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EARLY AIRWAY PRESSURE RELEASE VENTILATION PREVENTS ARDS—A NOVEL PREVENTIVE APPROACH TO LUNG INJURY

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ABSTRACT—Acute respiratory distress syndrome (ARDS) afflicts 200,000 patients annually with a mortality rate of 30% to 60% despite wide use of low tidal volume (LTV) ventilation, the present standard of care. High-permeability alveolar edema and instability occur early in the development of ARDS, before clinical signs of lung injury, and represent potential targets for therapy. We hypothesize that early application of a protective ventilation strategy (airway pressure release ventilation [APRV]) will stabilize alveoli and reduce alveolar edema, preventing the development of ARDS. Yorkshire pigs (30–40 kg) were anesthetized and subjected to two-hit injury: (*a*) intestinal ischemia-reperfusion, (*b*) peritoneal sepsis, or sham surgery. Following surgery, pigs were randomized into APRV (n = 4), according to current published guidelines for APRV; LTV ventilation (n = 3), using the current published ARDS Network guidelines (6 mL/kg); or sham (n = 5). The clinical care of all pigs was administered per the Surviving Sepsis Campaign guidelines. Animals were killed, and necropsy performed at 48 h. Arterial blood gases were measured to assess for the development of clinical lung injury. Lung tissue epithelial cadherin (E-cadherin) was measured to assess alveolar permeability. Bronchoalveolar lavage fluid (BALF) surfactant protein A was measured to assess alveolar stability. Lung edema content and histopathology were analyzed at 48 h. Airway pressure release ventilation pigs did not develop ARDS. In contrast, pigs in the LTV ventilation met ARDS criteria ($Pa_{O_2}/F_{I_{O_2}}$ ratio) (APRV: baseline = 471 ± 16; 48 h = 392 ± 8; vs. LTV ventilation: baseline = 551 ± 28; 48 h = 138 ± 88; $P < 0.001$). Airway pressure release ventilation preserved alveolar epithelial integrity demonstrated by higher levels of E-cadherin in lung tissue as compared with LTV ventilation ($P < 0.05$). Surfactant protein A levels were higher in BALF from the APRV group, suggesting APRV preserved alveolar stability. Quantitative histologic scoring showed improvements in all stigmata of ARDS in the APRV group versus the LTV ventilation ($P < 0.05$). Airway pressure release ventilation had significantly lower lung edema (wet-dry weight) than LTV ventilation ($P < 0.05$). Protective ventilation with APRV immediately following injury prevents development of ARDS. Reduction in lung edema, preservation of lung E-cadherin, and surfactant protein A abundance in BALF suggest that APRV attenuates lung permeability, edema, and surfactant degradation. Protective ventilation could change the clinical paradigm from supportive care for ARDS with LTV ventilation to preventing development of ARDS with APRV.

KEYWORDS—Acute respiratory distress syndrome, acute lung injury, airway pressure release ventilation, sepsis, shock, mechanical ventilation, ARDS, ALI, systemic inflammatory response syndrome

ABBREVIATIONS—ARDS — acute respiratory distress syndrome; LTV — low tidal volume; APRV — airway pressure release ventilation; PS — peritoneal sepsis; I/R — ischemia-reperfusion; PEEP — positive end-expiratory pressure; IL-6 — interleukin 6; ELISA — enzyme-linked immunosorbent assay; BALF — bronchoalveolar lavage fluid; SP-A — surfactant protein A; ANOVA — analysis of variance; SOFA — Sequential Organ Failure Assessment; C_{stat} — static compliance; P_{mean} — mean airway pressure; P/T_P — pressure-time profile; ARDSnet — Acute Respiratory Distress Syndrome Network; RR — respiratory rate; PEFR-peak expiratory flow rate; RM-ANOVA — repeated-measures ANOVA

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a serious clinical problem with more than 200,000 cases annually (1), which is resistant to treatment once the syndrome is fully clinically established (2, 3). Acute respiratory distress syndrome has a mortality rate of 30% to 60%, with significant costs of care and debilitating lifelong sequelae for survivors (3, 4). Despite decades of research, only one therapeutic modality, low tidal volume (LTV) ventilation, has been demonstrated to modestly improve ARDS-related mortality (9%) (5). Low tidal volume ventilation is a supportive therapy intended to limit the exacerbation of ARDS by mechanical ventilation (i.e., minimizing ventilator-induced lung injury) rather than altering the pathophysiology of the primary disease. However, since 1994, the mortality of ARDS has remained unchanged, calling into question the efficacy of LTV ventilation (3). The severity of established ARDS, the ineffectiveness of current therapy, and the long-term consequences of the disease

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suggest that preventive rather than supportive treatment strategies be sought.

Current therapy for lung injury is usually initiated when all of the clinical criteria for ARDS are met. This practice is consistent with the long-standing clinical concept that this disease is a binary phenomenon: ARDS is perceived as either present or absent (2, 5–7). However, recent population data have challenged this concept, demonstrating that ARDS is rarely present at the time of hospital admission but rather develops over a period of hours to days (8). Collectively, these data imply that there is a temporal window of opportunity to intervene with preventive therapies such as protective ventilation targeting early drivers of ARDS pathophysiology. We hypothesize that the preemptive application of protective ventilation with a sufficiently elevated airway pressure-time profile (P/T_P) will prevent ARDS by targeting prevention of alveolar edema, maintenance of alveolar stability throughout the ventilatory cycle (preventing atelectrauma), and maintenance of maximum alveolar recruitment (9, 10).

Airway pressure release ventilation (APRV) maintains a sustained airway pressure over a large proportion of the respiratory cycle, and therefore this ventilation strategy has a high P/T_P. We have previously shown the application of APRV before lung injury prevents ARDS in a translationally applicable porcine model of sepsis and ischemia-reperfusion (I/R)–induced ARDS (9). We hypothesized that the primary mechanism operant in this type of protective ventilation was the prevention of alveolar flooding (9). Alveolar edema deactivates pulmonary surfactant triggering alveolar instability, which in turn causes mechanical injury via atelectrauma and subsequently propagates ARDS progression through the lung (11, 12). Thus, preventing pulmonary edema could block the pathologic cascade of surfactant deactivation and alveolar instability proximally and thereby avert the development of ARDS (9).

The present study builds on this prior work by comparing preemptive APRV to the standard of care Acute Respiratory Distress Syndrome Network (ARDSnet) LTV ventilation in a high-fidelity model of peritoneal sepsis (PS) + I/R–induced lung injury. Airway pressure release ventilation was applied to animals 1 h following injury according to current published guidelines (13). Low tidal volume ventilation was administered according to published ARDSnet guidelines once ALI criteria (Pao_2/Fio_2 [P/F]< 300) are met (5). The goal of this study was to compare the effectiveness of APRV at preventing ARDS, against the effectiveness of the current standard-of-care LTV ventilation at treating ARDS. Our data show that early application of APRV prevents clinical lung injury, whereas LTV ventilation allows the progression of disease to fulminant ARDS. These findings indicate that ARDS is preventable and suggest a paradigm shift in the approach to management of patients at risk of developing ARDS from treating fully established ARDS to preventing it from developing.

MATERIALS AND METHODS

Animals

All techniques and procedures described were reviewed and approved by the Committee for the Human Use of Animals at Upstate Medical University. Healthy female Yorkshire pigs (30–50 kg) were anesthetized using continuous infusion of ketamine/xylazine/propofol to maintain a surgical plane of anesthesia. Animals were continuously monitored and cared for by the investigators for the full 48-h duration of the experiment. Under sterile conditions, animals underwent tracheostomy, arterial and venous catheterization, and bladder catheterization. Baseline (BL) measurements were taken after surgical preparation and before injury.

