

Preemptive mechanical ventilation can block progressive acute lung injury

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Abstract

Mortality from acute respiratory distress syndrome (ARDS) remains unacceptable, approaching 45% in certain high-risk patient populations. Treating fulminant ARDS is currently relegated to supportive care measures only. Thus, the best treatment for ARDS may lie with preventing this syndrome from ever occurring. Clinical studies were examined to determine why ARDS has remained resistant to treatment over the past several decades. In addition, both basic science and clinical studies were examined to determine the impact that early, protective mechanical ventilation may have on preventing the development of ARDS in at-risk patients. Fulminant ARDS is highly resistant to both pharmacologic treatment and methods of mechanical ventilation. However, ARDS is a progressive disease with an early treatment window that can be exploited. In particular, protective mechanical ventilation initiated before the onset of lung injury can prevent the progression to ARDS. Airway pressure release ventilation (APRV) is a novel mechanical ventilation strategy for delivering a protective breath that has been shown to block progressive acute lung injury (ALI) and prevent ALI from progressing to ARDS. ARDS mortality currently remains as high as 45% in some studies. As ARDS is a progressive disease, the key to treatment lies with preventing the disease from ever occurring while it remains subclinical. Early protective mechanical ventilation with APRV appears to offer substantial benefit in this regard and may be the prophylactic treatment of choice for preventing ARDS.

Key words: Mechanical ventilation; Acute lung injury;

Acute respiratory distress syndrome; Airway pressure release ventilation

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Core tip: Mortality from acute respiratory distress syndrome (ARDS) remains unacceptably high. Treating fulminant ARDS, however, is currently relegated to supportive care measures only. Thus, the best treatment for ARDS may lie with preventive measures. Indeed, since ARDS is a progressive disease, treating this disease in its subclinical phases may prevent the disease from ever occurring. In this regard, early protective mechanical ventilation with airway pressure release ventilation appears to offer substantial benefit and may be the prophylactic treatment of choice for preventing ARDS.

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ACUTE RESPIRATORY DISTRESS SYNDROME AND ITS SEQUELAE REMAIN A MAJOR AND COSTLY PUBLIC HEALTH CARE BURDEN

Acute respiratory distress syndrome (ARDS) and its sequelae remain a significant public health care burden in North America and worldwide^[1-3]. The mean hospital costs for a patient with ARDS can easily cross the \$100000 mark before discharge; this figure does not include the cost of subsequent hospital visits for complications from ARDS or any outpatient services including physical therapy, in-home nursing, or pharmaceuticals^[1].

Compounding this significant cost is the broad spectrum of disability suffered by ARDS patients^[2-6]. These disabilities are both physical and psychological, and they can last for at least 5 years after the initial ARDS insult^[1-6]. Most importantly, the sum total of these disabilities ultimately leads to a quality of life for ARDS patients that is significantly reduced compared to both the general population and other patients without ARDS who survived a critical illness^[4,6].

It would appear that the most effective way to reduce the economic, physical, and psychological burden of ARDS would be *via* prevention of the disease process from ever occurring. Fulminant ARDS is resistant to all current treatment therapies, be they pharmacologic, mechanical, or a combination of the two^[7-9]. We believe, however, that employment of a protective ventilation

strategy early in the course of acute lung injury (ALI) or in patients at risk for ALI can block progression of this disease and prevent ARDS. Thus, our goal with this review is to detail the longstanding futility of treating established ARDS while examining the evidence that preemptive protective mechanical ventilation can reduce ARDS incidence. Furthermore, we will examine both the basic science and clinical studies demonstrating that airway pressure release ventilation (APRV) is the premier mode of ventilation for delivering an optimal protective breath with a specific mechanical breath profile (MBP) that prevents progression to ARDS for those patients at risk.

ONCE ESTABLISHED, THERE ARE NO EFFECTIVE TREATMENTS FOR ARDS

The landmark ARDSnet trial in 2000 marked the first time in decades that a significant, positive treatment effect was noted in patients with ALI and ARDS. In this trial, patients with ALI or ARDS were randomized to a "traditional", high-tidal volume (12 cc/kg) ventilation group or a low-tidal volume (6 cc/kg) ventilation group. The trial was terminated after enrollment of 861 patients, as mortality was significantly lower in the low-tidal volume ventilation group compared to the high-tidal volume ventilation group (31% vs 38.9%, $P = 0.007$)^[10].

