Original Investigation | ASSOCIATION OF VA SURGEONS

Airway Pressure Release Ventilation Prevents Ventilator-Induced Lung Injury in Normal Lungs

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IMPORTANCE Up to 25% of patients with normal lungs develop acute lung injury (ALI) secondary to mechanical ventilation, with 60% to 80% progressing to acute respiratory distress syndrome (ARDS). Once established, ARDS is treated with mechanical ventilation that can paradoxically elevate mortality. A ventilation strategy that reduces the incidence of ARDS could change the clinical paradigm from treatment to prevention.

OBJECTIVES To demonstrate that (1) mechanical ventilation with tidal volume (V_T) and positive end-expiratory pressure (PEEP) settings used routinely on surgery patients causes ALI/ARDS in normal rats and (2) preemptive application of airway pressure release ventilation (APRV) blocks drivers of lung injury (ie, surfactant deactivation and alveolar edema) and prevents ARDS.

DESIGN, SETTING, AND SUBJECTS Rats were anesthetized and tracheostomy was performed at State University of New York Upstate Medical University. Arterial and venous lines, a peritoneal catheter, and a rectal temperature probe were inserted. Animals were randomized into 3 groups and followed up for 6 hours: spontaneous breathing ventilation (SBV, n = 5), continuous mandatory ventilation (CMV, n = 6), and APRV (n = 5). Rats in the CMV group were ventilated with V_T of 10 cc/kg and PEEP of 0.5 cm H_2O. Airway pressure release ventilation was set with a P_{High} of 15 to 20 cm H_2O; P_{Low} was set at 0 cm H_2O. Time at P_{High} (T_{High}) was 1.3 to 1.5 seconds and a T_{Low} was set to terminate at 75% of the peak expiratory flow rate (0.11-0.14 seconds), creating a minimum 90% cycle time spent at P_{High}. Bronchoalveolar lavage fluid and lungs were harvested for histopathologic analysis at necropsy.

RESULTS Acute lung injury/ARDS developed in the CMV group (mean [SE] Pao_2/FiO_2 ratio, 242.96 [24.82]) and was prevented with preemptive APRV (mean [SE] Pao_2/FIO_2 ratio, 478.00 [41.38]; $P < .05$). Airway pressure release ventilation also significantly reduced histopathologic changes and bronchoalveolar lavage fluid total protein (endothelial permeability) and preserved surfactant proteins A and B concentrations as compared with the CMV group.

CONCLUSIONS AND RELEVANCE Continuous mandatory ventilation in normal rats for 6 hours with V_T and PEEP settings similar to those of surgery patients caused ALI. Preemptive application of APRV blocked early drivers of lung injury, preventing ARDS. Our data suggest that APRV applied early could reduce the incidence of ARDS in patients at risk.

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After treatment of arrhythmias, continuous mandatory ventilation (CMV) is the most common therapeutic intervention used in the intensive care unit.[1] Recent studies have shown that up to 25% of patients with normal lungs when placed on mechanical ventilation will develop acute lung injury (ALI). A primary driver of this injury is believed to be the use of higher tidal volumes (VT), presenting a serious medical problem.[2-5] With limited options for treating established ALI,[6] strategies for preventing ventilator-induced lung injury (VILI) are needed. Currently, low VT ventilation is the only strategy used in attempts to reduce the incidence of ALI in normal lungs.[5] Our group has shown that airway pressure release ventilation (APRV), using our specific settings and applied preemptively,[7] prevents the development of sepsis-induced ALI and acute respiratory distress syndrome (ARDS).[8] Because APRV prevented ARDS in these animals at high risk for developing lung injury,[9] we hypothesized that preemptive application of APRV in normal rats would also prevent ARDS driven by CMV with eupneic VT in lower-risk, nonseptic rats.

Herein, we showed that CMV causes ARDS within 6 hours of application, while preemptive mechanical ventilation with APRV prevented the development of ALI/ARDS by blocking the drivers of lung damage (ie, surfactant deactivation and alveolar edema).

Methods

All techniques and procedures described were fully approved by the Committee for the Humane Use of Animals at Upstate Medical University. Male Sprague-Dawley rats (400-500 g, Taconic Farms) were anesthetized using an intraperitoneal ketamine (90 mg/kg) and xylazine (10 mg/kg) mixture to maintain a surgical plane of anesthesia.

