Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation

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1Pathophysiology Research Laboratory, National Children’s Medical Research Center, Tokyo 154-8509, Japan; and 2Division of Respiratory and Critical Care, Department of Medicine, St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada M5B 1W8

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Imai, Yumiko, Satoshi Nakagawa, Yushi Ito, Toshio Kawano, Arthur S. Slutsky, and Katsuyuki Miyasaka. Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation. J Appl Physiol 91: 1836–1844, 2001.—This study compared pathophysiological and biochemical indexes of acute lung injury in a saline-lavaged rabbit model with different ventilatory strategies: a control group consisting of moderate tidal volume (VT) (10–12 ml/kg) and low positive end-expiratory pressure (PEEP) (4–5 cmH2O); and three protective groups: 1) low VT (5–6 ml/kg) high PEEP, 2–3 cmH2O greater than the lower inflection point; 2) low VT (5–6 ml/kg), high PEEP (8–10 cmH2O); and 3) high-frequency oscillatory ventilation (HFOV). The strategy using PEEP > inflection point resulted in hypotension and barotrauma. HFOV attenuated the decrease in pulmonary compliance, the lung inflammation assessed by polymorphonuclear leukocyte infiltration and tumor necrosis factor-α concentration in the alveolar space, and pathological changes of the small airways and alveoli. Conventional mechanical ventilation using lung protection strategies (low VT high PEEP) only attenuated the decrease in oxygenation and pulmonary compliance. Therefore, HFOV may be a preferable option as a lung protection strategy.

ventilator-induced lung injury; volume recruitment; tumor necrosis factor; conventional mechanical ventilation

MECHANICAL VENTILATION IS essential for patients with respiratory or ventilatory failure. However, the ventilatory strategies used in many patients with the acute respiratory distress syndrome (ARDS) or acute lung injury may worsen the lung injury. A number of experimental studies have demonstrated that a ventilatory strategy that overdistends alveolar units and/or allows repeated tidal collapse and reopening of damaged lung units may induce lung injury. This indicates that both the magnitude of cyclic fluctuations of alveolar volume (tidal volume [VT]) and the level of end-expiratory alveolar volume may be important in ventilator-induced lung injury (VILI) (11, 31, 40).

Various “lung protection” strategies have been developed to minimize VILI. One strategy uses conventional mechanical ventilation (CMV) with decreased VT and increased positive end-expiratory pressure (PEEP), titrated to the pressure-volume (P-V) curve. Amato and co-workers (2) showed improved survival and decreased incidence of barotrauma in a group treated with an “open lung” approach that employed volume recruitment maneuvers, higher PEEP levels (adjusted on the basis of an initial P-V curve), and a VT of 6 ml/kg. Ranieri and co-workers (34) used a similar strategy and reported a decrease in pulmonary and systemic cytokines in patients with ARDS. More recently, the ARDS Net investigators reported a 22% decrease in mortality of patients with ARDS using a protective conventional strategy aimed at reducing end-inspiratory stretch. This study used a small VT (6 ml/kg predicted body wt) with a PEEP that averaged ~9 cmH2O (1).

These strategies are based on the same concepts underlying the protective advantages of high-frequency oscillatory ventilation (HFOV) (13, 26). HFOV allows the use of extremely small VTs, often less than the anatomical dead space. During HFOV, it is possible to maintain end-expiratory lung volume higher up on the deflation P-V relationship without inducing concurrent overdistention because of the much smaller VTs used (13). There are convincing animal data indicating reduced lung injury with HFOV. Studies in premature primates and saline-lavaged adult rabbits demonstrated that, when compared with conventional ventilation, HFOV improves gas exchange, promotes uniform lung inflation, and reduces lung injury (10, 27, 45). HFOV is also associated with reduced inflammatory mediators and granulocytes in lung lavage samples when compared with conventional ventilation (18, 25, 42, 43).