Experimental groups—Sham group (n = 5). Following surgical preparation, animals underwent laparotomy and dissection of the superior mesenteric artery (SMA) without clamping and cecotomy followed by closure of cecotomy. No fecal clot was placed in the peritoneum. These animals were then connected to a Hamilton G5 ventilator (Hamilton, Reno, Nev), and ventilator settings were as follows: tidal volume (Vt) = 10 mL/kg, positive end-expiratory pressure (PEEP) = 5, respiratory rate (RR) = 12, and Fio_2 = 21%. Respiratory rate was adjusted to maintain $Paco_2$ within normal limits; no other ventilatory adjustments were made.

Following surgical instrumentation and BL measurements, secondary lung injury was induced using a "two-hit" model as previously described (14). Briefly, (*a*) I/R: the SMA was clamped for 30 min to induce intestinal ischemia then released; (*b*) PS: stool was harvested from a cecotomy and mixed with blood to create a fecal clot, which was implanted in the abdomen before abdominal closure. Time zero (T0) measurements were taken immediately after the induction of injury (i.e., removal of SMA clamp and placement of fecal clot) upon closure of the abdomen.

One hour following injury (T1), animals were randomized into two groups: airway pressure release ventilation (APRV, n = 4) or LTV ventilation.

Low tidal volume group (LTV n = 3). Animals were connected to a Dräger Evita XL ventilator (Dräger, Lubeck, Germany), with initial settings identical to sham group. Animals were transitioned to LTV ventilation (Vt = 6 mL/kg) when they met ARDSnet clinical criteria of P/F less than 300 per ARDSnet protocol. Appropriate adjustments in RR were made to maintain adequate minute volume. Positive end-expiratory pressure and Fio_2 were adjusted in response to changes in Sao_2 along the "high PEEP, low Fio_2" scale (5). If airway plateau pressure (P_{plat}) rose above 30 cmH_2O, Vt was further reduced by 1 mL/kg increments to 4 mL/kg with appropriate adjustments in RR to maintain equivalent minute volume per ARDSnet guidelines. The upper limit for RR was 35 breaths/min with titrations made in Vt if respiratory acidosis was detected (pH <7.15) according to the ARDSnet protocol.

APRV group (n = 4). The technique of administering APRV in this study has been described previously (13). Animals were connected to a Dräger Evita XL ventilator (Dräger) with the same preinjury settings as sham. At 1 h after injury (T1), the ventilator mode was switched to APRV with the following initial settings: high pressure (P_{high}) was initially set at the P_{plat} from the volume-cycled setting used for BL measurements. Low pressure (P_{low}) was set at 0 cmH_2O for the entire 48 h to minimize expiratory resistance and maximize peak expiratory flow rate (PEFR). Duration of P_{high} (T_{high}) was set at 3.9 to 6.0 s to equal 90% to 95% of the respiratory cycle. Duration of release phase was set using T_{low} and ranged between 0.40 and 0.55 s to achieve a termination of PEFR equal to 75% of PEFR. This parameter was calculated and monitored for adjustment based on the angle of deceleration noted on the expiratory flow waveform (13). Adjusting the T_{low} to maintain 75% of PEFR generated release volumes in a range of 10 mL/kg. Adjustments to P_{high} and T_{high} were made to ensure that the APRV animals were not inadvertently receiving LTV ventilation. The P_{high}, T_{high}, T_{low}, and Fio_2 were titrated throughout the study to minimize lung derecruitment, limit airway pressures, optimize the efficiency of CO_2 clearance, and minimize dead space ventilation. These adjustments were based on interpretation of expiratory flow waveform, static compliance (C_{stat}), calculated resistance, Vt, and arterial blood gases (13).

Clinical management

Broad-spectrum antibiotics (ampicillin 2 g i.v. [Bristol Myers Squibb, Princeton, NJ] and metronidazole 500 mg i.v. [Baxter, Deerfield, Ill]) were given following abdominal closure and every 12 h until the end of the study. Animals were treated with i.v. fluid resuscitation and vasopressors in a protocol adapted from the early goal-directed therapy strategy (15). This strategy is considered standard of care for management of hemodynamic collapse in sepsis. Maintenance i.v. fluid requirements were calculated by body weight and given via continuous infusion. Ringer's lactate was used for maintenance and resuscitation. Hemodynamic parameters were assessed to determine the need for resuscitative fluid bolus according to parameters described by Rivers et al. (15). According to early goal-directed therapy guidelines, continuous infusion of norepinephrine was started when the animal was no longer responsive to fluid bolus. Vasopressin and epinephrine were added when norepinephrine was no longer effective.

Physiologic measurements

Hemodynamic parameters were measured (CMS-2001 System M1176A, with Monitor M1094B; Agilent, Böbingen, Germany) using Edwards transducers (Pressure Monitoring Kit [PXMK1183]; Edwards Lifesciences, Irvine,

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Calif). Pulmonary parameters were measured or calculated by the Dräger ventilator. Blood was drawn every 6 h. Measurement of blood gases and chemistries were made with Roche blood gas analyzer (Cobas b221; Roche, Basel, Switzerland). Clinical pathology and blood cultures were performed by the Upstate Medical University pathology laboratory facility.

Systemic inflammation

Plasma was frozen every 6 h for enzyme-linked immunosorbent assay (ELISA) quantification of interleukin 6 (IL-6) levels in systemic circulation.

Calculation of P/T_P

We have developed a novel method to analyze the force imparted on the lung by mechanical ventilation, incorporating the pressure and time over which pressure is sustained during each breath. This relationship, termed the *pressure-time profile* (P/T_P), is defined as the area under the airway pressure waveform for each breath and is therefore the integral of airway pressure over time during each breath (Eq. (1)). Pressure-time profile is a unique characteristic of any given ventilatory mode.

$$P/T_P = \int_{T_{insp}}^{T_{exp}} P dt \quad (1)$$

where P = airway pressure (in cmH_2O), t = time (in seconds), T_{insp} = the time at the beginning of inspiration, and T_{exp} = the time at end expiration. This calculation was performed hourly for each experimental group.

Necropsy

After 48 h, the experimental protocol was terminated, animals were killed, and necropsy was performed. The lungs, liver, spleen, kidney, and small intestine were removed and preserved in formalin. Lungs were inflated to 25 cmH_2O using stepwise increases in PEEP to standardized lung volume history and grossly photographed. The left lung was filled with 10% formalin to a height of ~25 cm, clamped, and immersed in formalin. This technique standardized the inflation pressure necessary for quantitative histologic measurements.

Bronchoalveolar lavage fluid and lung tissue

The right middle lobe of the lung was lavaged with 60 mL of normal saline, spun at 3,500 revolutions/min at 4°C, and snap-frozen for later analysis. The concentration of IL-6 was determined in the plasma and bronchoalveolar lavage fluid (BALF) using ELISA according to the manufacturer's recommendations. Western blot analyses of surfactant protein A (SP-A) abundance in the BALF as well as of epithelial cadherin (E-cadherin) in lung tissue homogenates were performed (16, 17).

Quantitative histology—The quantitative histologic assessment of the lung was based on image analysis of 120 photomicrographs (10 per animal), made at high-dry magnification following a validated, unbiased, systematic sampling protocol (14). Each photomicrograph was scored using a four-point scale for each of five parameters: atelectasis, fibrinous deposits and blood in air space, vessel congestion, alveolar wall thickness, and leukocytes (14).

