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Cardiovascular responses to high-frequency oscillatory ventilation during acute lung injury in sheep

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Abstract

Purpose. The present study was designed to evaluate pulmonary and systemic hemodynamics and blood gas changes on switching from conventional mechanical ventilation (CMV) to high-frequency oscillatory ventilation (HFOV) in a large animal model of acute lung injury.

Methods. Eleven anesthetised sheep chronically instrumented with vascular monitoring were prepared. Animals received oleic acid ($0.08\,ml \cdot kg^{-1}$) intravenously and were ventilated for 4 h h after the administration of oleic acid. The animals were then randomized into the two following different ventilation modes: CMV (tidal volume [V_T], $6\,ml \cdot kg^{-1}$; respiratory rate [RR], $25 \cdot min^{-1}$) with positive end-expiratory pressure (PEEP) of $12\,cmH_2O$; or CMV under the same settings without PEEP. HFOV was then switched. The setting of mean airway pressure with a fixed stroke volume was changed between 25, 18, and $12\,cmH_2O$ every 20 min. Mean pulmonary artery pressure, pulmonary artery occlusive pressure (Paop), left atrium pressure, systemic arterial pressure, cardiac output (CO), and blood gas composition under each setting were measured before and after HFOV.

Results. Switching to HFOV, from without PEEP, resulted in significant increases in Paop and Pa_{O_2} and a decrease in CO at higher (25, $18\,cmH_2O$) mean airway pressure. However, when changed from low V_T and PEEP, HFOV produced further improvements in oxygenation without any deterioration of cardiovascular depression. Thus, switching to HFOV from CMV with low V_T and high PEEP may have little influence on pulmonary or systemic hemodynamics in acute lung injury.

Conclusion. We conclude that hemodynamic responses are dependent on the predefined setting of PEEP during CMV, and on applied mean airway pressure during HFOV.

Key words Acute lung injury · Open lung strategy · Ventilation-induced lung injury

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Introduction

Mechanical ventilation remains the main type of supportive therapy for patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). However, there is evidence that mechanical ventilation itself may cause progression of the existing lung injury, from overdistension during inspiration, from the repeated opening and closing of alveoli, or from excessive stress at the margins between aerated and atelectatic lung regions [1,2]. Various strategies have been designed to prevent ventilator-induced lung injury. Based on numerous clinical trials, mechanical ventilation using relatively low tidal volumes (V_T) and adequate levels of positive end-expiratory pressure (PEEP) are recommended for managing patients with ARDS requiring mechanical ventilation [3,4].

High-frequency oscillation (HFO) is a ventilation strategy employing very high respiratory frequencies with extremely low V_T [5,6]. HFO ventilation (HFOV) has been demonstrated to have benefits over conventional mechanical ventilation (CMV) in neonatal models of ALI [7], and in neonatal patient populations [8]. Despite disappointing results for HFOV in early clinical trials in adults with ARDS [9–11], there is renewed interest in the application of HFOV in adults with ALI [5,12–15], because of the increasing evidence of the usefulness of the open-lung strategy in the management of ARDS, as described above.

Experimental studies have shown that HFOV, especially with high mean airway pressure, can decrease the venous return of the systemic circulation due to overdistension of the alveoli, which may decrease cardiac output (CO) [16–19]. Furthermore, the net effects of high mean airway pressure and decreased CO may lead to the compression of pulmonary capillaries and increase pulmonary vascular resistance [16–18]. These hemodynamic compromises should be minimized for the clinical application of HFOV. Several clinical trials

have reported a brief but significant increase in pulmonary artery occlusive pressure (Paop) during HFOV [13,14]. In addition, adverse cardiovascular events, including decreases in CO and systemic artery pressure during HFOV, were actually observed in a few adult patients in previous clinical trials [14]. However, the pre-existing physiological conditions in the patients who showed these adverse cardiovascular responses to HFOV were not reported. In addition, results in experimental studies on the effects of HFOV on hemodynamics were conflicting [16–20] and these studies were performed mainly in small animals without injury.