Thus there are two general ventilatory approaches to lung protection, one based on conventional ventilation and one based on high-frequency ventilation. It is unclear from the literature whether there is an advantage of one approach over the other. The present study set out to examine this issue using a rabbit lung lavage model. We compared different ventilatory strategies: a

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control group consisting of moderate VT (10–12 ml/kg) and low PEEP (4–5 cmH2O) (MVLP), and three protective groups: 1) low VT (5–6 ml/kg) high PEEP, 2–3 cmH2O greater than the lower inflection point (Pinf); 2) low VT (5–6 ml/kg), high PEEP (8–10 cmH2O) (LVHP); and 3) HFOV. End points were pathophysiologic indexes of acute lung injury: gas exchange, lung compliance, the number of polymorphonuclear leukocytes (PMN), levels of tumor necrosis factor-α (TNF-α) in lung lavage fluid, and lung pathology.

METHODS

The study protocol was reviewed and approved by the Institutional Animal Research Committee.

Animal Preparation

Adult male Japanese White rabbits (2.5–3.2 kg) were premedicated with an intramuscular injection of ketamine hydrochloride (10 mg/kg). A venous line was established for fluid maintenance, and the animals were anesthetized and paralyzed by a continuous intravenous infusion of ketamine (8 mg/h) and pancuronium bromide (0.3 mg/h) in 10 ml/kg−1 h−1 of 5% dextrose in Ringer lactate solution. A tracheostomy was performed, and a 4.0-mm-ID endotracheal tube was inserted and fixed in place while the animal was manually ventilated at an inspired O2 fraction (FIO2) of 1.0 for 3–4 min. Immediately after tracheostomy, ventilation was initiated with a piston pump HFOV ventilator (Humming V; Senko Medical Instrument Manufacturers, Tokyo, Japan). We used HFOV for preparation and stabilization, as described later in detail, because we and others have previously demonstrated that HFOV minimizes lung injury in this salinelavaged rabbit lung model (16, 18, 25, 42, 43). Sinusoidal volume changes were delivered at an FIO2 of 1.0, an oscillatory frequency of 15 Hz, and a mean airway pressure (MAP) of 7 cmH2O. The stroke volume was adjusted to keep arterial CO2 partial pressure (Paco2) levels between 30 and 50 Torr. Blood pressure was measured through a fluid-filled catheter in the carotid artery. Arterial blood gases were intermittently measured by a pH/blood-gas analyzer (model 178, Corning, Medfield, MA). Systemic arterial blood pressure was continuously monitored by a pressure transducer (CDX-3, Cobe Laboratories), and body temperature was maintained between 38 and 39°C with a servo-controlled radiant heater and a heating pad.

After stabilization, the rabbits' lungs were lavaged with 30 ml/kg of warmed normal saline to remove lung surfactant. The solution was flushed in and out of the lungs five times, and the saline was gently sucked out at the end of each lavage. This procedure was repeated two times by using the same protocol described by Hamilton et al. (16). The fluid obtained from the lavage procedure was stored and analyzed as the “before ventilation” control. The percentage of lavage fluid recovered was 81 ± 6%.

MAP was raised by 5 cmH2O, and a sustained inflation (SI) to 30 cmH2O for 15 s was performed several times after the lavage for all experiments. After completion of this procedure, MAP was set at 15 cmH2O and stabilized, Paco2 levels were maintained between 30 and 50 Torr by adjusting stroke volume, and the frequency was fixed at 15 Hz during HFOV. With several SI maneuvers, the arterial O2 partial pressure (PaO2) of the animals soon returned to prelavage levels, i.e., >350 Torr.

