Preemptive mechanical ventilation based on dynamic physiology in the alveolar microenvironment: Novel considerations of time-dependent properties of the respiratory system

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MECHANICAL VENTILATION AND LUNG INJURY

Identification of acute respiratory distress syndrome (ARDS) as a syndrome and the possibility that a mechanical ventilator setting could reduce ARDS mortality led to a large number of physiologic studies investigating the optimal ventilator setting for the ARDS patient.[1,2] What these studies found was that mechanical ventilation can significantly reduce ARDS morbidity and mortality when set properly, but can exacerbate lung damage by causing a secondary ventilator-induced lung injury (VILI) when set improperly.[1] Dreyfuss and Saumon[3] described the transpulmonary pressure (Ptp) gradient across the alveolus caused alveolar strain (i.e., alveolar volume change) as the major mechanism of VILI rather than just the magnitude of airway pressure (volutrauma vs. barotrauma). Further work from Gattinoni et al.[4,5] in ARDS patients demonstrated that dependent lung areas demonstrate preferential loss of lung volume, whereas nondependent lung areas have relatively normal ventilation. The term "baby lung" was coined for this remaining normal residual lung tissue, and it was postulated that overdistension would occur in the more compliant "baby lung" if a normal size tidal volume (Vt) were delivered to the ARDS patient. The mechanism of atelectrauma is excessive shear-stress as the collapsed alveolar walls pull apart during inflation and stress-concentration, which occurs between patent and totally collapsed or edema-filled alveoli.[6]

These physiologic and clinical studies suggested that VILI might be minimized if (*a*) Ptp was reduced in order to lower alveolar strain; (*b*) Vt and plateau pressure (Pplat) were lowered to prevent lung overdistension; and (*c*) adequate positive end-expiratory pressure (PEEP) was used to minimize atelectrauma.[7,8] Using these data as proof of concept, several small clinical trials were conducted, with some studies showing no improvement in lung protection with low Vt (LVt) strategy using 6 mL/kg,[9–11] whereas other studies suggested that LVt was lung protective.[12–14] In 2000, the ARDS Network (ARDSnet) published a large randomized controlled trial (RCT) demonstrating that LVt significantly reduced mortality in ARDS patients (from 39% to 31%). Since this study, LVt has remained the current standard-of-care protective ventilation strategy for patients with established ARDS.[15]

STAGNATION IN REDUCING ARDS MORTALITY

Understanding the pathophysiology associated with ARDS and how it can be exacerbated with mechanical ventilation led to the development of protective ventilation strategies.[15] These strategies combined with better hemodynamic and fluid resuscitation management significantly reduced mortality from 1967 when ARDS was first identified until present.[16] However, there has not been a further significant reduction in ARDS-related mortality over the last 17 years.[16–21] The lack of reduced mortality suggests that the pathophysiology caused by mechanical ventilation in alveoli and alveolar ducts (the microenvironment) is not fully understood.[22] Without this knowledge, it is impossible deduce the optimal combination of macrocomponents including Vt, Ptp, Pplat, PEEP, set on the ventilator needed to block mechanical damage to the microenvironment of the pulmonary parenchyma.

There remain significant gaps in our knowledge of the precise characterization of VILI-induced lung tissue damage including (1) the significance of each mechanical breath profile (MB_P) component (i.e., all airway pressures, volumes, flows, rates, and the duration that they are applied during both inspiration and expiration) on lung injury or protection,[23] and (2) the potential synergy among MB_P components and other factors, such as increased inflammation (biotrauma) secondary to the mechanical injury (volutrauma and atelectrauma), which injure or protect the lung. Since the lung changes volume as a dynamic viscoelastic system,[6] the macrocomponents of the mechanical breath that are dialed into the ventilator must account for the dynamic nature of lung physiology, with adjustments being continually made directed by changes in this physiology. Without the ability to continually adjust components of the MB_P with evolving lung pathophysiology (as the lung gets either better or worse), it will be impossible to protect alveoli and alveolar ducts in the microenvironment, which is necessary to reduce VILI and decrease ARDS mortality.[23–26]

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Genetic predisposition is another risk factor for developing ARDS. It has been shown that patients with ARDS can be separated into two phenotypes, and mortality for each is different. In addition, four biomarkers have been identified that can predict these two phenotypes.[27] A new hypothesis on the inflammatory mechanism of ARDS is purinergic signaling (i.e., extracellular release of ATP following cellular damage), which may be the molecular focal point driving progressive acute lung injury (ALI).[28] A recent publication has demonstrated that the Time-Controlled Adaptive Ventilation (TCAV) protocol significantly reduced lung Diffuse Alveolar Damage score, expression of biomarkers, and extracellular matrix homeostasis in both primary and secondary ARDS rat models.[29]