In the present study, we evaluated the pulmonary and systemic hemodynamic and blood gas changes, on switching from CMV with low V_T and adequate PEEP to HFOV, in a large animal model of ALI. In addition, we examined how these effects were modulated by the mean airway pressure applied during HFOV and/or the pre-existing PEEP level of CMV.

Methods

The study protocol was approved by the Institutional Review Board for the Care of Animals of Shinshu University. Care and handling of animals were performed in accordance with the guidelines of the National Institutes of Health.

Animal preparation

Eleven sheep, weighing 35–44 kg, were used. The sheep were anesthetized by the intravenous administration of pentobarbitone sodium at a dose of 12.5 mg·kg^{-1} and then ventilated with 0.5%–1.0% halothane, using positive-pressure ventilation. Through left thoracotomy, we directly implanted a silicone catheter into the left atrium to measure the pressure. A silicone tube was inserted into the thoracic aorta via the carotid artery. An 8-Fr catheter sheath introducer (Cordis Laboratories, Miami, FL, USA) was also placed in the superior vena cava, via the right jugular vein, and a 7-Fr thermodilution Swan-Ganz catheter was passed into the pulmonary artery through the Cordis introducer.

Measurements

Systemic arterial (Psa), pulmonary arterial (Ppa), and left atrial (Pla) pressures were measured continuously and recorded using calibrated pressure transducers (Statham P50; Gould, Statham, Oxnard, CA, USA) and a recorder (WT-68; Nihon Koden, Tokyo, Japan), respectively. Pulmonary artery occlusive pressure (Paop) and CO were measured before and after each experimental setting. CO was determined by the thermodilution method, using a CO computer (model 9520; Edwards, Santa Ana, CA, USA). Pulmonary (PVR) and systemic vascular resistance (SVR) were calculated by the following equations; (mean Ppa–mean Pla)/CO, and mean Psa/CO, respectively. Blood samples for blood gas analysis were drawn from systemic artery lines. Blood gas analysis (Pa_{O_2}, Pa_{CO_2}, and pH) was performed using a blood gas analyzer (ABL-2; Radiometer, Copenhagen, Denmark).

Experimental protocols (Fig. 1)

After surgical preparation, stable baseline was observed for at least 30 min. Then, sheep received administration of oleic acid (0.08 ml·kg^{-1}) intravenously to induce ALI. Animals were infused with normal saline at a rate of 60 ml·h^{-1} and treated by CMV with V_T of 10 ml·kg^{-1} and respiratory rate (RR) of 20·min^{-1} with 70% oxygen for 4 h. The sheep were divided into two experimental groups. For experiment 1 (without PEEP; $n = 6$); before conversion to HFOV, animals were maintained under

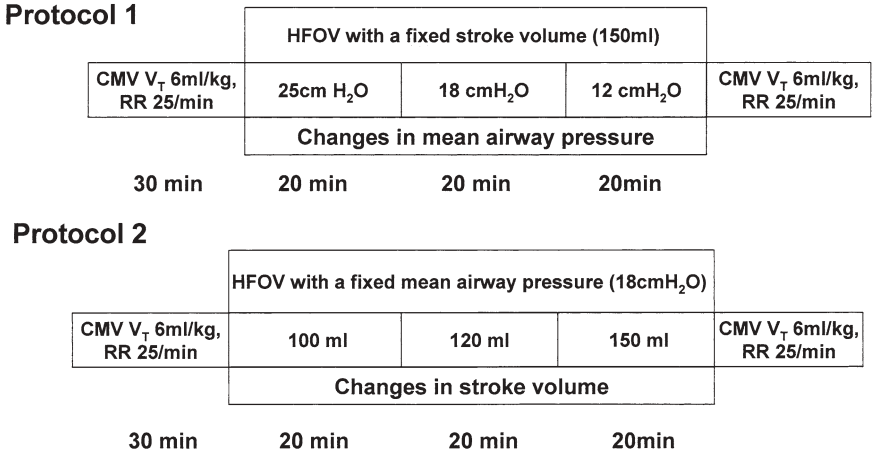

Fig. 1. Experimental protocols and the time course of changes in ventilation mode. These two protocols were performed in both experiment 1 (without positive end-expiratory pressure [PEEP]) and experiment 2 (with PEEP). *CMV*, conventional mechanical ventilation; *HFOV*, high-frequency oscillatory ventilation; V_T, tidal volume; *RR*, respiratory rate