Experimental Protocol

Pilot study using a PEEP > lower Pinf strategy. To determine whether HFOV is better or worse than a conventional strategy requires the use of a specific conventional strategy. Because there is no generally agreed on optimal strategy, we chose to study two strategies that have been shown to decrease mortality in two recent randomized controlled trials: 1) a strategy similar to that of Amato et al. (2) with small VT and PEEP > Pinf, and 2) a strategy similar to the National Institutes of Health (NIH) trial (1) using small VT and PEEP ~10 cmH2O. We started with a pilot study to assess the feasibility of using a strategy based on Pinf in this rabbit model. In eight animals, after preparation of the animals and lung lavage as described above, we inflated the lungs twice to an airway opening pressure of 30 cmH2O and then measured a quasi-static P-V curve of the respiratory system. The quasi-static P-V curve was constructed by slowly, manually inflating the lungs using fixed-volume steps up to a pressure of 30 cmH2O. The deflation loop of the static P-V curve was then constructed by withdrawing air in the same manner. The Pinf was determined as described by Matamis et al. (24). After a SI to 30 cmH2O for 15 s was performed several times, the animals were ventilated by using the CMV mode of the Humming V (time-cycled with pressure-limited ventilation mode) with a low VT (5–6 ml/kg) and PEEP 2–3 cmH2O > Pinf (n = 4) for 4 h using an FIO2 of 1.0. VT was maintained at 5–6 ml/kg by adjusting peak inspiratory pressure (PIP), VT, PIP, and MAP were monitored at the proximal end of the endotracheal tube with the airway monitoring mode of a pulmonary function monitor (model GM250 navigator; Newport Medical Instruments, Newport Beach, CA). PEEP was monitored at the same site with a pressure transducer. Arterial blood gases were measured every hour, and systemic arterial blood pressure was continuously monitored. Although we achieved excellent oxygenation, three of four animals developed systemic hypotension and metabolic acidosis and/or pneumothorax. Therefore, in the second set of experiments, we used a value of PEEP = 8–9 cmH2O at the beginning of the first h and 10 cmH2O over the following 3 h in the low VT, high PEEP (LVHP) group. We also used a VT of 5–6 ml/kg in the LVHP group, volumes that are very similar to those used in the recently reported NIH ARDS Net trial (1).

Main experiment. Given the results of the pilot study, the main set of experiments was carried out with the use of a protective ventilatory strategy that is similar to the recently reported NIH trial (1). The rabbits were randomly divided into three groups [MVLP (n = 7), LVHP (n = 6), and HFOV (n = 6)] and were then ventilated for 4 h at an FIO2 of 1.0. In the MVLP group, PEEP was 4–5 cmH2O and VT was maintained at 10–12 ml/kg by adjusting PIP. In the LVHP group, PEEP was set at 8–9 cmH2O for the first hour and then gradually increased to 10 cmH2O over the following 3 h, so as to minimize the systemic hypotension. VT was maintained at 5–6 ml/kg by adjusting PIP. In the HFOV group, MAP was set at 15 cmH2O. Normocapnia was achieved by altering the stroke volume of the piston. Arterial blood gases were measured every hour with a blood-gas analyzer (model 178, Corning). Total respiratory compliance (Crs) was measured before lung lavage and after 4 h of ventilation. The animals were killed by KCl injection at the termination of the experiment, and the lungs were excised via a midline sternotomy. The left lung was then lavaged twice using 15 ml/kg aliquots of normal saline. The drained lavage fluid was collected as in the sample after ventilation. The percentage of lavage fluid recovered was 67 ± 9%. The right lung was fixed.
with an instillation of 10% buffered formalin at a transpulmonary pressure of 15 cmH\textsubscript{2}O. We compared pathophysiological indexes as follows: gas exchange, Crs before lung lavage and after 4 h of ventilation, numbers of PMN, the levels of TNF-a in the lung lavage fluid, and lung pathological findings at the end of the experiment.

Measurement of Crs

We measured Crs with the static occlusion method by using the passive mechanics (occlusion) mode of a pulmonary function monitor (model GM250 navigator, Newport Medical Instruments). Airway pressures and volumes were measured both at the beginning of inspiration and at the occlusion plateau by using pressure and flow transducers. Crs was then automatically calculated by using linear regression as the chord slope of the P-V line.

Cells, PMN, and Macrophage Counts in Lung Lavage Fluid

The total number of lavaged cells was counted by a standard hemocytometer. Cells were differentiated by use of Wright-Giemsa-stained preparations, and the percent of PMN and macrophages was assessed.

Measurement of TNF-a Concentrations in the Lung Lavage Fluid

TNF-a concentrations in the lung lavage fluid were assayed using a sandwich ELISA based on the cytokine ELISA protocol of PharMingen (San Diego, CA) as described previously (17). These assays were performed using a purified polyclonal goat anti-rabbit TNF-a antibody as a capture antibody and biotinylated polyclonal goat anti-rabbit TNF-a antibody for detection. The rabbit TNF-a-conditioned medium (PharMingen) was used as a standard, and samples were run in duplicate. The limit of detection in this assay was 50 pg/ml, and linear standard curves were obtained ranging from 75 to 15,000 pg/ml.

