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EXPERIMENTAL

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The open lung concept: pressure controlled ventilation is as effective as high frequency oscillatory ventilation in improving gas exchange and lung mechanics in surfactant-deficient animals

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Abstract *Objective:* To demonstrate in experimental animals with respiratory insufficiency that under well-defined conditions, commercially available ventilators allow settings which are as effective as high frequency oscillatory ventilators (HFOV), with respect to the levels of gas exchange, protein infiltration, and lung stability.
Design: Prospective, randomized, animal study.
Setting: Experimental laboratory of a university.
Subjects: 18 adult male Sprague-Dawley rats.
Interventions: Lung injury was induced by repeated whole-lung lavage. Thereafter, the animals were assigned to pressure-controlled ventilation (PCV) plus The Open Lung Concept (OLC) or HFOV plus OLC (HFO_{OLC}). In both groups, an opening maneuver was performed by increasing airway pressures to improve the arterial oxygen tension/fractional inspired oxygen (PaO_2/FIO_2) ratio to $\geq$ 500 mm Hg; thereafter, airway pressures were reduced to minimal values, which kept $PaO_2/FIO_2 \geq 500$ mm Hg. Pressure amplitude was adjusted to keep CO_2 as close as possible in the normal range.
Measurements and results: Airway pressure, blood gas tension, and arterial blood pressure were recorded every 30 min. At the end of the 3-h study period, a pressure-volume curve was recorded and bronchoalveolar lavage was performed to determine protein content. After the recruitment maneuver, the resulting mean airway pressure to keep a $PaO_2/FIO_2 \geq 500$ mm Hg was 25 ± 1.3 cm H_2O during PCV_{OLC} and 25 ± 0.5 cm H_2O during $HFOV_{OLC}$. Arterial oxygenation in both groups was above $\geq$ 500 mm Hg and arterial carbon dioxide tension was kept close to the normal range. No differences in mean arterial pressure, lung mechanics and protein influx were found between the two groups.
Conclusions: This study shows that in surfactant-deficient animals, PCV, in combination with a recruitment maneuver, opens atelectatic lung areas and keeps them open as effectively as HFOV.

Key words High frequency oscillatory ventilation · Pressure control ventilation · Surfactant deficiency · Alveolar recruitment · Open lung concept · Animal model

Introduction

It is becoming increasingly clear that besides inspiratory epithelial overstretching [1], the repeated collapse and reexpansion of alveoli, which leads to the development of shear forces, contributes to a great extent to ventilation-induced lung injury (VILI) [2]. It has been suggested that collapsed alveoli should be recruited before

starting long-term mechanical ventilation, and high inspiratory lung volumes should be avoided by using small pressure amplitudes [the Open Lung Concept (OLC)] [3].

More than 25 years ago, high frequency oscillatory ventilation (HFOV) was introduced as a new ventilatory technique for treating the neonatal respiratory distress syndrome (RDS) [4]. The small pressure amplitudes applied during HFOV were expected to reduce VILI, but it has been demonstrated that HFOV only leads to less lung damage when it is applied to reexpanded lungs (i.e., open lungs) by use of a relatively high mean airway pressure (MAwP) [5, 6]. This is called the high-lung volume strategy; the results of recent pilot studies in neonates with RDS applying this strategy are encouraging [7–10].

The idea has become established that, due to the larger pressure swings, conventional mechanical ventilation (CMV) recruits alveoli at inspiration but cannot prevent them from collapse at end-expiration and that only an increase in positive end-expiratory pressure (PEEP) during CMV would reduce the amount of alveolar derecruitment at the cost of higher peak inspiratory pressures [11, 12]. Studies comparing CMV and HFOV with respect to gas exchange seem to support this idea [5, 6, 13–15]. These studies showed that, although the lung can be opened during CMV with relatively high peak inspiratory pressures, the lung could not be kept open during the ventilation period. The required high level of PEEP and high tidal volumes to keep the lung open and provide adequate gas exchange in these studies resulted in barotrauma and circulatory impairment [5, 6]. However, earlier studies with CMV using a pressure-controlled time-cycle mode (PCV) applying small pressure amplitudes combined with high levels of PEEP and high inspiratory pressure for a short time, have shown that PCV can effectively recruit alveoli and keep them open during the entire respiratory cycle [16, 17].

Therefore, in the present study in experimental animals with respiratory insufficiency, we investigated whether, under well-defined conditions, commercially available ventilators allow settings which are as effective as HFOV with respect to the levels of gas exchange, protein infiltration, and lung stability.