Statistical analysis

Data are mean ± SEM. Repeated-measures analyses of variance (RM-ANOVA) with pig number and treatment as random effects were performed to compare differences within and between treatment groups for continuous parameters; probability values less than 0.001 were considered significant. Post hoc Tukey tests were performed on continuous data at specific time points only if significance was found in the group × time effect using RM-ANOVA. Categorical data were compared using an unpaired Student t test. Quantitative histology data were analyzed using Mann-Whitney U test after testing for normality. $P < 0.05$ was considered significant. All analyses were performed using JMP version 5.1.1 software (Cary, NC).

RESULTS

Hemodynamics and laboratory data

The APRV and LTV ventilation groups demonstrated hemodynamic compromise consistent with shock: tachycardia, progressive hypotension, and high resuscitative fluid and vasopressor requirements. As expected, the sham group did not exhibit any of these hemodynamic derangements (Table 1). Mean arterial pressure (MAP) decreased more rapidly in the LTV ventilation group than in the APRV group, with significant differences appearing by 24 h ($P < 0.05$; Table 1). Consistent with this trend in hemodynamic deterioration, lactate levels and norepinephrine requirements increased more rapidly in the LTV ventilation group as compared with the APRV group, with significant differences appearing by 24 h ($P < 0.05$).

All animals in both APRV and LTV ventilation groups developed polymicrobial bacteremia in blood cultures, typical of this animal model (9). There were no differences between the APRV and LTV ventilation groups in hemoglobin/hematocrit, white blood cell count, platelets, or coagulation parameters (data not shown). There was a significant time trend toward leukopenia, thrombocytopenia, anemia, and coagulopathy in both APRV and LTV ventilation groups. Plasma IL-6 levels were equivalent between APRV and LTV ventilation at BL and increased for both groups by 48 h; however, they were significantly higher in LTV ventilation ($P < 0.05$ vs. APRV).

Fluid balance

The sham group animals did not develop significantly positive fluid balance ($P < 0.05$ vs. APRV and LTV ventilation), nor did they require bolus fluids above the maintenance i.v. fluid requirements. All animals in APRV and LTV ventilation groups experienced severe shock requiring aggressive i.v. fluid resuscitation and exhibited similarly positive fluid balances that were not statistically different between the APRV and LTV ventilation groups.

Sequential Organ Failure Assessment scores

To estimate shock severity, Sequential Organ Failure Assessment (SOFA) scores were calculated. The SOFA score of the sham group was normal for 48 h, reflecting neither critical illness nor instability, and was significantly different from the other two groups ($P < 0.05$ vs. APRV and LTV ventilation, respectively). The SOFA scores of the APRV group were 6.75 ± 1.31 at 12 h and 9.75 ± 1.79 at 48 h, reflecting severe, progressive critical illness. The SOFA scores for the LTV ventilation group at 12 h were 10.33 ± 2.33 and 16.5 ± 0.96 at 48 h, reflecting severe, progressive critical illness, which progressed more rapidly than in the APRV group.

Organ injury—The animals in both the APRV and LTV ventilation groups exhibited nonpulmonary organ injury. Three of four animals in the APRV group and all animals in the LTV ventilation group developed abdominal compartment syndrome (ACS), with elevated bladder pressure, acute increases in airway pressure, reduction in MAP, and acute decrease in urine output. These animals underwent urgent decompressive laparotomy as clinically indicated. All animals in both groups developed both gross and microscopic intestinal inflammation with mucosal necrosis, villous sloughing, and inflammatory cellular infiltration (data not shown). All animals in both APRV group and LTV ventilation groups developed gastric stress ulceration. Liver histology in animals from both groups demonstrated paracentral hepatonecrosis characteristic of "shock liver." All animals in both LTV ventilation and APRV groups developed oliguric renal failure (<0.5 mL/kg urine output per hour) for the final 2 to 3 h of life.

Pulmonary Data

The development of clinical lung injury was determined by P/F ratio and C_{stat} (Fig. 1, A and B). The APRV and sham

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TABLE 1. **Hemodynamic parameters**

	Group	BL	6 h	12 h	18 h	24 h	30 h	36 h	42 h	48 h	$P > 0.05$
HR, beats/min	Sham	132.0 ± 13.5	106.8 ± 3.8	93.0 ± 5.5	91.0 ± 3.7	90.2 ± 4.3	93.0 ± 5.2	83.8 ± 5.9	78.6 ± 6.2	81.6 ± 6.2	
	APRV	98.7 ± 2.4	125.3 ± 9.5	108.0 ± 7.1	104.0 ± 7.9	108.0 ± 9.4	116.5 ± 10.6	125.5 ± 16.0	110.3 ± 14.3	126.3 ± 25.2	
	LTV	96.3 ± 12.8	106.3 ± 20.9	102.0 ± 21.0	92.0 ± 12.7	96.0 ± 5.0	105.7 ± 11.3	103.0 ± 6.9	99.0 ± 13.9	91.7 ± 6.9	
MAP, mmHg	Sham	124.8 ± 8.2	84.2 ± 9.8	85.6 ± 5.3	76.0 ± 6.2	67.0 ± 4.6	68.6 ± 4.5	69.6 ± 3.8	66.2 ± 4.4	65.8 ± 5.1	*
	APRV	112 ± 2.7	70.3 ± 7.8	83.5 ± 7.7	79.3 ± 5.3	80.0 ± 7.1†	81.5 ± 16.6	82.8 ± 12.2	73.8 ± 4.1	76 ± 7.2†	
	LTV	125.0 ± 5.9	71.0 ± 9.5	68.3 ± 9.0	58.0 ± 4.9	53.3 ± 7.0†	48.7 ± 4.3	57.0 ± 10.0	41.3 ± 2.2‡	46.0 ± 7.5†	
Lactate, mmol/L	Sham	2.0 ± 0.3	4.0 ± 1.2	1.5 ± 0.4		0.9 ± 0.1		1.0 ± 0.3		0.7 ± 0.1	
	APRV	1.5 ± 0.3	6.7 ± 2.6	3.6 ± 1.8		2.0 ± 0.7		2.0 ± 1.4		6.0 ± 3.1	
	LTV	1.6 ± 0.2	5.0 ± 1.8	5.2 ± 2.8		7.6 ± 5.4		11.6 ± 4.1‡		14.0 ± 2.3‡	
Norepinephrine dose, μg/min	Sham	0	0	0	0	0	0	0	0	0	*
	APRV	0	1.3 ± 1.3	1.8 ± 1.2	2.0 ± 1.2	2.0 ± 1.2	4.5 ± 1.5	5.2 ± 1.7	8.0 ± 3.7	6.3 ± 4.3	
	LTV	0	2.0 ± 2.0	5.3 ± 5.3	3.3 ± 3.3	8.0 ± 6.1‡	11.5 ± 4.3‡	20.3 ± 3.2‡	21.7 ± 2.2‡	23.7 ± 1.9‡	
Bladder pressure	Sham	3.0 ± 1.3	4.0 ± 1.6	4.2 ± 1.5‡	6.8 ± 2.4	3.0 ± 1.6‡	2.4 ± 0.5‡	7.6 ± 2.6†	7.0 ± 2.2	2.6 ± 0.7†	
	APRV	5.3 ± 2.0	10.0 ± 2.7	13.5 ± 3.2	14.0 ± 3.5	11.8 ± 3.4	14.0 ± 2.0	17.0 ± 4.3	15.5 ± 2.8	15.8 ± 3.2†	
	LTV	3.0 ± 1.6	14.3 ± 7.4	17.0 ± 5.6	15.7 ± 6.2	17.0 ± 5.5	27.3 ± 8.1	24.7 ± 2.8†	26.7 ± 0.9‡	26.7 ± 0.9†	

*$P > 0.05$ following RM-ANOVA.
†$P < 0.05$ between groups following post hoc analysis with Tukey test.
‡$P < 0.05$ following post-hoc analysis with Tukey test.
HR indicates heart rate.