PATHOPHYSIOLOGY OF ARDS

Because the physiologic state of the lung is critical to understanding the impact of the mechanical breath on lung pathophysiology, the key pathologic components associated with ALI must be understood. There are four well-accepted components of ARDS pathology that result in significant changes in the anatomical, mechanical, and functional aspects the lung. These include (1) increased vascular permeability, (2) alveolar flooding with edema, (4) loss of pulmonary surfactant function that causes alveolar collapse (atelectasis), and (4) alveolar instability altering dynamic alveolar ventilation and ultimately resulting in repetitive alveolar collapse and expansion (RACE) (Fig. 1).[30] This tetrad of pathology is interdependent in that increased vascular permeability leads to alveolar flooding, causing surfactant deactivation, which impacts alveolar mechanics. Surfactant can be deactivated by pulmonary edema, which in turn reduces surfactant production by type II cells. Because these pathologies result in a heterogeneous lung injury, it produces a wide range of both alveolar opening and collapse time constants, making protective mechanical ventilation of the heterogeneous lung without causing VILI very difficult.

The microenvironment of the pulmonary parenchyma is complex, with alveoli sharing walls in a honeycomb fashion forming an interdependent structure.[31] This interdependence greatly adds to the structural integrity of each individual alveolus, but this structural integrity is lost with heterogeneous alveolar instability or collapse. There is a current misconception that alveoli change volume in a linear elastic fashion much like a balloon, whereas alveoli actually change volume nonlinearly, being a part of the viscoelastic lung system.[32–34]

The importance of this knowledge cannot be overestimated when designing the optimally protective mechanical breath. Viscoelastic behavior dictates that there will be a fast and slow component to both alveolar recruitment and collapse. Thus, a percentage of alveoli will recruit rapidly with the applied force (i.e., Vt), but many others will take a much longer time to open at the same airway pressure. Conversely, when the force is removed, a percentage of alveoli will collapse very rapidly, while others will take a much longer time to collapse at the same airway pressure. Therefore, it is not only the airway pressure and flow that are important but also the duration during which they are applied. An extended time at inspiration would gradually recruit alveoli, opening the lung, while minimal time at expiration would prevent alveolar collapse, stabilizing the lung.[6] When combined with the knowledge that both alveolar opening[35] and closing[23,36] time constants are dramatically modified in ALI, the importance of inspiratory and expiratory time in the protective mechanical breath becomes apparent.

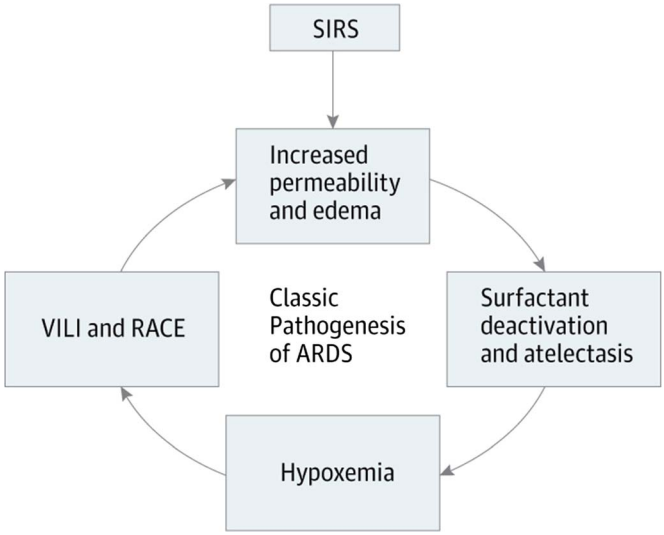

Figure 1. The tetrad of ARDS pathophysiology. A major insult (severe sepsis, hemorrhagic shock, trauma, burns, etc.) causes a systemic inflammatory response syndrome (SIRS), which initially increases pulmonary vascular permeability. Increased permeability results in alveolar flooding with edema fluid, which is known to deactivate surfactant function. The combination of edema and atelectasis caused by surfactant dysfunction results in hypoxemia. Functional surfactant is necessary for normal alveolar mechanics so that loss of function results in significant alveolar collapse and instability, with alveoli collapsing and reopening with each breath. Each of these pathologic components contributes to the development of ARDS individually and synergistically.[30]

Clinically measured lung dynamics in the heterogeneously injured lung are the summed effect of all lung areas, normal, unstable, and atelectatic. This brings into question if we can continually adjust the MB_P "on the fly" by measuring changes in the macro-components, which are a summation of the changes in a heterogeneous micro-environment. However, with our preemptive ventilation strategy of "never give the lung a chance to collapse," the micro-environment becomes identical (i.e., all alveoli inflated), and the clinically measured macrodynamics now represent the entire lung.