Materials and methods

The study protocol was approved by the institutional Animal Investigation Committee. Care and handling of the animals were in accordance with European Community guidelines (86/609/EC). The study was performed in 18 adult male Sprague-Dawley rats (body weight 280–350 g). Anesthesia was induced with 2% enflurane and 65% nitrous oxide in oxygen. Immediately after induction of anesthesia, 6 animals were killed, the thorax was opened, and static pressure-volume curves (P/V curves) were recorded and a bronchoalveolar lavage (BAL) was performed. These animals served as a healthy nonventilated control group (healthy). In the remaining animals, a polyethylene catheter (0.8-mm outer diameter) was inserted into the right carotid artery for drawing arterial blood samples, and for continuous monitoring of arterial pressure to adjust hemodynamic support. Before tracheotomy, the animals received 30 mg/kg pentobarbital sodium, intraperitoneally (Nembutal; Algin, Maassluis, The Netherlands). After tracheotomy, muscle relaxation was induced with pancuronium bromide 0.6 mg/kg intramuscularly (Pavulon; Organon Teknika, Boxtel, The Netherlands) immediately followed by connection to the ventilator and to a pressure transducer (Siemens Sirecust 1280, Siemens, Danvers, Mass., USA) for continuous arterial pressure monitoring. The animals were mechanically ventilated with a Servo Ventilator 300 (Siemens-Elema, Solna, Sweden) in a pressure-controlled time-cycled mode, at fractional inspired oxygen concentration (FIO_2) of 1.0, frequency of 30 breaths per minute (bpm), peak inspiratory pressure (PIP) of 12 cm H_2O, PEEP of 2 cm H_2O, inspiratory/expiratory I/E ratio of 1 : 2. Anesthesia was maintained with pentobarbital sodium (Nembutal; 30 mg/kg); neuromuscular block was maintained with pancuronium bromide, i.m. (Pavulon; 0.6 mg/kg). Body temperature was kept within the normal range by means of a heating pad. Initially, PIP was increased to 20 cm H_2O for 30 s to open up atelectatic regions in the lungs due to the surgical procedure. After this procedure to open up the lungs, the ventilator settings were reset to the previous ones and a 0.15 ml blood sample was taken and replaced by heparinized (10 IU/ml) saline (0.9% NaCl). Arterial oxygen tension (PaO_2) and carbon dioxide tension ($PaCO_2$) were measured by conventional methods (ABL 505, Radiometer Copenhagen, Denmark). Next, respiratory failure was induced by repeated whole-lung lavage as described by Lachmann et al. [18]. Each lavage was performed with saline (32 ml/kg body weight) heated to 37 °C. Just before the first lavage, PIP and PEEP were elevated to 26 and 6 cm H_2O, respectively. Lung lavage was repeated five to seven times with 5-min intervals to achieve a $PaO_2/FIO_2 \leq 85$ mm Hg. Within 10 min after the last lavage, the animals were randomized to one of the following groups ($n = 6$ per group). In the first group, PCV_{OLC}, a procedure to open up the lungs (defined as $PaO_2/FIO_2 \geq 500$ mm Hg), at the following ventilator settings: PIP 40 cm H_2O, static PEEP 12 cm H_2O, I/E ratio 4 : 1, FIO_2 1.0, respiratory frequency 150 bpm. After 1 to 2 min at these settings, a blood sample was drawn to verify that PaO_2/FIO_2 was ≥ 500 mm Hg. After this recruitment procedure, total PEEP (PEEPt = static PEEP plus intrinsic PEEP) was decreased in approximately in 2- to 3-min steps to the minimal level which kept $PaO_2/FIO_2 \geq 500$ mm Hg. Then the pressure amplitude was set to keep $PaCO_2$ as close as possible to the normal range and was not changed thereafter [19, 20]. The second group, $HFOV_{OLC}$, was ventilated with HFOV (type OHF-1, Dufour, Villeneuve d'Ascq, France); an opening maneuver was performed by setting the ventilator to oscillation mode without sigh, respiratory rate at 10 Hz, oscillatory pressure amplitude of 28 cm H_2O, FIO_2 1.0. The MAwP was initiated at 28 cm H_2O. After about 1–2 min at these ventilator settings, a blood gas sample was drawn to verify that PaO_2/FIO_2 was ≥ 500 mm Hg. Thereafter, the level of MAwP was decreased in 2- to 3-min steps, to the minimal level which kept $PaO_2/FIO_2 \geq 500$ mm Hg. Then, the oscillatory pressure amplitude was set to maintain $PaCO_2$ as close as possible to normal range and was not changed thereafter.

