Mechanical Ventilation as a Therapeutic Tool to Reduce ARDS Incidence

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Trauma, hemorrhagic shock, or sepsis can incite systemic inflammatory response syndrome, which can result in early acute lung injury (EALI). As EALI advances, improperly set mechanical ventilation (MV) can amplify early injury into a secondary ventilator-induced lung injury that invariably develops into overt ARDS. Once established, ARDS is refractory to most therapeutic strategies, which have not been able to lower ARDS mortality below the current unacceptably high 40%. Low tidal volume ventilation is one of the few treatments shown to have a moderate positive impact on ARDS survival, presumably by reducing ventilator-induced lung injury. Thus, there is a compelling case to be made that the focus of ARDS management should switch from treatment once this syndrome has become established to the application of preventative measures while patients are still in the EALI stage. Indeed, studies have shown that ARDS incidence is markedly reduced when conventional MV is applied preemptively using a combination of low tidal volume and positive end-expiratory pressure in both patients in the ICU and in surgical patients at high risk for developing ARDS. Furthermore, there is evidence from animal models and high-risk trauma patients that superior prevention of ARDS can be achieved using preemptive airway pressure release ventilation with a very brief duration of pressure release. Preventing rather than treating ARDS may be the way forward in dealing with this recalcitrant condition and would represent a paradigm shift in the way that MV is currently practiced.

ABBREVIATIONS: ALI = acute lung injury; APRV = airway pressure release ventilation; CMV = conventional mechanical ventilation; LVt = low tidal volume; MBP = mechanical breath profile; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; PTI = pressure-time integral; RACE = repetitive alveolar collapse and expansion; RM = recruitment maneuver; SIRS = systemic inflammatory response syndrome; THigh = duration at high pressure; TLow = duration at low pressure; VILI = ventilator-induced lung injury; VT = tidal volume; μ-strain = microstrain

ARDS as defined by the Berlin definition is a serious clinical syndrome with 190,000 cases and 74,000 deaths/y in the United States and is refractory to treatment once established. Work has shown that secondary ARDS develops slowly over a period of many hours or days due to excessive inflammation known as the systemic
inflammatory response syndrome (SIRS). This initial stage of ARDS is known as early acute lung injury and may exist even before the patient is intubated. However, subsequent mechanical ventilation (MV) with inappropriate ventilator settings can cause a secondary ventilator-induced lung injury (VILI) that, when combined with SIRS, acts to advance lung injury toward ARDS (Fig 1). The fact that lung injury develops slowly potentially gives caregivers time to block progression of acute lung injury (ALI) in its early stages, thus reducing the chances of it developing into full-blown ARDS. Nevertheless, current treatments for ARDS, which have proven largely disappointing, are supportive in nature and are applied only once lung injury has become well established. Preventing ARDS from developing would, thus, represent a paradigm shift in the way that medicine is practiced. Accordingly, in this article, we focus on the evidence suggesting that the incidence of ARDS can be significantly reduced if appropriately set protective MV is administered to at-risk patients well before any overt clinical signs of ALI are present.

Current Treatments for Established ARDS
To date, all attempts at pharmacologic prevention of ARDS have been ineffective, so supportive treatment of the established syndrome has been seen as the only clinical option. Unfortunately, success at treating established ARDS has been generally dismal. Preventing ARDS from developing would, thus, represent a paradigm shift in the way that medicine is practiced. Accordingly, in this article, we focus on the evidence suggesting that the incidence of ARDS can be significantly reduced if appropriately set protective MV is administered to at-risk patients well before any overt clinical signs of ALI are present.

