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Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation and high-frequency oscillation

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Abstract *Objective:* To determine whether using a small tidal volume (5 ml/kg) ventilation following sustained inflation with positive end-expiratory pressure (PEEP) set above the critical closing pressure (CCP) allows oxygenation equally well and induces as little lung damage as high-frequency oscillation following sustained inflation with a continuous distending pressure (CDP) slightly above the CCP of the lung.
Material and methods: Twelve surfactant-depleted adult New Zealand rabbits were ventilated for 4 h after being randomly assigned to one of two groups: group 1, conventional mechanical ventilation, tidal volume 5 ml/kg, sustained inflation followed by PEEP > CCP; group 2, high-frequency oscillation, sustained inflation followed by CDP > CCP.
Results: In both groups oxygenation improved substantially after sustained inflation ($P < 0.05$) and remained stable over 4 h of ventilation without any differences between the groups. Histologically, both groups showed only little airway injury to bronchioles, alveolar ducts, and alveolar airspace, with no difference between the two groups. Myeloperoxidase content in homogenized lung tissue, as a marker of leukocyte infiltration, was equivalent in the two groups.
Conclusions: We conclude that a volume recruitment strategy during small tidal volume ventilation and maintaining lung volumes above lung closing is as protective as that of high-frequency oscillation at similar lung volumes in this model of lung injury

Key words Intermittent positive pressure ventilation · Positive end-expiratory pressure · High-frequency oscillation · Volume recruitment maneuvers · Pulmonary mechanics · Lung volume

Introduction

Alveolar recruitment and stabilization are important in the diseased lung to improve ventilation/perfusion matching and arterial oxygenation. To achieve adequate lung volume recruitment the lung must be inflated past the pressure at which atelectatic lung units begin to open (lower inflection point, P_{inf}) and then to be main-

tained above the pressure at which lung closing occurs (i. e., critical closing pressure, CCP). These two pressure points can be estimated from the overall pressure-volume (PV) curve of the respiratory system.

In the clinical application of high-frequency oscillation (HFO) oxygenation is the endpoint used to manipulate the operating continuous distending pressure (CDP) and demonstrates a linear relationship to lung volume [1]. The poor initial results of HFO in lung injury models [2] were disappointing because the small "tidal" volumes in combination with low mean airway pressures failed to recruit lung volume. To overcome this phenomenon the concept of sustained inflation maneuvers (SI) was introduced [3, 4]. This consists of applying a high pressure to the lung (usually 30 cmH_2O) sustained for a short period (30 s) before returning to the previous mean airway pressures, boosting the lung, in the presence of PV hysteresis, from the inflation limb to the deflation limb [1, 3, 5] of the PV curve, thus gaining lung volume and allowing an improvement in oxygenation and a decrease in the ventilator-induced lung injury. Once accepted, this approach showed evidence of clinical benefit with a substantial reduction in chronic lung disease in both neonates and preterm infants [6, 7].

Historically, conventional mechanical ventilation (CMV) uses repetitive large convective flows to achieve lung volume recruitment to avoid progressive decrease in compliance [8], making every breath a sigh [9, 10]. With increasing evidence that not only high peak pressures but also large volume distention [11, 12, 13, 14] and the repetitive closing and reopening of terminal airways [15, 16] can cause very significant lung injury, tidal volumes (V_Ts) were been reduced substantially below 10–12 ml/kg, and positive end-expiratory pressure (PEEP) was pushed above P_{inf} on the PV curve, in the belief that it is this pressure that is required to maintain lung volume (according the inflation characteristics of the lung) and thus avoid the repetitive opening and closing of alveoli and the associated lung injury [15, 16, 17, 18, 19, 20, 21]. However, the clinical relevance of this high lung volume–small tidal volume (V_T) approach remains controversial [22, 23].

From the use of HFO we have learned that oxygenation depends less on the mean airway pressure than on whether the oscillatory cycle is placed on the inflation limb or the deflation limb of the PV curve [1, 3, 4, 24]. We have shown that similar principles can be applied to CMV [25, 26]. Therefore we hypothesized that small V_T ventilation (5 ml/kg) with SI (CMVSI) should allow optimal recruitment and its physiological benefits while having similar lung injury to HFO with SI (HFOSI).

Material and methods

The study was conducted in accordance with National Institutes of Health guidelines for the use of experimental animals, and with the approval of the Institutional Animal Care and Use Committee of the Hospital for Sick Children.

We used the previously described bronchoalveolar warm saline lavage model of acute lung injury [3, 5, 25, 27, 28, 29] in adult New Zealand rabbits (2500–3500 g body weight). The rabbits were premedicated with acepromazine (0.5 mg/kg intramuscularly) and anesthetized with sodium pentobarbital (10–20 mg/kg intravenously). A tracheotomy was performed, and a 3.5- or 4.0-mm endotracheal tube was inserted. Animals were paralyzed with pancuronium bromide intravenously (bolus of 0.2 mg/kg, followed by a continuous infusion of 0.2 mg/kg per hour) and ventilated in a pressure controlled mode with a target V_T of 10 ml/kg [PEEP 0 cmH_2O, inspired fraction of oxygen (FiO_2) 1.0, respiratory rate 24/min]. Peripheral venous access was established for fluid management. A peripheral arterial line was inserted for continuous blood pressure monitoring (Hewlett-Packard model 1280) and sampling of blood gases.

After a control period of 30 min, respiratory failure was induced by repeated lung lavage with aliquots of 25 ml/kg of warmed normal saline. PEEP was increased to 5 cmH_2O immediately after the first lung lavage and V_T was reduced to 5 ml/kg to avoid high peak airway pressures. Lavage was considered to have been adequate if the PaO_2 was reduced to below 60 mmHg (8 kPa) and remained low over a stabilization period of 30 min at the following ventilator settings: PEEP 5 cmH_2O, V_T 5 ml/kg, FiO_2 1.0, respiratory rate 30/min. Animals were randomized to one of two groups (group 1. CMVSI; group 2, HFOSI) and ventilator settings were then changed according to the protocol. CMV was provided by an infant ventilator (Sechrist Infant ventilator IV-100B, Sechrist Industries, Anaheim, Calif., USA), HFO by a piston-driven high-frequency oscillator (High Frequency Oscillatory Ventilator 3100, Sensor Medics Corporation, Yorba Linda, Calif., USA). SI was applied by an inspiratory hold for 30 s at a pressure of 30 cmH_2O during CMV and by increasing the mean airway pressure to 30 cmH_2O for 30 s during HFO for all animals.