Airway pressures were continuously monitored with a tip catheter pressure transducer (Raychem EO 2 A 121, USA), using a water column as a reference pressure, connected with a Y-piece to the tracheal tube, and recorded (Siemens Sirecust 1280, Siemens, Danvers, Mass., USA). Additionally, intrinsic PEEP was determined by subtracting set PEEP from total PEEP in the PCV_{OLC} group

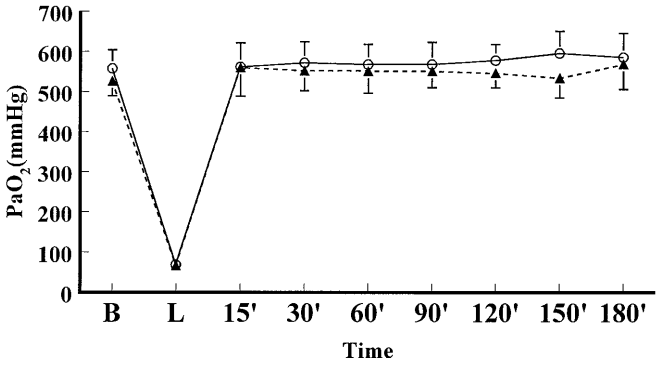

Fig. 1 PaO_2 values (mean ± SD) over the whole study period. *B* before lavage, *L* after lavage. Pressure-controlled time-cycled ventilation with open lungs (*continuous line*) and high frequency oscillatory ventilation with open lungs (*dashed line*). No statistical differences within or between the two groups over time were found after the Open Lung Concept was applied

Table 1 Data on arterial carbon dioxide tension $PaCO_2$ and mean arterial pressure *MAP* over time in the groups with pressure-controlled ventilation with open lungs (PCV_{OLC}) and high frequency oscillatory ventilation with open lungs ($HFOV_{OLC}$). Values are mean ± SD

	Time (min)	PCV_{OLC}	$HFOV_{OLC}$
$PaCO_2$ (mm Hg)	Basal	40 ± 6.4	37 ± 6.2
	Lavage	64 ± 9.0	54 ± 5.7
	15	32 ± 8.6*	32 ± 7.5*
	30	37 ± 8.3*	37 ± 6.4*
	60	33 ± 6.6*	35 ± 6.0*
	90	35 ± 8.4*	37 ± 5.5*
	120	36 ± 10.0*	37 ± 4.5*
	150	38 ± 13.0*	34 ± 3.2*
	180	34 ± 10.0*	32 ± 4.3*
MAP (mm Hg)	Basal	134 ± 22.5	144 ± 14.7
	Lavage	90 ± 21.0	100 ± 9.0
	15	115 ± 13.0	121 ± 14.3
	30	122 ± 12.1	122 ± 23.2
	60	126 ± 10.0	114 ± 19.0
	90	123 ± 14.5	114 ± 11.9
	120	125 ± 13.0	108 ± 14.0
	150	122 ± 12.4	108 ± 18.9
	180	118 ± 14.4	101 ± 17.0

* vs after lavage $p \leq 0.05$

and in the $HFOV_{OLC}$ total PEEP was defined as the lowest pressure within the oscillatory pressure amplitude. The highest pressure within the oscillatory pressure amplitude was defined as PIP.

After surfactant depletion and performance of the recruitment procedure, airway pressures were determined and blood gas samples were taken at 15, 30, 60, 90, 120, 150, and 180 min. At the same time points, arterial pressure was recorded. Hemodynamic support was provided by infusion of 1 ml saline 0.9% (to a maximum of 3 ml per h) when mean arterial pressure (MAP) decreased below 100 mm Hg.