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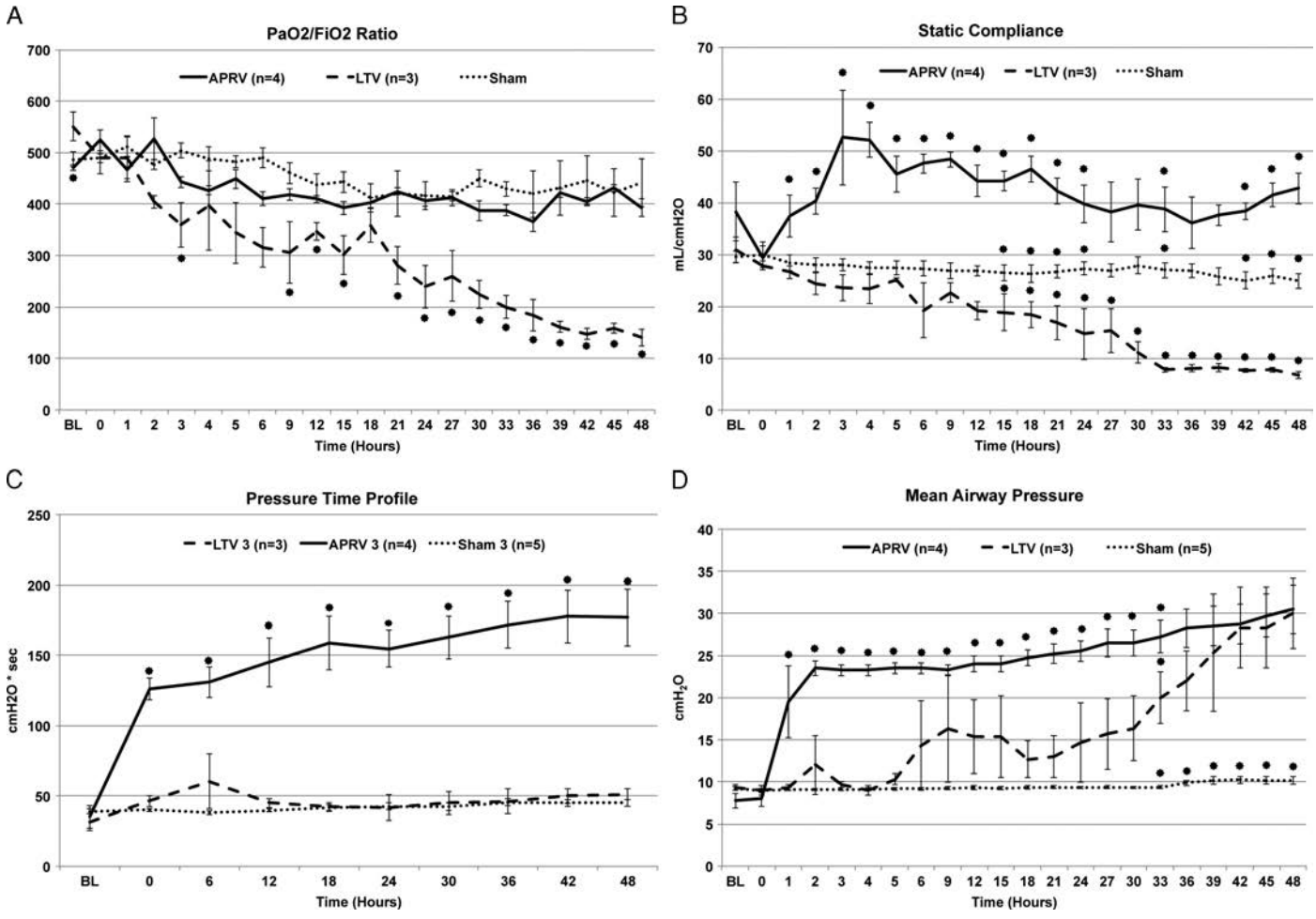

FIG. 1. **Pulmonary data**. A, P/F Ratio: APRV maintains a normal P/F ratio throughout the 48-h study with no significant difference from uninjured sham animals. Low tidal volume ventilation develops ALI (P/F < 300) by 19 h and ARDS (P/F < 250) by 33 h; ventilation strategy does not alter steady progression of increasing hypoxemia ($P < 0.001$ vs. APRV and sham). B, Static compliance (C_{stat}): the APRV shows significant increase in C_{stat} after transition from volume-cycled mode to APRV ($P < 0.001$ vs. sham and LTV ventilation). Sham maintained a normal C_{stat} level throughout the course of the study. In contrast, the LTV ventilation group developed progressive decreases in C_{stat} to less than 50% of BL. C, Mean airway pressure: sham group maintained normal P_{mean} throughout 48-h significantly different from both APRV and LTV ventilation ($P < 0.001$). P_{mean} was significantly higher in APRV than in both sham and LTV ventilation after transition from conventional ventilation at 1 h. Because of stepwise increases in PEEP per the ARDSnet protocol, the P_{mean} was identical from 39 to 48 h for LTV ventilation and APRV. D, Pressure-time profile (P/T_P): APRV group had significantly higher P/T_P than did both other groups as soon as the transition was made from volume-cycled ventilation ($P < 0.001$ vs. sham and LTV ventilation). In the LTV ventilation group, P/T_P remained low and did not change over the 48-h course of the study. Sham group animals also had low P/T_P, which was not significantly different from the LTV ventilation group throughout the study.

groups had normal P/F ratios throughout the 48-h experiment. There were no significant differences in P/F ratio between these two groups (Fig. 1A). The APRV group had a significant increase in C_{stat} after being transitioned from volume-cycled ventilation to APRV (Fig. 1B). As compared with the sham group, the APRV group maintained a "supranormal" C_{stat} level throughout the course of the study. In contrast, the LTV ventilation group developed progressively severe lung injury, with declining P/F ratio and C_{stat} over the course of the study (Fig. 1, A and B). The P/F ratio in the LTV ventilation group decreased to meet the American-European Consensus Criteria for acute lung injury (ALI) (<300) by 19 h and ARDS criteria (<200) by 33 h (Fig. 1A) (11). This progression to lung injury in the LTV ventilation group was corroborated by steadily declining C_{stat} to less than 50% of BL by the end of the study, consistent with the stiff, noncompliant lungs characteristic of ARDS (Fig. 1B).

The sham group maintained normal mean airway pressures (P_{mean}) throughout the 48-h study ($P < 0.001$ vs. APRV and LTV ventilation groups; Fig. 1C). Mean airway pressure was significantly higher in APRV than in both sham and LTV ventilation after transition from conventional ventilation at 1 h (Fig. 1C). Because of stepwise increases in PEEP per the ARDSnet protocol, the P_{mean} were identical from 39 to 48 h for LTV ventilation and APRV (Fig. 1C). Tidal volume was initially ~10 mL/kg for all groups at BL and remained at this level for 48 h in the sham and APRV groups. In contrast, the Vt in the LTV ventilation group was lowered in response to development of ALI (Table 2). Positive end-expiratory pressure was initially at 5 cmH_2O for all groups at BL and remained at this level for the sham group throughout the study (Table 2). The LTV ventilation group required progressive increases in PEEP in response to refractory hypoxemia throughout the study (Table 2).