**Figure 1 – Sequence of events from initial injury to the development of ARDS. Trauma, hemorrhagic shock, or sepsis results in SIRS, causing EALI. As the disease progresses the patient is intubated and if placed on mechanical ventilation with nonprotective breath, would greatly exacerbate lung injury causing a secondary VILI. Thus, SIRS and VILI often work together to drive acute lung injury, which if unblocked will cause ARDS. EALI = early acute lung injury; SIRS = systemic inflammatory response syndrome; T/H/S = trauma/hemorrhagic shock/sepsis; VILI = ventilator-induced lung injury.**

Indeed, the only therapeutic strategies that have been shown to significantly reduce mortality are low tidal volume (LVR) MV, prone positioning, and neuromuscular blockade. Even so, the mortality from ARDS remains unacceptably high at > 40%. To make matters worse, patients who survive ARDS often develop chronic lung and neurologic dysfunction. Although MV is a lifesaving therapy, when applied inappropriately it will increase the incidence and mortality of ARDS by causing a secondary pathology known as VILI (Fig 1). The inflammatory mediators produced by VILI can then injure distant organs, leading to the development of multiorgan dysfunction syndrome that is frequently the ultimate cause of death in patients with ARDS. Since treatment of established ARDS is very difficult, and the only strategy demonstrated to reduce ARDS mortality involves protective MV, the question arises: Would it be possible to use the ventilator as a therapeutic device in at-risk patients to prevent ARDS in the same preemptive manner in which drugs are used to prevent other diseases?

**Clinical Studies Demonstrating ARDS Incidence Can Be Reduced**

**Patients in the ICU**

Clinical meta-analyses have shown that early application of protective ventilation in both high-risk patients...
in the ICU and surgical patients can reduce the incidence of ARDS. Multiple studies in patients in the ICU have shown that preemptive protective MV can reduce ARDS incidence. This has been shown with conventional MV (CMV) using a combination of LVT, positive end-expiratory pressure (PEEP), and recruitment maneuvers (RMs), including a preemptive randomized clinical trial demonstrating that ARDS incidence can be reduced in high-risk patients in the ICU. ARDS occurrence in trauma patients has also been lessened with early application of airway pressure release ventilation (APRV).

Patients Undergoing Major Surgery
Reduced ARDS incidence has also been demonstrated in a group of patients with normal lungs who underwent extensive abdominal surgery and, thus, were at high risk for developing ARDS. The group ventilated with high tidal volume (Vt) (12 mL/kg) plus zero PEEP developed significantly more complications, including pneumonia, sepsis, septic shock, acute respiratory failure, and death, than did the group ventilated with LVT (6 mL/kg) plus 6 to 8 cm H2O PEEP combined with RMs.

These studies demonstrate clinical proof of concept that either early CMV using a combination of LVT, PEEP, and RMs or early APRV can reduce ARDS incidence. Nevertheless, the optimally protective mechanical breath for reducing ARDS incidence remains unknown. Indeed, LVT with low PEEP has been shown to actually increase mortality in surgical patients at high risk for ARDS.

Minimizing a Ventilation Injury Cost Function
MV can be delivered in a near limitless variety of configurations according to the value of the various parameters that define its characteristics. The parameters most commonly manipulated in patients with ARDS include Vt (the current goal being 6 mL/kg ideal body weight), plateau pressure (the desired maximum being typically 30 cm H2O), and PEEP (the goal being to reduce derecruitment at the end of expiration). It seems natural to postulate that there must exist an optimal combination of mechanical breath parameters (ie, airway pressures, volumes, flows, rates, and their respective durations throughout each breath), which we have termed the mechanical breath profile (MBP), that would minimize progressive lung injury. We hypothesize that the optimal mechanical breath can be defined with respect to some function of the MBP parameters that quantifies the injury potential of a given breath. One simple possibility for such a function is the pressure-time integral (PTI) defined as:

\[ PTI = \int_0^{T_{\text{tot}}} P(t)dt \]

where \( T_{\text{tot}} \) is the duration of the entire breath during inspiration and expiration. The PTI provides a general

