The impact of mechanical ventilation strategies that minimize atelectrauma in an experimental model of acute lung injury

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Abstract

Objective: To evaluate whether ventilation strategies that target alveolar stabilization and prevention of atelectrauma would be associated with more favorable physiologic outcomes in a combined model of acute lung injury.

Methods: Thirty-nine rabbits were instrumented and ventilated with FiO_2 of 1.0. Combined lung injury was induced by an infusion of lipopolysaccharide and tracheal saline lavage. Animals were randomized to receive conventional ventilation with tidal volume of 10 ml/kg, PEEP of 4 cm H_2O; conventional ventilation with surfactant (Infasurf, 3 mg/kg IT); partial liquid ventilation (18 ml/kg of perflubron IT); or high-frequency oscillatory ventilation with mean airway pressure of 14 cm H_2O and frequency of 4 Hz. Uninjured ventilated animals served as controls. Conventional ventilation with surfactant, partial liquid ventilation and control groups were ventilated with settings identical to the conventional ventilation group. Animals were studied for 4 hours, during which serial blood gas measurements were obtained. After sacrifice, lungs were harvested for injury grading by a microscopic lung injury score and measurement of 4-hydroxy-nonenal, a marker of lipid peroxidation.

Results: Conventional ventilation resulted in hypoxia and greater evidence of lung injury. Animals treated with partial liquid ventilation, high-frequency oscillatory ventilation or conventional ventilation with surfactant had adequate oxygenation, but conventional ventilation with surfactant resulted in higher lung injury scores and increased pulmonary oxidative damage.

Conclusion: Strategies that minimize atelectrauma (partial liquid ventilation and high-frequency oscillatory ventilation) are associated with adequate oxygenation and attenuated lung injury. Surfactant improves oxygenation in comparison to conventional ventilation alone but resulted in increased injury, presumably because the inadequately low PEEP was insufficient to stabilize the alveoli during expiration.

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Introduction

It is known that injury to alveolar capillary units associated with microcirculatory dysfunction, alveolar fluid accumulation and functional surfactant abnormalities lead patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) to exhibit a severe imbalance between ventilation and perfusion, resulting in significant hypoxemia.[1] In addition, the exaggerated work of breathing due to increased dead space and reduced pulmonary compliance leads to respiratory failure marked by hypercapnia and respiratory acidosis.[1] As a result, the vast majority of patients with ALI and ARDS require mechanical ventilation in order to achieve respiratory stability and to buy time for treatment of the underlying condition and for the natural resolution of the pulmonary process.[2] Despite advances in general intensive care therapies, the dramatic alterations of respiratory physiology described above mean that patients with ALI and ARDS continue to exhibit significant mortality, varying between 35% and 71%.[3-5]

Mechanical ventilation can no longer be seen merely as a supportive therapy in ALI and ARDS, but as a treatment modality capable of significantly influencing the course of pulmonary disease and clinical outcome.[5,6] Mechanical

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ventilation strategies employing large tidal volumes, thus resulting in cyclic alveolar overdistension during inspiration, are clearly associated with worsening of lung disease (volutrauma) in experimental models[7,8] and clinical trials.[5,6] On the other hand, the exact contribution made by cyclical alveolar collapse during expiration alternated with reopening during inspiration (atelectrauma)[9] in aggravating lung injury is less obvious. Despite proof that the use of ventilation strategies that avoid atelectrauma (using an adequate PEEP) result in attenuation of biological lung injury markers,[10,11] a recent clinical trial comparing the use of high PEEP and low PEEP for patients with ARDS was abandoned due to futility as there were no significant differences between the two groups.[12]

In this experiment, our aim was investigate the impact of ventilation strategies that reduce or prevent atelectrauma, such as high-frequency oscillatory ventilation (HFOV), partial liquid ventilation with perfluorochemicals (PLV) and conventional mechanical ventilation (CMV) with surfactant, compared with a strategy that is known to cause atelectrauma, such as CMV with too low a PEEP,[11] in a combined model of acute lung injury. We hypothesized that ventilation strategies capable of preventing atelectrauma would be associated with better oxygenation, reduced microscopic injury and attenuation of oxidative lung damage.