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TABLE 2. **Pulmonary data**

	Group	BL	6 h	12 h	24 h	36 h	48 h	$P > 0.05$
Vt, L	Sham	10.2 ± 0.1	10.2 ± 0.2	10.0 ± 0.2	9.9 ± 0.2	10.2 ± 0.3	10.0 ± 0.2*	†
	APRV	9.9 ± 0.2	10.3 ± 0.4	10.3 ± 0.5	10.3 ± 0.4	11.8 ± 0.8	12.0 ± 0.8*	
	LTV	10.0 ± 0.1	9.8 ± 0.2	8.5 ± 1.2	7.4 ± 1.4	5.7 ± 0.3‡	5.8 ± 0.4*	
PEEP, cmH_2O	Sham	5.0 ± 0.0	5.0 ± 0.0*	5.0 ± 0.0	5.0 ± 0.0*	5.0 ± 0.0	5.0 ± 0.0	†
	LTV	5.0 ± 0.0	9.3 ± 3.4	7.3 ± 2.3	8.7 ± 3.7	15.3 ± 2.9‡	20.0 ± 2.3‡	
RR, breaths/min	Sham	13.6 ± 0.9	18.7 ± 2.7*	14.9 ± 2.3*	12.6 ± 1.4	9.8 ± 0.6	10.1 ± 0.8	†
	APRV	18.0 ± 4.7	10.8 ± 0.6*	11.0 ± 1.5*	10.0 ± 0.7	11.8 ± 2.5	11.3 ± 2.3	
	LTV	17.0 ± 2.1	17.0 ± 2.9	18.0 ± 4.0	22.0 ± 3.8‡	29.7 ± 0.9‡	32.0 ± 3.1‡	
$Paco_2$, mmHg	Sham	36.1 ± 2.2	34.6 ± 2.9	37.0 ± 2.2	37.7 ± 1.7	36.6 ± 1.3	34.7 ± 2.5	
	APRV	39.6 ± 1.1	42.5 ± 4.6	38.8 ± 2.0	43.3 ± 2.2	43.9 ± 3.0	38.6 ± 1.2	
	LTV	34.6 ± 1.4	40.6 ± 1.7	38.6 ± 1.9	42.9 ± 3.0	57.0 ± 9.4	64.0 ± 8.8	

*$P < 0.05$ between groups following post hoc analysis with Tukey test.
†$P < 0.05$ following RM-ANOVA.
‡$P < 0.05$ following post hoc analysis with Tukey test.

Figure 1D shows that the APRV group had a significantly higher P/T_P than both other groups as soon as the transition was made from volume-cycled ventilation (Fig. 1D). Furthermore, despite progressive increases in PEEP (Table 2) in the LTV ventilation group, P/T_P remained low and did not change over the 48-h course of the study (Fig. 1D). Sham group animals also had low P/T_P, which was not significantly different from the LTV ventilation group throughout the course of the study. Pressure-time profile in both the sham and LTV ventilation groups remained similarly low and did not change over the course of the study, despite substantial increases in PEEP (Table 2). This is explained by the quantities that contribute to P/T_P. As lung injury progressed in the LTV ventilation group RR was increased to clear CO_2. However, to maintain an inspiratory-to-expiratory ratio of 1:2 as required by LTV ventilation protocol, the inspiratory time was decreased simultaneously. Because time and pressure are equally weighted in P/T_P (Eq. (1)), this decrease in inspiratory time had the effect of maintaining a low P/T_P in LTV ventilation despite increases in PEEP.

Gross pathology

The APRV-treated animals exhibited normal, pink, homogenously well-inflated lung tissue with no evidence of inflammation and no evidence of atelectasis and appeared to be inflated nearly to total lung capacity (TLC) (Fig. 2A). The cut surface of the representative APRV lung specimen shows neither bronchial nor septal edema (Fig. 2B). The lungs of the LTV ventilation group were predominantly atelectatic with heterogeneous parenchymal inflammation (Fig. 2C). In addition, gel-like edema occupied the interlobular septae of the lung, and airway edema was present in the bronchial openings (Fig. 2D) in the LTV ventilation group.

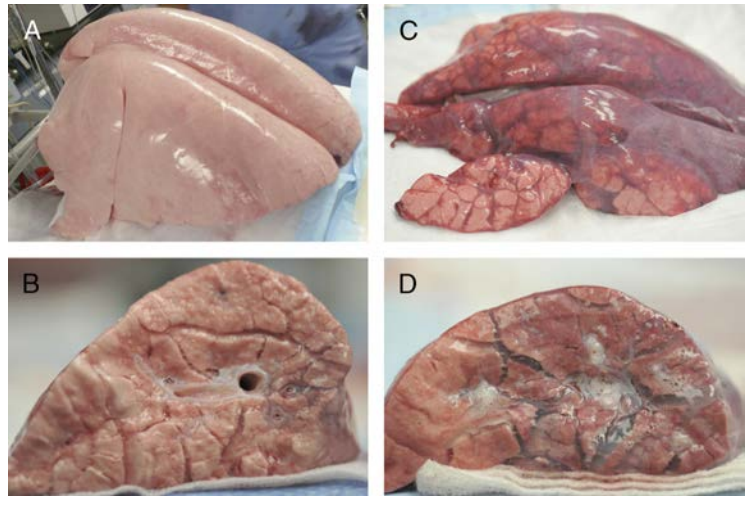

FIG. 2. **Gross pathology: Representative specimens of gross lungs from LTV ventilation and APRV groups are shown**. A, Airway pressure release ventilation whole lung: animals exhibited normal, pink, homogenously well-inflated lung tissue with no evidence of inflammation and no evidence of atelectasis and appeared to be inflated nearly to TLC. B, Airway pressure release ventilation cut surface: the cut surface of the representative APRV lung specimen shows neither bronchial nor septal edema. C, Low tidal volume ventilation whole lung: the lungs were predominantly atelectatic with heterogeneous parenchymal inflammation. D, Low tidal volume ventilation cut surface: the cut surface shows gel-like edema filling the interlobular septae of the lung in the LTV ventilation group and airway edema in the bronchial openings.

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TABLE 3. **Quantitative histologic scoring of lung injury**

	Histopathology scores*		
	Sham operation	LTV (2-hit)	APRV (2-hit)
Atelectasis	0.28 ± 0.07†	0.05 ± 0.07	0.00 ± 0.07
Fibrinous deposits	1.30 ± 0.13†	0.68 ± 0.13	0.38 ± 0.13†
Blood in alveoli	0.23 ± 0.13†	0.20 ± 0.13	0.30 ± 0.13
Capillary congestion	2.15 ± 0.13	1.90 ± 0.13	0.83 ± 0.13†
Thick alveolar wall	1.75 ± 0.17	1.70 ± 0.17	0.25 ± 0.17†
Leukocyte infiltration	1.18 ± 0.13†	2.10 ± 0.13†	1.80 ± 0.13†

*Values are mean ± SEM (n = 40).
†Significantly different from the other two treatment conditions ($P < 0.05$).