CMVSI animals were then ventilated with a PEEP > CCP (optimal PEEP), a concept that we have previously described. In brief, "optimal PEEP" was defined as the pressure level derived from the deflation limb of the quasistatic PV curve corresponding to a theoretical lung volume of 50 % of total lung capacity (TLC; i. e., lung volume above FRC at 30 cmH_2O airway pressure). This definition is based on our and others observations [25, 30, 31] determining the level at which derecruitment occurs to be at an end-expiratory lung volume (EELV) of approximately 40–45 % of TLC. Lowering PEEP below this level would result in a substantial drop in PaO_2, suggesting closure of major lung units, indicative of the CCP of the lung [25]. HFOSI animals were ventilated at a CDP level 4–5 cmH_2O above CCP level using the following parameters (frequency 15 Hz, oscillation pressure amplitude 36–50 cmH_2O, FiO_2 1.0, I:E 33 %). We accepted normoventilation or mild hypoventilation (pCO_2 40–60 mmHg) during both modes of ventilatory support.

The concept of ventilator settings is explained using a schematic drawing (Fig. 1) and the time-course of the whole experiment is outlined in Fig. 2.

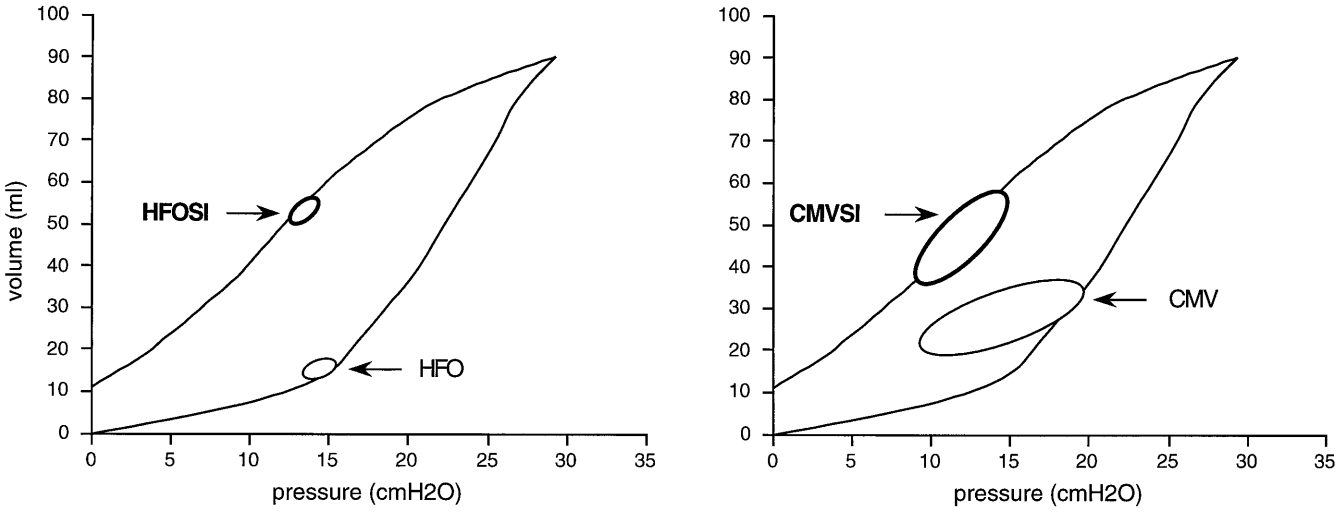


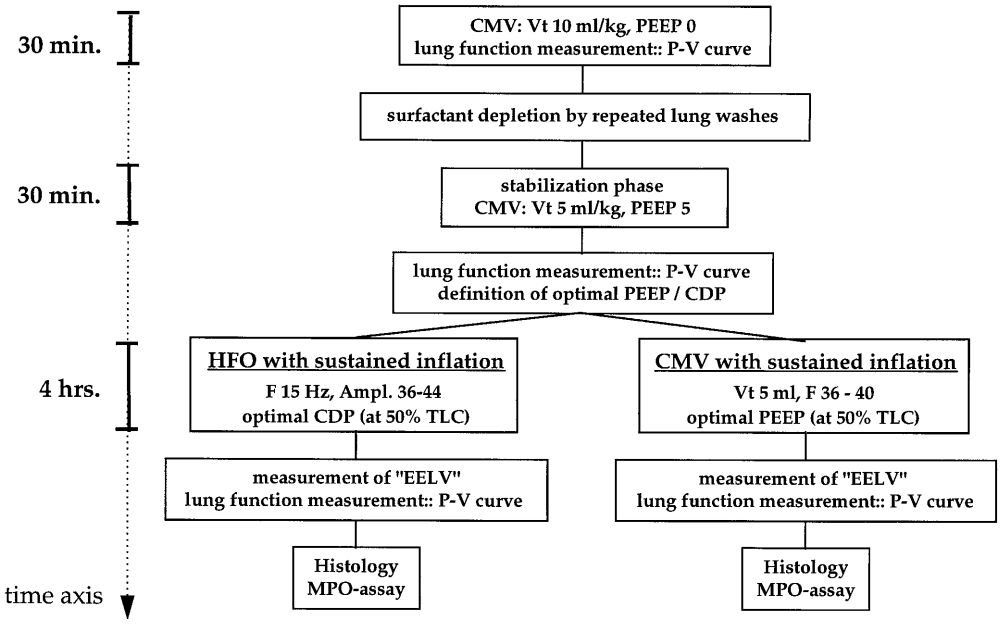
Fig.1 Schematic drawing to illustrate the position of the dynamic loops in relation to the overall pressure-volume curve during high-frequency oscillation and conventional ventilation, before (*HFO/CMV*) and after a sustained inflation (*HFOSI/CMVSI*). (See [25, 26])

Lung function measurements

Dynamic and static lung function measurements were performed before lung lavage, after lung lavage, and at the end of the 4 h ventilation protocol. V_T was measured with a low dead space (1.3 ml) thermistor pneumotachograph (BEAR NVM-1, BEAR Medical Systems, Riverside, Calif., USA) inserted between the endotracheal tube and the ventilator adapter. The flow signal was digitally integrated to volume. Airway pressures were recorded using a Validyne MP 45 pressure transducer (Validyne Engineering, Northridge, Calif., USA) connected to a side port of the ETT adapter. Both flow/volume and pressure signals were recorded by an online IBM computer using AD conversion at a sampling rate of 250 Hz (DT2801A, Marlboro, Mass., USA) and software package ANADAT/lABDAT (McGill University, Montreal, Canada).