CMV (V_T, 6 ml·kg^{-1}; RR, 25·min^{-1}) without PEEP for 30 min. For experiment 2 (with PEEP; $n = 5$), animals were maintained under CMV (V_T, 6 ml·kg^{-1}; RR, 25·min^{-1}) with 12 cm H_2O PEEP for 30 min. In addition, each experiment consisted of two different protocols during HFOV. In protocol 1, mean airway pressure was changed with a fixed stroke volume and the cardiovascular parameters were measured. The initial mean airway pressure was 25 cm H_2O, with a fixed stroke volume of 150 ml. After observation for 20 min, mean airway pressure was changed to 18 and 12 cm H_2O. The observation was performed for 20 min under each setting. Protocol 2 was then performed after protocol 1; animals were switched to CMV again, with or without PEEP, after the protocol 1 experiment. After stable baseline measurement over 30 min, HFOV was again started, with a fixed mean airway pressure and various stroke volume settings. The first stroke volume setting was 100 ml, with a fixed mean airway pressure of 18 cm H_2O. Using the same time course as that in protocol 1, the stroke volume was changed to 120 ml and 150 ml. These experimental protocols are summarized in Fig. 1. Throughout the experiments, sheep were anesthetised by propofol infusion (3 mg·kg^{-1}·h^{-1}) and paralyzed with pancuronium bromide (0.1 mg·kg^{-1}) initially and as needed to suppress any spontaneous movements. Sodium bicarbonate was not used to correct pH.

In the present study, we used a newly developed HFO ventilator (R100; Metran, Saitama, Japan) for adults. Compared to previous HFO ventilators with a reciprocating pump, this machine has a rotary valve, which can generate higher oscillatory frequency (5–15 Hz) and greater amplitude (approximately 100 ml stroke volume at 15 Hz). This machine also allows the use of conventional mode, including pressure or volume control modes, and pressure supportive ventilation. Thus, the ventilation mode can be switched readily using this apparatus. In the present study, an oscillatory frequency of 15 Hz, percent inspiratory time of 33%, and fraction of inspired oxygen ($F_{I_{O_2}}$) of 0.7 were maintained throughout the experiments. After each step, hemodynamics and blood gas were analyzed. Finally, CMV was controlled (V_T, 6 ml·kg^{-1}; RR, 25·min^{-1}) in the same mechanical mode as that used prior to HFOV, and measurements were repeated.

Statistical analysis

The data values are expressed as means ± SD. Changes in measured variables over time and between groups were analyzed by two-way analysis of variance (ANOVA), and the differences were tested by Fisher's exact test. $P < 0.05$ was accepted as significant.

Results

Comparisons of cardiovascular and blood gas responses to HFOV with various mean airway pressure settings following CMV with and without PEEP (protocol 1)

Hemodynamic responses to HFOV with a fixed stroke volume of 150 ml and blood gas analysis are shown in Tables 1 and 2, respectively. Before switching to HFOV, the values for mean airway pressure during CMV were 4.5 ± 1.3 cmH_2O in experiment 1 (without PEEP) and 16.8 ± 1.0 cmH_2O in experiment 2 (with PEEP). After switching to HFOV in experiment 1, HFOV with 25-cmH_2O mean airway pressure induced significant increases in Paop and Pla, and decreases in CO and Psa. The significant increase in Paop and decrease in CO were sustained in HFOV with 18 cmH_2O. Ppa decreased but the effect was not statistically significant. On the other hand, the values of Paop and Pla in experiment 2 were significantly higher than those in experiment 1 (without PEEP). HFOV with 25 cmH_2O did not cause significant changes in systemic or pulmonary hemodynamic parameters. HFOV resulted in small but significant decreases in Ppa at 18 and 12 cm H_2O, compared to that before HFOV. We calculated the percentage change in Paop after switching to HFOV, and the results are graphed in Fig. 2. The percentage change of Paop during HFOV was increased significantly compared with that in CMV without PEEP, which showed a significant difference from that with PEEP. The P/F ratio improved significantly during HFOV with