Materials and methods

This trial was performed in the experimental laboratory of the Division of Pediatric Critical Care, in the Biomedical Research Center, State University of New York at Buffalo, United States of America. The experimental protocol was approved by the Institutional Animal Care and Utilization Committee of the State University of New York at Buffalo. Chemical reagents were obtained from Sigma Chemical (St. Louis, Missouri, USA), except when otherwise stated.

Animals and randomization

Animals were treated according to the guidelines published by the National Institutes of Health of the United States of America. Thirty-nine juvenile New Zealand White rabbits weighing between 1.9 kg and 2.5 kg were used. Animals were randomized before induction of anesthesia through a system of identical envelopes with an equal chance of entering into any one of the five experimental groups.

Anesthesia and sedation

Animals were anesthetized and sedated with an intramuscular injection of 25 mg/kg of ketamine (Fort Dodge Animal Health, Fort Dodge, IA, USA), and 4 mg/kg of xylazine (The Butler Company, Columbus, OH, USA). Pre-oxygenation was performed under spontaneous breathing with continuous gas flow (10 l/min) of 100% oxygen through a facemask. Venous access was obtained via lateral auricular vein puncture (22 gauge jelco, Johnson & Johnson, Arlington, TX, USA). Muscle relaxation was induced by intravenous

administration of 0.2 mg/kg of pancuronium (Baxter HealthCare Corp., Irvine, CA, USA) and maintained with additional doses of 0.1 mg/kg every hour. Anesthesia and sedation were maintained by continuous intravenous administration of 10 mg/kg/hour of ketamine and 4 mg/kg/hour of xylazine until completion of the experiment.

Instrumentation

The anesthetized animals were positioned in the supine position and the anterior neck was rapidly dissected for a tracheostomy. A cuffed tracheal tube (3.0 to 3.5 mm, Sheridan Catheter, Argyle, NY, USA) was introduced through the tracheal incision and secured with umbilical tape. During dissection, the internal jugular vein and common carotid artery were isolated. A single-lumen vascular catheter (Intramedic Polyethylene Tubing, Beckton Dickinson, Sparks, MD, USA) was inserted into the common carotid artery and advanced to the intrathoracic portion of this vessel. A double lumen venous catheter (4 French, 8 cm, Cook Incorporated, Bloomington, IN, USA) was introduced to the junction between the right atrium and the upper vena cava via the internal jugular vein. Both catheters were connected to a patient monitor (Horizon 2000, Mennen Medical, Clearance, NY, USA) for continuous measurement of arterial and central venous pressures.

Core body temperature was monitored with an esophageal sensor and normal body temperature was maintained with an electrical warming pad. Maintenance fluids were continuously administered by infusion of 0.9% saline solution with 5% dextrose at 4 ml/kg/hour.

During the instrumentation process, all animals were ventilated with a Servo 300 ventilator (Siemens-Elema, Solna, Sweden) with FiO_2 of 1.0, tidal volume of 10 ml/kg, PEEP of 4 cmH_2O and a respiratory frequency of 25 cycles per minute. These parameters were maintained for a stabilization period of 15 minutes until induction of acute lung injury.

Volume-pressure curves

Static volume-pressure curves of the respiratory system were obtained at the end of the stabilization period and after induction of acute lung injury. Airway pressure was measured with a transducer (P23XL, Spectramed, Ounard, Califórnia, USA) coupled to a side port of the tracheal tube, that transmitted signals to a multi-channel chart recorder (TA6000, Gould Instruments, Valley View, Ohio, USA).[11]

Induction of Lung injury

Acute lung injury was induced by intravenous endotoxin administration[13] and pulmonary lavage with saline solution.[13,14] *Escherichia coli* lipopolysaccharides were reconstituted in saline to a final concentration of 0.5 mg/kg and infused for five minutes. This procedure was followed by endotracheal pulmonary lavage with three 30 ml/kg aliquots of saline solution warmed to 38 ºC.[14] The animals were stabilized for 15 minutes, after which an arterial blood gas

measurement was performed to confirm the degree of hypoxemia necessary for the next stage of the experimental protocol ($PaO_2 < 100$ torr).