Quantitative and descriptive histology

The quantitative histologic technique used in this study allows for an unbiased comparison of degree of tissue injury to the lungs between the LTV ventilation and APRV groups. The histologic lesions analyzed are considered pathognomonic for ARDS when the clinical context is appropriate (11). These lesions include atelectasis, fibrinous deposits, capillary congestion, leukocyte infiltration, intra-alveolar hemorrhage, and alveolar wall thickness. Airway pressure release ventilation resulted in significantly reduced fibrinous exudates, capillary congestion, leukocyte infiltration, and alveolar wall thickness ($P < 0.05$ vs. LTV ventilation and sham; Table 3). Sham animals exhibited more severe histologic injury than LTV ventilation and APRV animals in the categories of atelectasis, fibrin deposits, leukocyte infiltration, and intra-alveolar hemorrhage ($P < 0.05$; Table 3).

Histologic section of the lung of a representative LTV ventilation animal (Fig. 3B) shows stigmata of lung injury including atelectasis, fibrinous exudates, intra-alveolar hemorrhage, congested capillaries, thickened alveolar walls, and leukocytic infiltrates. A histologic section of the lung from the APRV group (Fig. 3C) shows preservation of normal pulmonary architecture and none of the stigmata of lung injury described. Notably, APRV animals exhibited prominent perivascular edema cuffs and dilated lymphatics as compared with LTV ventilation animals. Furthermore, APRV animals exhibited normal alveolar patency, whereas LTV ventilation animals exhibited intra-alveolar fibrin as well as alveolar collapse. The sham group exhibited signs of histologic lung injury (although there had been no clinical evidence of this throughout the 48-h experiment) including mild to moderate atelectasis, fibrinous exudates, intra-alveolar hemorrhage, congested capillaries, thickened alveolar walls, and leukocytic infiltrates (Fig. 3A).

Wet-Dry Weight Ratio

To assess the degree of pulmonary edema, we assessed wet-dry (W:D) weight ratio. The LTV ventilation group had significantly higher W:D weight ratio (10.63 ± 1.72) than the APRV group (7.18 ± 1.12) ($P < 0.05$). Both ARDSnet and APRV groups had higher W:D weight than did the sham group (5.63 ± 0.51). There were no differences between groups in W:D weight ratios for liver, kidney, intestine, or spleen.

BALF and lung tissue

Surfactant composition was assessed by quantifying SP-A in BALF by Western blot. Surfactant protein A was significantly lower in the LTV ventilation group ($P < 0.05$ vs. APRV; Fig. 4B). All LTV ventilation animals exhibited total degradation of the SP-A protein monomer, whereas SP-A monomer bands were expressed at higher levels in the APRV group ($P < 0.05$) (Fig. 4B). Interleukin 6 levels in BALF were analyzed by ELISA (Fig. 4C) and showed that APRV was associated with significantly lower pulmonary IL-6 than LTV ventilation ($P < 0.05$ vs. APRV and sham, respectively). The APRV group expressed significantly higher levels of E-cadherin in lung tissue homogenates than did the LTV ventilation group ($P < 0.05$; Fig. 4A) as measured by Western blot.

DISCUSSION

The present study strongly suggests that early intervention using a ventilator mode with a high P/T_P may successfully prevent ARDS, based on studies in our clinically relevant porcine model of lung injury. Airway pressure release ventilation applied 1 h after injury preserved oxygenation (P/F ratio), lung compliance, surfactant protein abundance, histologic lung architecture, and alveolar epithelial integrity (E-cadherin) compared with standard-of-care LTV ventilation treatment. Airway pressure release ventilation also reduced pulmonary edema and lung inflammation (BALF IL-6) compared with

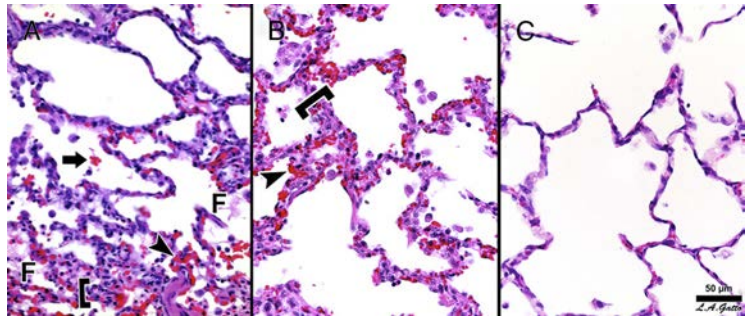

FIG. 3. **Histology: Photomicrographs of representative lung sections of specimens from each treatment group at 40× magnification**. F = fibrinous deposit in the air compartment; arrow = blood in alveolus; arrowhead = congested alveolar capillary; bracket = thickened alveolar wall. A, Sham: animals received 48 h of mechanical ventilation without PS + I/R injury. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, and thickened alveolar walls. B, Low tidal volume ventilation: animals received PS + I/R injury and LTV ventilation after onset of ALI. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, leukocyte infiltration, and thickened alveolar walls. C, Airway pressure release ventilation: animals received APRV 1 h following PS + I/R injury. Specimen shows normal pulmonary architecture, alveoli are well expanded and thin walled, and there are no exudates.

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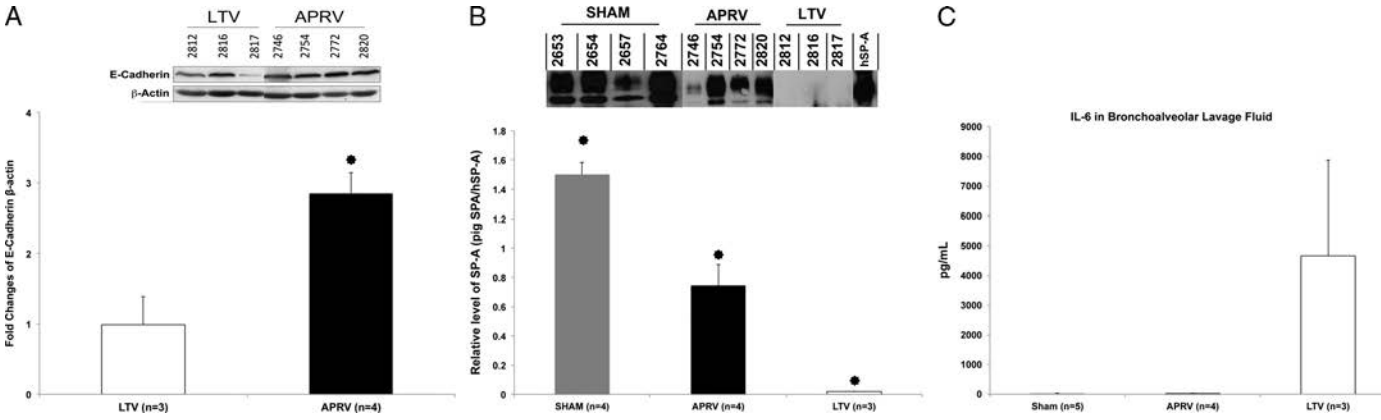

FIG. 4. **Bronchoalveolar lavage and lung tissue analysis**. A, Epithelial cadherin in Lung tissue: APRV had significantly greater E-cadherin abundance in lung tissue than LTV ventilation ($P < 0.05$). B, Surfactant Protein A in BALF: APRV had significantly higher SP-A abundance in BALF than LTV ventilation ($P < 0.05$). C, Interleukin 6 in BALF: APRV had significantly lower IL-6 in BALF than LTV ventilation ($P < 0.05$).