Although this certainly was a step forward in ARDS treatment, the optimism of this study should be tempered with the following considerations. First, the patient population studied in this trial underrepresents certain patient groups at high risk for ARDS. In particular, trauma patients only accounted for 13% of the patients in the low-tidal volume group and 9% of the patients in the high-tidal volume group^[10]. Many trauma patients have well-known risk factors for ARDS development including: Injury severity scores > 16, thoracic injury or pulmonary contusions with abbreviated injury scale score of > 3, longbone and/or pelvic fractures, and transfusion of > 2 units of blood products within the first 24 h of injury^[11]. Second, although the results of the study were statistically significant, in-hospital mortality from ARDS remained quite high at 31%. Lastly, and perhaps most importantly, the overall mortality of ARDS worldwide has not substantially changed since the original ARDSnet study was published and remains static at approximately 40%^[12-14].

ARDS is a progressive disease, and there is a treatment window early in this progression that can be exploited

Why has ARDS remained a vexing clinical entity, highly resistant to all of our attempts at effective treatment? The answer to this question may lie in the way we view the disease process itself. For decades, ARDS has been viewed through the lens of a binary construct: the disease is either present or it is not. However, this

paradigm has started shifting in recent years, and this shift may hold the key to effectively combating ALI and ARDS. In particular, ARDS is now being viewed as a progressive disease with an early treatment window that can be targeted^[15-25]. To that end, ARDS investigators are turning their attention toward identifying patients at-risk for developing ALI/ARDS and investigating preventive treatment strategies.

Unfortunately, identifying at-risk patients for ALI has proven difficult. The complexity of this process is highlighted by a recent prospective observational study in three Spanish teaching hospitals. In this study, 815 patients were identified with at least one clinical insult, the most common being sepsis, pneumonia, and pancreatitis^[26]. However, the majority of patients in this study with risk factors for developing ALI/ARDS never developed lung injury at all^[26]. What is clear across multiple studies, however, is the fact that ALI is rarely present on initial presentation and develops over hours to days while patients are in the hospital^[27-30]. Thus, there is a window of opportunity early in the progression of developing lung injury that can be exploited with the following caveat: whatever intervention is used, it must be benign and without deleterious side effects so it can be applied to all patients at high-risk for developing lung injury.

What is clinically needed to make this a reality is a reliable risk factor model that accurately identifies, with a high sensitivity and specificity, those patients who will develop ALI/ARDS. One model that may prove helpful in this regard is the Lung Injury Prediction score (LIPS). The LIPS score is calculated based on a set of predisposing conditions and risk modifiers that are catalogued before the onset of ALI including the presence of shock, sepsis, pneumonia, acute abdomen, smoke inhalation, lung contusion, multiple fractures and acidosis^[31]. Benefits of the LIPS score include the use of clinical variables closely associated with lung injury that are easily available on hospital admission and are a usual part of the patient chart^[31]. In addition, this model identifies at-risk patients before they are admitted to the intensive care unit (ICU) or suffer a "second hit" that can hasten the progression to ALI^[31].

The only successful treatments thus far are those involving methods of protective mechanical ventilation instituted early in the disease course

Although a clinical predictive tool like the LIPS score may ultimately prove useful for identifying those patients at risk for developing ALI/ARDS, successfully preventing progression to lung injury has proven equally difficult to solve. To be sure, maximizing supportive care measures and following a standardized bundle of lung injury prevention measures is an important part of this process^[15,22]. However, there is no clearly defined treatment to date, either pharmacologic or mechanical, that definitively prevents lung injury.

With this in mind, there is an increasing body of

literature demonstrating the beneficial effects of early protective mechanical ventilation on halting the progression toward lung injury. For example, patients undergoing major abdominal, cardiac, or thoracic surgery represent a large patient population at risk for developing ALI^[32-34]. The method and technique of mechanical ventilation during surgery, therefore, represent a potential therapeutic intervention for preventing the development of ALI/ARDS in these at-risk surgery patients. One constant across these studies is the following: Protective ventilation strategies in the operating room, using low tidal volume ventilation strategies (6-8 cc/kg), lower the risk of lung injury and pulmonary complications as compared to conventional mechanical ventilation with higher tidal volumes^[34]. Employing selective positive end-expiratory pressure (PEEP) levels and using recruitment maneuvers in the operating room may provide further lung protection as well. For example, Futier *et al.*^[35] (add 35 here as well) demonstrated a 69% decrease in the number of patients requiring ventilatory support within the first seven days after major abdominal surgery. The ventilation strategy used in the operating room was low tidal volume ventilation (tidal volume 6-8 cc/kg) along with a PEEP of 6-8 cmH₂O and recruitment maneuvers every 30 min after intubation^[35].