Experimental groups

Animals in the HFOV group were ventilated with a SensorMedics 3100A oscillator (Viasys Healthcare, Yorba Linda, CA, USA). The remaining experimental groups were ventilated with a Servo 300 ventilator in volume control mode. During the four-hour intervention phase of the experiment, FiO_2 was maintained at 1.0. The injured animals were randomized into one of four experimental groups: 1) conventional mechanical ventilation (CMV, n = 7): ventilation with a tidal volume of 10 ml/kg, PEEP of 4 cm H_2O, inspiratory time of 1 second and respiratory frequency from 25 to 40 cycles per minute, adjusted according to $PaCO_2$; 2) surfactant (CMV-S, n = 8): ventilation identical to the CMV group, with the addition of a 3 mg/kg endotracheal dose of natural exogenous surfactant (Infasurf, ONY, Inc., Amherst, NY, USA); 3) partial liquid ventilation (PLV, n = 7): ventilation identical to the CMV group, with the addition of an 18 ml/kg endotracheal dose of perflubron (Alliance Pharmaceutical, Corp., San Diego, CA, USA). Every hour, these animals were disconnected from the respirator to check for the presence of a liquid meniscus in the endotracheal tube. If a meniscus was not observed, 2 ml/kg of perflubron was administered to replace evaporative losses; 4) high-frequency oscillatory ventilation (HFOV, n = 8): ventilation with mean airway pressure of 14 cm H_2O, inspiratory time of 33%, frequency of 10 Hz and the amplitude necessary to maintain $PaCO_2$ at physiologic levels. A group of healthy animals were instrumented and ventilated in an identical manner to the CMV group and used as the control (n = 9).

Arterial blood gas analysis was performed at baseline, after injury, (for the experimental groups) and every 30 minutes during the four-hour ventilation protocol. Immediately prior to completion of the experiment, animals received a dose of heparin (100 units/kg, IV) and were sacrificed by rapid administration of pentobarbital (100 mg/kg, IV).

Sample collection

Immediately after sacrifice, the endotracheal tube was occluded and the thorax carefully opened to rule out the presence of an occult pneumothorax, to confirm ideal position of vascular catheters and tracheal tube, and to collect tissue samples.

The right lung was isolated by placement of an occlusive loop of umbilical tape at the level of the hilum. The left atrium was phenestrated and the pulmonary artery was cannulated with a catheter for the infusion of 100 ml of heparinized saline solution. The left lung was dissected in axial slices which were flash frozen in liquid nitrogen and preserved at -70 ºC for subsequent analysis. The right lung was dissected into 0.5 cm thick axial slices and the central slice (at the level of the hilum) was fixed in 10% formalin for microscopic analysis.

Analysis of oxidative damage

Oxidative pulmonary damage was quantified by measuring levels of 4-hydroxy-nonenal (4-HNE), a specific marker of lipid peroxidation, using the method of Esterbauer and Cheeseman.[15,16]

Microscopic analysis

Axial lung slices were stained with hematoxylin / eosin and independently examined and by two investigators, in a blinded fashion. On each slide, the specimen was divided into two distinct zones representing the dependent (dorsal) and the non-dependent (ventral) regions of the lung. Ten microscopic fields were randomly selected, five in each of the regions. A microscopic lung injury score which assesses seven variables, each with five individual degrees of severity, was used to objectively quantify the magnitude of injuries by means of an optical microscope.[17,18]

Statistical analysis

Results were expressed as means and standard deviations and analyzed using SigmaStat 2.03 (SPSS, Chicago, IL, USA). Variables with normal distribution were compared among the various experimental groups using analysis of variance (ANOVA), with subsequent multiple comparisons between pairs made with the Student-Newman-Keuls test. Variables with non-normal distribution were compared among the various experimental groups using the Kruskal-Wallis ANOVA, and subsequent comparisons between pairs using the Dunn test. The behavior of variables over time was analyzed using the Friedman repeated measures ANOVA, with post hoc multiple comparisons between pairs by the Dunnett method. A 5% statistical significance level was adopted (alpha = 0.05).

Results

Changes to respiratory system compliance

All animals subjected to lung injury by intravenous endotoxin administration and surfactant lavage exhibited significant worsening in respiratory system compliance, measured by volume and static pressure relationships in the post-injury period compared to the baseline (Figure 1). All injured groups exhibited a lower inflection point at approximately 12 to 13 cmH_2O.