The *quasistatic* PV curve of the respiratory system was constructed by slowly, manually inflating the lungs using fixed volume steps up to a plateau pressure of 30 cmH_2O at the external opening of the endotracheal tube. The deflation loop of the quasistatic PV curve was then constructed by withdrawing air in the same manner [32]. Volumes were held at each step until a plateau was observed on the pressure tracing. Before each measurement the FiO_2 was reduced to 0.21 for at least 1 min to minimize O_2 uptake throughout the apneic period, which would lead to a net loss of thoracic gas volume [33]. The animals were then disconnected for a short period from the ventilator circuit to allow the lungs to collapse passive-

Fig.2 Flowchart showing the time-course of the experiments



ly to FRC. This was followed by two large breaths to standardize volume history of the lungs immediately before quasistatic PV curves were constructed.

EELV above FRC was measured using the airway occlusion technique [34]. In practice, the endotracheal tube was briefly occluded at end-expiration and then opened to atmosphere to allow deflation to FRC and this expired volume from end-expiration (EELV) was recorded. Volume was measured under stable conditions after at least 5 min of ventilation at each ventilator setting (before and after SI) at the beginning of the experiment after completed lung lavage before the animals were submitted to the randomly allocated ventilatory protocol.

Lung histology

The animals were killed by an intravenous injection of pentobarbital. Lungs were removed and fixed by intratracheal instillation of 10% neutral-buffered formalin to a volume equal to 50% of the volume at TLC as measured at the beginning of the experiment. Following intratracheal fixation the lungs were immersed in a 10% neutral-buffered formalin solution for 48 h. The lungs were sectioned in coronal plane and two random sections from the left upper, left middle, and left lower lobe (total of six sections) were processed for histological analysis. Tissues were embedded in paraffin, sectioned at 5 μm and stained, with hematoxylin and eosin. Each section (two per lobe) was examined by two independent pathologists (J.C.P. and C.M.) who were blinded to the experimental group. The sections were examined using two slightly different procedures. The first, evaluating the distribution pattern of the lesions, gave particular reference to bronchiolar epithelial lesions (necrosis and epithelial sloughing) and hyaline membrane formation in alveolar ducts using a modification of the method described by Nilsson et al. [35] and later Muscedere et al. [16]. A total of at least 100 alveolar ducts per slide and all of the membranous and respiratory bronchioles in the same microscopic views were analyzed. Individual injury scores for membranous and respiratory bronchioles and alveolar ducts were obtained as a percentage of injured airways of each airway type.

The second procedure evaluated the sections according to criteria adapted from Hamilton et al. [28] and Ginsberg et al. [36]. This system scores in a semiquantitative way the gravity of bronchiolar epithelial lesions (airway score) and of the alveolar ducts (airspace score). The lungs were surveyed, and the severity of histopathological changes was graded as 0–4 (0, normal; 1, questionable change; 2, minimal change; 3, moderate change; 4, marked change). The criteria used to evaluate histopathological changes in airways included sloughing of respiratory epithelium, flattening of respiratory epithelium, and the presence of proteinaceous exudate in airways/alveoli. The categories of histopathological changes used to evaluate the airspace included the presence of heterophils in alveoli, the presence of macrophages in alveoli, signs of overinflation or emphysema of alveoli, and the amount of hyaline membrane formation.

Lung tissue myeloperoxidase

Several small lung tissue samples, always taken from the right lower lobe, were immediately frozen in liquid nitrogen and stored at –70 °C for measurement of the myeloperoxidase (MPO) concentration, a quantitative method measuring pulmonary leukostasis [37]. Thawed lung samples (0.75–0.8 g wet weight) were homogenized (Polytron PT 10/35, Brinkman Instruments, Westburg, N.Y., USA) in 20 ml 10 mM potassium phosphate (pH 7.4) for 1 min. The homogenate was centrifuged at 12000 *g* (20 min, 4 °C). The pellet was rehomogenized in 20 ml 50 mM potassium phosphate (pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide. This suspension was frozen overnight at –70 °C, thawed the next morning at room temperature, rehomogenized for 1 min, and sonicated at 40 W (VC 50T, Sonics & Materials, Conn., USA) for 1 min. After centrifugation (12,000 *g*, 20 min, 4 °C), the supernatant was collected and used for both MPO and protein assay.

MPO activity was assessed using the spectrometric technique with tetramethylbenzidine as substrate [37]. Each cuvette contained 25 μl of the undiluted sample, 25 μl of 16 mM 3,3′,5,5′-tetramethylbenzidine dissolved in *N*,*N*-dimethylformamide and 175 μl 220 mM potassium phosphate buffer containing 110 mM NaCl. The reaction was initiated by addition of 25 μl 3.0 mM H_2O_2. The change in absorbance at 655 nm during the first 3 min was measured using the Cobas FARA II Chemistry System (Roche Diagnostic Systems, Montclair, N.J., USA) at pH 5.4 and 37 °C. Results are expressed as the MPO content per milligram of protein.

The protein content of the samples was determined utilizing the Pierce BCA protein assay (Pierce, Rockford, Ill., USA). Spectrometric determination of the assay was performed using the Cobas FARA II Chemistry System. Standard dilutions of bovine serum albumin in 50 mM potassium phosphate (pH 6.0, containing 5% hexadecyltrimethylammonium bromide) were prepared to generate a standard curve.

Statistical methods

Results are given as mean ± SD for parametric data. Repeated measures analysis of variance with a posthoc Bonferroni correction for multiple comparisons was used to determine the effects of group-time interaction for each parameter measured repeatedly. The two treatment groups were compared using parametric testing (unpaired *t* test). For multiple comparisons between the two groups one-way analysis of variance was performed followed by the Bonferroni multiple comparison test. Statistical significance was accepted at $P < 0.05$ for all comparisons [38].

Results

We ventilated 12 surfactant-depleted adult New Zealand rabbits (6 in each group) for 4 h: group 1, CMVSI (V_T 5 ml/kg, SI followed by PEEP > CCP); group 2, HFOSI (HFO, SI followed by CDP > CCP and 4–5 cmH_2O). The two groups were identical for baseline characteristics, such as weight (3.1 ± 0.1 vs. 3.1 ± 0.2 kg), number of lung washes (6.3 ± 1.4 vs. 5.9 ± 0.8), amount of recovered lavage fluid (89 ± 4% vs. 89 ± 5%), and static compliance (0.84 ± 0.17 vs. 0.96 ± 0.07 ml/cmH_2O) and pO_2 values (53 ± 4 vs. 53 ± 8 mmHg) after completed lavage. Furthermore, PEEP at 50% TLC values (PEEP > CCP), as previously defined, were similar (9.4 ± 0.5 vs. 10.9 ± 1.0 cmH_2O) for both groups. Lavaged lungs of both groups were recruitable with an EELV (above FRC) of 19.5 ± 9.0 ml for the CMVSI group vs. 15.5 ± 6.0 ml for the HFOSI group before a sustained inflation was applied, and an EELV (above FRC) of 34.9 ± 12.4 ml (CMVSI) vs. 34.3 ± 5.8 ml (HFOSI) after a sustained inflation at a PEEP at 50%