After 180 min, all animals were killed with an overdose of pentobarbital sodium injected through the penile vein. Then static P/V curves were recorded using the syringe technique. After the thorax and diaphragm were opened, the tracheostomy catheter was connected to a pressure transducer with a syringe attached to it (Validyne model DP 45–32, Validyne Engineering, Northridge, Calif., USA), and pressures were recorded on a polygraph (Grass model 7B, Grass Instrument, Quincy Mass., USA). Using a syringe filled with nitrogen (N_2) the lungs were first inflated (within 10 s) to an airway pressure of 35 mm H_2O, which was maintained for 5 s, followed by deflation to an airway pressure of 0 cm H_2O was reached. Each inflation step took 1–2 s followed by a 5-s pause to allow pressure equilibration. After this, in the same way, the lungs were then deflated until an airway pressure of 0 cm H_2O was reached. The volume of N_2 left in the syringe was recorded. Maximal compliance (C_{max}) was calculated from the steepest part of the deflation limb [21]. Total lung capacity (TLC_{35}) was defined as lung volume at inflation with a distending pressure of 35 cm H_2O.

The Gruenwald index, which characterizes the surfactant system in situ, was calculated from the pressure-volume curve, defined as $(2V_5 + V_{10})/2V_{max}$, where V_5, V_{10} and V_{max} are the lung volumes at transpulmonary pressures of 5, 10, and 35 cm H_2O from the deflation limb, respectively [22].

After P/V recordings, BAL was performed five times with saline-$CaCl_2$ 1.5 mmol/l. Thereafter, cell debris was removed from BAL by centrifugation at 400 *g* for 10 min, and protein concentration was measured using the Bradford method (Biorad protein assay, Munich, Germany) [23].

Statistical analysis was performed using the Instat 2.0 biostatistics package (Graph Pad Software, San Diego, Calif., USA). Analysis of variance was performed to compare intragroup and intergroup differences at every time point; if $p < 0.05$, a Tukey post hoc test was performed. All data are reported as mean ± standard deviation (SD).

Results

Blood gas values before and immediately after lavage were comparable for both groups (Fig. 1, Table 1). None of the animals died during the 3-h study period. Carbon dioxide values decreased significantly from 64 ± 9.0 mm Hg after lung lavage to 32 ± 8.6 mm Hg 15 min after the recruitment procedure ($p < 0.01$) and from 54 ± 5.7 to 32 ± 7.5 mm Hg ($p < 0.01$) in PCV_{OLC} and $HFOV_{OLC}$, respectively, and remained comparable during the entire observation period (Table 1).

Figure 2 shows the mean airway pressures recorded from the tip catheter pressure transducer 3 h after the recruitment procedure. PIP and PEEPt values were significantly lower in the PCV_{OLC} group than in the $HFOV_{OLC}$ group. However, the driving pressure amplitude was significantly higher in the PCV_{OLC} group (18.8 ± 2.2 cm H_2O) compared with the $HFOV_{OLC}$ group (14.0 ± 1.6 cmH_2O, $p < 0.05$). The MAwP were not significantly different between the two groups (25 ± 1.3 cm H_2O in PCV_{OLC} and 26 ± 0.5 cm H_2O in $HFOV_{OLC}$). The total PEEP in PCV_{OLC} consisted of 10 ± 0.3 cm H_2O static PEEP and 3 ± 2.4 cm H_2O intrinsic PEEP.

In PCV_{OLC}, mean values of MAP (Table 1) 15 min after the recruitment maneuver were kept above 100 mm Hg, and no intergroup differences were found

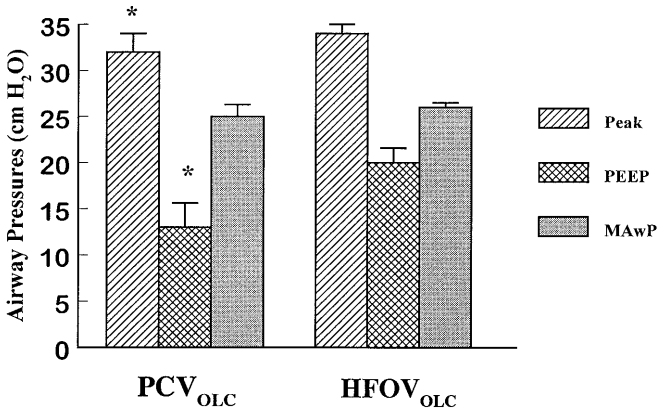

Fig. 2 Airway pressures (mean ± SD) recorded with the tip catheter pressure transducer 3 h after the recruitment maneuver. In pressure-controlled time-cycled ventilation with open lungs (PCV_{OLC}) there was a significantly (*$p < 0.05$) lower peak pressure *Peak* and lower positive end-expiratory pressure *PEEP* compared with high frequency oscillatory ventilation with open lungs ($HFOV_{OLC}$), at the same mean airway pressure *MAwP*

during the 3-h study period. However, intragroup differences were observed in the $HFOV_{OLC}$ group where the mean values of MAP were significantly lower at the end of the study period. Fluid replacement after the recruitment maneuver was required in 2 animals in the PCV_{OLC} group and in 3 animals in the $HFOV_{OLC}$ group. There was no statistical difference in the rate of saline infusion during the 3-h study period between groups, with 0.5 ml/h in PCV_{OLC} and 0.8 ml/h in $HFOV_{OLC}$.