Oxygenation

The distribution of PaO_2 measurement for the various experimental groups is shown in Figure 2. All groups exhibited normal oxygenation prior to induction of lung injury. Immediately after induction of injury, all groups exhibited a significant decrease in PaO_2, compared with the baseline. The CMV group maintained significantly lower PaO_2 in comparison to the other groups throughout the experiment. The PLV group, in a similar manner, maintained PaO_2 between 380 mmHg and 400 mmHg, which, despite being statistically lower than the remaining groups, is
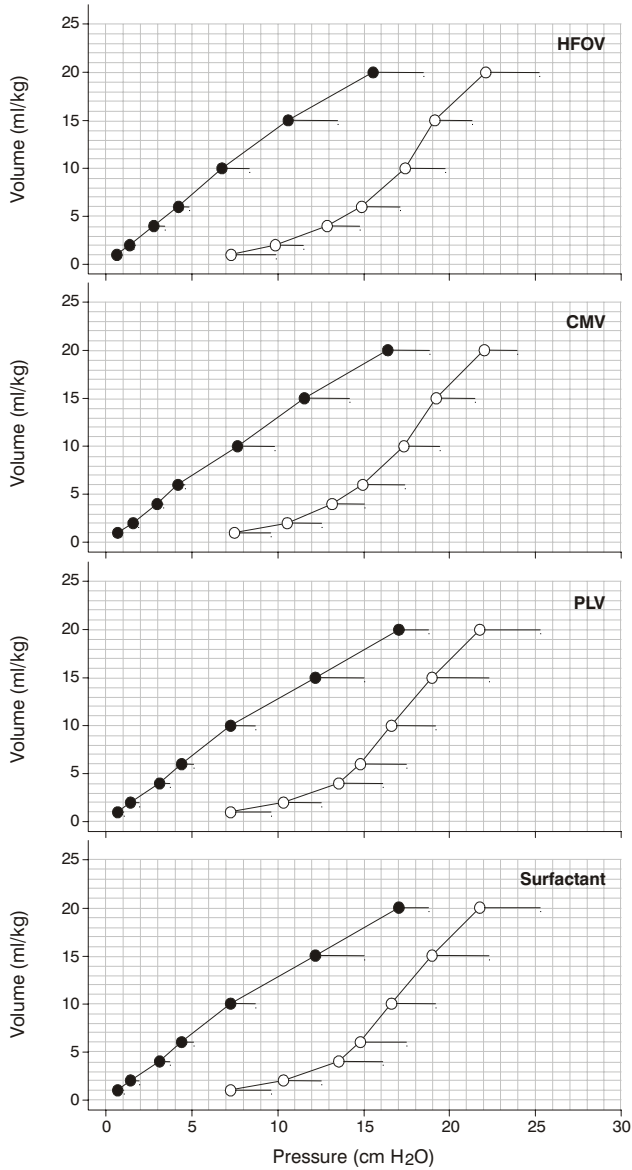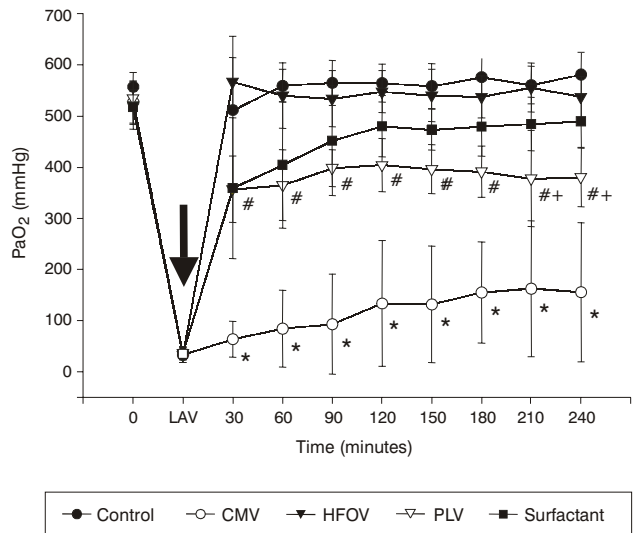
HFOV: high frequency oscillatory ventilation; CMV: conventional mechanical ventilation; PLV: partial liquid ventilation

Figure 1 - Volume and static airway pressure relationship for animals at baseline (closed circles) and after induction of pulmonary injury (open circles)

compatible with oxygenation of normal lungs when subjected to this procedure.[19,20] Animals treated with CMV-S exhibited a gradual improvement in oxygenation as the experiment progressed, presumably due to progressive alveolar recruitment. These animals had significantly higher PaO_2 than those treated with PLV at 210 and 240 minutes of observation. Animals treated with HFOV exhibited the highest PaO_2 levels among the injured groups, promptly returning to values compatible with the pre-injured state and comparable to the control group, indicating optimal pulmonary recruitment.