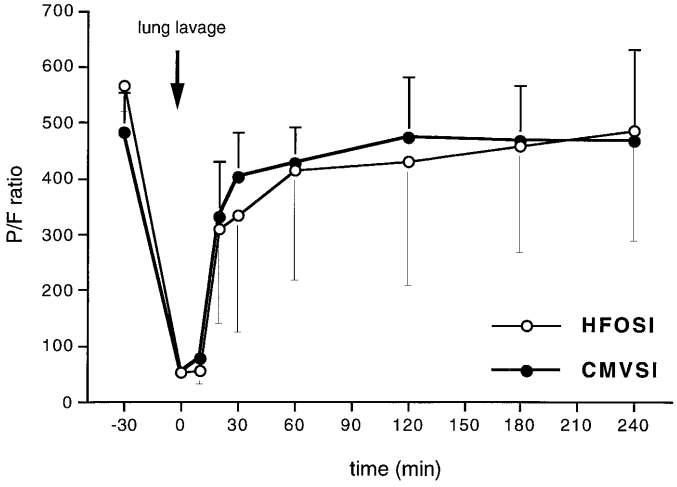


Fig.3 PaO_2/FiO_2 (mean ± SD), HFO (*open circles*) versus CMV (*closed circles*) over time. Differences between the two groups are not significant

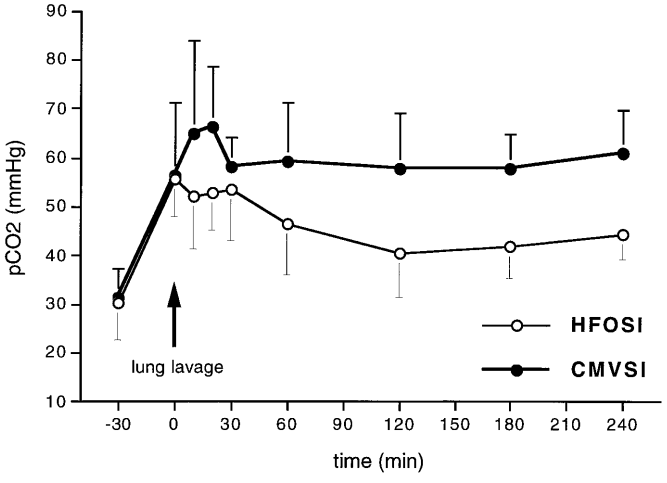
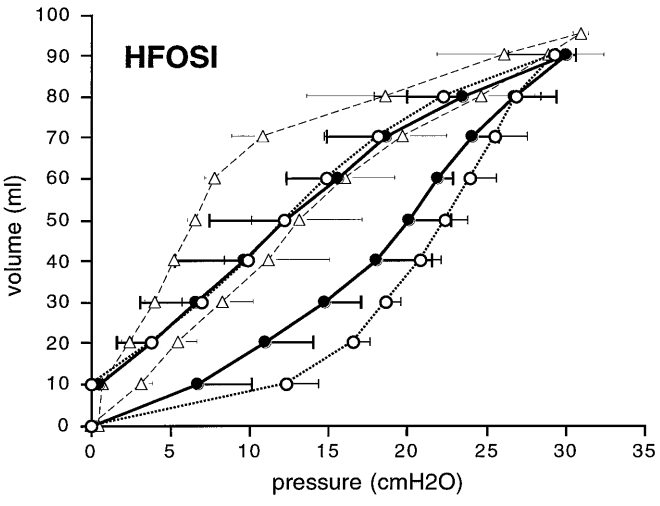


Fig.4 $PaCO_2$ values (mean ± SD), HFO (*open circles*) versus CMV (*closed circles*) over time. Differences between the two groups reflect the difference between the two ventilator strategies used



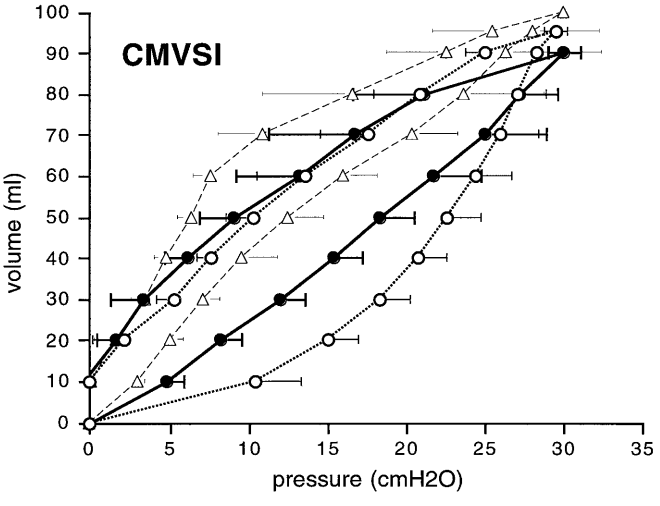


Fig.5 Composite pressure-volume curves before lung lavage (*open triangles*), after lung lavage (open circles), and after 4 h of ventilation (closed circles) for both groups. Note that the lower inflection point (P_{inf}) became lost after 4 h of ventilation in both groups. Differences between the two groups are not significant

TLC. Operating mean airway pressures were nearly identical in the two groups (CMVSI, 14.3 ± 1.0 cmH_2O; HFOSI, 14.5 ± 1.0 cmH_2O) with PEEP set at 9.4 ± 0.5 cmH_2O (PEEP > CCP) in the CMVSI group, and CDP at 14.5 ± 1.0 cmH_2O (i.e., 4–5 cmH_2O above CCP) in the HFOSI group.

Gas exchange

Oxygenation improved significantly but equally in the two groups after a SI (from 79 ± 18 to 330 ± 100 mmHg, and from 57 ± 25 to 311 ± 172 mmHg, respectively, at an FiO_2 of 1.0), remained stable over 4 h of ventilation, and was very similar in the two groups at the end of the ventilation protocol (468 ± 163 vs. 469 ± 198 mmHg, $P = 0.34$; Fig. 3). CO_2 levels over the 4 h ventilation protocol were dissimilar and are given for both groups in Fig. 4.