Figure 3 shows the P/V curves from the healthy, PCV_{OLC}, and $HFOV_{OLC}$ groups. No statistical differences were found in TLC_{35} between groups (43 ± 2 ml/kg in the healthy control group, 41 ± 6 ml/kg in PCV_{OLC}, and 42 ± 2 ml/kg in $HFOV_{OLC}$). As expected, in the healthy control group C_{max} was significantly higher (4.0 ± 0.2 ml/cm H_2O per kg) than in the surfactant-depleted lungs ventilated either with PCV_{OLC} or $HFOV_{OLC}$ (2.4 ± 0.6 and 2.5 ± 0.2 ml/cm H_2O per kg, respectively). Obviously, the Gruenwald index was also significantly higher in the healthy control group than in PCV_{OLC} (1.06 ± 0.20 vs 0.67 ± 0.13; $p < 0.01$) and $HFOV_{OLC}$ (1.06 ± 0.20 vs 0.53 ± 0.15, $p < 0.001$).

The protein concentration of BAL fluid was not significantly different between the three groups: 0.44 ± 0.20 in the healthy control group, 0.55 ± 0.23 in PCV_{OLC}, and 0.59 ± 0.28 in $HFOV_{OLC}$.

Discussion

This study shows in experimental animals with respiratory insufficiency that under well-defined conditions, commercially available ventilators allow settings which are as effective as HFOV with respect to the level of gas exchange, protein infiltration, and lung stability.

In the present study we used the lung lavage model, which has proved to be a consistent and convenient model of acute lung injury [18]. It has been postulated that, in the acute phase, this model reflects more a primary surfactant deficiency, as seen in neonatal RDS [16, 17]. Despite the fact that the lung injury in this study is not exactly representative of the pathology seen in humans with RDS, this model is ideal for testing various therapeutic interventions for RDS [16, 17].

It has been demonstrated that arterial oxygenation increases with increasing functional residual capacity as alveoli reexpand and shunt flow decreases [5, 6, 20, 24]. Therefore, in the present study we used arterial oxygenation as a parameter to characterize the state of alveoli recruitment. Previous studies in rabbits with acute lung injury have shown that HFOV applied with

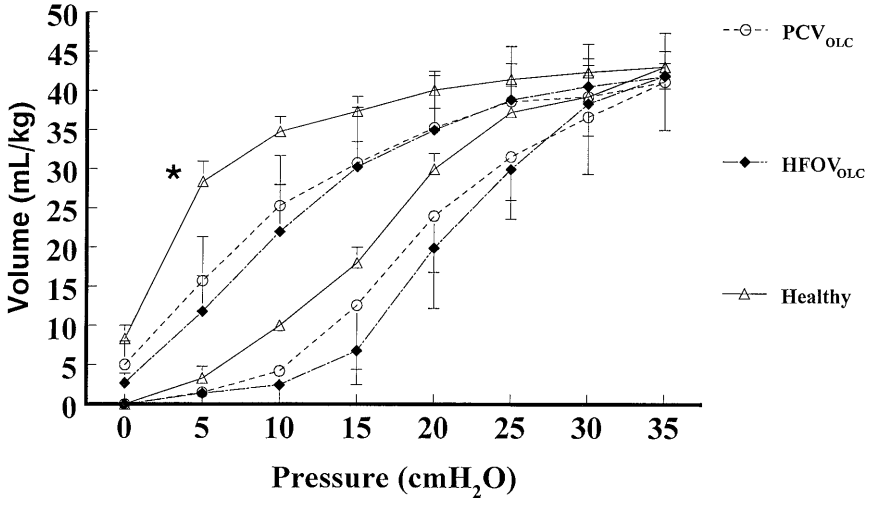

Fig. 3 Pressure-volume curves (mean ± SD). At total lung capacity, no statistical differences were found between the three groups. In the healthy, nonventilated controls (*Healthy*) C_{max} was significantly higher than those in the pressure-controlled time-cycled ventilation with open lungs (PCV_{OLC}) and high frequency oscillatory ventilation with open lungs ($HFOV_{OLC}$) (*$p < 0.001$)