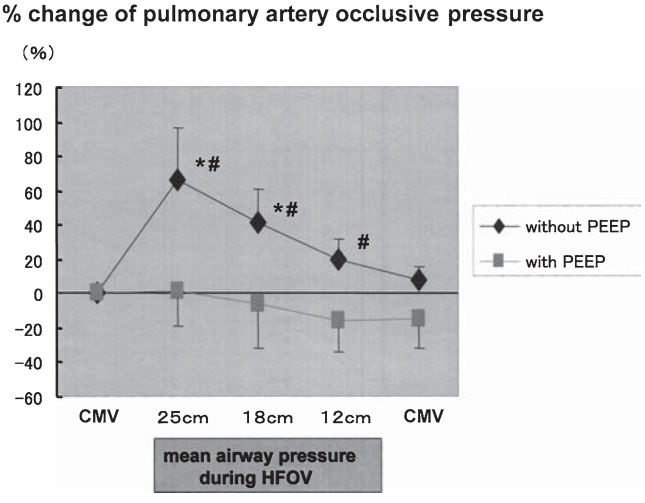

Fig. 2. Comparison of percentage increases in pulmonary artery occlusive pressure (Paop) during high-frequency oscillatory ventilation (*HFOV*) following conventional mechanical ventilation (*CMV*) with and without positive end-expiratory pressure (*PEEP*). *Significantly different from baseline (before HFOV); #significantly different between with and without PEEP

Table 1. Comparison of cardiovascular responses to HFOV with various mean airway pressures and a fixed stroke volume setting following CMV with and without PEEP

Mechanical ventilation	Ppa (cmH_2O)	Paop (cmH_2O)	Pla (cmH_2O)	CO ($l \cdot min^{-1}$)	Psa (mmHg)	PVR ($cmH_2O \cdot l^{-1} \cdot min^{-1}$)	SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$)
Experiment 1							
Baseline (before oleic acid)	19.6 ± 3.5	9.4 ± 0.5	2.8 ± 0.8	3.6 ± 0.9	138.9 ± 10.5	4.9 ± 1.3	41.4 ± 11.7
CMV ($6 ml \cdot kg^{-1}$) without PEEP (before HFOV)	31.2 ± 7.0	8.3 ± 1.0	4.6 ± 0.6	3.3 ± 1.7	125.0 ± 28.5	10.2 ± 6.6	47.5 ± 24.8
HFOV (mean airway pressure/stroke volume)							
25 cmH_2O/150 ml	27.3 ± 4.2	13.7 ± 2.6*	6.1 ± 0.5*	1.8 ± 0.7*	94.4 ± 30.6*	13.0 ± 5.8	61.8 ± 33.6
18 cmH_2O/150 ml	25.3 ± 4.1	11.6 ± 1.9*	5.5 ± 0.8	2.1 ± 0.7*	101.9 ± 31.0	10.2 ± 3.5	55.8 ± 29.2
12 cmH_2O/150 ml	26.5 ± 5.5	9.8 ± 1.2	4.4 ± 0.9	2.4 ± 0.8	111.1 ± 33.7	9.9 ± 4.0	49.3 ± 15.9
CMV ($6 ml \cdot kg^{-1}$) without PEEP (after HFOV)	30.1 ± 8.5	8.8 ± 0.9	4.8 ± 0.9	2.5 ± 0.8	111.1 ± 37.2	11.7 ± 7.6	46.9 ± 18.2
Experiment 2							
Baseline (before oleic acid)	20.0 ± 4.0	8.6 ± 1.0	2.3 ± 1.0	3.3 ± 0.4	122.9 ± 10.7	5.6 ± 1.4	38.4 ± 7.2
CMV ($6 ml \cdot kg^{-1}$) with PEEP (before HFOV)	32.4 ± 3.3	12.6 ± 2.7**	6.9 ± 1.0**	3.2 ± 0.6	106.9 ± 21.0	8.3 ± 1.5	34.8 ± 8.4
HFOV (mean airway pressure/stroke volume)							
25 cmH_2O/150 ml	24.4 ± 3.5	12.5 ± 1.8	7.3 ± 3.8	2.2 ± 1.1	91.7 ± 13.2	7.6 ± 2.0	41.2 ± 8.1
18 cmH_2O/150 ml	22.3 ± 1.8*	11.5 ± 2.3	7.8 ± 2.9	3.0 ± 1.1	95.8 ± 12.3	5.8 ± 3.7	35.9 ± 14.3
12 cmH_2O/150 ml	21.3 ± 8.2*	10.4 ± 2.1	6.0 ± 3.7	4.3 ± 2.1	104.2 ± 16.6	6.0 ± 5.8	30.6 ± 15.9
CMV ($6 ml \cdot kg^{-1}$) with PEEP (after HFOV)	30.3 ± 7.6	10.7 ± 1.5	6.0 ± 2.6	4.3 ± 1.0	96.3 ± 28.0	6.0 ± 2.7	24.2 ± 11.3