Histopathological Examination

After fixation, the right lung was floated in 10% formalin for at least 24 h. The lung was then serially sectioned in a coronal fashion from apex to base, and four random sections from a lung were processed for pathological analysis and embedded in paraffin. Thereafter, each section was sliced to 5 \textmu m and was stained with hematoxylin-eosin and Masson’s trichrome. We assessed the lungs (four sections per lung) using a five-point scale according to combined assessments of alveolar congestion, hemorrhage, infiltration or aggregation of neutrophils in the air space or vessel walls, thickness of the alveolar wall, and hyaline membrane formation. The scoring was as follows: 0 = minimal (little) damage, 1+ = mild damage, 2+ = moderate damage, 3+ = severe damage, and 4+ = maximal damage.

Membranous bronchioles are conducting airways without cartilage and include terminal bronchioles, which are the most distal generation of membranous bronchioles and the patent generation to respiratory bronchioles. Four membranous bronchioles per section (16 bronchioles per lung) were processed for pathological scoring. Six pathological abnormalities were evaluated, including degree of inflammatory cell infiltration, fibrosis, smooth muscle hypertrophy, presence of pigment, goblet cell metaplasia, and squamous cell metaplasia. We assigned a score ranging from 0 (normal) to 3 for each of these pathological variables. The airway changes were evaluated by the method of Wright et al. (51), compared with a panel of standard photographs (kindly provided by J. C. Hogg, St. Paul’s Hospital, Vancouver, Canada).

Data Analysis

Results are presented as means ± SD. We used a two-way ANOVA to determine the statistical significance of intergroup differences in blood-gas data at different time points, Crs, numbers of PMN in the final lavage fluid, the levels of TNF-a in the lung lavage fluid before and after ventilation, and the scoring of lung pathology. A P value <0.05 was considered statistically significant.

RESULTS

Pilot Study

After lung lavage, the lower P\textsubscript{inf} was 9.3 ± 1.1 cmH\textsubscript{2}O. As described above, because we had profound hypotension and gross barotrauma in this group of animals, we did not complete any other analysis on this group.

Main Experiment

Gas exchange. The ventilation protocols resulted in no significant differences in MAP (Fig. 1). P\textsubscript{aO\textsubscript{2}} was highest in the HFOV group and lowest in the MVLP group. P\textsubscript{aO\textsubscript{2}} of the LVHP group was between the values of HFOV and MVLP groups (Fig. 2). P\textsubscript{aCO\textsubscript{2}} was higher in the LVHP group than in the MVLP or HFOV groups, and pH was lower in the LVHP group than in the MVLP or HFOV groups (Fig. 3). The values of Crs after ventilation were lower in the MVLP group than in the HFOV and LVHP groups (P < 0.01) and were also lower in the LVHP group than in the HFOV group (P < 0.05) (Fig. 4).
Cell and PMN count. Following the ventilatory period, the recovered cells from the lung lavage included macrophages and PMN. The number of PMN was lower in the HFOV group than in the LVHP and MVLP groups ($P < 0.01$). No significant differences were seen between the LVHP and MVLP groups (Fig. 5).

Levels of TNF-$\alpha$ in the lung lavage fluid before and after ventilation. Levels of TNF-$\alpha$ in the lung lavage fluid before ventilation were not significantly different among the three groups. Levels of TNF-$\alpha$ after ventilation were lower in the HFOV group ($436 \pm 177$ pg/ml) than in the MVLP group ($7,366 \pm 5,023$ pg/ml) ($P < 0.01$) or in the LVHP group ($4,310 \pm 1,091$ pg/ml) ($P < 0.05$). No significant differences were seen between the MVLP and LVHP groups, although there was a tendency to lower levels in the LVHP group (Fig. 6).