Figure 2 – Pathologic tetrad of acute lung injury (ALI) culminating in ARDS: increased permeability, surfactant deactivation, alveolar edema, and RACE all contribute to progressive ALI. The diagram depicts an air sac consisting of several individual alveoli. Each alveolus is lined with a liquid hypo-hase (blue) to which pulmonary surfactant (black dots with tails) is adhered. Increased vascular permeability: Follow injury (trauma, hemorrhage, or sepsis) pulmonary capillaries (red circles) begin to leak (black arrows) edema fluid (tan) into the alveolar lumen resulting in mild to moderate hypoxia. Surfactant deactivation: When hypoxia become sufficiently severe, the patient would be placed on mechanical ventilation and, if nonprotective, would work synergistically with the alveolar edema to further damage the surfactant film (surfactant sloughed into the alveolar lumen) and increase alveolar flooding (tan). Alveolar edema: Over time, nonprotective ventilation plus increased capillary permeability will completely destroy the surfactant film resulting in total alveolar flooding (tan). RACE: At a certain level of surfactant disruption, alveoli become unstable, collapsing during expiration and reexpanding during inspiration. RACE significantly exacerbates lung damage by contributing to surfactant deactivation and to dynamic microstrain-induced increases in permeability (small black arrows) significantly exacerbating edema formation (solid red arrow). In addition, high alveolar surface tension secondary to surfactant deactivation alone causes edema and combined with increased permeability would greatly accelerate alveolar flooding (dotted red arrow). Once a portion of lung develops these key pathologic changes they establish a positive feedback loop exacerbating and accelerating progressive lung damage and if this sequence is unbroken will drive the lung into ARDS. RACE = repetitive alveolar collapse and expansion.
measure of both the degree of stress applied to the lungs and the duration over which the stress is applied during each breath. Even though PTI does not take into account the variable alveolar surface area being exposed to the ventilator pressure, it adds the important component of the duration over which the pressure is applied during a breath.

Our group has shown that the incidence of ARDS in both animals and patients is significantly reduced with the APRV mode of ventilation by extending the duration of the end-inspiratory plateau and by minimizing the duration of the pressure release, which greatly increases the PTI. In other words, protection against the development of ALI is conferred by much more than simply the values of $V_t$, plateau pressure, and PEEP that are used; the durations over which these parameters are applied also determine whether lung injury will progress. Mode acronyms such as APRV or CMV, thus, do not encompass all the features of a mechanical breath that determine its injurious or protective impact because the temporal details of the mechanical breath can be critical to this impact. As a means of understanding the details of the MBP on the development of VILI, we have recently developed a computational model of a lung that is mechanically ventilated that simulates the tissue stresses and strains generated by various modes of MV. By fitting this model to dynamic airway pressure and lung volume data measured in rats we demonstrated that the MBP associated with appropriately set APRV is superior to protective CMV at recruiting the lung, maintaining homogeneous ventilation, and preventing repetitive alveolar collapse and expansion (RACE) during exhalation.

The Optimally Protective Breath

Mechanisms of VILI

There are several plausible mechanisms that could underlie the protective benefits of APRV relative to the pathogenesis of ARDS (Fig 2). In secondary ARDS, trauma, hemorrhagic shock, or sepsis can incite SIRS and cause an increase in capillary permeability that ultimately results in surfactant deactivation that, together with alveolar flooding, alters alveolar mechanics and, in particular, can lead to RACE. Lung tissue injury caused by RACE can be exacerbated by the development of

Figure 3 – Lung histology at inspiration and expiration to determine the microstrain ($\mu$-strain) caused by mechanical ventilation on the terminal airway (individual alveoli and conducting airways: respiratory bronchiole, alveolar duct, and alveolar sac) (hematoxylin and eosin). We defined alveoli as individual structures not connecting adjacent alveoli (lilac), the conducting airways were defined as airways extending from the alveolar duct proximally connecting multiple alveoli (green) and the remaining structures including interstitium, blood vessels, and lymphatics (magenta). The control group was uninjured, showing normal changes in the terminal airway during ventilation. Note the relative small size of the conducting airways (green) and the open and well-inflated alveoli (lilac). In the remaining groups, ARDS was caused by Tween instillation. Two settings for the time set at duration at low pressure (TLow) using APRV and two PEEP levels with a tidal volume ($V_t$) set at 6 mL/kg were studied with conventional mechanical ventilation (CMV). In the APRV group with improperly set TLow at 10% (ie, 90% of the lung volume was exhaled), there is a dramatic overdistension of the conducting airways (green) and increased dynamic $\mu$-strain with ventilation. CMV with PEEP5 again showed a large dynamic $\mu$-strain on conducting airway with more alveolar collapse (lilac). PEEP16 improved alveolar inflation (lilac) and reduced but did not eliminate conducting