LVT AS A PROTECTIVE VENTILATION STRATEGY

Assuming that VILI is a core pathology driving progressive ALI and increasing ARDS mortality, why has the current LVt standard-of-care ventilation strategy been ineffective at reducing ARDS mortality even further for nearly two decades?[16–21] From a physiologic perspective, the ARDSnet protocol may not be an effective strategy to block components of the ARDS tetrad (Fig. 1) for a number of reasons:

First, the strategy is not preemptive but rather is typically applied after the patient has significant lung injury with a

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suggested target P/F ratio of less than 300 or arterial oxygen saturation of less than 88% for treatment.[15] Thus, lung disease has already progressed to the point of heterogeneous collapse with stress risers and unstable alveoli, both key VILI mechanisms. The ARDSnet protocol was designed to protect the remaining healthy "baby lung," rather than to "open the lung and keep it open," which is the key pathology associated with ARDS that makes the lung so vulnerable to a secondary VILI.

Second, the one-size-fits-all concept that 6 mL/kg Vt is optimal for all patients is not likely true. Indeed, Deans et al.[37] found there were 2,587 patients who met enrollment criteria in the ARDSnet study but were not enrolled in the study for various technical reasons. These patients were subjected to routine treatment including ventilation with Vt 10 mL/kg. Thus, 10 mL/kg Vt was the actual standard of care for patients, not 12 mL/kg that was used in the ARDSnet study.[15] Thus, the observational cohort receiving 10 mL/kg Vt would be a more accurate group to compare against the 6 mL/kg LVt treatment group. This standard-of-care group (Vt 10 mL/kg) and LVt strategy (6 mL/kg) were found to have identical mortality rates. They also showed that the patients with the more compliant lungs at the time of randomization did poorly with LVt, whereas if the compliance was worse, the patients did better with LVt. Thus, a one-size-fits-all approach to mechanical ventilation, standardizing every patient to 6 mL/kg, may not be ideal and suggests that Vt should be directed by changes in lung physiology such as compliance. The LVt strategy can even be harmful if used in patients with more compliant lungs, as evident by increased mortality.[38]

Third, changes in PEEP and Vt are set by changes in blood oxygenation on a sliding scale.[15] Oxygenation is not a reliable marker of altered alveolar mechanics (i.e., the dynamic change in alveolar size and shape during tidal ventilation) in the acutely injured lung.[39–42] This fact may help to explain the reason why in the ARDSnet study oxygenation improved in the 12 mL/kg group but mortality was increased.[15] It has been shown that a better strategy would be to personalize the size of the Vt to the physiologic parameters of the patient's lung, using parameters such as compliance and driving pressure.[37,43,44]

Fourth, LVt strategy for ARDS causes loss of alveolar surface area, resulting in hypercapnia and acidosis, and the impact on patient outcome of this acidosis is unknown. Although studies have suggested that hypercapnia may be lung protective reducing mortality,[45–47] it has also been suggested that hypercapnia is harmful and increases mortality.[9] A recent clinical study showed that hypercapnic acidosis during the first 24 hours in the intensive care unit (ICU) is associated with increased mortality[48]; thus, the acidosis associated with LVt may be one explanation for the sustained high mortality of ARDS.

With this understanding, we should consider reevaluating the current standard-of-care protective ventilation strategy (i.e., ARDSnet protocol) in which the focus is largely on limiting VILI in the remaining normal lung tissue while the acutely injured lung tissue remains collapsed.[15] The novel strategy must prevent the lung from every collapsing or rapidly (within hours) reopen the lung as soon as the patient is intubated. This would eliminate all of the pathologic problems associated with ventilating a heterogeneously collapsed lung. Preemptive ventilation would be a paradigm shift in protective ventilation from treating the acutely injured lung, to preventing ARDS from ever developing.