It is important to remember that these preemptive strategies of protective mechanical ventilation are not restricted to surgical patients or those patients undergoing major abdominal or thoracic surgery. For those patients with critical illness who are in the ICU setting, protective mechanical ventilation strategies may be of utmost importance as well. Specifically, Determann *et al.*^[36] compared the effect of conventional tidal volume ventilation (10 cc/kg of predicted body weight) vs low tidal volume ventilation (6 cc/kg of predicted body weight) in critically ill patients without ALI at the onset of mechanical ventilation. This trial was stopped prematurely as the development of lung injury was significantly higher in the conventional tidal volume group^[36].

PREEMPTIVE, PROTECTIVE MECHANICAL VENTILATION INSTITUTED BEFORE THE DEVELOPMENT OF CLINICAL MANIFESTATIONS HAS THE POTENTIAL TO REDUCE THE INCIDENCE OF ARDS

It seems clear, therefore, that mechanical ventilation and the way it is implemented are key factors in determining whether or not patients at-risk for lung injury progress to ALI/ARDS. Thus, if used correctly, mechanical ventilation has the potential to dramatically decrease the incidence of ARDS. This brings up another important question: What method of mechanical ventilation provides the optimal protective breath-to-

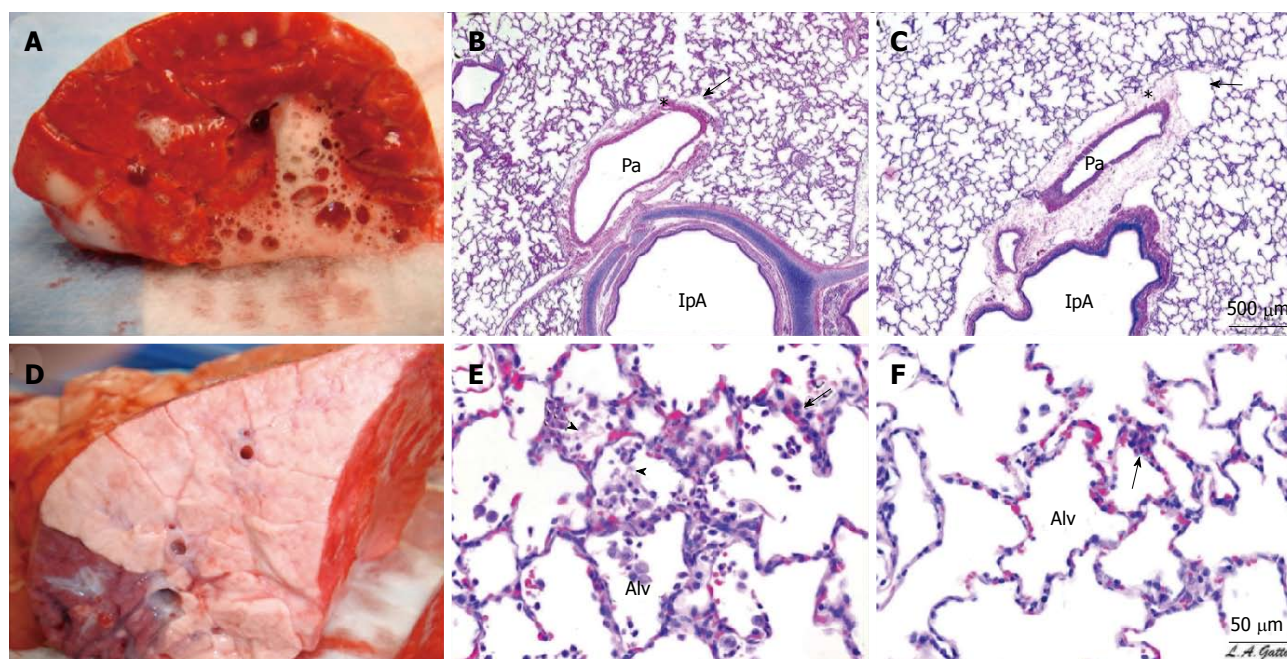


Figure 1 A gross and histological comparison between airway pressure release ventilation and nonpreventative ventilation. A and D: Gross pathology of the cut surface of the right lower lobe of the lung of representative animals from (A) the NPV and (D) the APRV group. The NPV shows severe inflammation, bronchial edema, and areas of hemorrhage. The APRV group demonstrates normal, pink, homogeneously inflated lungs with little injury on gross appearance; B, C, E, F: Histological comparison of four pigs, two NPV (B and E) and two APRV (C and F) at low (B and C) and high (E and F) magnification. The NPV animals show classic stigmata of ARDS including atelectasis, fibrinous exudates, intra-alveolar hemorrhage, congested capillaries, thickened alveolar walls, and leukocytic infiltrates. The APRV animals demonstrate preservation of nearly normal pulmonary architecture. Published with permission from Ref^[38]. APRV: Airway pressure release ventilation; NPV: Nonpreventative ventilation; ARDS: Acute respiratory distress syndrome; Alv: Alveoli.

breath strategy for preventing lung injury?

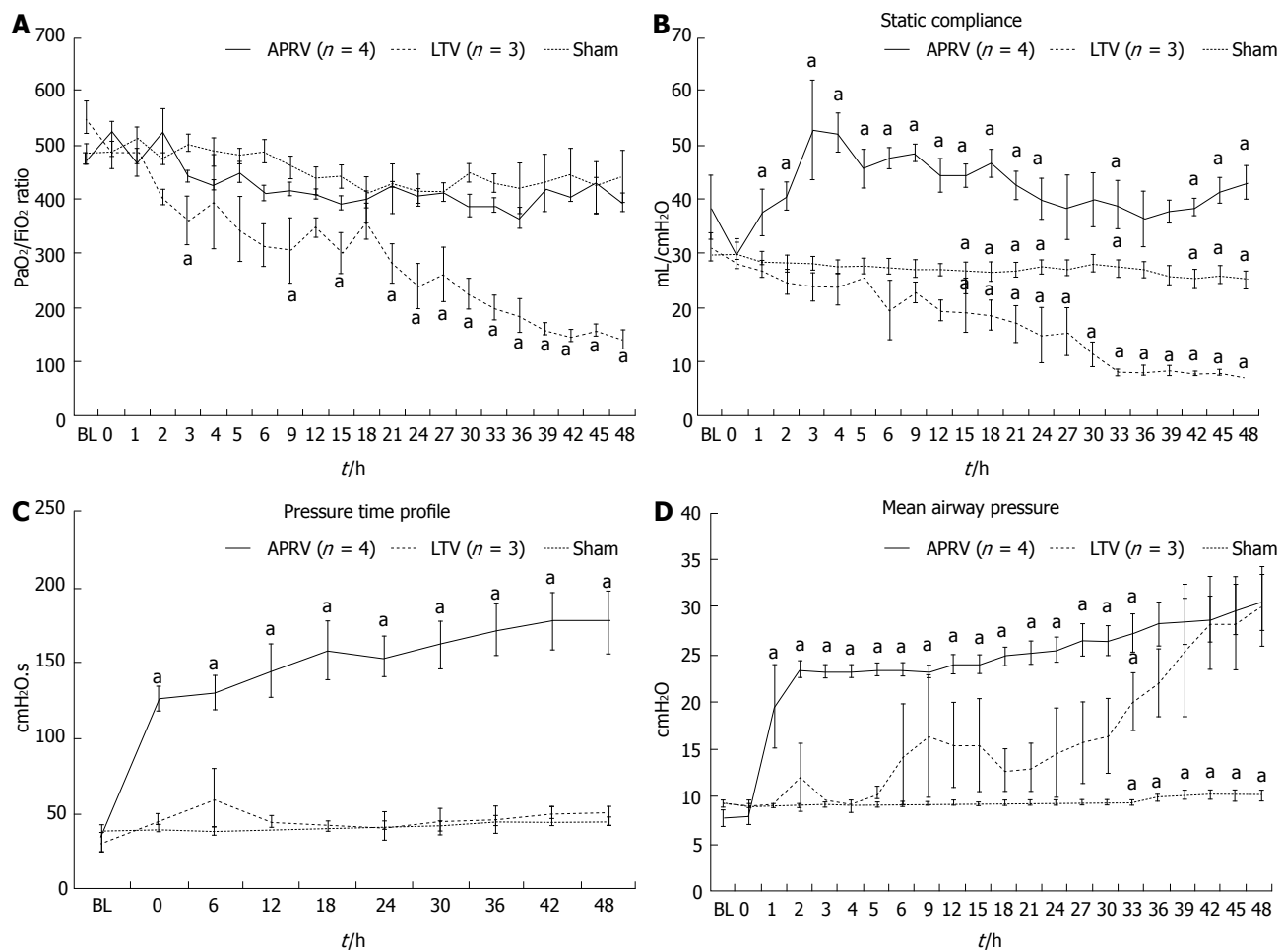
Both basic science and clinical studies suggest that APRV is the ideal ventilation strategy for delivering the optimal protective breath