airway overdistension. APRV with properly set TLow at 75% (25% of the lung volume was exhaled) was the closest to control with reduced conducting airway size and $\mu$-strain during ventilation and open, well-inflated alveoli (lilac). PEEP = positive end-expiratory pressure. (Reprinted with permission from Kollisch-Singule et al. 44)
stress concentrations between air-filled alveoli and alveoli that are either collapsed or edema filled. Thus, heterogeneous ventilation, which creates stress concentrators, can also cause excessive strain on alveolar walls and combined with RACE drive progressive lung injury.

LVT, PEEP, and RM"s

The factors that constitute an optimally protective breath for reducing ARDS incidence are currently unknown. Nevertheless, it is safe to assume that these factors include both reducing stress concentrations by maximizing the homogeneity of ventilation and minimizing RACE. Indeed, clinical studies have shown that early application of LVT ventilation with various levels of PEEP significantly reduces the incidence of ARDS, presumably by reducing tissue overdistension in areas of stress concentration and by preventing RACE.

However, a recent study demonstrated that LVT alone applied to the normal lung during surgery in patients at high risk for developing ARDS was associated with increased mortality and that LVT with high but not low PEEP increased postoperative pulmonary complications. In contrast, Futier et al showed that the combination of LVT, PEEP, and RM"s significantly reduced acute respiratory failure and mortality in patients undergoing major surgery. These studies suggest that the optimally protective CMV breath will involve some appropriate combination of VT, PEEP, and RM"s.

Airway Pressure Release Ventilation

Currently, APRV is thought of as a “rescue mode” to be used only in patients with ARDS who are refractory to any other ventilator strategy. Theoretically, APRV should minimize the primary physiologic mechanisms of VILI by maintaining an “open lung,” resulting in homogeneous lung ventilation. In addition, APRV gradually inflates or “nudges” the lung open, which minimizes the tissue damage associated with aggressive recruitment maneuvers. Given that APRV is superior to CMV for the most severely injured lungs (ie, rescue mode) and that the MBP of APRV is theoretically ideal for minimizing ventilator injury cost function, we chose to study the efficacy of this mechanical breath at reducing ARDS incidence. We hypothesized that the mechanism by which APRV protected the lung was reduced alveolar microstrain (µ-strain). We found that appropriately set APRV with an extended duration at plateau pressure (duration at high pressure [THigh]) and a very brief duration at pressure release (duration at low pressure [TLow]) is essential to minimizing µ-strain in the alveoli and the alveolar ducts (Figs 3, 4).

µ-Strain is defined as the change in size and shape of the alveoli and alveolar ducts in response to a given stress. In this case the stress applied is airway pressure. Both THigh and TLow can be adjusted dynamically and specifically to target an individual’s pathophysiology via closed-loop feedback and together achieve lung protection via two mechanisms: (1) An extended THigh progressively recruits and stabilizes alveoli, which results in homogenous ventilation and elimination of stress.