*Significantly different from CMV condition (before HFOV); **significantly different between with and without PEEP (both, $P < 0.05$)
CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; baseline, before oleic acid administration; Ppa, pulmonary artery pressure; Paop, pulmonary artery occlusive pressure; Pla, left atrial pressure; CO, cardiac output; Psa, systemic arterial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance

Table 2. Comparison of blood gas analysis following HFOV with various mean airway pressures and a fixed stroke volume setting following CMV with and without PEEP

Mechanical ventilation	P/F ratio	Pa_{CO_2}	pH
Experiment 1			
Baseline (before oleic acid)	421.8 ± 38	36.2 ± 5.5	7.42 ± 0.09
CMV (6 ml·kg^{-1}) without PEEP (before HFOV)	83.8 ± 10.2	72.6 ± 11.6	7.13 ± 0.09
HFOV (mean airway pressure/stroke volume)			
25 cmH_2O/150 ml	136 ± 48.4*	41.7 ± 14.4*	7.24 ± 0.14
18 cmH_2O/150 ml	110.6 ± 31.4	31.7 ± 15.0*	7.29 ± 0.14
12 cmH_2O/150 ml	72.7 ± 13.5	34.3 ± 13.1*	7.35 ± 0.19*
CMV (6 ml·kg^{-1}) without PEEP (after HFOV)	81.1 ± 13.2	67.1 ± 13.3	7.14 ± 0.14
Experiment 2			
Baseline (before oleic acid)	443.2 ± 44.2	30.8 ± 8.9	7.45 ± 0.08
CMV (6 ml·kg^{-1}) with PEEP (before HFOV)	99.6 ± 1.9	54.8 ± 5.6	7.17 ± 0.07
HFOV (mean airway pressure/stroke volume)			
25 cmH_2O/150 ml	159.2 ± 38.5*	26.0 ± 3.3*,**	7.46 ± 0.08*,**
18 cmH_2O/150 ml	232.6 ± 97.9*	22.9 ± 4.6*,**	7.53 ± 0.14*,**
12 cmH_2O/150 ml	85.9 ± 5.9	24.9 ± 8.3*,**	7.53 ± 0.2*,**
CMV (6 ml·kg^{-1}) with PEEP (after HFOV)	144.1 ± 65.5	56.7 ± 11.4	7.14 ± 0.15

* Significantly different from CMV condition (before HFOV); ** significantly different between with and without PEEP (both, $P < 0.05$)
CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; baseline, before oleic acid administration

25 cmH_2O and Pa_{CO_2} fell significantly during HFOV in both experiments regardless of the mean airway pressure (Table 2). In addition, the acid-base balance also improved after switching to HFOV. There were significant differences in Pa_{CO_2} and pH between experiments with and without PEEP.

