

EFFECTS OF HIGH-FREQUENCY OSCILLATORY VENTILATION AND PARTIAL LIQUID VENTILATION ON ACUTE LUNG INJURY INDUCED BY STEAM INHALATION IN NEW ZEALAND RABBITS

Wang S.-G., Guo G.-H., Fu Z.-H., Zhou S.-F.

Burn Institute of the First Affiliated Hospital, An Hui Medical University, Nanchang, People's Republic of China

SUMMARY. Objective: to investigate the beneficial effects of high-frequency oscillatory ventilation (HFOV) and partial liquid ventilation (PLV) in treating acute lung injury induced by steam inhalation. Design: a prospective, randomized, controlled, multiple-group study. Setting: an animal research centre laboratory in a university burns centre. Subjects: New Zealand rabbits ($n = 30$; 2.25 ± 0.25 kg) of either sex. Interventions: the animals were ventilated by HFOV with a mean airway pressure of 10 cm H₂O, a frequency of 10 Hz, an amplitude of 20 cm H₂O, an I:E ratio of 1:1, and an FiO₂ of 1.0. After the induction of acute lung injury by steam inhalation, the animals were randomly assigned to receive either HFOV alone or a combined therapy of HFOV + PLV. The animals were grouped as HFOV, HFOV + PLV, and control group (without ventilation after recovery from muscular relaxation). Measurements and main results: arterial blood gases, cardiovascular haemodynamics, dynamic lung compliance, and total lung injury scores were measured. After steam inhalation, all three groups displayed low PaO₂ and low dynamic lung compliance. In the control group all the animals died within 3 h. In the HFOV and HFOV + PLV groups, all the animals displayed significant improvements in dynamic lung compliance, oxygenation, and histological outcomes; HFOV + PLV showed the best results. Conclusion: in a New Zealand rabbit model of steam inhalation injury, HFOV improved oxygenation, increased dynamic lung compliance, and alleviated lung histological injury. Combined therapy with HFOV + PLV was clearly superior to that with HFOV alone during the observation period.

Introduction

Severe steam inhalation injury can cause acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and respiratory failure, which have been researched in our university medical centre for nearly twenty years, showing high mortality and morbidity both clinically and in the laboratory. ALI is known to have many pathophysiological consequences, including diffuse bronchoalveolar damage, pulmonary oedema, lung inflammation, surfactant deficiency, and deterioration of pulmonary function, and it may progress to ARDS.¹⁻³ Patients with ALI have a high mortality and often require the assistance of mechanical ventilation, which may further aggravate the ALI owing to the risk of barotraumas, volutraumas, and biotraumas.⁴ For these reasons a search for an optimal therapy of respiratory care to treat these patients is warranted.

To improve respiratory support and diminish the risk of chronic lung disease, high-frequency oscillatory ventilation (HFOV) was developed as a rescue and lung-protective ventilation strategy. Chronic lung disease can be reduced in pre-term infants using HFOV and a defined strategy to improve alveolar recruitment.^{5,6} HFOV has the characteristics of low tide volume, high frequency, and a constant, less variable airway pressure, which are an optimal ventilation mode for ARDS. It allows stable lung in-

flation and the recruitment of alveolar space, reduces the risks of high peak airway pressure and airway stretching, and improves V/Q matching. It is also reported that HFOV can suppress the inflammatory response of lung tissue and alveolar macrophages.⁷ It can therefore be considered the best ventilatory mode for ALI/ARDS.

PLV with perfluorocarbon (PFC) is performed by using a high-frequency oscillatory ventilator and filling the lungs with a volume of PFC liquid equal to the functional residual capacity.^{8,9} PFC is a liquid with high solubility for oxygen and CO₂. Therefore, when a gas is delivered by a ventilator during PLV, oxygenated PFC liquid can convey oxygen to, and remove CO₂ from, the alveoli, including collapsed units in injured lungs, thus improving gas exchange in a situation of ALI/ARDS.^{8,9} It has been suggested that PLV improves lung compliance, minimizes the risk of barotraumas, clears airway debris, washes out inflammatory mediators, and reduces pathological fluid infiltration in injured lungs; it has also been found that the washing, cleaning, and clearing of PLV are especially suitable for steam inhalation injury.¹⁰

Some animal and clinical studies have demonstrated the beneficial effects both of HFOV alone and of HFOV with PFC pre-treatment on ALI induced by causes other than steam inhalation.^{11,12} Hence it would seem that additional experimental data are required to define the roles of

HFOV alone and the combination of HFOV with PLV for steam inhalation injury.