Surgical Methods

Under aseptic conditions, a tracheostomy was performed with a 14-gauge angiocatheter in the CMV and APRV groups. The carotid artery and the external jugular vein were cannulated using polyethylene 50 tubing, an 8F Foley catheter (DeRoyal) was placed in the abdomen for anesthesia and temperature. Body temperature was measured and maintained at a mean (SE) of 37°C (0.5). All groups received an intravenous infusion of lactated ringers solution for resuscitation via the venous line using Alaris infusion pumps (Cardinal Health). Arterial blood gases were analyzed every 30 minutes using a Cobas b221 blood gas analyzer (Roche Diagnostics). Blood was drawn at baseline and at 6 hours postmechanical ventilation, spun in an Eppendorf Ag Centrifuge (Eppendorf Nordic) and the plasma snap frozen. During the 6-hour experiment, hemodynamic and lung function parameters (mean arterial pressure, heart rate, oxygen saturation, plateau pressure, peak inspiratory pressure, positive end-expiratory pressure [PEEP], mean airway pressure, minute ventilation, respiratory rate, VT, resistance, compliance, and fraction of inspired oxygen [FIO_2]) were measured every 30 minutes, as well as arterial blood gas samples. Maintenance intravenous lactated ringers solution was given to all rats calculated by body weight (4 cc/kg/h) and adjusted for mean arterial pressure (range for rats, 60-70 mm Hg) and heart rate (range for rats, 200-300 beats/min). Intravenous rocuronium (500 mg/100 mL) was given at 5 cc/h to the ventilated animals to minimize spontaneous breathing.

Ventilator Protocols

Following surgical intervention, animals were randomized into 3 groups based on ventilation strategy and followed up for 6 hours: (1) spontaneous breathing ventilation (SBV) with no mechanical ventilation (n = 5); (2) CMV, including VT of 10 cc/kg and PEEP of 0.5 cm H_2O (n = 6); and (3) APRV using the specific settings described here (n = 5). Animals in the SBV group received no mechanical ventilation but did receive supplemental oxygen by nasal hood for the entire experiment (6 hours). The CMV and APRV groups were ventilated with an Evita Infinity v500 ventilator (Dräger). The animals in the CMV group were placed on volume control ventilation at VT of 10 cc/kg, PEEP of 0.5 cm H_2O, respiratory rate of 55 to 75 and inspiratory to expiratory ratio of 1:2. Airway pressure (P) release ventilation settings and time (T) were as follows: P_{High} set to the plateau pressure on CMV (15-20 cm H_2O), P_{Low} set at 0 cm H_2O, T_{High} set to 1.3 to 1.5 seconds, and T_{Low} set to terminate at 75% of the peak expiratory flow rate, creating a minimum 90% of the total cycle time spent at P_{High}.[7] The respiratory rate in the CMV group and P_{High}/T_{High} in the APRV group were adjusted to maintain $PaCO_2$ between 30 and 50 mm Hg. In the CMV group, FIO_2 was set at 30% and increased as necessary for either oxygen saturation as measured by pulse oximetry of less than 88% or PaO_2 of less than 55 mm Hg, according to Acute Respiratory Distress Syndrome Network (ARDSnet) protocol.[10] The FIO_2 in the APRV group did not require adjustment because they maintained a PaO_2 of more than 55 mm Hg on 30% FIO_2 throughout the study.

Necropsy

Six hours following mechanical ventilation, the animals were euthanized and lungs were excised en bloc. To standardize lung volume history, the lungs were inflated to the last recorded peak inspiratory pressure at 6 hours and the trachea was clamped. The lungs were removed surgically through midline sternotomy with care to protect vascular and lung tissue. The right lung was isolated and fixed in formalin at peak inspiratory pressure. Following 24 hours of fixation, the lung was cross-sectioned and stained with hematoxylin and eosin for histopathologic analysis.

Bronchoalveolar Lavage Fluid Cytokine and Surfactant Analysis

The left lobe of the lung was lavaged with 2.5 mL of normal saline. This bronchoalveolar lavage fluid (BALF) was spun at 1734*g* at 4°C and snap frozen for later analysis of the following parameters: Western blot analyses of surfactant protein A (SP-A) and surfactant protein B (SP-B) expression was performed as previously described.[11] Total protein and interleukin 6 (IL-6) levels in the BALF were determined by the bicinchoninic acid and enzyme-linked immunosorbent assay method as previously described, respectively.[8,9]

Quantitative Histology

The quantitative histological assessment of the lung was based on image analysis of 150 photomicrographs (10 per animal) of alveolar parenchyma, made at high-dry magnification following an unbiased, systematic sampling protocol that did not include mainstem airways and central vessels. Each photomicrograph was scored using a 4-point scale for each of 6 parameters: atelectasis, fibrinous deposits, blood in air spaces, vessel congestion, alveolar wall thickness, and leukocyte infiltration, as described previously.[8]

Histology Alveolar Air Space Analysis

In addition, the air compartment was assessed in the same tissue being scored. Alveolar lumina were quantified in each photomicrograph using the ImagePro digital image analysis system (Media Cybernetics) and expressed as percentages of total area. Random photomicrographs of lung histology were taken to identify airspace by hand and quantified by the ImagePro analysis to express data as percentages of the image occupied by air.