Histopathology. Similar to previous studies (16, 17, 20, 25) the pathological findings from the animals in the MVLP group showed extensive hyaline membrane formation and severe PMN infiltration (Fig. 7A). Expanded lung parenchyma with well-preserved alveoli and less hyaline membranes were seen in the lung samples in the HFOV group (Fig. 7C). In the LVHP group, alveolar injury was severe and similar to the findings in the MVLP group (Fig. 7, A and B). The pathological scores are summarized in Table 1. The quantitative alveolar pathological scores were higher in the MVLP and LVHP groups than in the HFOV group ($P < 0.01$). No significant differences were seen between the MVLP and LVHP groups (Table 1). Pathological findings of the membranous bronchioles in the MVLP group exhibited a high degree of bronchiolar inflammation, a moderate degree of goblet cell and squamous cell metaplasia, and a low degree of fibrosis and muscular hypertrophy (Fig. 8A). In the HFOV group, the degree of bronchiolar injury was less, especially with regard to inflammation and squamous cell metaplasia (Fig. 8C). In the LVHP group, the degree of injury was between the scores of the MVLP and HFOV groups (Fig. 8B). Results of the individual scores are presented in Table 2. The pathological score with respect to membranous bronchioles was higher in the MVLP group than in the LVHP and HFOV groups ($P < 0.01$).

DISCUSSION

The major findings of this study were 1) ventilation with low VT and high PEEP attenuated the decrease in oxygenation and pulmonary compliance observed with moderate VT and low PEEP but did not attenuate lung inflammation characterized by PMN infiltration and TNF-$\alpha$ production, 2) HFOV attenuated the decrease in oxygenation and pulmonary compliance, as well as PMN infiltration and TNF-$\alpha$ production, compared with strategies using moderate VT and low PEEP or low VT and high PEEP, and 3) HFOV attenuated the injury to the alveoli and membranous bronchioles.

The major question in interpreting the results of this study is whether the protective ventilatory strategy using CMV was optimal or at least an accepted conventional lung protective strategy.
LVHP strategy thus fulfilled the two criteria mentioned above for an adequate lung protective strategy: PIP was <25 cmH2O, below values thought to be safe (39), and PaO₂ was >300 Torr, indicating adequate recruitment. Further evidence for the adequacy of this approach comes from Rimensberger and colleagues (35), who documented that volume recruitment maneuvers allowed expansion of atelectatic lung units during small VT (5 ml/kg) ventilation and that a PEEP above P_{inf} was not necessary to maintain recruited lung volume in the same model we used, the saline-lavaged rabbit. Thus it is reasonable to treat the LVHP group as a protective conventional strategy (albeit, possibly not optimal).

Compared with the MVLP group, the LVHP group had improved oxygenation and respiratory compliance. This finding has a number of possible explanations. Mechanical ventilation can result in surfactant loss and in the conversion of surfactant from large aggregates to functionally inferior small aggregates, which may occur to a greater extent in injured lungs. A study in a rabbit lung injury model showed that conversion of large to small aggregates was minimized with a low VT (5 ml/kg) strategy (19). Reduced surfactant conversion to small aggregates may have improved compliance and facilitated oxygenation in the LVHP group. Using computed tomography, Gattinoni and colleagues (14) examined the topographic distribution of gas in injured lungs of ARDS patients and documented that the inflated portion of the lung represents a small portion of the total lung volume ("baby-lung" concept). To the extent that certain regions of the lung did not maintain recruitment in the MVLP group, this concept could partly explain the decreased compliance observed in the MVLP group compared with the lungs of the LVHP group. More recently, using parenchymal marker technique, Mar-

**Fig. 5.** Numbers of polymorphonuclear leukocyte (PMN) cells in the lung lavage fluid at termination of ventilation. Values are means ± SD. Numbers of PMN were significantly higher in the MVLP and LVHP groups than in the HFOV group. **P < 0.01 compared with HFOV group; n.s., not significant.

**Fig. 6.** Levels of tumor necrosis factor-α (TNF-α) in the lung lavage fluid before ventilation and at termination of ventilation in the MVLP, LVHP, and HFOV groups. Values are means ± SD. *P < 0.05 compared with HFOV. **P < 0.01 compared with HFOV. Levels of TNF-α after ventilation were higher in the MVLP and LVHP groups than in the HFOV group, and no significant differences were seen between MVLP and LVHP groups.
tynowicz and colleagues (23) documented that regional tidal expansion of dependent regions was significantly reduced after oleic acid injury and was restored by application of PEEP, although oleic acid injury did not lead to the collapse of dependent lung units at functional residual capacity, suggesting an alternative mechanism for topographic variability in regional impedance and lung expansion after injury in a model characterized by marked alveolar flooding.