In the present study we aimed to investigate two issues: 1. How HFOV can improve oxygenation, increase lung compliance, and alleviate lung histological injury in treating ALI induced by steam inhalation injury; 2. whether the combined therapy of HFOV and PLV possesses synergism in the treatment of steam inhalation.

Materials and methods

All the protocols used in this study were in accordance with the guide for the care and use of laboratory animals published by the National Institute of Health and were approved by the Committee of Jiangxi Science Council, Nanchang, China.

Animal preparation. New Zealand rabbits, 2.25 ± 0.25 kg, were anaesthetized with intramuscularly administered atropine (0.1 mg/dose) and ketamine (40 mg/kg/dose) before the surgical procedures. All animals were placed in a supine position for tracheostomy. After placing of a 4.0-mm inside-diameter Portex uncuffed tracheal tube, HFOV was established using a volume-controlled infant ventilator (SLE5000, UK) with an MAP of 10 cm H₂O, a frequency of 10 Hz, an amplitude of 20 cm H₂O, an I:E ratio of 1:1, and an FiO₂ of 1.0 under muscular relaxation. These ventilatory settings were kept constant throughout the experiments. A 4-Fr double-lumen catheter (Arrow, USA) was inserted into the right jugular vein for infusion, sedation, and muscular relaxation and for the monitoring of central venous pressure (CVP). After induction of anaesthesia, normal saline was infused at a rate of 15 ml/kg/h. A 3.5-Fr umbilical vessel catheter (Arrow, USA) was placed in the left carotid artery for continuous recording of arterial pressure. A fine cannula catheter was placed in the right femoral artery for blood sampling. Body temperature was maintained at approximately 39 ± 0.5 °C throughout the experiment with a servo-controlled heating blanket.

Physiological monitoring. Throughout the experiment, CVP and carotid mean blood pressure were monitored and recorded every hour using pressure transducers on a multi-channel thermal array recorder (Japan). Respiratory flow and ventilator mechanical parameters were monitored continuously during observation of the experiment and recorded every hour via the monitoring device of the SLE 5000 infantile ventilator; the ventilation mode was changed to conventional mandatory ventilation with a tidal volume of 10 ml/kg, a frequency of 30 cycles/min, an I:E ratio of 1:1, and an FiO₂ of 1.0. Arterial blood samples were taken for measurements of pH, PaO₂, PaCO₂, and oxygen saturation using an automatic blood gas system (Denmark).

Steam generation and induction of ALI. Steam came from a controlled temperature and pressure electronic de-

vice made by our own university.¹³ When the parameter settings of temperature (110 °C) and pressure (0.04 mPa/cm²) were obtained, the ejecting time was adjusted to 1 sec. The steam of 1 sec was ejected from the rubber tube, which caused repeated scalding by ejecting steam into the intubation of prepared rabbits three times. The steam scalding interval was 5 min. After steam inhalation, the animals were observed for 60 min, during which time they were given an additional 100 ml of normal saline. Arterial blood gases were measured every 10 min until PaO₂ decreased to 200 mm Hg at FiO₂ 1.0 and Cdyn decreased to 60% of the mean pre-injury value. Animals not matching the criteria were excluded.

PLV. After induction of ALI the lungs were filled with room-temperature, pre-oxygenated (bubbling with pure oxygen 3-5 ml/min for 5 min) PFC (6 ml/kg/h, once per h [England]), via a side port of the endotracheal tube adaptor within 5-10 min. Gas ventilation of the liquid-filled lungs was continued at pre-installation settings.

Histological preparations and examinations. Immediately after excision, the airways and lungs were fixed by immersion in a 10% formaldehyde solution for 24 h. Four blocks (0.5-1.0 cm³), including non-dependent and dependent sites of the right lung, were obtained. Tissue specimens were embedded in paraffin and cut into sections, which were subsequently stained with haematoxylin and eosin. The sections were examined in blinded manner using light microscopy and scored by a qualified pathologist using a quantitative scoring system. The injury variables scored were alveolar and interstitial inflammation, alveolar and interstitial haemorrhage, oedema, atelectasis, and necrosis, as described in other studies. Injury severity was graded according to the following scale: no injury = 0; injury to 25% of field = 1; injury to 50% of field = 2; injury to 75% of field = 3; diffuse injury = 4. Multiple (>10) fields of section for each tissue sample were examined in order to minimize regional variations.

