Literature List
APRV
2016
## APRV Literature List

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**Categories**

- **CLIN** = Clinical Study
- **REV** = Review
- **CASE** = Case study
- **ANM** = Animal Study
Clinical research about airway pressure release ventilation for moderate to severe acute respiratory distress syndrome.

Rationale and Objectives: To evaluate clinical effects of airway pressure release ventilation (APRV) in patients suffering from moderate to severe acute respiratory distress syndrome (ARDS). A patient presented with significant high aminotransferase levels due to the first human *R. aeschlimannii* infection ever detected in Italy. The hypothesis of rickettsiosis was made on the basis of a comprehensive medical history and was confirmed by serological tests. Molecular analyses made on a sample of hepatic tissue revealed the presence of a rickettsia species never found before in human liver.

Methods and Measurements: From August 2012 to August 2014, fifty-two cases with moderate to severe ARDS were randomly divided into two groups. The first group (APRV) used the airway pressure release ventilation method; the second group (SIMV) was ventilated using synchronized intermittent mandatory ventilation mode and positive end expiratory pressure (PEEP). Changes in oxygenation index, respiratory mechanics, extravascular lung water, functional residual capacity change and hemodynamics were recorded in both groups after mechanical ventilation. TNF-α and IL-10 levels in alveolar lavage were also measured. Acute physiology and chronic health evaluation (APACHE) II and Murray scores were evaluated. Pneumothorax and mediastinal emphysema during ventilation were also recorded. The probability of survival, the duration of ICU stay, days without organ failure and days without sedation were compared.

Main Results: Conditions in APRV were improved significantly. Oxygenation index was increased, airway peak pressure (Ppeak) was reduced, and the lung dynamic compliance improved, extravascular lung water was relieved, functional residual capacity increased and Murray score was improved. In APRV group ventilation central venous pressure (CVP) and systemic circulation resistance index (SVRI) were reduced, but cardiac index (CI) increased, and at the same time lactate and oxygen saturation of central venous blood (ScvO2) were improved. Free sedatives days were significantly reduced in APRV group while days without mechanical ventilation were increased and days in ICU were shortened significantly. TNF-α and IL-10 concentrations in the alveolar lavage, probability of survival and days without organ failure were similar in both groups.

Conclusion: In patients suffering from moderate to severe ARDS, application of APRV improved lung function and hemodynamics. It also reduced the need for sedatives and the duration of mechanical ventilation as well as days in ICU.
**Introduction:** Postoperative pulmonary edema is a fatal adverse event after a cardiac surgery. We here report successful management using airway pressure release ventilation (APRV) for severe hypoxia with pulmonary edema after a cardiac surgery.

**Presentation of Case:** A 58-year-old man underwent an uneventful mitral valve repair. Immediately afterwards, the patient became agitated and made vigorous inspiratory efforts. His oxygen saturation dropped to 90%. Coarse inspiratory rhonchi were heard on auscultation, and copious, pink, frothy sputum was obtained with suctioning. Initial chest radiograph showed right-sided patchy opacities and interstitial infiltrates. A transthoracic echocardiogram demonstrated normal cardiac function. With worsening respiratory failure on mechanical ventilation, APRV was attempted. His condition and blood gas was subsequently improved. Over the following 3 days, the patient experienced an uneventful postoperative course and was discharged to home on postoperative day 14.

**Discussion:** Extracorporeal membrane oxygenation (ECMO) is the most effective for severe hypoxia with pulmonary edema; however, ECMO is associated with hemorrhage and infectious complications. Alternatively, APRV was required for the successful management for severe hypoxia with pulmonary edema.

**Conclusions:** APRV could be effective for severe hypoxia with pulmonary edema after a cardiac surgery.

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**Background:** The optimal mode of ventilation in acute respiratory distress syndrome (ARDS) remains uncertain. Airway pressure release ventilation (APRV) is a recognized treatment for mechanically-ventilated patients with severe hypoxemia. However, contemporary data on its role as a rescue modality in ARDS is lacking. The goal of this study was to describe the clinical and physiological effects of APRV in patients with established ARDS.