A recent review discussed the physiology and methods used to personalize PEEP to lung pathology.[32] The goal is to develop a feedback loop using changes in lung physiology to maintain an open and stable lung (Fig. 2). A novel feedback loop approach used to stabilize the lung is known as time-controlled PEEP (TC-PEEP).[49] With this method, the clinician does not directly set PEEP on the ventilator but rather sets an expiratory time to be sufficiently brief not to allow the lung to fully empty, thereby maintaining lung volume and an end-expiratory pressure (TC-PEEP). An advantage of this method is that the expiratory duration may be targeted to be less than the collapse time constant of the alveoli such that, in addition to the end-expiratory pressure, the alveolus does not have time to collapse. Thus, TC-PEEP stabilizes the lung using two mechanisms: the brief expiratory duration does not allow sufficient *time* for alveoli collapse while maintaining a PEEP.[30] Time-controlled PEEP is one of the components of the TCAV protocol that will be discussed in detail below (Fig. 3).[49,50]

With TC-PEEP resulting in a high degree of alveolar stability, how is CO_2 effectively cleared? During the extended time at inspiration in the TCAV protocol, CO_2 diffuses from the alveoli into the large airways and trachea. During the very brief expiratory release phase, a large volume of CO_2 is removed because of the high concentration in the large airways. Thus, the TCAV protocol stabilizes alveoli using TC-PEEP without causing problems in ventilation.

Although several clinical trials have shown that open lung strategies in patients with ARDS did not reduce mortality,[51–53] more recent evidence suggests a survival benefit.[54,55] Thus, it

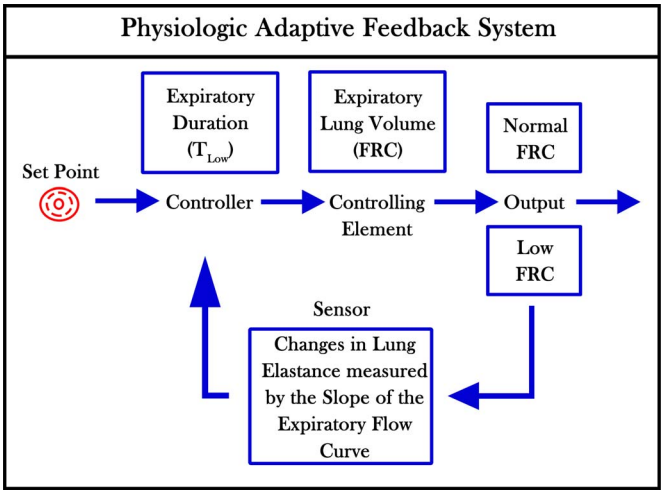

Figure 2. A schematic of a physiologic adaptive feedback system used to maintain lung functional residual capacity (FRC) during expiration. The *set point* is the physiologic FRC in normal humans. The *controller* in this feedback system is the expiratory duration and impacts the *controlling element,* which is the volume of FRC. The *output* is either a lung with *normal* or *low FRC* volume. Low FRC will be detected as a change in *lung elastance,* which is measured by the *slope of the expiratory flow curve* (Fig. 1B). A steeper slope will trigger the *controller* to shorten the expiratory duration that will cause an increase in FRC.[32]

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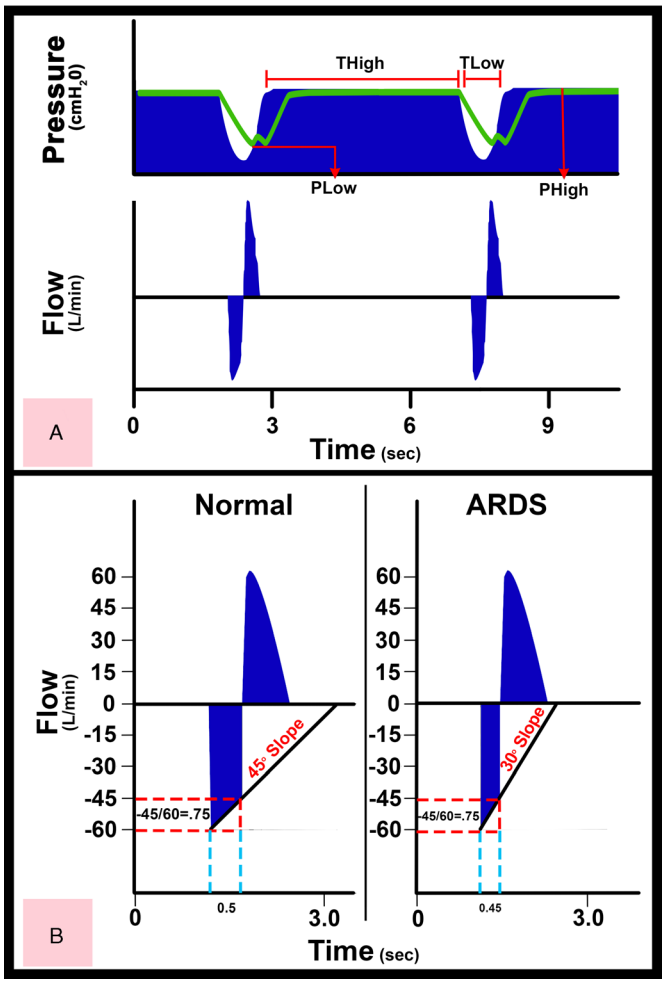