Lung mechanics

Static compliance increased similarly and significantly over the 4 h of ventilation in the two groups from their similar baseline measurements (i.e., lavaged lung) and

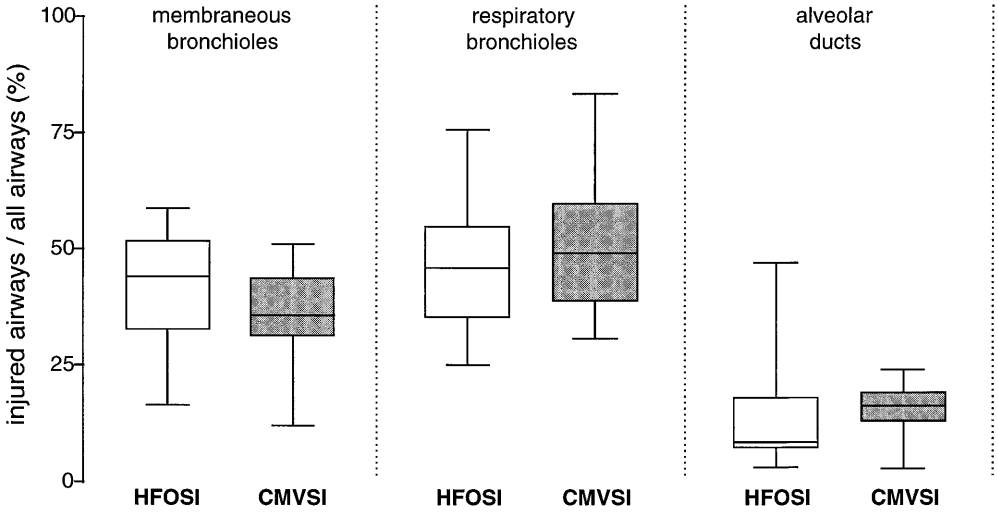


Fig.6 Box-and-whiskers graph of quantitative histopathological analysis showing the distribution pattern of airway and airspace injury. The importance of injury is given by the percentage of injured airways of each airway type. *Boxes* 25th and 75th percentiles, and the median; *whiskers* extend from the minimal to the maximal value. Differences between the two groups are not significant

did not differ at the end of the ventilation protocol between the groups (Fig. 5).

Lung histology

Histologically both groups showed only minimal airway injury of bronchioles, alveolar ducts, and alveolar airspace. Histology slides of both groups were characterized principally by mild, often widespread, sometimes only circumferential or segmental flattening of respiratory epithelium and sloughing of viable epithelial cells within the lumen of larger airways. The inflammatory cell infiltrate was mild and hyaline membranes were rarely seen in airspace. There was no significant difference between the groups ($P > 0.05$, analysis of variance) for any histopathological criteria assessed (Figs. 6, 7, 8).

Lung tissue myeloperoxidase

MPO content in homogenized lung tissue was equal in the two groups (0.84 ± 0.36 vs. 1.04 ± 0.43 /mg protein; $P = 0.39$).

Discussion

The pressures required to open conducting distal airways and alveolar units in the gas-filled lung exceed those required to prevent closure (i.e., PV hysteresis). This is certainly true in the surfactant-depleted lung. This behavior of the lung can be used to optimize lung recruitment, using maneuvers such as a sustained inflation. The point of maximal lung volume corresponds to the value at which TLC is reached. This is found to be at about 30 cmH_2O transpulmonary pressure for mammals, providing the rationale, at least in small animals with a highly compliant chest wall, of applying sustained inflation maneuvers to 30 cmH_2O airway pressure over a short period of time.

This allow the PV relationship of the respiratory system to be fully utilized, since the ventilatory cycle can be pushed onto the deflation limb of the overall PV curve [1, 25]. At end-expiration substantial airway closure occurs only if the end-expiratory airway pressure is too low to maintain the lung volume above critical lung closing [39]. This concept and its efficiency as a lung protective strategy after surfactant depletion has been well described by various authors [1, 3, 4, 5] during HFO, the extreme of a small V_T ventilation approach.

In this study we used the same concept during small V_T CMV as described previously [25] to test whether this ventilator strategy is as efficient as HFO with SI in preventing ventilator-induced lung injury and in achieving adequate gas exchange. We set the PEEP level after SI to an EELV corresponding to 50 % of TLC to maintain EELV slightly above critical lung closing. This was based on data from the literature [30, 31] showing that gas filled lung units start to close at lung volumes below 40–45 % of TLC. It is clear that this approach is quite arbitrary and perhaps may not be clinically applicable in as simple a manner.

Our results show that this strategy of lung recruitment during small V_T ventilation using a SI (CMVSI) allows similar improvement in oxygenation as during HFOSI. Furthermore, neither histological nor biochemical markers of lung injury differed between groups and, although widespread in their distribution, only minimal in their gravity. Ideally, a lung-protective ventilation strategy should allow the appearance of any morphological lesions at all to be avoided. In fact, this may be impossible to achieve when using a model of acute lung injury based on a primary insult (i.e., depletion of the

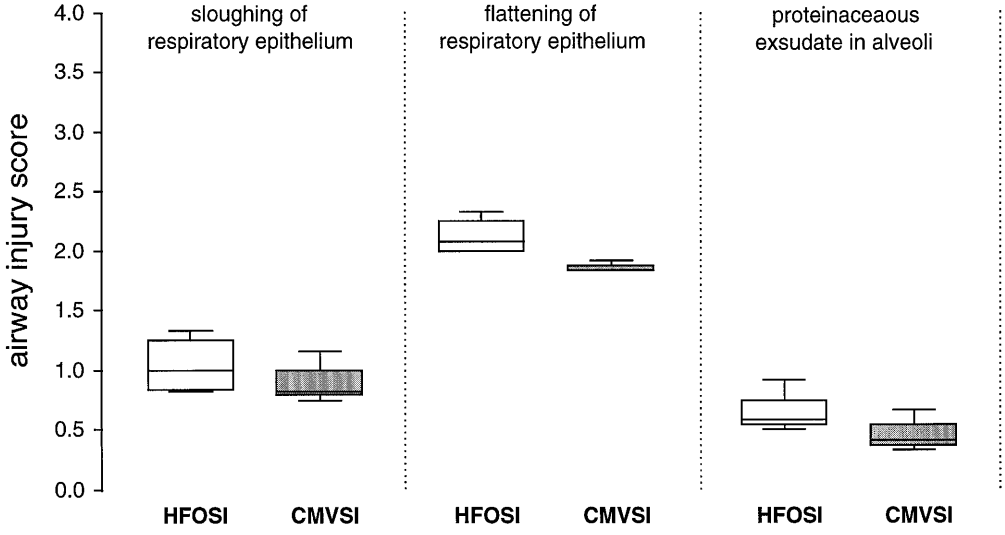


Fig.7 Box-and-whiskers graph of semiquantitative histopathological analysis showing the gravity of airway injury (score 0 – 4). *Boxes* 25th and 75th percentiles, and the median; *whiskers* extend from the minimal to the maximal value. Differences between the two groups are not significant

lungs of surfactant followed by a period of conventional, and somewhat injurious, ventilation to achieve stable model conditions). It is well known that the inflammatory response on any mechanical stress to the small airways and airspaces occurs within a few minutes after its onset, before any stable conditions are present, and before animals can be randomized to one or the other ventilation protocol in an experimental set-up. This was to some extent the case in our study. There was no significant difference in the groups when markers of lung injury were examined. This finding can be explained by the fact that (a) the repetitive stretching and collapsing, and (b) substantial overdistention of distal conducting airways was avoided during both modes of ventilation, since tidal cycles are placed within a "safe zone" on the deflation limb (Fig. 1). As the lung demonstrates hysteresis, and the lung is boosted onto the inflation limb, opening the lung with a sustained inflation and maintaining lung volume with an adequate distending pressure is what avoids injurious ventilation. In brief, our study indicates that to prevent ventilator induced lung injury it is of more importance to achieve and maintain alveolar expansion than to choose one or another type of ventilator. This is well in accord with the findings of Gommers et al. [40], who have shown similar results when comparing HFO and CMV in a model of acute lung injury in which recruitment was achieved by means of surfactant therapy.