Statistics

Data are expressed as mean (standard error [SE]). Repeated measures analysis of variance with rat number and treatment as random effects were performed to compare differences within and between treatment groups for continuous parameters. Probability values less than 0.05 were considered significant. Posthoc Tukey tests were performed on continuous data at specific points only if significance was found in the group × time effect using repeated measures analysis of variance.

Results

Hemodynamics and Fluid Resuscitation

Mean (SE) arterial blood pressure was not significantly different between groups at any time during the 6-hour study, including the values at the end of the study (T6 = SBV, 61.60 [7.1]; CMV, 83.83 [10.4]; APRV, 56.5 [11.7] mm Hg; $P = .21$), although CMV trended higher. The mean (SE) amount of intravenous fluid infused during the experiment was similar in the CMV (56.16 [15.6] mL) and APRV (77.6 [15.1] mL) groups; however, mean (SE) fluid infusion in the SBV group (27.9 [5.9] mL) was significantly lower ($P < .05$) than in the APRV group but not the CMV group.

Lung Function

The Berlin definition of ALI/ARDS was used to identify the development of ARDS.[12] Clinically defined ALI/ARDS developed in the CMV group (mean [SE] Pao_2/FIO_2 [P/F] ratio, 242.96 [24.82]), and this was prevented with APRV (P/F ratio, 478.00 [41.38]; $P < .05$ vs CMV). None of the rats in the APRV group had a P/F ratio fall below 300 for the entire 6-hour experiment with the FIO_2 set to 30%. Conversely, the P/F ratio of all CMV rats fell below 300 at T5 and 40% of the CMV rats had a P/F ratio below 200 at T6. Final FIO_2 for both mechanically ventilated groups was not statistically different (mean [SE]: CMV, 0.37 [0.09]; APRV, 0.33 [0.02]). In the CMV group, oxygenation was normal for most of the study but fell rapidly and dramatically with the onset of ARDS, such that there was minimal time to increase FIO_2 before death. In addition, final plateau pressures were not statistically different between CMV and APRV (mean [SE]: CMV, 16.50 [1.26]; APRV, 18.80 [0.66]), although APRV trended higher.

Pulmonary Histology

No histopathologic lesions were observed in the SBV group (**Figure 1**, **Table**). Airways in the SBV group were open with round alveoli and slender walls (Figure 1). Lung injury caused by CMV was heterogeneous, typical of ALI/ARDS histopathology (Figure 1).[13] Controlled mechanical ventilation caused marked alveolar flooding, fibrin deposits in the air compartment, and leukocyte infiltration into the alveoli and lung parenchyma (Figure 1, Table). Focal atelectasis was also seen evidenced by pleating and collapse of alveoli. Inflated alveoli were not as large or round as those in the SBV group, suggesting that the mechanics of the alveolus (ie, the dynamic change in alveolar size and shape with tidal ventilation) may have been altered (Figure 1).[14] Conversely, APRV prevented histologic features of ALI by maintaining open air spaces, round alveoli, and thin alveolar walls similar to the SBV controls (Figure 1, Table). Although the extent to which alveoli were open was not uniform, true atelectasis was minimal (Figure 1). Quantitative analysis of histologic lung injury revealed significantly protected lung architecture in the APRV treatment group (Table). Atelectasis, fibrinous deposits, and thickened alveolar wall lesions were more prevalent in CMV-ventilated rats than the APRV group ($P < .05$). Vessel congestion and blood in airspace were similar between CMV and APRV (Table). Leukocyte infiltration increased incrementally, with SBV having the lowest and CMV the highest cellular counts ($P < .05$) (Table).

Histologic Analysis of Alveolar Airspace

Quantitative analysis of images of the histology of the space in the alveoli showed significantly more alveolar air in the APRV lung compared with CMV lung (mean [SE]: SBV, 83.08% [0.97]; APRV, 75.59% [1.27]; CMV, 43.74% [2.07]; $P < .05$ vs all groups; **Figure 2**; Table).