Figure 3. Representative airway pressure and flow curves with APRV set by the TCAV protocol (spontaneous breaths are not shown). (*A*) There is an extended time at inspiration (T_{High}) and minimal time at expiration (T_{Low}). The high pressure (P_{High}) combined with the T_{High} determines the magnitude and duration of the CPAP. The end-expiratory airway pressure (T_{Low}) is always set to 0 cmH_2O, which allows unrestricted expiratory flow for accurate assessment of lung respiratory system elastance determined by the expiratory flow curve. However, P_{Low} never reaches 0 cmH_2O because T_{Low} is set sufficiently short to maintain both lung volume and pressure at end expiration. The green line is the measured tracheal pressure, which is the actual end-expiratory pressure seen by the alveolus. We have found that if expiratory duration is set properly the end-expiratory pressure (the actual P_{Low}) is approximately one-half of the P_{High}. (*B*) Using the slope of the expiratory flow curve (SEFC) to set the expiratory duration necessary to stabilize the lung. The SEFC of the normal lung is approximately 45°, which decreases to 30° in ARDS. Expiratory duration is calculated by terminating expiration at 75% of the peak expiratory flow (–60 L/min), which in this example would be at –45 L/min. Note that using this same ratio in both normal and ARDS lungs the expiratory duration is shorter (0.45 vs. 0.5 second) in the ARDS lung because of the steeper SEFC.[49]

appears that ventilation strategies that "open the lung and keep it open" may result in a mortality reduction, a hypothesis that is supported by the physiologic understanding of VILI.[56–61] However, a recent clinical trial has shown that a recruitment maneuver (RM) combined with titrated PEEP actually increased mortality as compared with the low PEEP group.[62] The inconsistency in reducing mortality using conventional volume-assist control ventilation with RM and titrated PEEP to "open the lung and keep it open" suggests that there is a problem with the ventilation strategy. It is possible that the treatment is applied too late in disease progression to be of much benefit. In an editorial on this article, Sahetya and Brower[63] suggest that because there are now four failed clinical trials using RM plus PEEP novel protective ventilation strategies need to be tested. Data from our laboratory suggest that the TCAV protocol may be the novel, more effective lung-protective strategy that Drs Sahetya and Brower suggest.

APPLY PROTECTIVE VENTILATION PREEMPTIVELY

Although LVt and LVt combined with open lung strategies have reduced mortality from the time ARDS was first identified in 1967,[15] there has not been a continual reduction in mortality over the past two decades.[16–21] The recent failed clinical trial showing that an open lung approach actually increased mortality suggests that once ARDS is established even an optimally protective ventilation strategy may not be effective at reducing mortality.[62] Thus, a better strategy would be to "never give the lung a chance to collapse" in patients ventilated with normal lungs but at high risk of developing ARDS. This would shift the paradigm from treating established ARDS to preventing ARDS before it developed.