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**Figure 4** - A. In vivo photomicrographs at inspiration and end expiration of subpleural alveoli (far left) following surfactant deactivation with Tween. To assess the µ-strain, individual alveoli were color-coded in yellow with nonalveolar tissue in red and the alveolar area calculated using computer image analysis at inspiration and expiration. Two settings for TLow using APRV and two PEEP levels with a VT of 6 mL/kg were studied with CMV. In the APRV group with improperly set TLow at 5% (ie, 90% of the lung volume was exhaled), there was large µ-strain on the alveoli as they recruited and collapsed with each breath. There was also significant µ-strain with CMV PEEP5 with less recruitment during inspiration. CMV PEEP16 reduced the µ-strain but failed to recruit all alveolar whereas APRV with properly set TLow at 75% (25% of the lung volume was exhaled) both recruited and stabilized (ie, minimal µ-strain) alveoli (original magnification x10). B. Percentage of alveolar air space occupancy as determined by computer image analysis at inspiration and expiration. Alveolar air space occupancy is expressed as a percentage (% of the photomicrograph containing inflated alveoli) at inspiration (light gray) and expiration (dark gray). The larger the difference in airspace occupancy between inspiration and expiration, the larger the alveolar µ-strain. Although the VT delivered to the lung with APRV 75% is approximately 12 mL/kg, the alveolar VT (ie, the volume change of the individual alveoli with each breath) is very small as measured by the standard measured µ-strain. Thus, it is not the size of the VT being delivered to the lung but the size of the change in individual alveolar VT that is critical in preventing ventilator damage to the pulmonary parenchyma. Data mean ± SEM; a = P < .05 for PEEP is APRV 10% vs PEEP5 75% 5; b = P < .05 for PEEP16 vs APRV 75%. PEFR = peak expiratory flow rate; T-PEFR = termination of peak expiratory flow rate. See Figure 3 legend for expansion of other abbreviations. (Reprinted with permission from Kollisch-Singule et al.)
concentrations, and (2) a very brief TLow does not allow enough time for alveolar collapse during exhalation, which minimizes alveolar \(\mu\)-strain.

We have shown significant reductions in ARDS development with the preemptive application of APRV in a rat model of VILI\(^{34}\) and in a rat hemorrhagic shock ARDS model.\(^{32}\) In addition, we have demonstrated near-complete lung protection in a high-fidelity clinically applicable porcine ARDS model,\(^{31,33}\) which was associated with high PTI (Fig 5B). These studies thus confirm, perhaps somewhat counterintuitively, that increasing PTI is actually protective, at least in the context of APRV, and reduces both alveolar and alveolar duct \(\mu\)-strain (Figs 3, 4).\(^{30,44}\) The result is reduced development of ARDS as measured by the \(Pao_2/Fio_2\) ratio (Fig 5A) and gross pathology (Fig 6).\(^{31}\)

APRV has also been shown to be effective at reducing ARDS incidence in patients in the ICU. We conducted a systematic review in high-risk trauma patients and demonstrated that preemptive MV with APRV blocks the progression of ALI (Fig 7).\(^{24}\) This analysis compared APRV applied preemptively with 15 studies using standard-of-care ventilation applied only after acute lung injury has developed. The patients in the APRV group had a greater mean Injury Severity Score and a lung injury prediction score of \(>\) 8 (indicating a \(>\) 30% risk

![Figure 5](http://journal.publications.chestnet.org/)

Figure 5 – A, B, Pressure/time profile (PTI) (A) and \(Pao_2/Fio_2\) ratio (B) over time (48 h) following peritoneal sepsis and gut ischemia/reperfusion (PS + I/R)-induced ARDS in anesthetized pigs. Two treatments groups were tested: (1) Preemptive APRV and (2) ARDSnet LTV applied after the animal desaturates similar to how it is currently used clinically. A sham group with surgery but without PS + I/R was also tested. APRV resulted in a significant increase in PTI that was associated with dramatic protection of lung function measured as a \(Pao_2/Fio_2\) ratio. Lung protection was so complete that the \(Pao_2/Fio_2\) ratio values in the APRV group were similar to the sham group, whereas the LTV group developed severe respiratory failure (ie, ARDS) with a mean \(Pao_2/Fio_2\) ratio well below 200. Data mean \(\pm SEM\). \(\ast\) = \(P < .05\) vs both groups. LTV = low tidal volume ventilation. See Figure 3 legend for expansion of other abbreviations. (Adapted with permission from Roy et al.\(^{31}\))
of developing ARDS), but a very low incidence of ARDS (1.3%) and in-hospital mortality (3.6%) (Fig 7). Thus, preemptive APRV can reduce ARDS incidence in high-risk patients similar to, or even better than, preemptive LTV ventilation with PEEP and RMs. 20,25,26,29,39,40,46