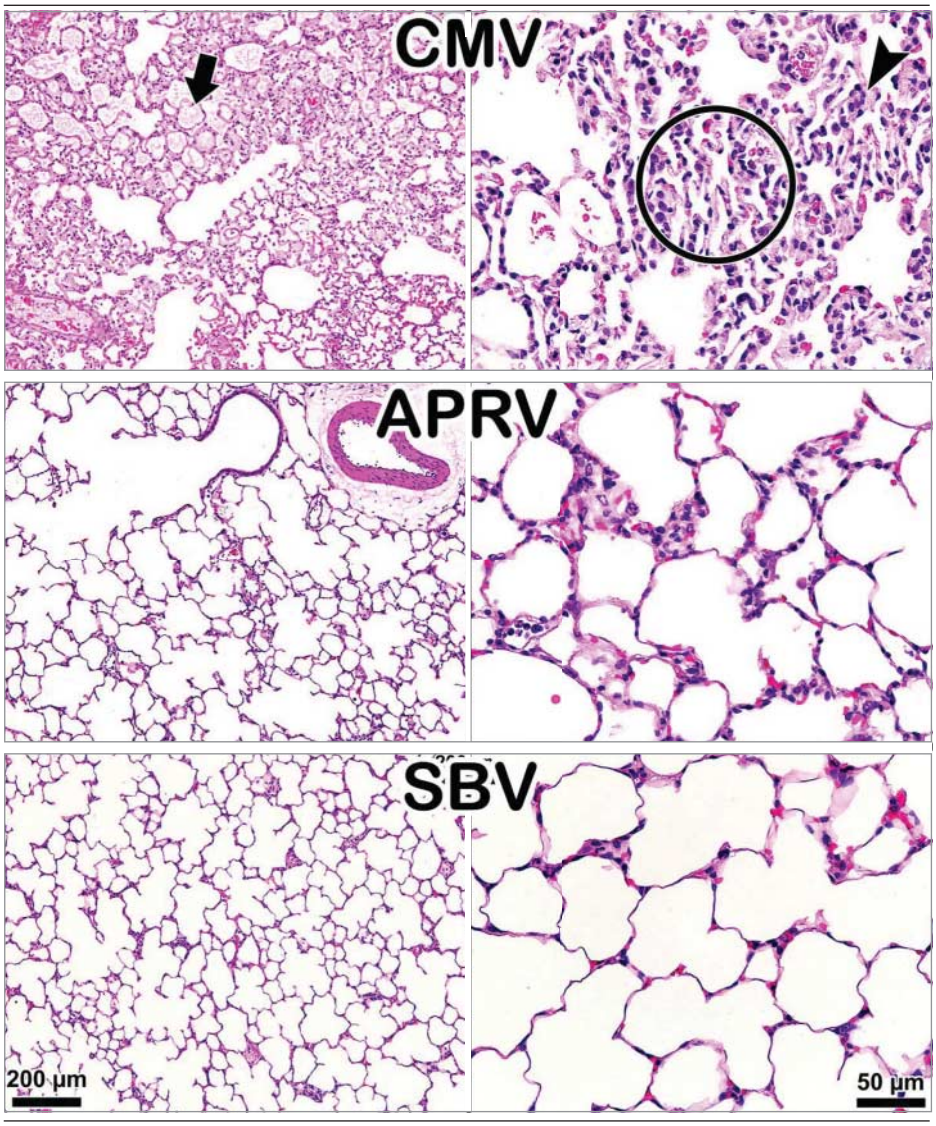
Total Protein, Cytokines, and Surfactant Proteins in BALF

The levels of total protein, IL-6, SP-A, and SP-B were measured at necropsy (T6). The results showed that total protein was significantly elevated in the CMV group compared with the SBV group (**Figure 3**A). No significant difference of BALF IL-6 levels was observed among the groups (Figure 3B). However, SP-A levels were significantly higher in the APRV ventilation group and SBV group compared with the CMV group, and SP-B levels were significantly higher in the SBV compared with CMV group (Figure 3C and D).

Discussion

Our study had 2 main findings. First, CMV in normal rats on eupneic ventilation settings, with V_T (10 cc/kg)[15,16] and PEEP

Figure 1. Lung Histology



Continuous mandatory ventilation (CMV) histopathology typical of acute respiratory distress syndrome includes atelectasis and thickened alveolar walls (circle), alveolar edema and fibrin (arrow), and cellular infiltration (arrowhead). Airway pressure release ventilation (APRV) histology was very similar to spontaneous breathing ventilation (SBV). Histology was conducted by L. A. Gatto.

Table. Histological Scores (1 to 4) and Percentage Areas on Photomicrographs

	Ventilation, Mean (SE)		
	Continuous Mandatory (n = 60)	Airway Pressure Release (n = 50)	Spontaneous Breathing (n = 50)
Atelectasis	1.90 (1.76)[a]	0.32 (0.71)	0.00 (0.00)
Fibrinous deposits	2.02 (1.61)[a]	0.64 (1.05)	0.22 (0.65)
Blood in air compartment	0.38 (0.80)	0.30 (0.46)	0.08 (0.34)[b]
Vessel congestion	1.03 (1.31)	0.98 (1.29)	0.04 (0.20)[a]
Thickened alveolar walls	2.77 (1.32)[a]	0.60 (0.93)	0.22 (0.62)
Cellular infiltration	3.08 (0.62)[a]	1.92 (1.05)[a]	0.04 (0.20)[a]
Air compartment, % area	44 (16)[a]	76 (9)[a]	83 (7)[a]

Abbreviation: SE, standard error.