Experimental protocol. In total, 30 animals were used in this study. After initial instrumentation, stabilization, and measurement of pre-injury base data, ALI was induced by steam inhalation. After induction of ALI, a period of 60 min was allowed for stabilization before post-injury physiological data were measured. Three animals did not reach the criteria of ALI at 60 min after induction and were thus excluded from the study. After meeting the ALI criteria, 27 animals were then randomly assigned to one of three groups: 1. HFOV group (n = 9), treated with HFOV only; 2. HFOV + PLV group (n = 9), treated with a combined therapy of HFOV and PFC; 3. control group (n = 9), no ventilation treatment. Physiological post-therapy data were measured at 1-h intervals for a total of 4 h or until death. At the end of the observation period, the animals were euthanized with a high dose of 15% potassium chloride. After the animals had been euthanized, the

Table I - Effects of steam inhalation on gas exchange, dynamic compliance, and haemodynamic variables in three groups of New Zealand rabbits

Time	Group	Weight (kg)	Age (days)	pH	PaO ₂ (mm Hg)	PaCO ₂ (mm Hg)	Heart rate (beats/min)
Pre-injury	Control	2.25 ± 0.21	80 ± 3	7.37 ± 0.04	474.5 ± 21.35	35.0 ± 2.67	230 ± 16
	HFOV	2.47 ± 0.18	80 ± 2	7.41 ± 0.06	482.4 ± 27.66	35.1 ± 2.96	218 ± 17
	HFOV+PLV	2.45 ± 0.27	80 ± 4	7.39 ± 0.04	479.2 ± 19.28	34.8 ± 2.75	220 ± 14
Post-injury	Control	–	–	7.28 ± 0.05 ^a	160.6 ± 17.19 ^a	29.3 ± 3.19	230 ± 18
	HFOV	–	–	7.26 ± 0.04 ^a	158.0 ± 19.42 ^a	30.5 ± 3.66	225 ± 16
	HFOV+PLV	–	–	7.29 ± 0.08 ^a	163.1 ± 21.33 ^a	29.9 ± 2.82	231 ± 21

Time	Group	MBP (mm Hg)	CVP (cm H ₂ O)	Cdyn (ml/cm H ₂ O/kg)	Resistance (cm H ₂ O/l/s)
Pre-injury	Control	78 ± 3	3 ± 1	1.52 ± 0.13	175.36 ± 28.26
	HFOV	76 ± 2	3 ± 1	1.49 ± 0.11	168.28 ± 31.42
	HFOV+PLV	75 ± 2	3 ± 0	1.50 ± 0.20	170.64 ± 29.97
Post-injury	Control	77 ± 3	2 ± 1	0.75 ± 0.11 ^a	239.52 ± 23.15 ^a
	HFOV	76 ± 3	2 ± 0	0.73 ± 0.14 ^a	240.49 ± 23.15 ^a
	HFOV+PLV	75 ± 2	2 ± 1	0.78 ± 0.17 ^a	237.56 ± 21.87 ^a

Cdyn = dynamic lung compliance; MBP = mean arterial pressure; CVP = central venous pressure; resistance = airway resistance; control = no ventilation; HFOV = high-frequency oscillatory ventilation alone; HFOV+PLV = combined therapy of HFOV+PLV; PLV = partial liquid ventilation.

^a $p < 0.05$ vs the corresponding pre-injury data.

Data are expressed as the mean ± SEM

Table II - Changes in arterial PaO₂, PaCO₂, and pH over time in New Zealand rabbits with steam inhalation injury in the various treatment groups

Time point	PaO ₂ (mm Hg)			PaCO ₂ (mm Hg)		
	Control	HFOV	HFOV+PLV	Control	HFOV	HFOV+PLV
0 h	161.6 ± 19.4	158.5 ± 17.7	163.1 ± 21.3	29.3 ± 3.1	30.5 ± 3.6	29.5 ± 2.8
1 h	76.5 ± 17.4	285.7 ± 23.4 ^a	297.7 ± 18.4 ^{ab}	46.1 ± 9.7	31.4 ± 2.8	35.5 ± 7.1
2 h	40.4 ± 24.6	318.6 ± 24.2 ^a	340.6 ± 30.6 ^{ab}	66.8 ± 8.5	35.5 ± 2.9	40.4 ± 2.2
3 h	–	241.5 ± 26.1 ^a	279.8 ± 40.2 ^{ab}	–	41.7 ± 2.8	42.3 ± 3.5
4 h	–	198.6 ± 36.1 ^a	225.8 ± 38.4 ^{ab}	–	51.7 ± 7.9	50.2 ± 6.5

Time point	pH		
	Control	HFOV	HFOV+PLV
0 h	7.28 ± 0.05	7.26 ± 0.04	7.29 ± 0.03
1 h	7.02 ± 0.35	7.32 ± 0.03 ^a	7.41 ± 0.03 ^a
2 h	6.67 ± 0.16	7.40 ± 0.04 ^a	7.40 ± 0.02 ^a
3 h	–	7.38 ± 0.05 ^a	7.43 ± 0.04 ^a
4 h	–	7.31 ± 0.04 ^a	7.32 ± 0.01 ^a

Control = no ventilation; HFOV = high-frequency oscillatory ventilation alone; HFOV+PLV = combined therapy of HFOV+PLV; PLV = partial liquid ventilation.