Mechanisms of APRV Protection
There are three possible mechanisms by which the extended PTI produced by APRV reduces ARDS incidence: (1) preserving the integrity of the blood-gas barrier and thereby reducing pulmonary edema formation (Fig 2, increased permeability), 47 thus blocking the sequence of events leading to surfactant deactivation, alveolar collapse, and subsequent alveolar instability (Fig 2, RACE); (2) minimizing alveolar collapse (Fig 3, RACE) with the very brief expiration that occurs during TLow, which limits the time for alveolar derecruitment to occur before the lung is reinflated (Figs 3, 4) 30,44; and (3) maximally recruiting the lung with the extended inspiratory duration THigh, which maintains distal airspace patency and creates a homogeneously ventilated lung so as to minimize stress concentrations in the parenchyma (Fig 4). 30 These factors have all been linked to lung protection. 47 For example, Protti et al 47 have shown that high static strain near total lung capacity causes minimal lung injury, whereas dynamic strain at the same lung volume results in severe lung damage with pulmonary edema. 47 Minimizing dynamic strain has also been shown to preserve surfactant function, which would further reduce edema and stabilize alveoli.
In a recent study, Amato et al\(^9\) reveal that the protective mechanical breath is complex and not just a function of \(V_t\).\(^4\) In a retrospective meta-analysis of ARDSnet data, the authors demonstrated that lower driving pressure (ie, \(V_t/\text{respiratory compliance}\)) was strongly associated with increased survival. We also found evidence that \(V_t\) is not the exclusive means of protecting the lung. Our preemptive application of APRV in a clinically applicable porcine sepsis plus ischemia/reperfusion ARDS model was highly lung protective, despite a \(V_t\) of 12 mL/kg, while a control group using a \(V_t\) strategy (ie, 6 mL/kg) resulted in less protection.\(^31\) Although driving pressure per se was not measured in this study, all published data suggest that the components of driving pressures in APRV would be in the normal range, since the respiratory compliance remained near baseline values throughout the entire experiment. The APRV groups in these studies demonstrate preservation of normal preinjury lung compliance, while accommodating 12 mL/kg \(V_t\) throughout the 48-h experiment.\(^31,33\) There is reason to expect that future studies will identify other parameters of the mechanical breath with a substantial protective role.

**Summary and Conclusions**

Although we believe that APRV is highly effective in treating established ARDS or as a “rescue mode” in patients with such serious lung disease that standard MV is ineffective, the exciting novel concept is the ability to significantly reduce ARDS incidence in patients at high risk. No controlled randomized phase 3 trials have been conducted using any preemptive ventilation strategy, however, this may provide future direction. In small clinical studies it has been shown that properly adjusted CMV can reduce the incidence of ARDS in both patients in the ICU\(^20,25,26,39,40,46\) and in patients undergoing major surgery.\(^26,28,29\) However the ideal combination of \(V_t\), PEEP, and RMs has yet to be determined. Our group has shown that preemptive APRV may be superior to CMV at reducing the incidence of ARDS in both animal\(^31-34\) and human\(^34\) studies. Ventilatory mode acronyms such as CMV, \(V_t\), or APRV do not express all the features of a mechanical breath that determine its injurious or protective impact, without also defining temporal details of the mechanical breath which are critical to clinical outcome. The essential protective mechanism of APRV appears to be related to never letting the lung collapse, which eliminates mechanical damage to the pulmonary tissue caused by stress concentrations arising from alveolar heterogeneity and by dynamic alveolar \(\mu\)-strain with alveolar collapse and reopening. These studies suggest that the ventilator can be used preemptively as a therapeutic tool to prevent ALI progression, thereby significantly reducing ARDS incidence. This echoes the comments of Villar and Slutsky\(^50\) that “ARDS is no longer a syndrome that must be treated, but is a syndrome that should be prevented.”

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**References**