Work in our laboratory over the past several years has led us to the conclusion that APRV, using a specific MBP, may be the best method of mechanical ventilation for providing the optimal protective breath and ultimately preventing the progression to ALI/ARDS. Our laboratory specializes in a porcine model of secondary ARDS caused by an intestinal ischemia/reperfusion injury and peritoneal sepsis^[37]. In 2012 we undertook a study to evaluate the effectiveness of APRV in preventing lung injury in this animal model. Yorkshire pigs were randomized to two mechanical ventilation groups: APRV (10–15 cc/kg tidal volume) and non-preventative ventilation (10 cc/kg tidal volume)^[38]. Despite similar markers of systemic inflammation, the APRV group did not develop ARDS and displayed decreased pulmonary inflammation with increased preservation of surfactant proteins^[38]. In addition, both the gross and histological appearance of the lungs demonstrated minimal lung injury in the APRV group, while the control group demonstrated significant lung injury and inflammation and progressed to fulminant ARDS (Figure 1)^[38].

The significant difference in lung injury between groups prompted us to further evaluate APRV and its effectiveness in preventing lung injury. As the ARDSnet

guidelines are the current standard of care for patients with ARDS, we decided to do a comparison study between APRV and the ARDSnet low tidal volume ventilation strategy with our porcine model of ARDS. As with our initial APRV experience, the APRV group in this study did not develop ARDS^[39]. In addition, the APRV group demonstrated preservation of lung E-cadherin and surfactant protein A, suggesting APRV can attenuate lung permeability, edema, and surfactant degradation^[39]. The ARDSnet ventilation group, on the other hand, developed significant lung injury and ARDS, based on pulmonary parameters along with both the gross and histological appearance of the lungs (Figure 2)^[39]. It is important to keep in mind that in this study, low tidal volume protective ventilation was applied after lung injury had developed, similar to current clinical practice. We are currently conducting a study in which low tidal volume ventilation and APRV are both applied preemptively in an attempt to identify the optimally protective breath to block progressive ALI.

The results of these two former studies were clearly dramatic and prompted us to evaluate the mechanical breath profile of APRV to further elucidate its potential for lung protection. To examine the mechanical breath profile of APRV, we used a rat model of lung injury induced by polysorbate lavage^[40]. Animals were randomized to one of two groups: A controlled mandatory ventilation group and an APRV group^[40]. In the controlled mandatory ventilation group, different levels of PEEP (5, 10, 16,