Within-group analysis: ^a $p < 0.05$ vs post-injury. Between-group analysis: ^b $p < 0.05$.

Data are expressed as the mean ± SEM.

trachea was clamped at the end of expiration with a positive end-expiratory pressure of 5 cm H₂O and the lungs were removed for histological preparations.

Statistical analysis. For each time point measured (pre-injury, post-injury, post-treatment), comparisons of car-

diopulmonary data among the groups were evaluated by one-way analysis of variance, followed by Fisher's least significant difference procedure when appropriate. Comparisons of baseline and post-injury data within each group were made using a paired Student's *t*-test. A two-way re-

peated measures analysis of variance on a one-factor general linear model was further used to compare the continuous cardiopulmonary data as a function of both time and group, followed by the Student-Newman-Keuls test for multiple comparisons. The histological scores were compared using the Kruskal-Wallis test followed by the Mann-Whitney U test for pair-wise comparisons. The data are presented as the mean $\pm$ SEM. Significance was accepted at the $p < 0.05$ level.

Results

Mean body weight and age did not vary significantly in the three groups (*Table I*). Also, before steam inhalation, the mean arterial blood gases, arterial pH, Cdyn, heart rate, MAP, and CVP did not vary in the three groups (*Table I*). Immediately after induction of ALI, all the animals developed evidence of severe lung injury characterized by a significant decrease in mean Cdyn to a value of less than 60% of its baseline, a dramatic increase in mean airway resistance up to a value of more than 150% of its baseline, and a dramatic decrease in mean PaO₂ to a level of less than 200 mm Hg (*Table I*). In addition, a significant decrease in mean arterial pH after steam inhalation

was noted (*Table I*). However, mean PaCO₂, heart rate, MAP, and CVP did not significantly change in these animals immediately after induction of ALI (*Table I*).

Changes in arterial blood gases and arterial pH during the 4-h observation period are presented in *Table II*. As can be seen, the mean values of PaO₂/FiO₂ with HFOV treatment displayed a trend of improvement over time compared with post-injury. HFOV + PLV showed better results with PaO₂/FiO₂ over time versus the HFOV group, and the control group had the worst result, with all animals dying within 3 h. Both the HFOV and the HFOV + PLV groups had their best PaO₂ at the 2-h time point. However, the changes in the mean values of PaCO₂ and pH fluctuated over time, without attaining statistical significance regarding HFOV and HFOV + PFC, except when comparing the corresponding post-injury values.

Table III shows the changes in heart rate, MAP, and CVP during the 4-h observation period. In the HFOV and the HFOV + PLV groups, the mean values of heart rate, MAP, and CVP remained fairly stable over time, except that the heart rate and MAP measured at the 4-h time point were significantly lower.

Table IV shows the changes in Cdyn and resistance during the 4-h observation period. There were significant

Table III - Changes in heart rate (HR), mean blood pressure (MBP), and central venous pressure (CVP) over time in New Zealand rabbits with steam inhalation injury in the various treatment groups

Time point	Control	HR HFOV	HFOV+PLV	Control	MBP HFOV	HFOV+PLV	Control	CVP HFOV	HFOV+PLV
0 h	230 $\pm$ 18	225 $\pm$ 16	231 $\pm$ 21	77 $\pm$ 3	76 $\pm$ 3	75 $\pm$ 2	3 $\pm$ 1	3 $\pm$ 1	3 $\pm$ 1
1 h	320 $\pm$ 28	215 $\pm$ 25	312 $\pm$ 12	63 $\pm$ 5	77 $\pm$ 4	77 $\pm$ 2	3 $\pm$ 2	3 $\pm$ 1	3 $\pm$ 1
2 h	83 $\pm$ 34	210 $\pm$ 29	310 $\pm$ 14	32 $\pm$ 8	78 $\pm$ 3	76 $\pm$ 2	3 $\pm$ 2	3 $\pm$ 2	3 $\pm$ 2
3 h	–	228 $\pm$ 26	314 $\pm$ 20	–	72 $\pm$ 4	73 $\pm$ 3	–	4 $\pm$ 2	4 $\pm$ 2
4 h	–	160 $\pm$ 28 ^a	180 $\pm$ 12 ^a	–	50 $\pm$ 5 ^a	51 $\pm$ 3 ^a	–	4 $\pm$ 2	4 $\pm$ 2

Control = no ventilation; HFOV = high-frequency oscillatory ventilation alone; HFOV+PLV = combined therapy of HFOV+PLV; PLV = partial liquid ventilation.