**Methods:** This retrospective observational study was performed in a 23-bed adult intensive care unit in a tertiary extracorporeal membrane oxygenation (ECMO) referral center. Patients with ARDS based on Berlin criteria were included through a prospectively-collected APRV database. Patients receiving APRV for less than six hours were excluded.

**Measurements and Results:** Fifty patients fulfilled the eligibility criteria. Prior to APRV initiation, median Murray Lung Injury Score was 3.5 (interquartile range (IQR) 2.5-3.9) and PaO2/FiO2 was 99mmHg (IQR 73-137). PaO2/FiO2 significantly improved within twenty-four hours post-APRV initiation (ANOVA F(1, 27)=24.34, P<.005). Two patients (4%) required intercostal catheter insertion for barotrauma. Only one patient (2%) required ECMO after APRV initiation, despite a majority (68%) fulfilling previously established criteria for ECMO at baseline. Hospital mortality rate was 38%.

**Conclusions:** In patients with ARDS-related refractory hypoxemia treated with APRV, an early and sustained improvement in oxygenation, low incidence of clinically significant barotrauma and progression to ECMO was observed. The safety and efficacy of APRV requires further consideration.

Rationale and Objectives: To evaluate intensive care unit (ICU) incidence and outcome of ARDS and to assess clinician recognition, ventilation management, and use of adjuncts—for example prone positioning—in routine clinical practice for patients fulfilling the ARDS Berlin Definition.

Design, Settings, and Participants: The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) was an international, multicenter, prospective cohort study of patients undergoing invasive or noninvasive ventilation, conducted during 4 consecutive weeks in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across 5 continents.

Main Outcomes and Measures: The primary outcome was ICU incidence of ARDS. Secondary outcomes included assessment of clinician recognition of ARDS, the application of ventilatory management, the use of adjunctive interventions in routine clinical practice, and clinical outcomes from ARDS.

Conclusions and Relevance: Among ICUs in 50 countries, the period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be underrecognized and undertreated and associated with a high mortality rate. These findings indicate the potential for improvement in the management of patients with ARDS.


Abstract: Airway pressure release ventilation (APRV) was first described in 1987 and defined as continuous positive airway pressure (CPAP) with a brief release while allowing the patient to spontaneously breathe throughout the respiratory cycle. The current understanding of the optimal strategy to minimize ventilator-induced lung injury is to "open the lung and keep it open". APRV should be ideal for this strategy with the prolonged CPAP duration recruiting the lung and the minimal release duration preventing lung collapse. However, APRV is inconsistently defined with significant variation in the settings used in experimental studies and in clinical practice. The goal of this review was to analyze the published literature and determine APRV efficacy as a lung-protective strategy. We reviewed all original articles in which the authors stated that APRV was used. The primary analysis was to correlate APRV settings with physiologic and clinical outcomes. Results showed that there was tremendous variation in settings that were all defined as APRV, particularly CPAP and release phase duration and the parameters used to guide these settings. Thus, it was impossible to assess efficacy of a single strategy since almost none of the APRV settings were identical. Therefore, we divided all APRV studies divided into two basic categories: (1) fixed-setting APRV (F-APRV) in which the release phase is set and left constant; and (2) personalized-APRV (P-APRV) in which the release phase is set based on changes in lung mechanics using the slope of the expiratory flow curve. Results showed that in no study was there a statistically significant worse outcome with APRV, regardless of the settings (F-APRV or P-APRV). Multiple studies demonstrated that P-APRV stabilizes alveoli and reduces the incidence of acute respiratory distress syndrome (ARDS) in clinically relevant animal models and in trauma patients. In conclusion, over the 30 years since the mode's inception there have been no strict criteria in defining a mechanical breath as being APRV. P-APRV has shown great promise as a highly lung-protective ventilation strategy.