Histopathologic lung damage

Animals in the control group exhibited normal pulmonary architecture, in contrast with samples from the CMV group, in which both the non-dependent and the dependent regions exhibited dense inflammatory infiltrates, proteinaceous edema, alveolar and interstitial hemorrhage and atelectasis (Figure 3). The pulmonary architecture of animals treated with HFOV, PLV or CMV-S was better preserved in comparison

CMV: conventional mechanical ventilation; HFOV: high frequency oscillatory ventilation; PLV: partial liquid ventilation; LAV: tracheal lavage (injury). The arrow indicates a significant reduction in PaO_2 for all experimental groups in comparison to baseline ($p < 0.05$). *$p < 0.05$ in comparison to the other experimental groups. #$p < 0.05$ in comparison to control and HFOV. +$p < 0.05$ in comparison with the surfactant group.

Figure 2 - PaO_2 measurements for the various experimental groups
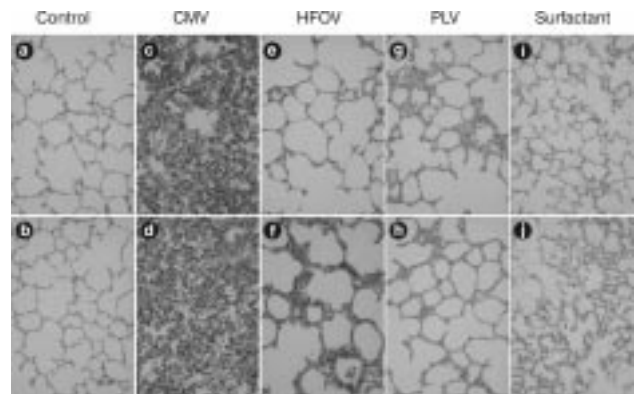
CMV: conventional mechanical ventilation; HFOV: high frequency oscillatory ventilation; PLV: partial liquid ventilation.

Figure 3 - Digital photomicrographs of light microscopy (200x, hematoxylin & eosin) examination of representative lung samples for the various experimental groups, including samples from the non-dependent region (upper panel: a,c,e,g,i) and samples from the dependent regions (b,d,f,h,j)

with those ventilated conventionally. Samples from the HFOV group exhibited less injury in the non-dependent region, with a tendency to a greater degree of damage in the dependent region. In contrast, animals treated with PLV presented more evidence of injury in the non-dependent region, compared with the dependent region. Animals treated with CMV-S revealed more evidence of injury than those treated with either HFOV or PLV, despite exhibiting less damage than the animals treated with CMV. Microscopic lung injury in animals treated with surfactant was more pronounced in the dependent lung region.

The objective global histopathologic injury scores for the various experimental groups are shown in Figure 4. As was expected, samples from the control group showed minimal evidence of injury. In contrast, the CMV group exhibited significantly greater damage than the others. Animals treated with HFOV and PLV exhibited low global scores, in contrast with those treated with CMV-S.
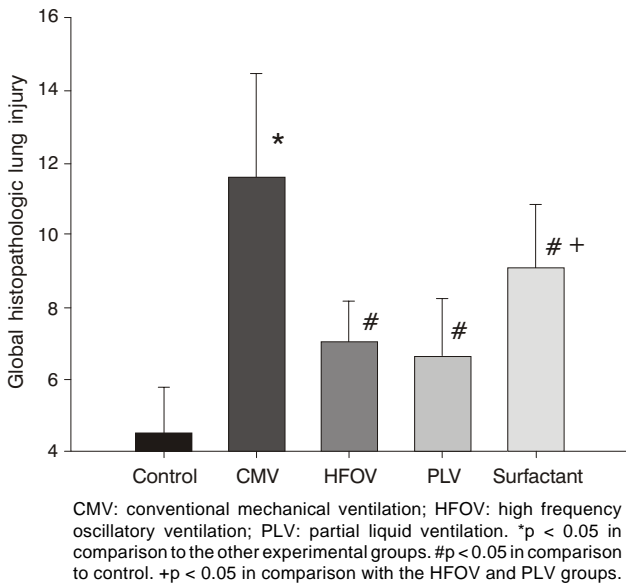
Discussion

This study employed an experimental model involving the combination of intravenous *E. coli* endotoxin infusion (lipopolysaccharide) and pulmonary lavage with saline solution to deplete surfactant. The objective of this methodology was to provide an animal model relevant to the study of ARDS in pediatric patients, since neither of the above models alone offers the investigator a chance to study the inflammatory characteristics and the pulmonary compliance alterations inherent to ARDS in a clinical environment, in a short period of time.