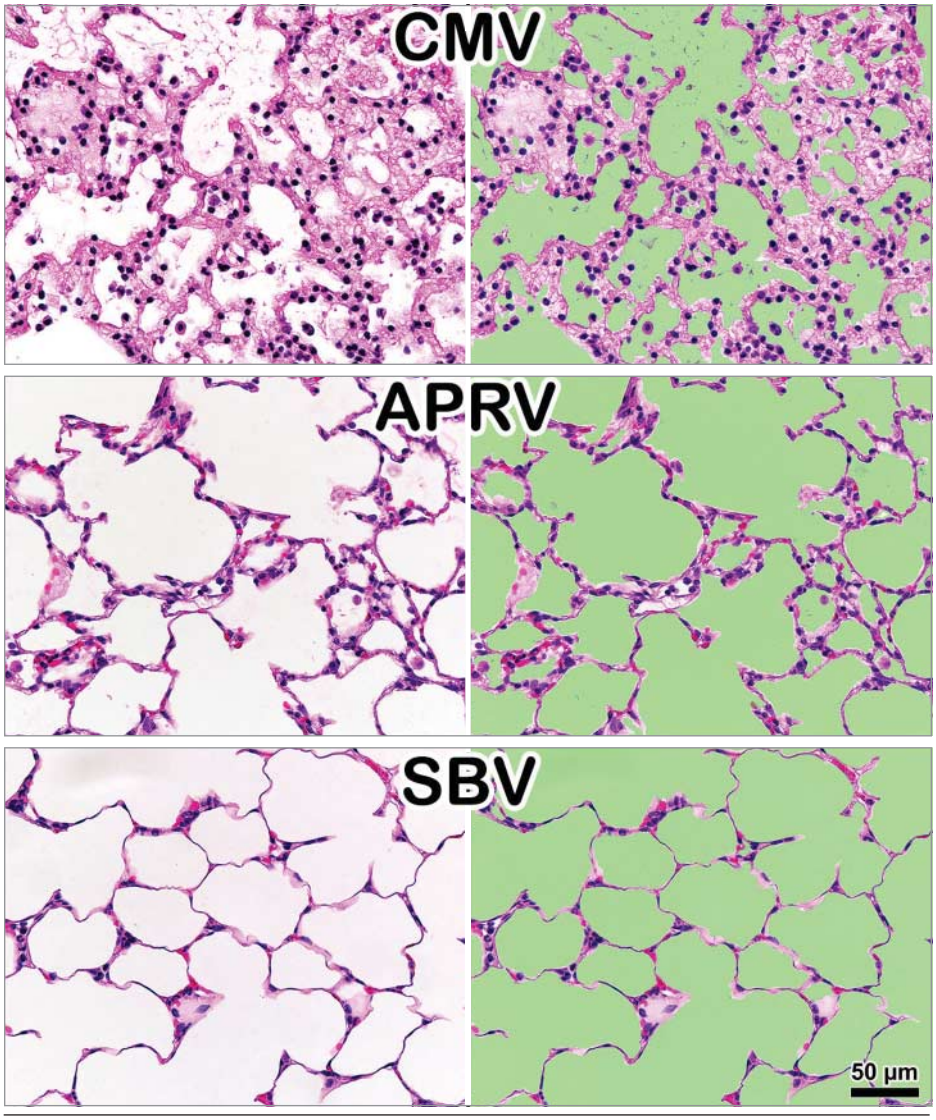
[a] $P < .05$ vs all groups.

[b] $P < .05$ vs continuous mandatory ventilation.

levels (0.5 cm H_2O) routinely used on surgery patients,[5,17] can cause the clinical (ie, hypoxemia, respiratory failure, and death), histologic, and molecular (ie, SP-A, SP-B, and total BALF protein concentrations) pathologies associated with ARDS. Second, APRV applied to the normal animal before lung injury can prevent this VILI-induced ARDS.