Conclusions: P-APRV allows for a personalized control of lung stability on a breath-to-breath basis that is not possible with other modes of ventilation. P-APRV is an adaptive, flow directed, duration dependent ventilation strategy that adapts the setting to each patient regardless of their lung pathophysiology. This personalized, adaptive mechanical breath may prove more efficacious at treating and preventing ARDS than the current standard of care.
**REV**  
Sadowitz B. et al.  
*Preemptive mechanical ventilation can block progressive acute lung injury.*  

**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.

**Conclusions:** 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 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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**ANM**  
Arrindell EL Jr. et al.  
*Lung volume recruitment in a preterm pig model of lung immaturity.*  

**Abstract:** A translational preterm pig model analogous to infants born at 28 wk of gestation revealed that continuous positive airway pressure results in limited lung recruitment but does not prevent respiratory distress syndrome, whereas assist-control + volume guarantee (AC+VG) ventilation improves recruitment but can cause injury, highlighting the need for improved ventilation strategies.

We determined whether airway pressure release ventilation (APRV) can be used to recruit the immature lungs of preterm pigs without injury. Spontaneously breathing pigs delivered at 89% of term (model for 28-wk infants) were randomized to 24 h of APRV (n = 9) vs. AC+VG with a tidal volume of 5 ml/kg (n = 10). Control pigs (n = 36) were provided with supplemental oxygen by an open mask. Nutrition and fluid support was provided throughout the 24-h period. All pigs supported with APRV and AC+VG survived 24 h, compared with 62% of control pigs. APRV resulted in improved lung volume recruitment compared with AC+VG based on radiographs, lower Pco2 levels (44 ± 2.9 vs. 53 ± 2.7 mmHg, P = 0.009) and lower inspired oxygen fraction requirements (36 ± 6 vs. 44 ± 11%, P < 0.001), and higher oxygenation index (5.1 ± 1.5 vs. 2.9 ± 1.1, P = 0.001). There were no differences between APRV and AC+VG pigs for heart rate, ratio of wet to dry lung mass, pro-inflammatory cytokines, or histopathological markers of lung injury.

Lung protective ventilation with APRV improved recruitment of alveoli of preterm lungs, enhanced development and maintenance of functional residual capacity without injury, and improved clinical outcomes relative to AC+VG. Long-term consequences of lung volume recruitment by using APRV should be evaluated.

Abstract: The standard treatment for acute respiratory distress syndrome (ARDS) is supportive in the form of low tidal volume ventilation applied after significant lung injury has already developed. Nevertheless, ARDS mortality remains unacceptably high (> 40%). Indeed, once ARDS is established it becomes refractory to treatment, and therefore avoidance is key. However, preventive techniques and therapeutics to reduce the incidence of ARDS in patients at high-risk have not been validated clinically. This review discusses the current data suggesting that preemptive application of the properly adjusted mechanical breath can block progressive acute lung injury and significantly reduce the occurrence of ARDS.

Conclusions: To our knowledge we are the only group that is conducting experiments investigating the optimal mechanical breath necessary to reduce the incidence of ARDS in animal models of secondary ARDS (i.e., hemorrhagic shock and sepsis). Our work clearly shows that preemptive APRV using the settings developed by our group will reduce ARDS incidence in a rat trauma/hemorrhagic shock model and in a high fidelity, clinically applicable porcine ARDS model [27,35]. Because our animal model so closely represents the clinical progression from injury (i.e., hemorrhagic shock and sepsis) to established-ARDS, it is considered “good evidence” that any treatment shown efficacious in this model will be successful in a clinical trial [57]. In addition, we have shown that part of the protective mechanism of preemptive APRV is minimizing μ-strain in the alveolus and alveolar ducts, highlighting the importance of understanding the impact of any given PTI on the microenvironment [16,17]. The meta-analysis on severely injured trauma patients showed an order of magnitude reduction in ARDS incidence and mortality with preemptive application of APRV strongly suggesting that a prospective clinical trial is warranted. In conclusion, the optimal method of protecting a patients lung with established ARDS, as described by Dr. Lachmann[60] in 1992, is to “Open the Lung and Keep it Open” and likewise, the goal of preemptive mechanical ventilation to reduce ARDS incidence is to “Never let the Lung Collapse”.