Within-group analysis: ^a $p < 0.05$ vs post-injury.

Data are expressed as the mean $\pm$ SEM.

Table IV - Changes in dynamic lung compliance (Cdyn) and airway resistance over time in New Zealand rabbits with steam inhalation injury in the various treatment groups

Time point	Control	Cdyn (ml/cmH ₂ O/kg) HFOV	HFOV+PLV	Control	Resistance (cmH ₂ O/l/s) HFOV	HFOV+PLV
0 h	0.75 $\pm$ 0.11	0.73 $\pm$ 0.14	0.79 $\pm$ 0.17	239.5 $\pm$ 17.8	240.4 $\pm$ 23	237.5 $\pm$ 21.8
1 h	–	0.97 $\pm$ 0.18 ^a	1.04 $\pm$ 0.25 ^a	–	210.3 $\pm$ 26.4 ^a	200.8 $\pm$ 20.1 ^a
2 h	–	1.30 $\pm$ 0.28 ^a	1.42 $\pm$ 0.11 ^{ab}	–	208.6 $\pm$ 20.7 ^a	170.4 $\pm$ 18.9 ^{ab}
3 h	–	1.18 $\pm$ 0.24 ^a	1.26 $\pm$ 0.29 ^{ab}	–	225.8 $\pm$ 25.5 ^a	190.3 $\pm$ 24.2 ^{ab}
4 h	–	0.84 $\pm$ 0.26 ^a	0.97 $\pm$ 0.25 ^{ab}	–	236.4 $\pm$ 34.2	201.4 $\pm$ 42.2 ^{ab}

Control = no ventilation; HFOV = high-frequency oscillatory ventilation alone; HFOV+PLV = combined therapy of HFOV+PLV; PLV = partial liquid ventilation.

Within-group analysis: ^a $p < 0.05$ vs post-injury. Between-group analysis: ^b $p < 0.05$.

Data are expressed as the mean $\pm$ SEM.

Table V - Lung injury scores in New Zealand rabbits with steam inhalation injury in the various treatment groups

Group		Alveolar inflammation	Interstitial inflammation	Alveolar haemorrhage	Interstitial haemorrhage
HFOV	Mean	0.7 ± 0.2	0.9 ± 0.4	1.5 ± 0.5 ^a	1.1 ± 0.4
	Dependent	0.8 ± 0.1	1.0 ± 0.3	1.7 ± 0.6	1.2 ± 0.5
	Nondependent	0.4 ± 0.2 ^b	0.8 ± 0.4	1.4 ± 0.3 ^b	1.1 ± 0.3
HFOV + PLV	Mean	0.4 ± 0.2 ^a	0.9 ± 0.3	1.2 ± 0.3 ^a	1.0 ± 0.5
	Dependent	0.5 ± 0.1 ^a	0.9 ± 0.2	1.3 ± 0.3 ^a	1.1 ± 0.3
	Nondependent	0.3 ± 0.2	0.9 ± 0.4	1.1 ± 0.4 ^a	1.0 ± 0.5

Group		Oedema	Necrosis	Atelectasis	Total
HFOV	Mean	2.2 ± 0.3	0.9 ± 0.5	1.9 ± 0.5	9.2 ± 0.4
	Dependent	2.3 ± 0.4	0.9 ± 0.6	2.1 ± 0.6	10.1 ± 0.3
	Nondependent	2.1 ± 0.2	0.9 ± 0.3	1.8 ± 0.3	8.7 ± 0.2
HFOV + PLV	Mean	1.6 ± 0.2 ^a	0.9 ± 0.3	1.4 ± 0.5 ^a	7.3 ± 0.3 ^a
	Dependent	1.6 ± 0.6 ^a	0.9 ± 0.4	1.7 ± 0.5 ^a	8.1 ± 0.4 ^a
	Nondependent	1.5 ± 0.3	0.9 ± 0.1	1.3 ± 0.4 ^a	7.0 ± 0.3 ^a

Control = no ventilation; HFOV = high-frequency oscillatory ventilation alone; HFOV+PLV = combined therapy of HFOV+PLV; PLV = partial liquid ventilation.

^a $p < 0.05$ vs the HFOV group of the corresponding data.

^b $p < 0.05$ vs the data of the dependent site in the same group.

Data are expressed as the mean ± SEM.

changes in Cdyn and resistance compared with the zero-h time point. Also, at the 2- and 3-h time points, the HFOV + PLV group showed significantly better results in Cdyn and resistance than the HFOV alone group.