It is well known that improperly set mechanical ventilation can exacerbate ALI caused by systemic inflammation (ie, trauma, hemorrhagic shock, or sepsis) or by direct pulmonary injury, such as pneumonia or aspiration, significantly increasing mortality.[1,2,5,13] Additionally, application of protective mechanical ventilation to these injured lungs can reduce

Figure 2. Histologic Alveolar Airspace



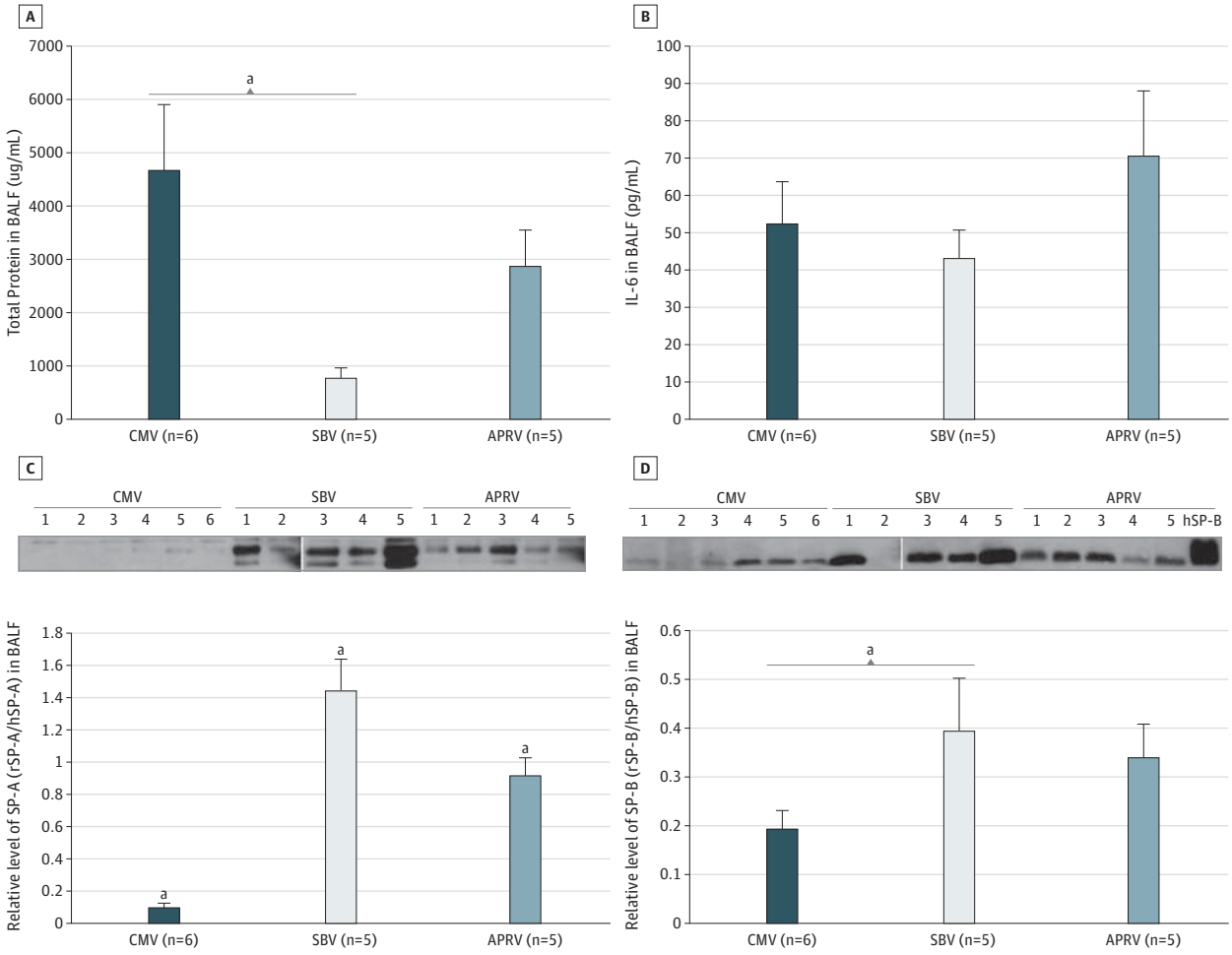
Quantitative airspace percentage in alveoli was highest in the spontaneous breathing ventilation (SBV) lung, reduced slightly with airway pressure release ventilation (APRV) and markedly reduced in the continuous mandatory ventilation (CMV) group (Table). The green areas indicate air and the red areas indicate tissue/edema. $P < .05$ vs all groups. Histology was conducted by L. A. Gatto.

ARDS-induced mortality.[10,18,19] More recently, it has been suggested that even patients with normal lungs who are at risk for developing ARDS can benefit from protective mechanical ventilation.[2,3,20,21] Our study supports this recent hypothesis by showing that, even in animals at low risk (ie, no systemic or pulmonary inflammation), ARDS can develop with VT and PEEP settings commonly used on surgery patients.[5,17,20,22,23] Our data also support the findings of Wolthuis et al,[24] who showed that clinically relevant ventilator settings cause ARDS in normal mice.