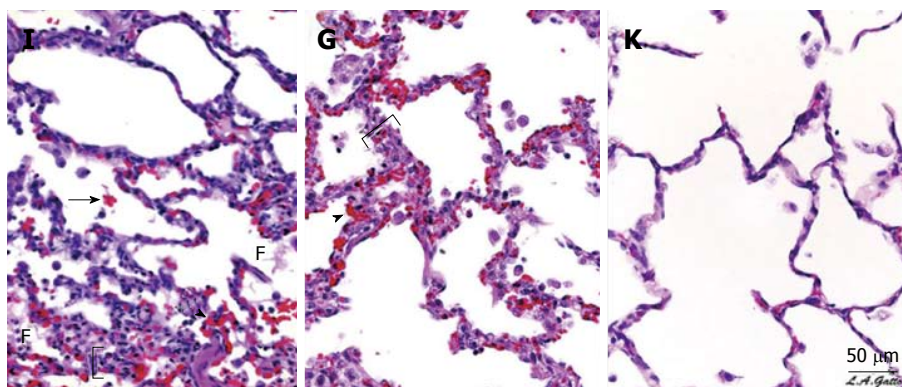


Figure 2 Pulmonary, gross and histologic representation between airway pressure release ventilation, LTV and sham animals. Top: Pulmonary data: A: P/F Ratio: APRV maintains a normal P/F ratio throughout the 48-h study with no significant difference from uninjured sham animals. Low tidal volume ventilation develops ALI (P/F G 300) by 19 h and ARDS (P/F G 250) by 33 h; ventilation strategy does not alter steady progression of increasing hypoxemia (P G 0.001 vs APRV and sham); B: Static compliance (Cstat): the APRV shows significant increase in Cstat after transition from volume- cycled mode to APRV (P G 0.001 vs sham and LTV ventilation). Sham maintained a normal Cstat level throughout the course of the study. In contrast, the LTV ventilation group developed progressive decreases in Cstat to less than 50% of BL; C: Mean airway pressure: sham group maintained normal Pmean throughout 48-h significantly different from both APRV and LTV ventilation (P G 0.001). Pmean 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 Pmean was identical from 39 to 48 h for LTV ventilation and APRV; D: Pressure-time profile (P/TP): APRV group had significantly higher P/TP than did both other groups as soon as the transition was made from volume-cycled ventilation (P G 0.001 vs sham and LTV ventilation). In the LTV ventilation group, P/TP remained low and did not change over the 48-h course of the study. Sham group animals also had low P/TP, which was not significantly different from the LTV ventilation group throughout the study; Middle: Gross appearance. Representative specimens of gross lungs and cut surface of gross lungs from LTV ventilation (F and H) and APRV (E and G) groups are shown. Bottom I-K: Histological appearance. Photomicrographs of representative lung sections of specimens from each treatment group at 40 × magnification are shown. 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 and no 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 aforementioned ischemic injury along with peritoneal sepsis 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 aforementioned ischemic injury and peritoneal sepsis. Specimen shows normal pulmonary architecture, alveoli are well expanded and thin walled, and there are no exudates. Republished with permission from Ref^[39]. APRV: Airway pressure release ventilation; PEEP: Positive end-expiratory pressure; ALI: Acute lung injury.

20, 24 cmH₂O) were tested; in the APRV group, the T_{low} was set to achieve ratios of the end-expiratory flow rate to peak expiratory flow rate (EEFR to PEFR) of 10%, 25%, 50%, and 75% - the smaller this ratio is, the more time the lung is exposed to low pressure during the release phase^[40]. A PEEP of 16 cmH₂O in the controlled mandatory ventilation group and an EEFR to PEFR ratio of 75% in the APRV group both minimized alveolar microstrain (*i.e.*, the dynamic change in alveolar size during tidal ventilation) in this study. However, alveolar recruitment was greater in the APRV group with an EEFR to PEFR ratio of 75% (Figure 3)^[40].

From a purely clinical perspective, APRV has demonstrated tremendous potential in preventing ALI/ARDS as well. In particular, Dr. Nader Habashi's clinical work with APRV has demonstrated the benefits of utilizing APRV in trauma patients at risk for developing lung injury. In a systematic review published in 2013, outcomes for patients with early application of APRV at the R Adams Cowley Shock Trauma Center in Maryland from 2002 to 2005 were compared to patient populations at other trauma centers to evaluate rates of ARDS development and in-hospital mortality^[11]. Relevant studies were identified through PubMed and MEDLINE searches from 1995 to 2012 using the keywords trauma and acute respiratory distress syndrome or ARDS and trauma and acute lung injury or ALI^[11]. Sixteen studies met the inclusion criteria of being a prospective or retrospective

observational studies or cohort studies enrolling 100 or more adult trauma patients with reported ALI/ARDS incidence and in-hospital mortality data^[11]. Although the patients at the Shock Trauma Center were in the upper quartile for their injury severity scores, both the incidence of ARDS (1.3%) and the in-hospital mortality (3.9%) were the lowest for this group of patients in whom early APRV was applied (Figure 4)^[11]. Although a prospective randomized controlled trial is needed to confirm these results, this systematic review provided convincing evidence that APRV may be precisely the protective mechanical ventilation mode that may be applied prophylactically to all patients as soon as they are intubated to prevent the progression to lung injury or ARDS. In addition, since APRV is a comfortable mode of mechanical ventilation with minimal negative side effects in patients with normal lungs, it can be applied prophylactically to all patients as soon as they are intubated (unpublished observations).