Background: Adult respiratory distress syndrome is often refractory to treatment and develops after entering the health care system. This suggests an opportunity to prevent this syndrome before it develops. The objective of this study was to demonstrate that early application of airway pressure release ventilation in high-risk trauma patients reduces hospital mortality as compared with similarly injured patients on conventional ventilation.

Methods: Systematic review of observational data in patients who received conventional ventilation in other trauma centers were compared with patients treated with early airway pressure release ventilation in our trauma center. Relevant studies were identified in a PubMed and MEDLINE search from 1995 to 2012 and included prospective and retrospective observational and cohort studies enrolling 100 or more adult trauma patients with reported adult respiratory distress syndrome incidence and mortality data.

Measurements and Main Results: Early airway pressure release ventilation as compared with the other trauma centers represented lower mean adult respiratory distress syndrome incidence (14.0% vs. 1.3%) and in-hospital mortality (14.1% vs. 3.9%).

Conclusions: These data suggest that early airway pressure release ventilation may prevent progression of acute lung injury in high-risk trauma patients, reducing trauma-related adult respiratory distress syndrome mortality.
Abstract: Acute respiratory distress syndrome (ARDS) affects 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 (30Y40 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 (PaO2/FiO2 ratio) (APRV: baseline = 471 T 16; 48 h = 392 T 8; vs. LTV ventilation: baseline = 551 T 28; 48 h = 138 T 88; P G 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 G 0.05). Inflammatory cytokine 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 G 0.05). Airway pressure release ventilation had significantly lower lung edema (wet-dry weight) than LTV ventilation (P G 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.

Conclusions: The current study demonstrates that systemic inflammatory response syndrome Y induced ARDS can be prevented with high airway P/TP 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/TP. Future studies are needed to elucidate the mechanical ventilation strategies that will offer the appropriate P/TP for prevention of ARDS.

Purpose of review: Patients who experience severe trauma are at increased risk for the development of acute lung injury and acute respiratory distress syndrome. The management strategies used to treat respiratory failure in this patient population should be comprehensive. Current trends in the management of acute lung injury and acute respiratory distress syndrome consist of maintaining acceptable gas exchange while limiting ventilator-associated lung injury.

Recent findings: Currently, two distinct forms of ventilator-associated lung injury are recognized to produce alveolar stress failure and have been termed low-volume lung injury (intratidal alveolar recruitment and de-recruitment) and high-volume lung injury (alveolar stretch and over distension). Pathologically, alveolar stress failure from low- and high-volume ventilation can produce lung injury in animal models and is termed ventilator-induced lung injury. The management goal in acute lung injury and acute respiratory distress syndrome challenges clinicians to achieve the optimal balance that both limits the forms of alveolar stress failure and maintains effective gas exchange. The integration of new ventilator modes that include the augmentation of spontaneous breathing during mechanical ventilation may be beneficial and may improve the ability to attain these goals.

Main Results: Airway pressure release ventilation is a mode of mechanical ventilation that maintains lung volume to limit intra tidal recruitment /de-recruitment and improves gas exchange while limiting over distension. Clinical and experimental data demonstrate improvements in arterial oxygenation, ventilation-perfusion matching (less shunt and dead space ventilation), cardiac output, oxygen delivery, and lower airway pressures during airway pressure release ventilation. Mechanical ventilation with airway pressure release ventilation permits spontaneous breathing throughout the entire respiratory cycle, improves patient comfort, reduces the use of sedation, and may reduce ventilator days.