There is an emerging concept that ARDS is not a syndrome that should be treated, but rather one that should be prevented.[1,5,20,25] Studies have shown that lower VT and higher PEEP applied to high-risk patients with normal lungs are associated with reduced inflammation, coagulopathy, mechanical ventilation duration, intubation time, intensive care unit length of stay, development of ALI/ARDS, and improved oxygenation.[2,5,19,20] We demonstrated that APRV applied preemptively to normal rats can reduce the incidence of ARDS, suggesting this method is a protective ventilation strategy.

We used preemptive APRV instead of low VT ARDSnet ventilation in this study as our previous data using a porcine sepsis plus ischemia-induced ARDS model demonstrated that APRV applied before lung injury was superior to ARDSnet applied when lung injury first developed (ie, oxygenation trigger established by the ARDSnet protocol[10]).[8] However, other protective ventilation strategies may have a similar beneficial effect. For example, the application of preemptive low VT ventilation was reported to prevent ARDS in a normal mouse model.[24] This mouse bench study supports clinical studies showing that lower VT reduces ARDS incidence in patients.[20] The clinical studies combined with mouse and rat data from this study all suggest that preemptive application of protective mechanical ventilation can reduce the incidence of ARDS.[5,15,19-21,24]

Figure 3. Bronchoalveolar Lavage Data

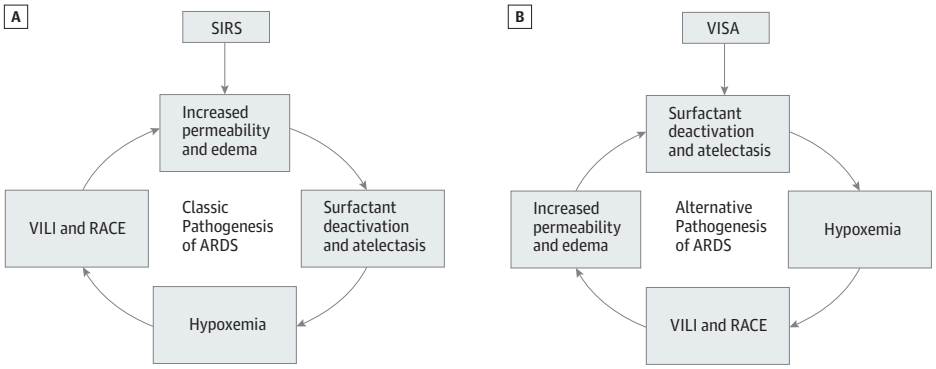


Bronchoalveolar lavage fluid (BALF) data including total protein (A), interleukin-6 (IL-6) (B), surfactant protein-A (SP-A) (C), and surfactant protein-B (SP-B) (D). APRV indicates airway pressure release ventilation; CMV, continuous mandatory ventilation; h, human; r, relative; SBV, spontaneous breathing ventilation.
[a]$P < .05$.

Although low VT and higher PEEP have been most studied as a preemptive ventilation strategy to prevent lung injury,[20-22] APRV has several theoretical advantages. The prolonged time (T_{High}) spent at the upper pressure (P_{High}) would recruit alveoli gradually over time, resulting in a more homogeneously ventilated lung reducing volutrauma. The extended time spent at P_{High} combined with the very brief T_{Low} (release phase) may stabilize patent alveoli, reducing atelectrauma secondary to alveolar recruitment/derecruitment or repetitive alveolar closure and expansion.[7-9] Early application of APRV in our study resulted in improved oxygenation and reduced lung injury, although we did not observe a significant reduction in inflammation. A possible explanation for the lack of impact on inflammation is the relatively short ventilation period (ie, 6 hours) and the fact that these were healthy rats at low risk for developing ARDS. Hong et al[26] had a similar finding showing that low VT and high PEEP did not result in a significant reduction in inflammatory mediators in normal pigs.

To understand the mechanism by which preemptive protective ventilation can prevent the development of ARDS, we must first understand the pathogenesis of the disease. The classic sequence of events leading to ARDS is depicted in **Figure 4**A.[13,27] Pathogenesis begins with an initiating injury that could be either a primary injury, such as pneumonia, or a secondary injury, such as trauma, sepsis, or hemorrhage, which results in a systemic inflammatory response syndrome (SIRS). The syndrome causes an increase in endothelial and epithelial permeability, resulting in alveolar flooding with edema, which deactivates pulmonary surfactant, causing alveolar collapse and instability. Pulmonary edema and atelectasis result in hypoxemia and the patient would then be placed on mechanical ventilation. Improper mechanical ventilation in an injured heterogeneously ventilated lung causes VILI secondary to alveolar overexpansion (volutrauma) and repetitive alveolar closure and expansion, also known as *atelectrauma*.[28,29]

Figure 4. Classic (A) and Alternative (B) Hypotheses for Acute Respiratory Distress Syndrome (ARDS) Pathogenesis



In the classic hypothesis, systemic inflammatory response syndrome (SIRS) initiates pathology, whereas in the alternative, ventilation-induced surfactant alteration (VISA) initiates pathology. RACE indicates repetitive alveolar collapse and expansion; VILI, ventilator-induced lung injury.