Comparisons of cardiovascular and blood gas responses to HFOV with various stroke volume settings following CMV with and without PEEP (protocol 2)

The values for mean airway pressure during CMV were 4.3 ± 0.8 cmH_2O without PEEP and 17.0 ± 1.4 cmH_2O with PEEP. The hemodynamic responses and results of blood gas analysis with a fixed mean airway pressure of 18 cmH_2O are shown in Tables 3 and 4, respectively. The cardiovascular responses were similar to those at a mean airway pressure of 18 cmH_2O mentioned above in protocol 1. Likewise, as in the protocol 1 experiment, Paop and Pla in CMV with PEEP were significantly higher than these values without PEEP. Paop rose significantly during HFOV regardless of the stroke volume value when switched from CMV without PEEP, but not with PEEP. Following the changes in stroke volume, CO in experiment 1 and Ppa in experiment 2 decreased significantly at a stroke volume of 150 ml. The changes in the P/F ratio improved significantly with higher stroke volume in experiment 1, and Pa_{CO_2} fell significantly regardless of the stroke volume value in both experiment 1 and experiment 2 (Table 4). Higher stroke volume was associated with a tendency toward a decrease in Pa_{CO_2}. There were significant differences in Pa_{CO_2} and pH between experiments with and without PEEP.

Discussion

In the present study, we examined the effects of conversion to HFOV from CMV on the systemic and pulmonary hemodynamics in a large animal model of acute lung injury (ALI). When ventilated with low V_T and adequate PEEP in CMV, switching to HFOV with relatively higher mean airway pressure produced improved oxygenation without any cardiovascular depression. With a lower mean airway pressure, oxygenation worsened. In contrast, switching to HFOV from CMV without PEEP caused a significant increase in Paop and a decrease in CO and Psa. Thus, the hemodynamic changes after HFOV were dependent on the mean airway pressure applied during HFOV and on PEEP during prior CMV. Compared with the changes in hemodynamic parameters following various mean airway pressure settings, the changes of stroke volume of HFOV had little effect on the hemodynamics.

Hemodynamic changes, including decreases in CO and increases in Paop during HFOV, were observed in previous clinical [13,14] and experimental [18] studies. Especially, the decrease in CO was parallel with the elevated mean airway pressure applied during HFOV [17–19]. Indeed, when we changed from CMV without PEEP, we found decreased CO at higher mean airway pressure settings. The initial mean airway pressure for HFOV has usually been set at 2–5 cm H_2O higher than that observed during CMV [9–15]. When compared with the initial mean airway pressure used during HFOV in other experimental and clinical studies, the initial mean airway pressure of 25 cmH_2O used in the present study was slightly higher than the recommended initial

Table 3. Comparison of cardiovascular responses to HFOV with various stroke volumes and a fixed mean airway pressure setting following CMV with and without PEEP