Table V shows light-microscopy assessments of lung tissues. As can be seen, marked pulmonary vascular congestion, alveolar haemorrhage, atelectasis, and inflammatory infiltration are visible in lung specimens of HFOV and of HFOV + PLV. These injury signs were greatly alleviated in lung specimens of HFOV + PLV. Table V presents the detailed data of semiquantitative lung injury scores of the dependent and non-dependent sites in each group. The lung injury scores in each injury variable presented no significant differences between dependent and non-dependent sites in each group, except for the analysis for oedema in the HFOV and the HFOV + PLV groups. When the injury scores from these two sites were summed together, the total lung injury scores in the HFOV + PLV group were significantly lower than those in the HFOV group.

Discussion and conclusions

The present study demonstrates the therapeutic effects of both HFOV alone and the combination of HFOV and PLV on ALI induced by steam inhalation injury during a 4-h experimental period. Compared with results in the HFOV group, animals treated with HFOV and PLV displayed better oxygenation, more favourable Cdyn, lower resistance, and more moderate lung tissue injury. The ef-

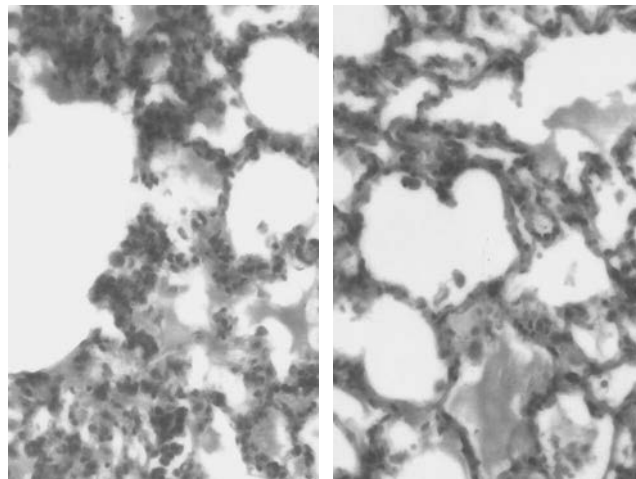


Fig. 1 - Lung histology (X200) of rabbits with steam inhalation injury in the various modes of ventilatory therapy. HFOV = high-frequency oscillatory ventilation; PLV+HFOV = combined therapy of partial liquid ventilation and high frequency oscillatory ventilation. Note that tissues in the HFOV groups displayed more serious pulmonary vascular congestion, alveolar haemorrhage, atelectasis, oedema, necrosis, and inflammatory infiltration than tissues in the PLV+HFOV groups.

fect of this rescue therapy did not however last throughout all the experiment period, showing a peak at the 2-h time point.

The major therapeutic effect of HFOV on ALI is known to be due to the characteristics of high frequency, low volume, and constant and less variable airway pressure, which

are now considered the optimal ventilation mode for ALI owing to the finding that it opens alveolar space and prevents atelectasis, avoids alveolar shearing and airway stretching, and decreases the risk of barotraumas and volutraumas. It has been shown to be effective in treating ALI in animals induced by repeated saline lavage and ARDS in pre-term infants. Recently it has been reported that HFOV can suppress inflammatory reactions in ventilated lung tissue.⁵⁻⁷

The improvements made by PLV in ALI have mainly been attributed to alleviations of alveolar inflammation, alveolar haemorrhage, pulmonary oedema, and atelectasis. It has been reported as successfully treating ALI due to various causes in clinical practice and in the animal laboratory.^{8,9} In our study we applied PLV within 1 h of steam inhalation injury. Our results are in good agreement with those reported by Fitzpatrick et al.,¹⁴ who demonstrated that the application of PLV within 60 min of the induction of smoke inhalation injury produced improvements in oxygenation, lung pathology, and survival rates in neonatal piglets. In contrast, Harrington et al.¹⁵ showed that delayed PLV performed within 2 to 6 h of the induction of steam inhalation injury showed no efficacy in the treatment of ALI using a similar model. Hence, it is evident that early application of PLV is required to obtain beneficial effects in the treatment of ALI induced by steam inhalation. It is well documented that the dosing strategy to perform PLV may influence the outcome.^{16,17} In this study, we gave an initial volume of PFC near to functional residual capacity with an hourly replacement at a dose of 6 ml/kg/h. This dosing strategy was sufficient to produce beneficial effects on gas exchange, lung compliance, and historical outcomes in our model. It was shown in a small animal model that a PFC dose at a volume of function residual capacity caused the most significant improvements in oxygenation.¹⁷ Small doses of PFC may allow the use of small tidal volumes as the lung protective ventilatory strategy to achieve improvements in histological outcomes and survival rates.¹¹ In this experiment we achieved the best result when we used HFOV and a small dose (6 ml/kg/h) of PFC to treat ALI induced by steam inhalation.