Many recent studies have shown the benefit of applying preemptive protective ventilation strategies on patients in the early stages of ALI, before clinical symptoms develop.[64–68] It is now known that ARDS is not a binary construct (i.e., either it is present or it is not) but rather is progressive, evolving through multiple stages.[69] Thus, early intervention with lung-protective ventilation would block progressive lung damage, just as it is better to implement prophylaxis to minimize the chance for a deep vein thrombosis rather than to treat the deep vein thrombosis or pulmonary embolism after it has formed. Indeed, preemptive protective mechanical ventilation has been continually applied earlier and has now been shown to be effective when initiated early in the operating[70] and emergency rooms.[71]

DETERMINING THE OPTIMAL PREEMPTIVE PROTECTIVE VENTILATION

To our knowledge, all studies performed with preemptive mechanical ventilation have used the same protective ventilation strategy that is currently used in established ARDS: LVt, PEEP, and RMs. Although recent studies have shown that a combination of preemptive LVt, PEEP and RM in patients without ARDS reduced the development of lung injury,[64–68] clinical outcomes have been inconsistent, demonstrating both an increase and decrease in mortality.[65,72,73] Neto et al.[65] conducted a retrospective study in 2,184 patients who were ventilated without ARDS, categorizing the ventilation strategy into low (≤7 mL/kg)

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intermediate (>7 and <10 mL/kg), and high (≥10 mL/kg) Vt groups. They found a dose-response relationship between lower Vt and a reduction in major pulmonary complications such as ARDS and pneumonia, which were associated with fewer ICU and hospital-free days and reduced mortality. However, another study showed that if lower Vt was combined with lower PEEP in anesthetized surgery patients the 30-day mortality rates were increased.[72] In contrast, Neto et al.[65] conducted a meta-analysis that confirmed the use of LVt protective in surgical patients but found that no added protection was offered by a higher PEEP.

The work of Neto et al. was supported by the multicenter PROVHILO RCT, showing that neither higher PEEP nor RMs reduce postoperative complications and suggested using LVt with low PEEP and no RMs as a protective preemptive ventilation strategy.[73] Combining these data clearly demonstrates that preemptive protective mechanical ventilation applied in the ICU or the operating room can reduce the incidence and severity of lung injury in patients at risk of ARDS development.

TCAV PROTOCOL

It is important to understand that, like the ARDSnet protocol, our TCAV protocol is an all-inclusive mechanical ventilation strategy that consists of the ventilator mode, the setting within that mode, and the adjustments made to these settings based on changes in lung physiology. Often in the literature, the mode is analyzed and critiqued in isolation, without regard to the entire protocol being used. For example, volume-assist control is the mode used within the ARDSnet protocol, but the mode itself means nothing without a detailed list of the settings and how these settings will be adjusted in response to changes in the patient's lung pathology (i.e., the ARDSnet protocol). The same is true for airway pressure release ventilation (APRV), which is the mode used within the TCAV protocol.

The first APRV publication was in 1987,[74] and since its inception, many vastly different settings have been used in both animal and clinical studies that have all been termed "APRV."[49] Jain et al.[49] discussed these differences in an article that reviewed the 30-year history of APRV and demonstrated the ventilator settings that were all called an "APRV" breath had significantly disparate settings. Figure 4 clearly shows the large differences in APRV settings used in four published studies.[74–77] These differences include, but not limited to, vastly different peak and end pressure, respiratory rate, and inspiratory and expiratory durations (Fig. 4). It is obvious that the settings in any ventilator mode are key to lung injury or protection.

Almost all mechanical ventilation review articles discuss the APRV mode in isolation, not as a treatment protocol. In addition, these review articles often use a very broad definition APRV, such as any mechanical breath with an inverse inspiratory to expiratory (I-E) ratio, regardless of what this ratio is or if vastly different ventilator settings are being used with the same I-E ratio (Fig. 4).[78] For these reasons, we named our protective ventilation strategy the TCAV protocol so that it will be analyzed as a whole, rather than only the ventilator mode within the protocol. The TCAV name is descriptive as to the impact it has on lung physiology: The "time-controlled" component (TCAV) of our protocol is the use of an extended inspiratory time to open the lung and a very brief expiratory time to keep the lung open. The "adaptive" component (TC**A**V) of our strategy is twofold: (1) because our Upper airway pressure is simply continuous positive airway pressure (CPAP) with a brief release, we do not set a Vt. Rather, the size of the Vt is adaptive to changes in lung volume; if lung volume is low, there is a small release volume (i.e., the volume of gas expired during the brief release, which is analogous to the set Vt using conventional ventilation); if lung volume is high, release volume will be larger; thus, Vt is not arbitrarily set on the ventilator but rather adapts to changes in lung volume; and (2) the expiratory duration is based on changes in the slope of the expiratory flow curve, which is a measure of respiratory system compliance. The faster the lung collapse, the briefer less release duration so that lung stability is adaptive to changes in lung physiology, regardless if the patient's lungs are getting better or worse.[49,50] Details of the TCAV protocol have been published previously[49,50] and will be discussed below.

