume by modification of HFOV settings according to each successive dose

of perflubron makes their results complicated to interpret. Sukumar et al. (18) also demonstrated that the combination of HFOV and perflubron administration significantly improved gas exchange and hemodynamic variables in preterm lambs with respiratory distress syndrome, compared with animals managed with HFOV alone. However, although HFOV settings were adjusted to achieve optimal gas exchange in both groups of animals, the optimization of gas exchange in HFOV only group was not accomplished over a 5-hr of experiment. The control animals receiving HFOV alone showed continued hypoxia, hypercarbia, and acidosis throughout the study. In the present study, we modified settings as to increase inspiratory time to 50% from 33% and to decrease frequency to 10 Hz from 15 Hz during HFOV, in order to achieve adequate chest vibration in anesthetized piglets immediately after the instillation of perfluorodecalin. We assumed that this might have optimized lung volume at each consecutive dose of 15 mL/kg of perfluorodecalin in our protocol. Actually, the parameters of gas exchange have already recovered to near their pre-injury levels by HFOV alone in our study. This difference in the extent of optimization of gas exchange in HFOV might have led to such a disparity in outcomes. The optimization of lung volume may be important for the proper evaluation of the additive effect of PLV on gas exchange over HFOV alone. However, there is also a possibility that there may be no room for further improvement by addition of PLV, if the injured lung has already recovered fully by HFOV alone. This may be the case in our present study, because the parameters of gas exchange have already recovered to near its pre-injury level by HFOV alone, as mentioned above. This might have influenced on the negative result of our study. The present study was our first study to evaluate the combined effect of HFOV and PLV. In the next step, it may be needed to set a lung injury model that is not recovered fully by HFOV alone, therefore enables us to evaluate, if any synergistic effect of additional PLV.

There have been also several negative studies regarding the combined effect of HFOV and PLV as well as our present study. Investigation of Gothberg et al. with a preterm lamb model of respiratory distress syndrome supports our results,

in which there were no significant differences in arterial oxygen tension or oxygenation index between HFOV and HFOV + PLV group (19). The results of Doctor et al.'s experiment with a swine model of lavage-induced acute lung injury is also similar to ours, in that they did not demonstrate a significant improvement in oxygenation when perflubron was added to HFOV (20). They suggested that there might be a region that, while recruited by perfluorocarbon, is still a source of intrapulmonary shunting, despite the tendency to perflubron to redistribute blood flow to nondependent lung. However, they proposed a possibility that the dose of perflubron they chose might not be optimal to achieve the most efficient gas exchange during the use of HFOV. The dose of perflubron was based on considerable experience with perflubron and conventional mechanical ventilation in larger animals. This is also the case in our study. We employed the dose of perfluorodecalin that was used in our previous study (21). In that study, perfluorodecalin was introduced in a conventional ventilation setting, and showed a dose-response relationship with respect to gas exchange. Therefore, the dose of perfluorodecalin used in that study might have not produced optimal results in our present study where HFOV was used. Doctor et al. (22) recently conducted an investigation to examine dose-response relationships regarding the efficiency of gas exchange and hemodynamic function during the combination of HFOV and PLV with an adult pig model of saline lavage-induced acute lung injury. In that investigation, there was optimal dose of perflubron (between 5 and 15 mL/kg) that enabled them to achieve the lowest oxygenation index during the combination of HFOV and PLV with perflubron. It thus appears that the further experiment concerning dose-response relationship to seek the optimal dose of perfluorodecalin in a HFOV setting deserves to be carried out.

There are reports of more favorable histopathologic outcome in case of the combination of HFOV and PLV (18, 20), although there is also a report of negative study (19). In our present study, the histopathologic data of the animals were not included, and this may be the shortcoming of our study.

In our newborn piglets with saline lavage-induced acute respiratory failure, we concluded that the addition of PLV with 30 mL/kg of perfluorodecalin to HFOV showed no detrimental effect on hemodynamic parameters, but did not produce significant improvement in gas exchange over a three-hour period, compared to HFOV alone.

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