Although the efficacy of a combination therapy of HFOV and PLV has not been studied in steam-induced ALI, it has been investigated in other ALI and ARDS models.^{11,12} Baden et al.¹¹ reported in their piglet model of saline

lavage-induced acute lung injury that low-dose (3 ml/kg) perflubron significantly increased arterial oxygenation compared with animals treated with HFOV alone, although additional doses of perfluorocarbon beyond the original dose of 3 ml/kg failed to demonstrate significant improvements in oxygenation. They conjectured that oxygenation was maximized only with small doses of perfluorocarbon in an HFOV setting and that increased doses of perfluorocarbon were not necessary to further recruit alveoli. However, the lack of attempts to optimize lung volume by modification of HFOV settings according to each successive dose of perfluorocarbon makes their results difficult to interpret. The dose we used (6 ml/kg/h) of PFC was based on our previous study.¹⁰ In the present study, we modified the settings so as to increase inspiratory time to 50% and amplitude to 20 cm H₂O and to decrease frequency to 10 Hz during HFOV in order to achieve adequate chest wiggle in anaesthetized piglets immediately after the instillation of PFC. There have also been several negative studies regarding the combined effect of HFOV and PLV. The investigation conducted by Gothberg et al.¹⁸ with a pre-term lamb model of respiratory distress syndrome suggested there were no significant differences in arterial oxygen tension or oxygenation index between the HFOV and the HFOV + PLV group. The result of Doctor et al.'s experiment¹⁹ with a swine model of lavage-induced ALI is similar, in that they did not demonstrate a significant improvement in oxygenation when PFC was added to HFOV. The cause of the varying results could be the different animal model with different causes of damage and treatment parameters of HFOV or conventional mandatory ventilation. In our experiment we obtained positive results using a combination therapy of HFOV and PLV to treat ALI induced by steam inhalation.

Despite the fact that lung conditions were improved by these rescue therapies, the arterial blood pressure and heart rate of all the animals studied deteriorated in the last 1-h period and oxygenation PaO₂/FiO₂ became gradually lower after the peak of 2-h time point, which may reflect deterioration of the cardiac function resulting from hypotension. Therefore, apart from advances in respiratory care therapy, it is conceivable that effective anti-inflammatory or other therapy may be required to manage ALI and ARDS induced by steam inhalation, such as aetiological treatment and anti-infection, a notion that will be further investigated in the future.

RÉSUMÉ. Objectif: investiguer les effets bénéfiques de la ventilation oscillatoire à haute fréquence (VOHF) et de la ventilation liquide partielle (VLP) dans le traitement des lésions aiguës pulmonaires induites par l'inhalation de vapeur. Dessin: une étude prospective, randomisée, contrôlée et à groupes multiples. Environnement: le laboratoire d'un centre de recherche sur les animaux dans un centre universitaire des brûlés. Sujets: des lapins néo-zélandais (n = 30; 2,25 ± 0,25 kg) des deux sexes. Interventions: les animaux ont été ventilés moyennant la VOHF avec une pression moyenne des voies aériennes of 10 cm H₂O, une fréquence de 10 Hz, une amplitude de 20 cm H₂O, un rapport I:E de 1:1 et un FiO₂ de 1.0. Après l'induction des lésions aiguës pulmonaires par

l'inhalation de vapeur, les animaux ont reçu au hasard ou la seule VOHF ou une thérapie associée de VOHF + VLP. Les animaux ont été groupés comme VOHF, VOHF + VLP et groupe témoin (sans ventilation après le rétablissement à la suite du relâchement musculaire). Mesures et résultats principaux: les gazes hématiques artériels, l'hémodynamique cardiovasculaire, la compliance pulmonaire dynamique et les scores totaux des lésions pulmonaires ont été mesurés. Après l'inhalation de vapeur, tous les trois groupes ont démontré un PaO_2 bas et une compliance pulmonaire dynamique basse. Dans le groupe témoin tous les animaux sont morts en moins de 3 h. Dans les groupes VOHF et VOHF + VLP, tous les animaux ont démontré des améliorations significatives dans la compliance pulmonaire dynamique, l'oxygénation et les résultats histologiques; la VOHF + la VLP présentaient les meilleurs résultats. Conclusion: dans un modèle de lapins néo-zélandais de lésions par inhalation de vapeur, la VOHF améliorait l'oxygénation, augmentait la compliance pulmonaire dynamique et allégeait les lésions histologiques pulmonaires. La thérapie associée de VOHF + VLP était manifestement supérieure à la seule VOHF pendant la période de l'observation.