When used alone, the intravenous endotoxin infusion model causes lung injury producing a series of abnormalities analogous to those observed during advanced septicemia and septic shock in humans,[21] which is the most common non-pulmonary cause of ALI and ARDS in human patients.[22] Concomitantly with the characteristic cardiovascular decompensation, endotoxemia activates a series of cascade
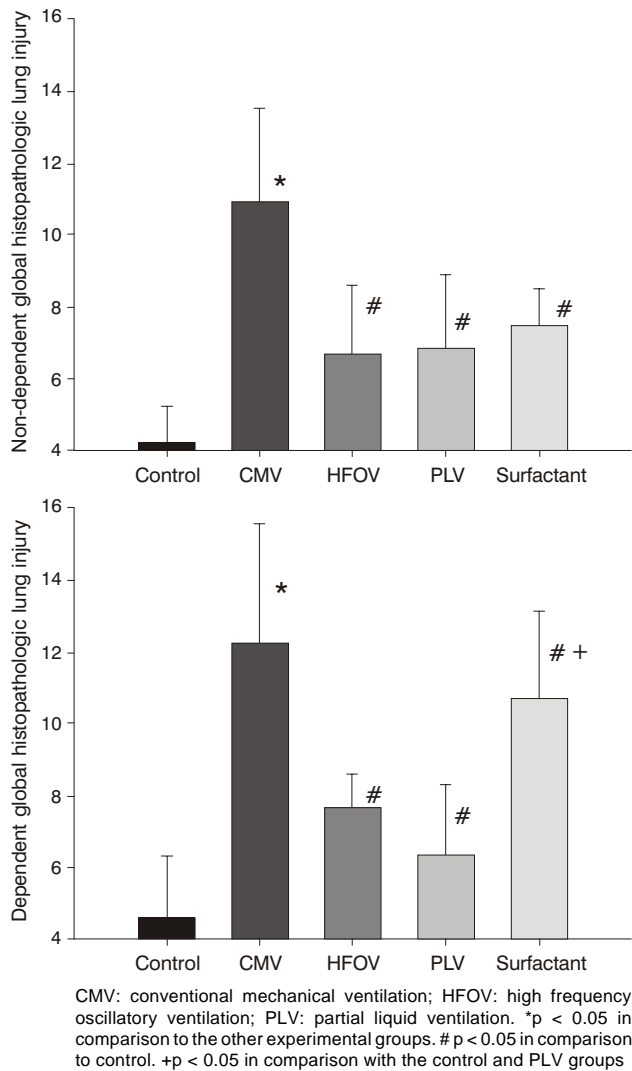

CMV: conventional mechanical ventilation; HFOV: high frequency oscillatory ventilation; PLV: partial liquid ventilation. *p < 0.05 in comparison to the other experimental groups. #p < 0.05 in comparison to control. +p < 0.05 in comparison with the HFOV and PLV groups.

Figure 4 - Global histopathologic lung injury observed in the various experimental groups

The results of the objective histopathologic injury score of dependent and non-dependent regions for each of the experimental groups are shown in Figure 5 and confirm the subjective impression observed in Figure 3.

Oxidative damage

Measurements of 4-HNE levels, a marker of oxidative damage and an indicator of lipid peroxidation, are shown in Figure 6. The group treated with CMV exhibited significantly higher levels of 4-HNE in comparison with the control group. The groups treated with PLV and HFOV had significantly lower 4-HNE levels than the CMV group. The CMV-S group had relatively low 4-HNE, but these measurements were not statistically different from those observed in the CMV group.

CMV: conventional mechanical ventilation; HFOV: high frequency oscillatory ventilation; PLV: partial liquid ventilation. *p < 0.05 in comparison to the other experimental groups. # p < 0.05 in comparison to control. +p < 0.05 in comparison with the control and PLV groups

Figure 5 - Dependent (lower panel) and non-dependent (upper panel) histopathologic lung injury observed in the various experimental groups.