In the LVHP group, there was a tendency to lower TNF-α concentrations than the MVLP group, but these values were markedly higher than the HFOV group. These results are similar to those of Tremblay and colleagues (44), who found that their MVHP group (VT = 15 ml/kg, PEEP = 10 cmH₂O) was associated with an ~50% decrease in TNF-α compared with a group with the same Vt but zero PEEP in isolated, ex vivo nonperfused rat lungs. This decrease in TNF-α was roughly the same as we observed, but the differences did not reach statistical significance in either study.

HFOV, compared with MVLP and LVHP, resulted in attenuation of the decrease in oxygenation, pulmonary compliance, as well as PMN infiltration and TNF-α production in the alveolar space. Our results suggest that the recruitment of lung volume and the limitation of alveolar pressure changes during the respiratory cycle using HFOV may reduce the lung injury caused by mechanical ventilation, compared with CMV with MVLP or even LVHP. Ranieri and colleagues (33) demonstrated that patients with ARDS often have no clear MVLP or even LVHP. Tobacco and Fredberg (47) studied the selection of frequency and PEEP values for ventilation of the atelectasis prone lung. They predicted that the range of “safe” frequency-PEEP combinations will be narrow and move to higher frequencies as lung compliance decreases, possibly suggesting the theoretical advantage of HFOV over CMV with MVLP or even LVHP in noncompliant lungs.

In our previous study using the same model, we confirmed that only 1 h of CMV (MVLP) produced large increases in TNF-α mRNA in intra-alveolar cells (43) and also found that the levels of TNF-α protein in lung lavage fluid were increased after 4 h of ventilation with CMV (17). Furthermore, polyclonal anti-TNF-α antibody attenuated lung injury and the decrease in oxygenation after lung lavage in animals ventilated with CMV (MVLP) (17), suggesting the importance of TNF-α in this model. In the present study, we found a significantly lower concentration of TNF-α in the lung lavage fluid in the HFOV group, compared with the MVLP or the LVHP group. In other models, injurious ventilatory strategies have been shown to increase TNF-α in the circulation draining an ex vivo perfused lung (50) or in the systemic circulation in vivo in an acid aspiration rat model (7). Ranieri et al. (34) demonstrated that a protective ventilatory strategy produced a significant decrease in lavage and serum TNF-α in humans. We do not mean to imply that TNF-α is the only, or even the key, mediator released during VILI. Indeed, other studies have suggested that TNF-α may not play a key role in VILI (32, 48, 49). Pugin et al. (32) and Vlahakis et al. (49) found no increase in TNF-α in stretched cell culture systems. Verbrugge and colleagues (48) used an in vivo rat lung lavage model and found that there were no statistically significant increases in bronchoalveolar lavage TNF-α concentrations among animals treated with different ventilatory strategies. Other chemokines or proinflammatory mediators such as interleukin (IL)-8 or IL-1β and anti-inflammatory mediators such as IL-10 have been measured in other studies, but these cytokines were not measured in the present study. The balance of these pro- and anti-

Table 1. Alveolar pathological score

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<th>Group</th>
<th>Total Score</th>
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<tr>
<td>MVLP</td>
<td>2.62 ± 0.35*</td>
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<tr>
<td>LVHP</td>
<td>2.21 ± 0.51*</td>
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<tr>
<td>HFOV</td>
<td>1.01 ± 0.40</td>
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Values are means ± SD; n = 24 lung sections per group. Score of 0 = minimal (little) damage; 1+ = mild damage; 2+ = moderate damage; 3+ = severe damage; and 4+ = maximal damage. MVLP, moderate tidal volume, low positive end-expiratory pressure (PEEP); LVHP, low tidal volume, high PEEP; HFOV, high-frequency oscillatory ventilation. *P < 0.01 compared with HFOV group. The pathological score was higher in the MVLP and LVHP groups than in the HFOV group (P < 0.01). No significant differences were seen between the MVLP and LVHP groups.
inflammatory mediators is known to be important in the cytokine network in the lung.