LTV ventilation. In fact P/F ratio, pulmonary mechanics, lung permeability, and inflammation in the APRV group were indistinguishable from the sham group, which received mechanical ventilation alone without PS + I/R injury. Low tidal volume ventilation resulted in significant gross and histologic lung injury with very high histologic lung injury scores. Airway pressure release ventilation preserved normal pulmonary histology despite significant systemic inflammation (plasma IL-6) and various indicators of critical illness (MAP, lactate, SOFA). Histologic lung injury scores for the APRV group were even lower than those for the sham group. The implications of these findings are both clinically and mechanistically significant to the understanding and management of ARDS.

The case for early intervention

Because established ARDS is accompanied by high mortality despite LTV ventilation (3), and ARDS survivors exhibit significant morbidities and limited quality of life (4), preventive approaches for this disease have been advocated in the literature (18). The current study describes a novel, preventive strategy of mechanical ventilation using high P/T_P, which effectively averts lung injury by targeting key elements in early ARDS pathophysiology. Preventive management of disease rests on a clear understanding of pathologic progression and identification of early drivers of pathophysiology, which may be targeted by therapy to block development of the fulminant disease (19). The shift in management of colorectal malignancy over the last three decades is exemplary of this strategy (19). As premalignant colonic mucosal lesions were identified and targeted, the management of colorectal cancer radically shifted from treatment of clinically evident disease to prevention at early asymptomatic stages in high-risk patients (19). The current study demonstrates that ARDS may have reversible preclinical stages during which targeted intervention prevents the development of established ARDS. The prevention of all stigmata of lung injury by APRV applied immediately after injury in our model suggests that blocking the key pathologic drivers of ARDS onset targeted by high P/T_P ventilation can halt the progression of pathology in the lung. Successful application of this preventive strategy will necessitate departure from the binary paradigm of understanding ARDS as either present or absent so that patients at risk may be selected early for preventive ventilation with APRV.

Identification of targets for early preventive therapy requires examination of the pathologic changes in the lung before the onset of clinical ARDS. The pathophysiology of ARDS onset follows from an insult (trauma/hemorrhage/sepsis) triggering systemic inflammation, which results in increased permeability causing pulmonary edema. Proteinaceous edema fluid floods alveoli, deactivating surfactant (11) and promoting alveolar instability with tidal ventilation (20). Mechanical ventilation in the context of unstable alveoli results in atelectrauma (21), which further propagates tissue injury and propels the lung toward ARDS (12). The pathologic tetrad of permeability, edema, surfactant deactivation, and alveolar instability is therefore the early driver of ARDS onset (11). We hypothesized that early mechanical ventilation with the appropriate P/T_P would specifically target these key elements of ARDS pathophysiology and prevent ARDS. The effect of sustaining pressure over time (high P/T_P) has three effects interrupting the pathologic tetrad, which are mechanisms for the success of APRV demonstrated in the present study. Sustained airway pressure (*a*) alters lung edema handling, preventing alveolar flooding; (*b*) maintains alveolar stability thereby blocking atelectrauma; and (*c*) recruits collapsed alveoli and prevents derecruitment. Each of these effects of P/T_P will be discussed in detail.

Pressure-time profile—targeting early drivers of ARDS pathophysiology

Because the only difference in management between APRV and LTV ventilation animals was the ventilatory strategy, the marked differences in outcome between these groups were likely related to the ventilatory forces applied at the alveolar surface, measured as P/T_P. The force exerted on the lung by mechanical ventilation is dependent on both pressure (P) and the duration of time (T) that this pressure is applied over the ventilatory cycle (22). We developed a novel method to quantify this concept by integrating the airway pressure curve over time (Eq. (1)). The P/T_P therefore reflects the combined pressure-time force effect exerted by mechanical ventilation on the lung tissue and represents a unique characteristic of any given ventilatory mode. Because P/T_P incorporates the temporal effect

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of pressure, this parameter is responsive to the dynamic forces of tidal respiration and differs significantly from static pressure measurements. The defining characteristic of APRV in the current study is the unique shape of the airway pressure curve during the entire breath as visualized by the airway pressure tracing (9, 13). Airway pressure release ventilation sustains a relatively constant airway pressure (P_{high}) for greater than 90% of the duration of the breath (T_{high}) with a brief subsecond release (T_{low}) to allow for CO_2 clearance (13). Thus, APRV is effectively continuous positive airway pressure (CPAP) with a release phase for ventilation (13). We postulate that it is this sustained pressure on the pulmonary interstitium that is the key mechanism of reduced pulmonary edema.

The current study demonstrates differences in outcome correlating closely with differences in P/T_P between the three separate ventilatory strategies examined. The highest P/T_P mode (APRV) had the best lung histology outcome, as well as reduction in edema, and preservation of alveolar epithelial integrity. Both low-P/T_P modes (LTV ventilation and sham) had measurable tissue injury at the histologic level, demonstrating that mechanical ventilation with low P/T_P is injurious, even in a normal lung (18). Low P/T_P combined with systemic inflammation in the LTV ventilation group was associated with significant lung injury, as assessed by clinical, molecular, and histologic parameters. These data suggest that both systemic inflammation and mechanical ventilation with low P/T_P are necessary for the development of ARDS. Our finding that injury to the normal lung can be caused by mechanical ventilation is consistent with recent literature (18). The most proximal event in the pathologic tetrad of ARDS onset is increased permeability resulting in alveolar edema. High P/T_P may attenuate edema formation to preempt ARDS as a potential mechanism of the success of APRV.

Pressure-time profile—attenuation of permeability and alveolar edema

The systemic inflammatory response syndrome disrupts the delicate alveolar-capillary fluid balance by increasing the vascular permeability (σ), which increases capillary filtration rate (Jv) as expressed in the Starling relationship (23). Ventilation with the appropriate P/T_P may shift the balance of the Starling equation from high capillary filtration to a significantly reduced filtration rate, even in the presence of increased σ (9). In the present study, the high P/T_P APRV group had lower lung edema (W:D ratio) and greater alveolar epithelial integrity (E-cadherin) than did the LTV ventilation group. Thus, mechanical ventilation with sustained airway pressure over time may alter the fluid-flux relationship to prevent edema flow into the alveolus.

There are several potential mechanisms by which sustained airway pressure (high P/T_P) might lead to reduced edema. Elevating and sustaining airway pressure by early increases in PEEP cause reduction in lung water in high-permeability edema (23), high alveolar surface tension edema (24), and barotraumatic edema (25). Sustained airway pressure over time increases the vascular transmural pressure secondary to an increase in the interstitial hydrostatic pressure (Pi), thereby opposing fluid movement out of the capillaries (23). Whereas these prior mechanistic studies were designed to prevent edema with airway pressurization, the current study was designed to efficaciously prevent ARDS in a translational ARDS model. The precise mechanisms by which high P/T_P delivered by APRV reduces lung edema and maintains alveolar epithelial integrity in this model remain to be determined.

Pressure-time profile stabilizes alveoli preventing cyclic recruitment and derecruitment, which is known to increase capillary permeability (26) and cause pulmonary edema (27). It is also possible that P/T_P normalizes σ by preventing the cyclic stretch of the alveolar endothelium (28). Lastly, P/T_P may act to support the integrity of the interstitial matrix. An intact interstitial matrix comparable to a low compliance glove surrounding the capillary plays a key role in restricting capillary fluid filtration (29). As long as the extracellular matrix is intact, edema is maintained within the interstitial space. Severe edema develops rapidly once damage to the extracellular matrix reaches a critical "tipping point" when the fluid restrictive component of the matrix is lost, allowing rapid efflux of fluid from the capillaries into the interstitial and alveolar space (30). The sustained pressure transmitted to the interstitial space (Pi) with P/T_P would prevent edema swelling-induced injury to the extracellular matrix, maintaining this important "edema safety factor," preventing the rapid influx of edema and alveolar flooding.