the "high-lung volume strategy" is able to reach oxygenation levels above 350 mm Hg and normocapnia [5, 6, 12]. A prerequisite for this latter strategy is that high pressures have to be applied for a short period to reaerate collapsed lung regions, which means that after reaeration oscillation takes place on the deflation limb of the P/V curve. Under this condition, carbon dioxide elimination is controlled by the oscillation pressure amplitude. However, according to Froese and Bryan's studies [6, 11, 12], the small swing in pressures and low tidal volumes produced by HFOV in the past could not be produced with CMV. In contrast to these latter studies, our study demonstrates that it is also possible to reach high levels of arterial oxygenation and normocapnia by applying small driving pressure amplitudes in the PCV_{OLC} mode. Pressure readings from the tip catheter pressure transducer showed that mean airway pressures were comparable in both OLC groups, with comparable good oxygenation. Hypercapnia was not observed and $PaCO_2$ levels were close to normal values during the 3-h study period in both groups. However, the driving pressure amplitude was almost 5 cm H_2O higher in the PCV_{OLC} group. Whether the latter observation has any clinical impact on VILI cannot be answered from this study. If one considers that protein influx is a sensitive parameter for VILI [25], then at least the higher driving pressure amplitude had no additional negative effect on the protein influx over the study period.

It is known that high MAwP can decrease venous return of the systemic circulation by impairment of the pulmonary circulation due to overdistention of alveoli, which results in compression of the pulmonary capillaries [17, 26]. When applying the OLC, hemodynamic compromise should be minimized by setting the MAwP finally at a level that just compensates for the increased tendency of the alveoli to collapse. However, if this still leads to hemodynamic compromise it should be compensated for by proper fluid management and hemodynamic support by inotropics [3, 19, 27, 28]. In our study, we observed a decrease in blood pressure only during the recruitment maneuver, which returned to normal levels within 1–2 min after reaching the airway pressures which kept the lungs open. After the recruitment maneuver, the MAwP in both OLC groups was the same, which resulted in mean MAP values above 100 mm Hg over the whole study period in both groups – and that is why the demand for fluids in both groups was not significantly different. These results agree with clinical trials which assessed the beneficial effects of open lungs in patients with adult RDS [27–30].

There was no difference between the groups in the amount of protein recovered in the BAL, nor when compared with healthy, normal nonventilated control animals.

The epithelium rather than the endothelium is rate-limiting for the transfer of protein across the alveoli capillary barrier [25]. Although peak inspiratory epithelial overstretching has been considered the main contributing factor for epithelial injury and intraalveolar protein infiltration [1, 31, 32] it is realized more and more that repeated alveolar collapse and reexpansion leads to shear stress with epithelial and endothelial damage, resulting in alveolar protein accumulation [33, 34]. In a surfactant-deficient model of acute lung injury, application of OLC decreases protein leakage [35]. It is known that counterbalancing the increased collapse tendency of the surfactant-deficient alveoli with appropriate airway pressures favors the shift of fluid from the alveoli to the interstitium by decreasing the pressure gradient across the alveolar-capillary membrane [36]. In addition, ventilating the alveoli with the smallest possible pressure amplitude will prevent epithelial overstretching. These two mechanisms may explain the comparable protein values in both groups compared with the healthy control group.

All changes in the P/V curve after surfactant depletion (e. g., decreased C_{max} and Gruenwald index and increased opening pressure) confirm earlier results in this animal model [5, 6, 12, 16, 17] on the one hand, and, on the other hand, demonstrate that the two modes of mechanical ventilation did not influence lung mechanics during the 3-h observation period.

In summary, this study shows that in surfactant-deficient animals, PCV in combination with a recruitment maneuver results in the same level of oxygenation, carbon dioxide elimination, protein infiltration, and lung mechanics as HFOV. Moreover, mean values of MAP were kept above 100 mm Hg in both modes of ventilation during the 3-h study period. These data indicate that the preferred use of high frequency oscillators for certain clinical conditions over pressure-controlled ventilators needs to be reconsidered. Rather than using special modes of mechanical ventilation in RDS, one should apply a general concept of ventilation which provides an open lung over the entire respiratory cycle, with the least possible hemodynamic compromise.

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