TCAV PROTOCOL USED AS A PREEMPTIVE VENTILATION STRATEGY

We now understand that the components of ARDS pathology that render the lung susceptible to a secondary VILI are the loss of lung volume, heterogeneous ventilation, and alveolar stability. This knowledge combined with our understanding of dynamic alveolar physiology in the acutely injured lung has directed us away from the standard-of-care LVt strategy. Instead, we have moved toward a mechanical breath that features the component of time at inspiration and expiration to open the lung and keep it open. This is critical because VILI would be dramatically reduced in a homogeneously ventilated lung. Our TCAV protocol focuses on maintaining adequate lung volume and homogeneous ventilation using an extended time at inspiration and minimal time at expiration, rather than focusing on a specific size of Vt. Indeed, an LVt strategy would favor lung collapse with concomitant alveolar instability and heterogeneity. In addition, the TCAV protocol is personalized to the specific pathology of each patient's lung and adaptive as the patient's lung gets better or worse.[49] We postulate that there are 3 main MB_P components necessary for optimal preemptive ventilation and that the TCAV protocol encompasses all three of these criteria.

The first component of the optimal preemptive ventilation strategy is it must be comfortable for the patient with relatively normal lungs so that the patient can spontaneously breathe. This would eliminate the high-frequency oscillatory ventilation mode because the patient cannot comfortably breathe spontaneously and must often be heavily sedated or paralyzed using neuromuscular-blocking agents. Also, an LVt with RM and higher PEEP protocol would not be comfortable or well tolerated in patients with early ALI and relatively normal lungs.

The TCAV protocol is simply CPAP with a brief release phase. Because of the open breathing system with CPAP, patients can spontaneously breathe with comfort at any point throughout the entire respiratory cycle, eliminating asynchrony as there is no physiologic stimulus (i.e., the lung is not collapsed, and the blood gases are in the normal range) to trigger a strong inspiratory effort with an open homogeneously ventilated lung. The CPAP phase maintains lung volume, thereby satiating mechanoreceptors and preventing large inspiratory pressure swings.[56] Patients can

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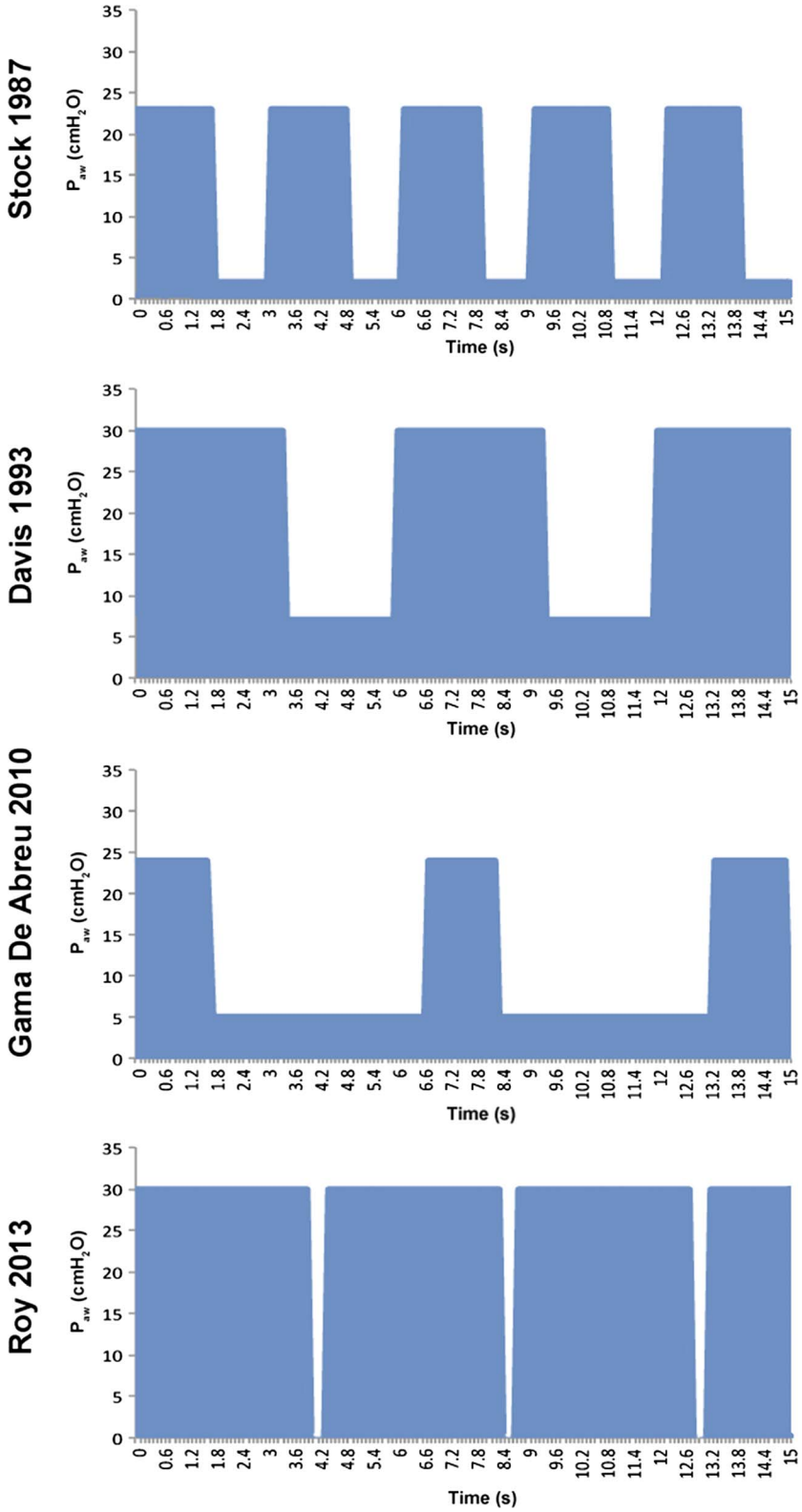