While it may be argued that the model of repeated lung lavage has insignificant injury to start, and that a 4-h ventilation protocol may entail insufficient time to see a significant change, we believe that it was the protective strategy of both modes of ventilation which avoided the progression to more severe lung injury. However, it has been shown many times in exactly the same animal model that oxygenation remains poor and histological lesions marked and widespread with more injurious ventilator strategies, such as low-PEEP large-V_T strategies or low mean airway pressures during HFO [5, 25, 28].

Our results seem to be controversial in comparison to the previous literature comparing the effects of lung volume recruitment during HFO and CMV. Kolton et al. [3] and later Bond and Froese [29] did not observe a similar recruitment during intermittent positive pressure ventilation. In retrospect, this was inevitable, as these studies used large V_T values, leading to high plateau pressures around 30 cmH_2O, and therefore every breath was in effect a sigh. Furthermore, PEEP values in the CMV group were low (5 cmH_2O), allowing for cyclic end-expiratory collapse of lung units, adding repetitive shear stress in the surfactant depleted lung during each tidal cycle. This is supported by the results of a more recent study [41] showing that to achieve and maintain full lung recruitment during HFO requires an inflation to TLC followed by relatively high continuous distending pressures, whereas during CMV relatively large V_T must be used with a level of PEEP higher than in the above studies to prevent end-expiratory collapse. Furthermore, under conditions of end-expiratory lung closing, as was the case in the Kolton et al. [3] and the Bond et al. [42] studies, the time allowed to re-recruit (i.e., inspiratory plateau time) might not have been long enough to achieve maximal recruitment during each respiratory cycle since recruitment is time dependent [43]. For these various reasons these authors [3, 42] were unable to show a beneficial effect of a SI (during CMV) on oxygenation or on histology.

In practice, lung volume recruitment during HFO is safely used for improving oxygenation in neonates with respiratory failure by applying mean airway pressures greater than those used with conventional ventilation

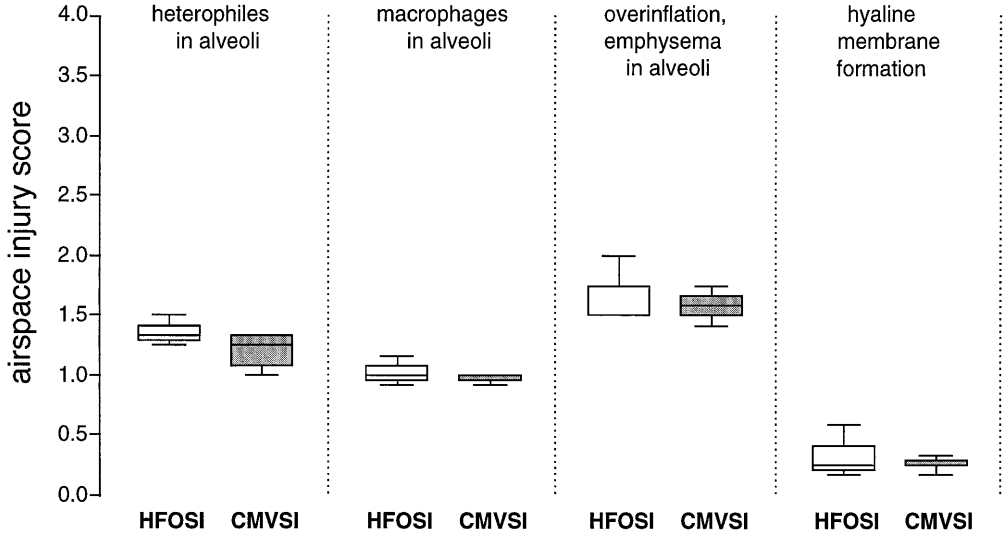


Fig.8 Box-and-whiskers graph of semiquantitative histopathological analysis showing the gravity of airspace injury (score 0 – 4). *Boxes* 25th and 75th percentiles, and the median; *whiskers* extend from the minimal to the maximal value. Differences between the two groups are not significant

[6, 7]. The rationale behind these differences in mean airway pressures required to match oxygenation is that during CMV recruitment occurs on a V_T basis, where peak inspiratory pressure recruits the lungs and PEEP maintains already recruited lung volume. HFO allows the use of extremely small V_T values, less than deadspace. Therefore during HFO maximum and minimum pressures are very close to the mean airway pressure, which means (a) that recruitment does not occur on a V_T basis, and (b) that end-expiratory lung volumes can be kept easily above critical lung closing.

Oxygenation was identical in the two groups; better CO_2 removal was achieved using HFO. However, although V_T reduction during CMV can be critical and has its limitations because of possibly unwanted systemic effects of CO_2 retention [44, 45, 46], CO_2 levels could be maintained within acceptable limits in our experiments, using small V_T values of only 5 ml/kg. Furthermore, there is some evidence in the recent literature that even larger V_T values may be acceptable, as long as airway pressures, or transpulmonary pressures, are limited to a maximum level of 35 cmH_2O [22, 23].