CONCLUSION

ARDS remains a troubling clinical entity with an unacceptably high mortality. Treating fulminant ARDS has proven futile for decades; there are currently no effective pharmacologic or mechanical ventilation strategies for curing ARDS, and treatment is relegated to aggressive supportive care measures. Thus, the key to

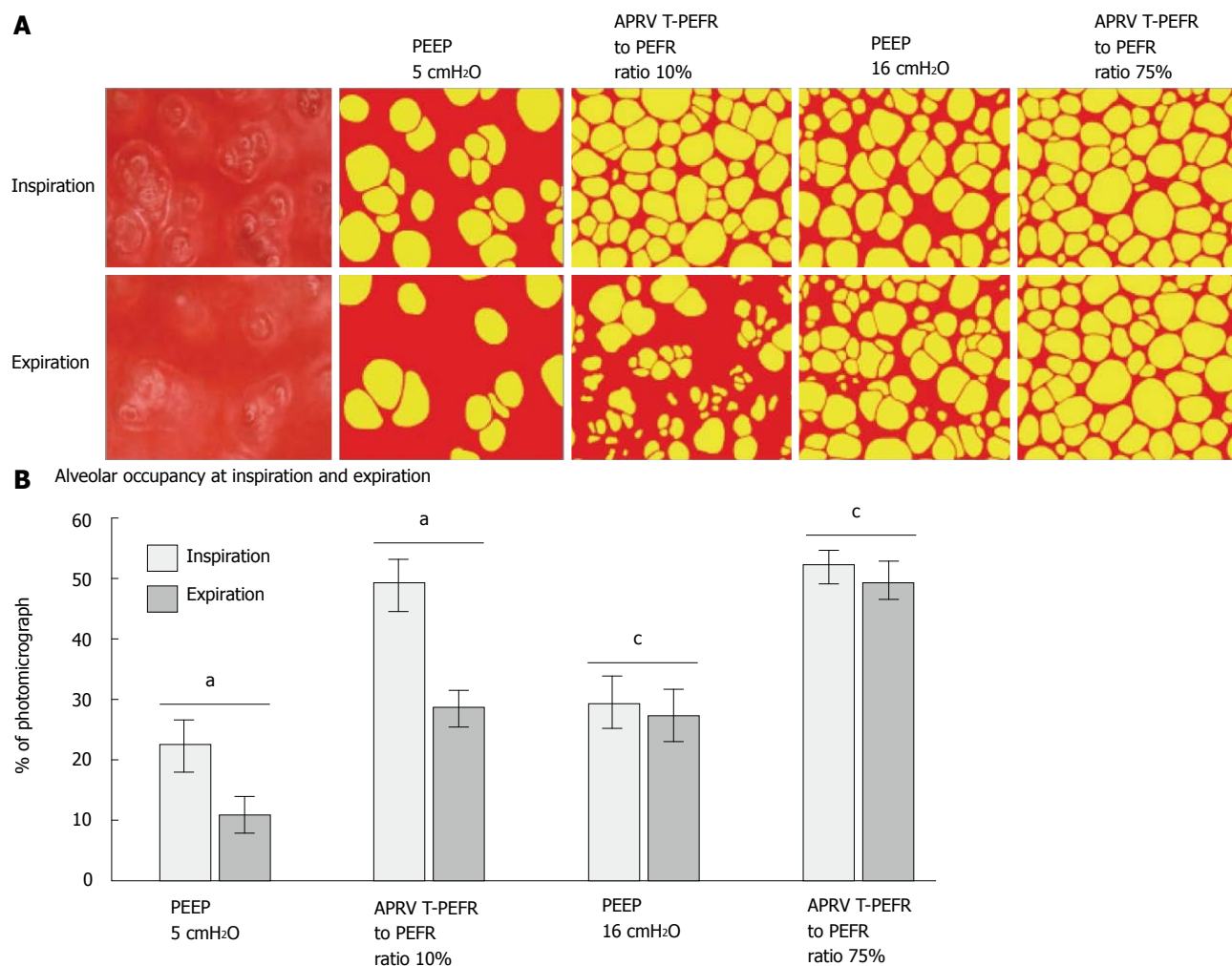


Figure 3 *In vivo* photomicrographs and percentage of alveolar air space occupancy at inspiration and expiration. A: *In vivo* photomicrographs at inspiration and expiration prior to coloring and for positive end-expiratory pressure (PEEP) of 5 cm H₂O, airway pressure release ventilation (APRV) ratio of termination of peak expiratory flow rate (T-PEFR) to peak expiratory flow rate (PEFR) of 10%, PEEP of 16 cm H₂O, and APRV T-PEFR to PEFR ratio of 75% (original magnification $\times 10$). Alveoli are colored in yellow; nonalveolar tissue, red; B: Alveolar air space occupancy is expressed as a percentage of the photomicrograph containing inflated alveoli (yellow in A) at inspiration and expiration. Data are shown as the mean; error bars indicate standard error of the mean. ^a $P < 0.05$ for PEEP of 5 cmH₂O vs APRV T-PEFR to PEFR ratio of 10%; ^c $P < 0.05$ for PEEP of 16 cmH₂O vs APRV T-PEFR to PEFR ratio of 75%. Republished with permission from Ref^[40].

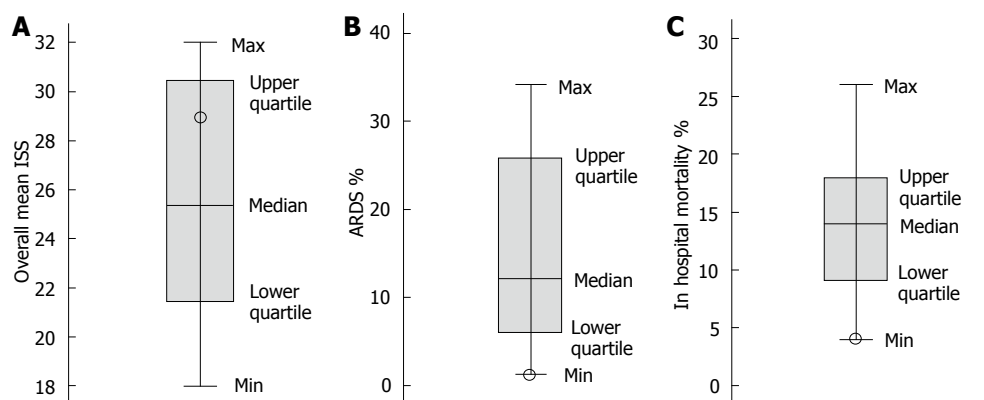