More recently, Albert[30] developed an alternative pathogenesis hypothesis to the classic theory just described, in which ventilation-induced surfactant deactivation in the normal lung (and not inflammation-induced increase in vascular permeability) is the initiating injury in ARDS pathogenesis (Figure 4A and B). Albert argues that spontaneous or mechanical ventilation of normal, homogeneously ventilated lungs in patients before they develop respiratory failure alters pulmonary surfactant function leading to atelectasis and hypoxemia. In this paradigm, surfactant disruption precedes the onset of ARDS (Figure 4B).[30] This initial ventilation-induced surfactant alteration (VISA) caused by either spontaneous or mechanical ventilation of the normal lung should not be confused with what we know as VILI. Ventilator-induced lung injury only occurs in the injured heterogeneously ventilated lung and exacerbates the lung injury caused by SIRS with secondary volutrauma, atelectrauma, and biotrauma.[30] On the other hand, VISA occurs in the normal homogeneously ventilated lung and initially only causes surfactant alteration.[30] Once there is sufficient surfactant deactivation and the lung becomes heterogeneously injured, VISA can be converted to VILI.

Multiple studies support Albert's hypothesis.[31-34] In the seminal study by Webb and Tierney,[35] they demonstrated that ventilating rats with a large VT and low PEEP caused hypoxemia and reduced compliance in the absence of histopathologic tissue disruption. The authors concluded that the atelectasis and hypoxemia resulted from surfactant depletion caused by the large change in alveolar volume with each breath. It is well known that the mechanical breath can cause the surfactant film to wear out and collapse, resulting in a significant increase in alveolar surface tension.[36,37] McClenahan and Urtnowski[36] demonstrated that repeated inflation of the excised rat lung caused a loss of surfactant function assessed by whole lung pressure/volume curves. Wyszogrodski et al[37] showed that hyperventilation in open-chested cats promoted the release of surfactant from alveolar Type II cells. However, released surfactant was inactive (ie, it did not lower surface tension measured on a surface film balance) and thus alveolar surface tension was increased.

Ventilation-induced surfactant alteration causes surfactant to wear out secondary to large changes in alveolar volume with each breath.[31,36,37] Sinclair et al[38] studied rabbits' spatial distribution of sequential ventilation, comparing 4 groups with VT of 6 and 12 cc/kg and PEEP of 0 and 8 cm H_2O. They found that ventilation was redistributed toward the dorsal-caudal lung with increasing VT. More importantly, this redistribution resulted in large changes of lung volume with each breath, exactly what is necessary to cause surfactant film to wear out and collapse. In addition, they noted that this large dynamic change in lung volume was eliminated with elevated PEEP and that lung damage was associated with the areas of the lung with the largest volume change.[38]

Our study supports Albert's hypothesis[30] of VISA-induced surfactant deactivation as the initiating sequence in ARDS pathogenesis in normal rats. We base this conclusion on the following evidence: (1) the rats were normal and thus there was no SIRS to cause an initial increase in vascular permeability; (2) the lack of SIRS was corroborated by no significant elevation of IL-6 in the CMV group; (3) the sizes of the VT and PEEP were not sufficient to cause a pathologic increase in airway pressure such that volutrauma was not the mechanism of lung injury; (4) the VT and PEEP settings in the CMV group were similar to those in the Sinclair et al[38] study that resulted in large changes in lung volume with each breath, which would cause surfactant film collapse; (5) the concentration of both surfactant proteins SP-A and SP-B were significantly reduced in the CMV group; and (6) preemptive application of a ventilation strategy that is associated with alveolar recruitment and stabilization (ie, APRV) prevented the decrease of SP-A, SP-B, hypoxemia, and histopathologic lung damage typical of ARDS.

In conclusion, this is the first study to demonstrate that preemptive application of APRV can prevent ARDS development in normal lungs without systemic injury. Our study supports the hypothesis that CMV, with VT and PEEP settings typical of those used on surgery patients, damages the normal lung sufficiently to cause ALI. Our data also support an alternative hypothesis of ARDS pathogenesis, with VISA being the initiating injury instead of a SIRS-induced increase in vascular permeability. And they support the concept that improper ventilation of the normal lung can cause lung injury and that preemptive application with a protective ventilation strategy can reduce the incidence of ARDS.

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