CMV: conventional mechanical ventilation; HFOV: high frequency oscillatory ventilation; PLV: partial liquid ventilation. *p < 0.05 in comparison to control. #p < 0.05 in comparison to CMV group.
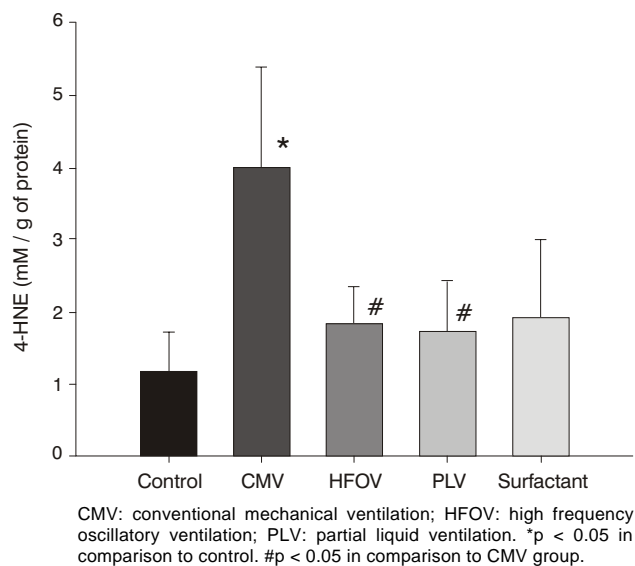
Figure 6 - 4-HNE measurements in the various experimental groups

systems, including coagulation, fibrinolysis and complement.[23] Activated neutrophils are in turn sequestrated in the pulmonary microsvasculature, where the release of reactive oxygen species, proteases and inflammatory cytokines are capable of inducing and exacerbating damage to pulmonary tissues.[23,24]

Pulmonary lavage with saline solution[14] has been used by a series of investigators because it causes surfactant depletion and dysfunction, alterations to pulmonary compliance and hypoxemia which are analogous to those observed in ARDS.[11,25] One criticism of this model is that it does not involve the systemic proinflammatory alterations found in ARDS, a limitation that is mitigated in the present study by intravenous administration of endotoxin to activate circulating neutrophils before tracheal lavage. The pulmonary lavage model causes a predictable change in compliance to the juvenile rabbit model. In a previous experiment, our laboratory demonstrated that three consecutive lavages with 30 ml/kg of saline are capable of causing a significant and consistent change in compliance in this experimental model, with animals developing a volume-pressure curve lower inflection point at approximately 12 to 13 cm H_2O.[11] This alteration is accompanied by significant hypoxemia, presumably caused by alveolar collapse since this hypoxemia can be promptly reversed with pulmonary recruitment manouvers.[11]

The current experiment employed four different ventilation strategies to support the injured animals: a conventional, non-protective strategy (CMV) and three other strategies (CMV-S, PLV and HFOV), conceivably protective because of their capacity to prevent atelectrauma and progression of lung injury. The tidal volume of 10 ml/kg did not produce any evidence of alveolar hyperinflation (which could cause volutrauma), since dynamic peak

inspiratory pressures were monitored by the ventilator and never exceeded 25 cm H_2O. The fact that the same tidal volume was applied to all groups, with the exception of the high frequency group, allowed for a balanced comparison of the impact of the other variables on the results of the experiment. All of the animals studied developed hypoxemia in a predictable manner after induction of lung injury. The acute nature of this hypoxemia indicates that it was primarily the result of the pulmonary lavage process[11,14,25] and not of neutrophil activation by the endotoxin, the effects of which are less abrupt.[13,18,26]

The decrease in PaO_2 observed after induction of lung injury was quickly reversed in animals subjected to HFOV. However, the mere initiation of HFOV does not guarantee improved oxygenation unless adequate mean airway pressure is employed, as was the case in the present study. At times, a significant improvement in oxygenation upon initiation of HFOV is only observed after the application of a dynamic sustained inflation maneuver with the goal of promoting rapid lung recruitment.[11,25,27] In the present study, animals treated with PLV exhibited rapid improvement in oxygenation, but PaO_2 remained limited to between 350 and 400 torr throughout the experimental period. While the PaO_2 of animals treated with PLV was significantly lower than the oxygenation presented by the group treated with HFOV, it was compatible with that found in other models of acute lung injury.[28] It is worth pointing out that even when used with health lungs, PLV is associated with reduced PaO_2, with levels between 350 and 450 torr, depending on the animal species being studied.[29,30] This phenomenon is explained by a relative oxygen diffusion barrier between the perfluorocarbon and the alveolar surfaces.[29,30] Animals treated with surfactant exhibited a progressive improvement in oxygenation, although with a trend to be lower than that of the group treated with HFOV (without statistical significance). The pattern of PaO_2 response in this group suggests progressive recruitment of alveolar units as the experiment progressed, despite the probability that these animals also suffered cyclical collapse and reopening of the more dependent alveoli, since the PEEP applied appeared to be insufficient to stabilize alveoli throughout the respiratory cycle.