Figure 4 Boxplots for mean individual severity score (A), acute respiratory distress syndrome % (B), and in-hospital mortality % (C). Mean ISS shows the range and distribution of ISS scores reported by 16 authors; 50% of them reported ISS between 30.5 and 23.2, with the middle score of 25.4 (median). The mean ISS of 29 for the preemptive APRV group belonged to the upper quartile of the boxplot. ARDS incidence % shows the range and distribution of scores reported by 16 authors; 50% of them reported ARDS incidence between 22.5% and 6%, with the middle score of 11.95% (median). The incidence of ARDS in the preemptive APRV group represented the minimum score at 1.3%. Mortality % shows the range and distribution of mortality scores reported by 16 authors; 50% of them reported mortality between 18.2% and 9.2%, with the middle score of 13.9% (median). The preemptive APRV group scored the minimum mortality rate of 3.9%. Republished with permission from Ref^[11]. ARDS: Acute respiratory distress syndrome; APRV: Airway pressure release ventilation; ISS: Individual severity score.

treating this highly morbid disease lies with preventing the disease from ever occurring. Indeed protective mechanical ventilation strategies are being employed in the operating room and in the intensive care unit before the development of lung injury. Moreover, data from both our laboratory and the clinical realm indicate that appropriately setting APRV generates a protective MBP that may be the most viable and accessible method of preventing lung injury and the subsequent progression to ARDS.

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