Mechanical ventilation	Ppa (cmH_2O)	Paop (cmH_2O)	Pla (cmH_2O)	CO ($l \cdot min^{-1}$)	Psa (mmHg)	PVR ($cmH_2O \cdot l^{-1} \cdot min^{-1}$)	SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$)
Experiment 1							
Baseline (before oleic acid)	19.6 ± 3.5	9.4 ± 0.5	2.8 ± 0.8	3.6 ± 0.9	138.9 ± 10.5	4.9 ± 1.3	41.4 ± 11.7
CMV ($6 ml \cdot kg^{-1}$) without PEEP (before HFOV)	28.3 ± 2.2	9.3 ± 1.9	5.3 ± 1.2	5.0 ± 2.7	131.1 ± 25.5	6.9 ± 4.4	36.6 ± 25.4
HFOV (mean airway pressure/stroke volume)	31.4 ± 3.4	11.2 ± 1.5*	4.9 ± 1.4	3.9 ± 1.5	112.2 ± 32.5	8.6 ± 3.9	34.8 ± 22.1
18 cmH_2O/100 ml							
18 cmH_2O/120 ml	27.8 ± 2.2	11.9 ± 1.2*	6.0 ± 1.3	2.8 ± 1.5	101.1 ± 33.4	11.5 ± 6.2	48.7 ± 37.4
18 cmH_2O/150 ml	25.7 ± 1.9	12.0 ± 1.2*	6.6 ± 0.9	2.5 ± 1.1*	88.9 ± 30.4	12.2 ± 9.7	49.4 ± 42.3
CMV ($6 ml \cdot kg^{-1}$) without PEEP (after HFOV)	28.5 ± 8.8	8.4 ± 1.4	5.2 ± 1.3	3.1 ± 1.7	111.1 ± 34.8	9.0 ± 4.8	44.2 ± 26.6
Experiment 2							
Baseline (before oleic acid)	20.0 ± 4.0	8.6 ± 1.0	2.3 ± 1.0	3.3 ± 0.4	122.9 ± 10.7	5.6 ± 1.4	38.4 ± 7.2
CMV ($6 ml \cdot kg^{-1}$) with PEEP (before HFOV)	31.8 ± 2.8	12.3 ± 1.8**	6.9 ± 0.5**	3.3 ± 0.5	111.1 ± 23.6	7.7 ± 1.3	34.2 ± 6.9
HFOV (mean airway pressure/stroke volume)							
18 cmH_2O/100 ml	26.0 ± 8.7	9.8 ± 1.4	5.0 ± 3.0	3.6 ± 0.9	100.0 ± 10.0	6.6 ± 4.7	29.3 ± 8.2
18 cmH_2O/120 ml	24.4 ± 5.8	10.0 ± 1.3	6.0 ± 2.0	3.8 ± 1.7	100.0 ± 11.1	6.2 ± 5.2	30.0 ± 8.1
18 cmH_2O/150 ml	23.0 ± 2.7*	11.4 ± 2.2	7.8 ± 2.2	3.0 ± 0.9	98.6 ± 11.5	5.8 ± 3.6	34.9 ± 9.7
CMV ($6 ml \cdot kg^{-1}$) with PEEP (after HFOV)	31.5 ± 5.2	10.8 ± 1.0	6.7 ± 1.5	4.0 ± 1.0	113.0 ± 14.0	6.5 ± 2.7	29.0 ± 4.2

*Significantly different from CMV condition (before HFOV); **significantly different between with and without PEEP (both, $P < 0.05$)

setting. However, in the present study, there was no cardiovascular depression when switching to HFOV from CMV with adequate PEEP.

The degree of increase in Paop was also associated with HFOV with elevated mean airway pressure [18]. The mechanism underlying the elevation of Paop has been proposed to be the extramural compression of pulmonary capillaries caused by increased alveolar pressure, which may be similar to the mechanism of PEEP [21,22]. The high pressure in the alveolar space leads to an increase in intrathoracic pressure, resulting in an increase in left-ventricular filling pressure [21,22]. We checked the left atrial pressure in the present study and found slightly elevated left atrial pressure during HFOV and/or CMV with PEEP. Although the elevation was not always significant, these results suggested an increase in intrathoracic pressure during HFOV and PEEP.

We compared these physiological changes with those on switching to HFOV from CMV without PEEP. A decrease in CO and an increase in Paop were noted on switching from CMV without PEEP. Although conversion to HFOV from CMV without PEEP is clinically uncommon, our findings suggested that the deterioration of cardiovascular responses to HFOV is dependent on the prior PEEP level during CMV. Thus, when we switch to HFOV, we should confirm the pre-existing ventilation condition and take into consideration the possibility that decreases in CO and/or Psa can occur in patients with ALI/ARDS during HFOV.

Ppa decreased after conversion to HFOV during ALI. In particular, Ppa was significantly decreased from the value seen in CMV with PEEP. In the present study, HFOV with higher mean airway pressure improved gas exchange and reversed respiratory acidosis during ALI. Acute respiratory acidosis can cause pulmonary hypertension [23,24] and may potentiate hypoxic pulmonary hypertension [25]. Thus, the decreased Ppa was mainly reflected by the improvement of blood gas parameters.