The concept of SI to recruit lung volume is based on the presence of hysteresis of the respiratory system. This is certainly true in the relatively homogeneous lung injury model of surfactant deficiency, whereas the presence of hysteresis remains controversial in established adult respiratory distress syndrome (ARDS) with a less homogeneous distribution of pulmonary lesions, due to a mixture of inflammatory reactions, lung tissue consolidation, and edema formation [32, 47, 48]. We recognize that as long as lung units are not allowed to collapse during end-expiration there is certainly little or no PV hysteresis present. This can be best achieved by setting PEEP high enough to avoid critical lung closing (i.e., optimum PEEP to prevent end-expiratory collapse) [25, 49]. Furthermore, when recording PV curves during mechanical ventilation (i.e., interruption methods, PEEP steps and others), it is not uncommon to observe no or only little hysteresis of the PV loop, constructed under somewhat dynamic conditions. Not only recruitment but also derecruitment is a time-dependent process. Therefore many of the recruited alveoli remain open at end-expiration according their specific time constant during ventilation despite a PEEP level below CCP, but tend to collapse when no PEEP is applied. Other alveoli are never recruited despite high end-inspiratory pressures. These two types of alveoli do not contribute to the PV relationship of the lung [50] and thus also not to hysteresis under dynamic conditions of ventilation with PEEP. In contrast, in the same ARDS patient PV hysteresis is observed when the quasistatic PV curve from functional residual capacity (i.e., prolonged expiration to 0 airway pressure) to TLC and back again is constructed by the syringe method [32]. This curve describes the outer envelope of possible positions that might actually occur during tidal ventilation, and within which we can deliberately place our tidal cycle [25]. Our concept of recruitment by SI is based on this hysteresis of the total quasistatic PV curve and has proven to be efficient for improvement in recruitment and oxygenation not only in our animal model of surfactant depletion, but also in patients with established ARDS, as recently reported by two different groups of investigators [51, 52].

The surfactant-depleted lung lavaged model that we used in our experiments may be more representative of the infant respiratory distress syndrome. However, this model does not differ substantially from acute lung injury in adults (i.e., early stages of ARDS) in terms of histological (hyaline membrane formation, cellular infiltration, epithelial sloughing, and necrosis) and pathophysi-

ological changes [27, 28, 53]. The criticism has repeatedly been expressed that the lung lavage model is not stable in terms of the PV relationship and the effect on oxygenation immediately after lung lavage. Interposing between lung lavage and PV measurements a stabilization period allowed us to have reproducible PV curves in the same animal and between different subjects as well. In the surfactant-depleted lung PV hysteresis is important initially but becomes less so when additional lung injury occurs, characterized by edema formation, cellular infiltration, and parenchymal consolidation. This is very similar to the situation in acute lung injury (ALI) or ARDS, in which PV hysteresis is most important in early stages and becomes less marked later in the course of the disease when widespread consolidation and cellular infiltrates are present [32]. The latter occurs earlier in ARDS from pulmonary disease than in ARDS from extrapulmonary disease and might explain the observation that a sigh maneuver is more effective in the latter than in the former [51]. It is therefore important to keep the timely concept in mind when trying to optimize mechanical ventilation in the clinical situation, either for infants or pediatric and adult patients with acute respiratory failure (i.e., ALI/ARDS).

In our experiments quasistatic PV loops showed less hysteresis at the end of the 4 h ventilation period than the PV curve after lung lavage, whereas static compliance, given by the slope of the PV relationship at TLC, did not change. The latter confirms the observation that almost no additional lung injury occurred during the ventilation period. Since lung history was carefully standardized before each measurement of lung function, we believe that the change in hysteresis indicates lowered alveolar surface tension, this being explained by some recovery of surfactant function. The shape of the deflation limb is related to the elastic recoil properties of the respiratory system and therefore remained unchanged.

We conclude that using a volume recruitment strategy during small V_T ventilation and maintaining lung volumes above the closing volume of the lung is as protective as using HFO at equal lung volumes, at least in this model of lung injury. However, gas exchange can be better optimized during HFO. Therefore HFO remains a promising ventilation mode not only in neonates [6], certainly when initiated very early in the course of disease [7], but also in children and adults with acute respiratory failure [54]. In any mode, we should be mindful of the lessons that we have learned during the use of HFO, which is first to recruit and then to keep once opened lung units open. This concept should be used for further trials of so-called protective ventilator strategies in neonates, children, and adults, using either small tidal ventilation or HFO. Any protective strategy must start early in the clinical course of ALI and ARDS, perhaps even in the patient at risk, to avoid further pulmonary deterioration by minimizing secondary, ventilator associated lung injury.

References

1. Suzuki H, Papazoglou K, Bryan AC (1992) Relationship between PaO_2 and lung volume during high frequency oscillatory ventilation. Acta Paediatr Jpn 34: 494–500
2. Thompson WK, Marchak BE, Froese AB, Bryan AC (1982) High-frequency oscillation compared with standard ventilation in pulmonary injury model. J Appl Physiol 52: 543–548
3. Kolton M, Cattran CB, Kent G, Volgyesi G, Froese AB, Bryan AC (1982) Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. Anesth Analg 61: 323–332
4. Walsh MC, Carlo WA (1988) Sustained inflation during HFOV improves pulmonary mechanics and oxygenation. J Appl Physiol 65: 368–372
5. McCulloch PR, Forkert PG, Froese AB (1988) Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. Am Rev Respir Dis 137: 1185–1192
6. Gerstmann DR, Minton SD, Stoddard RA (1996) The Provo multicentre early high frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 98: 1044–1057
7. Rimensberger PC, Beghetti M, Hanquinet S, Berner M (2000) "First intention" high-frequency oscillation (HFO) with early lung volume optimization improves pulmonary outcome in preterm infants with respiratory distress syndrome. Pediatrics (in press)
8. Mead J, Whittenberger JL, JR EPR (1957) Surface tension as a factor in pulmonary volume-pressure hysteresis. J Appl Physiol 10: 191–196
9. Hedley-White J, Laver MB, Bendixen HH (1964) Effect of changes in tidal ventilation on physiologic shunting. Am J Physiol 206: 891–897
10. Nunn JF, Bergman NA, Coleman AJ (1965) Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation. Br J Anaesth 37: 898–914
11. Dreyfuss D, Basset G, Soler P, Saumon G (1985) Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 132: 880–884
12. Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, Joris M (1987) Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. Am Rev Respir Dis 135: 312–315
13. Dreyfuss D, Soler P, Basset G, Saumon G (1988) High inflation pressure pulmonary edema respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137: 1159–1164
14. Tsuno K, Prato P, Kolobow T (1990) Acute lung injury from mechanical ventilation at moderately high airway pressures. J Appl Physiol 69: 956–961