BIBLIOGRAPHY

1. Rinaldo J.E., Rogours R.M.: Adult respiratory distress syndrome: Changing concepts of lung injury and repair. *N. Eng. J. Med.*, 306: 900-9, 1982.
2. McIntyre R.C., jr, Pulido E.J., Bensard D.D. et al.: Thirty years of clinical trials in acute respiratory distress syndrome. *Crit. Care Med.*, 28: 3314-31, 2000.
3. Lewis J.F., Jobe A.H.: Surfactant and the adult respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.*, 147: 218-33, 1993.
4. Speer C.P.: Inflammatory mechanisms in neonatal chronic lung disease. *Eur. J. Pediatr.*, 158 (suppl. 1): S18-22, 1999.
5. Clark R.H., Gerstmann D.R., Null D.M. et al.: Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. *Pediatrics*, 89: 5-12, 1992.
6. Courtney S.E., Durand D.J., Asselin J.M. et al.: High-frequency oscillatory ventilation versus conventional ventilation for very low birth weight infants. *N. Eng. J. Med.*, 347: 643-52, 2002.
7. Hardt K.V., Kandler M.A., Ellen Schoof L.F. et al.: High-frequency oscillatory ventilation suppresses inflammatory response in lung tissue and microdissected alveolar macrophages in surfactant-depleted piglets. *Pediatric Research*, 55: 339-46, 2004.
8. Wolfson M.R., Greenspan J.S., Shaffer T.H.: Liquid-assisted ventilation: An alternative respiratory modality. *Pediatr. Pulmonol.*, 26: 42-63, 1998.
9. Shaffer T.H., Wolfson M.R.: Liquid ventilation. An alternative ventilation strategy for management of neonatal respiratory distress. *Eur. J. Pediatr.*, 155: S30-34, 1996.
10. Guo Guanghua, Li Guohui, Zhu Feng: High-frequency partial liquid ventilation for steam inhalation. *Chinese Crit. Care Med.*, 13: 714-6, 2001.
11. Baden H.P., Mellema J.D., Bratton S.L. et al.: High-frequency oscillatory ventilation with partial liquid ventilation in a model of acute respiratory failure. *Crit. Care Med.*, 25: 299-302, 1997.
12. Sukumar M., Bommaraju M., Fisher J.E. et al.: High-frequency partial liquid ventilation in respiratory distress syndrome: Haemodynamics and gas exchange. *J. Appl. Physiol.*, 84: 327-34, 1998.
13. Wang Lian-Yun, Liu De-Wu, Li Guo-Hui et al.: Introduction of a new steam scalding device with controlled thermal and pressure. *Transactions of Jiangxi Medical College*, 4: 7, 2000.
14. Fitzpatrick J.C., Jordan B.S., Salman N. et al.: The use of perfluorocarbon-associated gas exchange to improve ventilation and decrease mortality after inhalation injury in a neonatal swine model. *J. Pediatr. Surg.*, 32: 192-6, 1997.
15. Harrington D.T., Jordan B.S., Dubick M.A. et al.: Delayed partial liquid ventilation shows no efficacy in the treatment of smoke inhalation injury in swine. *J. Appl. Physiol.*, 90: 2351-60, 2001.
16. Jeng M.J., Oliver R., Wolfson M.R. et al.: Partial liquid ventilation: Effect of initial dose and redosing strategy in acute lung injury. *Pediatr. Crit. Care Med.*, 3: 163-71, 2002.
17. Wolfson M.R., Kechner N.E., Roache R.F. et al.: Perfluorochemical rescue after surfactant treatment: Effect of perflubron dose and ventilatory frequency. *J. Appl. Physiol.*, 84: 624-40, 1998.
18. Gothberg S., Parker T.A., Abman S.H. et al.: High-frequency oscillatory ventilation and partial liquid ventilation after acute lung injury in premature lambs with respiratory distress syndrome. *Crit. Care Med.*, 28: 2450-6, 2000.
19. Doctor A., Mazzoni M.C., Delbalzo U. et al.: High-frequency oscillatory ventilation of the perfluorocarbon-filled lung: Preliminary results in an animal model of acute lung injury. *Crit. Care Med.*, 27: 2500-7, 1999.

This paper was received on 19 December 2005.

Address correspondence to: Dr Shao-gen Wang, Burn Institute of the First Affiliated Hospital of An Hui Medical University, 361 Ba Yi Rd, Nanchang 360033, People's Republic of China.