PVR was unchanged during HFOV in the present study. Traverse et al. [17] reported increased PVR during HFOV in the normal lung. A linear increase in PVR was observed with the elevation of mean airway pressure [17], the mechanism of which was shown to be the compression of pulmonary capillaries due to the increased intraalveolar pressure, which may cause an increase in right ventricular afterload. Indeed, when alveolar pressure exceeds pulmonary venous and capillary pressure, there is a possibility of decreased pulmonary blood flow and increased PVR [26,27]. There were no significant differences in the time course of PVR while switching from CMV to HFOV in the present study, which was consistent with the results of another experimental study of ALI [20].

Table 4. Comparison of blood gas analysis following HFOV with various stroke volumes and a fixed mean airway pressure setting following CMV with and without PEEP

Mechanical ventilation	P/F ratio	Pa_{CO_2}	pH
Experiment 1			
Baseline (before oleic acid)	421.8 ± 38.0	36.2 ± 5.5	7.42 ± 0.09
CMV (6 ml·kg^{-1}) without PEEP (before HFOV)	89.9 ± 21.5	71.7 ± 8.9	7.14 ± 0.14
HFOV (mean airway pressure/stroke volume)			
18 cmH_2O/100 ml	87.1 ± 19.2	58.9 ± 23.9	7.21 ± 0.19
18 cmH_2O/120 ml	137.3 ± 81.5*	47 ± 22.8*	7.27 ± 0.2
18 cmH_2O/150 ml	136 ± 48.4*	41.7 ± 14.4*	7.24 ± 0.14
CMV (6 ml·kg^{-1}) without PEEP (after HFOV)	82.1 ± 12.7	69.1 ± 12.4	7.22 ± 0.13
Experiment 2			
Baseline (before oleic acid)	443.2 ± 44.2	30.8 ± 8.9	7.45 ± 0.08
CMV (6 ml·kg^{-1}) with PEEP (before HFOV)	95.6 ± 6.8	58.1 ± 4.8	7.19 ± 0.07
HFOV (mean airway pressure/stroke volume)			
18 cmH_2O/100 ml	93.4 ± 12.9	33.3 ± 10.7*,**	7.43 ± 0.20*,**
18 cmH_2O/120 ml	89.6 ± 3.6	27.6 ± 6.8*,**	7.52 ± 0.20*,**
18 cmH_2O/150 ml	226.9 ± 83.5*	24.8 ± 4.0*,**	7.52 ± 0.01*,**
CMV (6 ml·kg^{-1}) with PEEP (after HFOV)	149.8 ± 76	58.9 ± 10.6	7.14 ± 0.12

* Significantly different from CMV condition (before HFOV); ** significantly different between with and without PEEP (both, $P < 0.05$)
CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; baseline, before oleic acid administration

There were some limitations of our study. We did not examine the effects of prolonged use of HFOV on the hemodynamics. Even slight changes in CO and/or Paop may influence microvascular fluid exchange in the lung. Pulmonary microvascular fluid exchange is an important factor in the treatment of patients with ALI/ARDS. The fluid balance may be influenced by the gradient between intracapillary and alveolar pressure. In an air embolism model, HFOV did not impair lymphatic balance during injury, compared with that during CMV [20]. In addition, HFOV, compared with CMV decreased lung damage in various experimental models of ALI in small animals [7]. However, the effect of HFOV on microvascular fluid exchange in the lung and progression to systemic inflammation from the lung may be an important issue for the clinical use of HFOV.

In summary, in a large animal model of ALI we showed that HFOV with an adequate mean airway pressure level led to improved oxygenation during ALI, without any adverse effects on cardiovascular parameters. The pulmonary and systemic circulation after HFOV was largely mediated by the mean airway pressure applied during HFOV and by the prior PEEP level during CMV. HFOV is a promising alternative open-lung strategy. We believe that HFOV is a safe and effective strategy for patients with ALI/ARDS, but further basic and clinical studies will be needed to determine the optimal settings for the application of HFOV.

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