No significant differences in pathological changes in the alveoli were seen between the MVLP and LVHP groups. Our results are different from those of some other investigators (3, 9, 37). Corbridge and colleagues (9) studied different ventilatory strategies in a canine acid-aspiration model and concluded that ventilation with high Vt and low PEEP augments lung edema and that PEEP protects against surfactant depletion. They used a Vt of 30 ml/kg in the high-Vt and low-PEEP group, which was markedly larger than our moderate Vt (10–12 ml/kg). In contrast, membranous bronchiolar pathological changes were greater in the MVLP group than in the LVHP group, consistent with the results of Muscedere and colleagues (28). During ventilation, a pressure wave is generated and travels down the airway, and at each point of the open airway the pressure is transmitted to the airway wall tangentially, producing large shear stresses, especially in regions where airways are collapsed; this may be responsible for the observed changes in the membranous bronchioles in the MVLP group. In the LVHP group, the degree of PEEP used may have been sufficient to keep the membranous bronchioles open at end-expiration. This could have protected these regions from repeated opening and closing, thus attenuating the trauma observed in the MVLP group. It is possible that membranous bronchioles were also held open during HFOV with a mean airway pressure of 15 cmH2O with only a small pressure oscillation around this and were not subjected to further trauma.

The increased injury in the MVLP group is unlikely to be due to the lower PaCO2 in this group because hypercapnic acidosis has been shown to attenuate lung injury in an isolated perfused rabbit model, possibly related to inhibition of endogenous xanthine oxidase (21, 22, 38). HFOV is thought to be an option of lung protection strategy without hypercapnia. In some clinical settings such as elevated intracranial pressure or inability to buffer CO2 adequately in the context of renal failure, these adverse effects of hypercapnia limit the use of “permissive hypercapnia.”

It has been suggested that mechanical ventilation used in patients with ARDS may serve to initiate and/or potentiate an inflammatory response in the lung that in turn propagates a vicious cycle of inflammation leading to tissue injury locally and possibly systemically (41, 46, 50). Results from our study suggest that the lower levels of lung inflammation and TNF-α in the HFOV group compared with CMV may be associated with a lower likelihood of propagation of this vicious cycle of inflammation.

Early prospective, controlled clinical trials were unable to demonstrate the superiority of HFOV over CMV (16a). No benefit of HFOV accrued in the high-frequency intervention trial, and HFOV was associated with an increased incidence of air leak, intracranial hemorrhage, and periventricular leukomalacia. It has been suggested that this lack of benefit in the HI FI study was related to the lack of an adequate volume recruitment strategy (5). Recent studies using a volume recruitment strategy demonstrated improved gas exchange, reductions in barotrauma, and overall improved outcome in neonatal patients receiving HFOV (8, 15, 29). More recently, a pilot study demonstrated that HFOV using a protocol designed to obtain recruitment and maintain optimal lung volume was both safe and effective in pediatric and adult patients with ARDS (4, 12). The present study suggests that HFOV may be the preferable option as a lung protection strategy. Further prospective, controlled, clinical trials are needed to compare these two different means of pursuing the same physiological treatment goal, namely, that of recruiting and maintaining lung volume. Furthermore, a strategy with PEEP above Pinf may not be always possible during CMV because of hemodynamic compromise, despite VT reduction, and HFOV, by allowing such recruitment, may be a better lung protective strategy.

In summary, in this lung lavage model HFOV attenuated pulmonary compliance, lung inflammation assessed by PMN infiltration, and TNF-α concentration in the alveolar space and pathological changes of the small airways and alveoli. CMV using a protection ventilatory strategy only attenuated the decrease in oxygenation and pulmonary compliance. HFOV may

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**Table 2. Pathological score in membranous bronchioles**

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<tr>
<th>Group</th>
<th>Total Score</th>
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<tr>
<td>MVLP</td>
<td>7.13 ± 1.65</td>
</tr>
<tr>
<td>LVHP</td>
<td>3.13 ± 1.18*</td>
</tr>
<tr>
<td>HFOV</td>
<td>2.94 ± 1.29†</td>
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Values are means ± SD; n = 96 bronchioles per group. *P < 0.01 compared with MVLP groups. †P < 0.01 compared with LVHP group. The pathological score was higher in the MVLP than in the LVHP and HFOV groups (P < 0.01) and higher in the LVHP group than in the HFOV group (P < 0.01).
therefore be a preferable option as a lung protection strategy.

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