The importance of PEEP, even for those animals treated with surfactant, is made clear in a study by Hartog et al.,[31] describing animals injured by pulmonary lavage with saline solution and ventilated with either high or low PEEP before treatment with exogenous surfactant.[31] Animals treated with high PEEP and surfactant exhibited significantly higher PaO_2 than animals treated with low PEEP and surfactant. Considering that in their experiment, animals with better oxygenation also exhibited lower levels of protein in alveolar lavage, it is impossible to differentiate between the role of atelectasis and lung injury and surfactant deactivation by plasma proteins in terms of the oxygenation of animals treated with low PEEP.[31,32] It could be speculated that, in the current study, oxygenation in the surfactant group could have been improved by increasing PEEP, in an attempt to

maintain the pulmonary recruitment obtained and prevent atelectrauma. This, however, would have interfered with the objective of comparing the effects of equivalent strategies with similar ventilator settings. In the current study, animals treated with conventional ventilation maintained low levels of oxygenation during the experimental period. This finding was not surprising, since hypoxemia is normally observed in this model when inadequately low PEEPs are employed.[11]

As expected, the healthy animals in the control group exhibited low lung injury scores. Animals treated with CMV demonstrated significantly higher histopathologic injury indices than the remaining experimental groups, in concert with oxygenation and ventilation measurements. These animals presented histopathologic injury in both dependent and non-dependent regions of the lung. In an analogy of what occurs in clinical practice, the injury score for the dependent region exhibited a trend to be greater than that observed for the non-dependent region, although this observation was not statistically significant. Animals treated with HFOV and PLV exhibited significant attenuation in histopathologic injury score in comparison with the CMV and CMV-S groups. This finding confirms the impression that the group treated with surfactant experienced atelectrauma, presumably because of the application of insufficient PEEP. The trend towards a lower microscopic injury score for the dependent regions of animals treated with PLV suggests that the high concentration of perfluorocarbon at this location may be associated with an increased local anti-inflammatory effect and with protection against oxidative tissue damage.[28] The fact that the surfactant, PLV and HFOV groups exhibited relatively low microscopic injury scores for the non-dependent regions is not surprising, since this region is less affected, both in human ARDS[1,33] and in experimental models.[11,18]

Neutrophil activation and sequestration in the lung during the initial phase of acute lung injury is associated with the production of reactive oxygen species and consequent oxidative damage.[34] The process of lipid peroxidation causes destruction of lipids present in the cellular membrane, resulting in the formation of lipid peroxides and aldehydes, such as 4-HNE.[15,35] In an earlier experiment we demonstrated elevated 4-HNE levels in animals injured with intravenous endotoxin and treated with conventional ventilation in contrast with animals treated with PLV that exhibited attenuated levels of 4-HNE.[16] In the current study, animals treated with CMV exhibited elevated levels of 4-HNE, in contrast with the control group. The PLV and HFOV strategies resulted in significantly lower 4-HNE levels than those found in the animals treated with CMV, demonstrating that, in addition to resulting in less histopathologic injury, these modes are also associated with reduced oxidative pulmonary damage. Animals treated with surfactant exhibited intermediate 4-HNE levels, which were not statistically greater than those found in the PLV and HFOV groups, but also not significantly lower than in animals treated with conventional ventilation.

In conclusion, in this experimental pediatric ARDS model, strategies that avoid atelectrauma, such as HFOV and PLV, resulted in adequate oxygenation, less evidence of histopathologic lung damage and attenuation of pulmonary oxidative damage, in comparison with CMV. The application of exogenous surfactant promotes improved oxygenation when compared with CMV, but results in increased lung injury, presumably because the inadequately low PEEP was insufficient to stabilize the alveoli during expiration, causing atelectrauma.

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