Pressure-time profile—alveolar stability

Alveolar instability, the dynamic opening and closure of alveoli during tidal ventilation, has been shown to result in atelectrauma, which is a key driver of ARDS (12) and represents a target of our high P/T_P preventive ventilation strategy. Although we did not directly measure alveolar stability in this study, we did measure the relative abundance of SP-A. Surfactant proteins convey functionality to alveolar surfactant, which stabilizes alveoli during tidal ventilation (11). If a ventilator mode induces or propagates alveolar instability, SP-A could be expected to be degraded in the BALF (9). The present study shows that APRV clearly preserved SP-A, whereas LTV ventilation clearly degraded this protein. These data suggest that APRV is capable of alveolar stabilization as a result of its high P/T_P-induced protection of surfactant function.

Pressure-time profile—lung recruitment

Sustained pressure over time takes advantage of the temporal component of recruitment (22), leading to progressive recruitment with each tidal breath. Over a short period, this pattern of ventilation results in near-total recruitment, resulting in the phenomenon that the lung is ventilated at near TLC. Examination of the gross lung specimens reveals the striking finding that APRV lungs appeared to be inflated to near TLC with no atelectatic segments (Fig. 2A), whereas a majority of lung parenchyma of LTV ventilation lungs was atelectatic, with only apical segments inflated (Fig. 2b). Recruitment of alveolar units is known to be a function of both pressure and time (22). It appears that the high P/T_P of APRV maintains recruitment of the entire lung ventilating very near TLC for the majority of the respiratory cycle. When the *ex vivo* lung was left connected to the ventilator at the same APRV settings, it

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was noted that the change in lung volume during release phase was nearly imperceptible (data not shown). Atelectasis with heterogeneously inflated lung parenchyma results in pressure gradients and stress-strain forces acting injuriously on lung tissue (31). Therefore, there is a clear advantage to ventilating near TLC where the lung is homogenously recruited, eliminating these injurious mechanical forces.

The current study utilizes a model in which PS is allowed to progress without source control, leading to escalating systemic inflammation, severe shock physiology, and organ failure. In the setting of this model, resuscitative fluid requirements increase throughout the course of the study, leading to extensive edema and ACS. Edema-induced extrapulmonary force vectors compress the lung from the abdominal contents and from the chest wall. We postulate that high P/T_P represents an intrapulmonary counterforce to these proatelectatic extrapulmonary forces and resists lung derecruitment and development of heterogeneity. Airway pressure release ventilation and LTV ventilation both had high fluid requirements, increasingly elevated intraperitoneal pressures, and eventual ACS. In response to this compression from the abdominal compartment, the LTV ventilation animals developed grossly evident atelectasis as the whole-lung specimens demonstrate. In contrast, APRV animals displayed fully recruited gross lung specimens despite similar extrapulmonary forces.

CLINICAL IMPLICATIONS

The present study was designed to detect a difference in ARDS incidence between preemptively applied APRV versus LTV ventilation applied according to present standards of care. In current clinical practice, LTV ventilation is typically not applied before respiratory failure but rather at the onset of hypoxemia (P/F <300), and stepwise increases in PEEP are made in response to oxygen desaturation. We showed that early, sustained airway pressurization (high P/T_P) delivered before the onset of lung injury prevents edema and the downstream sequelae (surfactant degradation, alveolar instability, atelectrauma, and parenchymal damage) associated with ARDS.

It is possible that early application of LTV ventilation with high PEEP could achieve similar effects provided that the P/T_P was equivalent to that of APRV. However, there are several reasons why we believe early application of APRV would be superior to high PEEP + low Vt. First, APRV has a significantly higher P/T_P than high PEEP + low Vt because of the extended time at P_{high}. For example, we calculated P/T_P for a high PEEP + low Vt breath from a preliminary study in the same two-hit porcine model, where PEEP = 20 cmH_2O, P_{plat} = 29 cmH_2O, T_{insp} = 1.3 s, and T_{exp} = 1.69 s. Inserting these numbers into Eq. (1), we find the calculated P/T_P is 71 cmH_2O * s. Thus, the P/T_P in the high PEEP + low Vt animal is much higher than in LTV ventilation or sham animals (range, 30–60 cmH_2O * s) but still significantly lower than the P/T_P for APRV (range, 130–190 cmH_2O * s) (Fig. 1D). This suggests that a substantially higher P/T_P than delivered by high PEEP + low Vt is necessary to achieve lung protection. This inadequate P/T_P is with a PEEP of 20 cmH_2O, which is significantly higher than typical clinical practice (6). We have not yet conclusively demonstrated that a higher P/T_P correlates with reduced lung injury, but the present study as well as unpublished data from our laboratory suggests that this relationship is true.

Second, application of APRV is more practical than applying a high-PEEP strategy to a relatively normal lung. High PEEP requires delivery of Vt above the PEEP level to ventilate, which can lead to barotrauma because additional mechanical force is applied to pulmonary tissue with Vt delivery. In contrast APRV, described as CPAP with a brief release phase, releases pressure from P_{high} to generate a ventilatory volume. Airway pressure release ventilation therefore harnesses the potential energy contained within the elastic properties of the respiratory system, causing the lung to recoil naturally to a lower lung volume to generate the Vt.

Clinically, APRV may be the most practical method to apply early high P/T_P. First, there are no prohibitive negative adverse effects from APRV, such that APRV can be applied to all patients at risk of developing ALI/ARDS. Second, because APRV is a form of CPAP and differs only in the added release phase, patients can comfortably breathe spontaneously at any point throughout the respiratory cycle. As a result of the CPAP element, APRV fulfills the spectrum from weaning to full support of patients on mechanical ventilation (13, 32). In addition, APRV is associated with increased patient comfort and less sedation.

Airway pressure release ventilation has been a standard-of-care mode of mechanical ventilation at the largest freestanding trauma center in the United States (R. Adams Cowley; Shock Trauma Center [STC]). At the STC, APRV is applied as the initial and sole mode of ventilation up to and through extubation including noninvasive applications (13, 32–35). Thus, STC uses a nonselective approach of early APRV application for nearly all patients with trauma and sepsis. Although not all individuals who are at risk actually develop ARDS, many of these patients do with serious morbidity and mortality. Early universal application of APRV to patients at risk is a preemptive measure to counter a potentially catastrophic outcome similar to the use of seatbelts, thromboprophylaxis, or stress ulcer prophylaxis.

CONCLUSIONS

The current study demonstrates that systemic inflammatory response syndrome–induced ARDS can be prevented with high airway P/T_P when APRV is used early in the course of mechanical ventilation in a clinically relevant translational porcine model of lung injury. Airway pressure release ventilation prevented clinical and histologic lung injury by preserving alveolar epithelial integrity, reducing lung edema, preserving surfactant, and maintaining alveolar stability. In summary, these data suggest that ARDS development involves a close interplay of both systemic inflammation as well as mechanical ventilation with low P/T_P. Future studies are needed to elucidate the mechanical ventilation strategies that will offer the appropriate P/T_P for prevention of ARDS.

The preemptive ventilation strategy presented in our study has the potential to change the current clinical practice paradigm from treating ARDS once it manifests to preventing it from

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ever developing. Because preemptive ventilation strategies such as APRV are already approved for use, clinical application can begin without delay with an immediate impact on patient care. If successful, our ventilation strategy would be the first prophylactic intervention of any kind to prevent ARDS.

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