15. Sandhar BK, Niblett DJ, Argiras EP, Dunnill MS, Sykes MK (1988) Effects of positive end-expiratory pressure on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome. Intensive Care Med 14: 538–546
16. Muscedere JG, Mullen JBM, Gan K, Slutsky AS (1994) Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 149: 1327–1334
17. Corbridge TC, Wood LDH, Crawford GP, Chudoba MJ, Yanos J, Sznajder JI (1990) Adverse effects of large tidal volume and low PEEP in canine acid aspiration. Am Rev Respir Dis 142: 311–315
18. Slutsky AS (1993) Barotrauma and alveolar recruitment. Intensive Care Med 19: 369–371
19. Amato MB, Barbas CS, Medeiros DM, Schettino GP, Filho GL, Kairalla RA, Deheinzelin D, Morais C, Fernandes EdO, Takagaki TY, de Carvalho CR (1995) Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 152: 1835–1846
20. Papadakos PJ, Apostokaols MJ (1996) High-inflation pressure and positive end-expiratory pressure. Injurious to the lung? Yes. Crit Care Clin 12: 627–634
21. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaski TY, de Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338: 347–354
22. Brochard L, Roudot-Thorwald F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clementi E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. Am J Respir Crit Care Med 158: 1831–1838
23. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Shouten BD, Todd TR, Slutsky AS (1998) Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med 338: 355–361
24. Byford LJ, Finkler JH, Froese AB (1988) Lung volume recruitment during high-frequency oscillation in atelectasis-prone rabbits. J Appl Physiol 64: 1607–6714
25. Rimensberger PC, Cox PN, Frndova H, Bryan AC (1999) The open lung during small tidal volume ventilation: concepts of recruitment and "optimal" PEEP. Crit Care Med 27: 1946–1952
26. Rimensberger PC, Pristine G, Mullen JBM, Cox PN, Slutsky AS (1999) Lung recruitment during small tidal volume ventilation allows minimal PEEP without augmenting lung injury. Crit Care Med 27: 1940–1945
27. Lachmann B, Robertson B, Vogel J (1980) In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol Scand 24: 231–236
28. Hamilton PP, Adebusola O, Smyth JA, Gillan JE, Cutz E, Froese AB, Bryan AC (1983) Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology. J Appl Physiol 55: 131–138
29. Bond DM, Froese AB (1993) Volume recruitment maneuvers are less deleterious than persistent low lung volumes in the atelctasis-prone rabbit lung during high-frequency oscillation. Crit Care Med 21: 402–412
30. Bachofen H, Hildebrandt J, Bachofen M (1970) Pressure-volume curves of air- and liquid-filled excised lungs – surface tension in situ. J Appl Physiol 29: 422–431
31. Frazer DG, Weber KC, Franz GN (1985) Evidence of sequential opening and closing of lung units during inflation-deflation of excised rat lungs. Respir Physiol 61: 277–288
32. Matamis D, Lemaire F, Harf A, Ansquer JC, Atlan G (1984) Total respiratory pressure-volume curves in the adult respiratory distress syndrome. Chest 86: 58–66
33. Dall'ava-Santucci J, Armaganidis A, Brunet F, Dhainaut JF, Chelucci GL, Monsallier JF, Lockhart A (1988) Causes of error of respiratory pressure-volume curves in paralyzed subjects. J Appl Physiol 64: 42–49
34. Kelly E, Bryan H, Possmayer F, Frndova H, Bryan C (1993) Compliance of the respiratory system in newborn infants pre- and postsurfactant therapy. Pediatr Pulmonol 15: 225–230
35. Nilsson R, Grossmann G, Robertson B (1978) Lung surfactant and the pathogenesis of neonatal bronchiolar lesions induced by artificial ventilation. Pediatr Res 12: 249–255
36. Ginsberg HS, Moldawer LL, Seghal PB, Redington M, Kilian PL, Chanock RM, Prince GA (1991) A mouse model for investigating the molecular pathogenesis of adenovirus pneumonia. Proc Natl Acad Sci USA 88: 1651–1655
37. Goldblum SE, Wu K, Jay M (1985) Lung myeloperoxidase as a measure of pulmonary leukostasis in rabbits. J Appl Physiol 59: 1978–1985
38. Motulsky H (1995) Intuitive biostatistics. Oxford University Press, Oxford, pp 255–261
39. Mansell AL, Bryan AC, Levison H (1977) Relationship of lung recoil to lung volume and maximum expiratory flow in normal children. J Appl Physiol 42: 817–823
40. Gommers D, Hartog A, Schnabel R, De Jaegere A, Lachmann B (1999) High-frequency oscillatory ventilation is not superior to conventional mechanical ventilation in surfactant-treated rabbits with lung injury. Eur Respir J 14: 738–744
41. Sznajder JI, Nahum A, Hansen DE, Long GR, Wood LD (1998) Volume recruitment and oxygenation in pulmonary edema: a comparison between HFOV and cmV. J Crit Care 13: 126–135
42. Bond DM, McAloon J, Froese AB (1994) Sustained inflations improve respiratory compliance during high-frequency oscillatory ventilation but not during large tidal volume positive-pressure ventilation in rabbits. Crit Care Med 22: 1269–1277
43. Suki B, Barbasi AL, Hantos Z, Petak F, Stanley HE (1994) Avalanches and power-law behaviour in lung inflation. Nature 368: 615–618
44. Feihl F, Perret C (1994) Permissive hypercapnia: how permissive should we be? Am J Respir Crit Care Med 150: 1722–1737
45. Hickling KG, Joyce C (1995) Permissive hypercapnia in ARDS and its effect on tissue oxygenation. Acta Anaesthesiol Scand 107 [Suppl]:201–208
46. Tasker RC, Peters MJ (1998) Combined lung injury, meningitis and cerebral edema: how permissive can hypercapnia be? Intensive Care Med 24: 616–619
47. Sydow M, Burchardi H, Zinserling J, Ische H, Crozier TA, Weyland W (1991) Improved determination of static compliance by automated single volume steps in ventilated patients. Intensive Care Med 17: 108–114
48. Beydon L, Svantesson C, Brauer K, Lemaire F, Jonson B (1996) Respiratory mechanics in patients ventilated for critical lung disease. Eur Respir J 9: 262–273

49. Hickling KG (1998) The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lung. Am J Respir Crit Care Med 158: 194–202
50. Carney DE, Bredenberg CE, Schiller HJ, Picone AL, McCann UG II, Gatto LA, Bailey G, Fillinger M, Nieman GF (1999) The mechanism of lung volume change during mechanical ventilation. Am J Respir Crit Care Med 160: 1697–1702
51. Pelosi P, Cadringher P, Bottino N, Panigada M, Carrieri F, Riva E, Lissoni A, Gattinoni L (1999) Sigh in acute respiratory distress syndrome. Am J Respir Crit Care Med 159: 872–880
52. Lapinsky SE, Aubin M, Metha S, Boiteau P, Slutsky AS (1999) Safety and efficacy of a sustained inflation for alveolar recruitment in adults with respiratory failure. Intensive Care Med 25: 1297–1301
53. Sugiura M, McCulloch PR, Wren S, Dawson RH, Froese AB (1994) Ventilator pattern influences neutrophil influx and activation in atelectasis-prone lung. J Appl Physiol 77: 1355–1365
54. Fort P, Farmer C, Westerman J, Johannigman J, Beninati W, Dolan S, Derdak S (1997) High-frequency oscillatory ventilation for adult respiratory distress syndrome – a pilot study. Crit Care Med 25: 937–947