Figure 4. Airway pressure release ventilation airway pressure waveforms, illustrating the dramatic variability APRV setting used in various protocols. Stock in 1987 used a T_{Low} of 1.27 seconds, 60% CPAP with and a respiratory rate (RR) of 20. Davis et al.[75] in 1993 used a similar %CPAP, prolonging T_{High} and T_{Low}, which decreased the RR. Gama de Abreau et al.[76] in 2010 with a prolonged T_{Low} and short T_{High}, which essentially simulated conventional ventilation. Roy et al.[77] in 2013 used the TCAV protocol comprising a very brief T_{Low} and 90% CPAP.[49]

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easily spontaneously breathe on an appropriate amount of CPAP without asynchrony or potential lung overdistension because there are no triggered mechanical breaths with the TCAV protocol. Indeed, CPAP is used by patients with sleep apnea and is well tolerated in the awake patient with perfectly normal lungs. Because the TCAV protocol is very comfortable for the patient, it can be applied preemptively, and it will keep the lung open, thereby meeting the first criterion of comfort for a preemptive protective breath strategy.

The second component of the optimal preemptive ventilation strategy is that it must be able to recruit and maintain an open lung because loss of lung surface area results in a strong respiratory drive leading to patient-ventilator asynchrony.[56] In addition, a homogeneously ventilated lung would eliminate stress risers and RACE, two key mechanisms of VILI, as well as normalize oxygenation and ventilation. Decreasing Vt using the LVt strategy would collapse, rather than recruit, the lung. Positive end-expiratory pressure is an expiratory phenomenon and prevents collapse but is not associated with lung recruitment. To open the lung, RMs are used and PEEP applied to keep the newly recruited alveoli open.[54] Direct visualization of subpleural alveoli has shown that an RM would open collapsed alveoli, but unless adequate PEEP was added, these newly recruited alveoli would derecruit or be subjected to RACE.[79] Lung recruitment has been shown to be highly variable in ARDS patients,[80] raising the question of how often and at what pressure RMs are required to open the lung and keep it open. A decremental PEEP titration following an RM is believed to be the best method of setting PEEP.[54] However, the optimal PEEP level will change as the patient's lung progressively improves or worsens, mandating dynamic RM and PEEP titration. This may help explain the results of a recent clinical trial demonstrating that RM and titrated PEEP increase ARDS mortality.[62]

Since alveoli recruit as a viscoelastic system, the longer the applied force (i.e., inflation pressure), the more alveoli that will recruit.[6] The TCAV protocol maintains a CPAP for ~90% of each respiratory cycle to maximize the recruiting force (Fig. 3A). We have shown in a rat ARDS model that alveoli continually recruit over a 40-second CPAP phase without an increase of airway pressure (Fig. 4).[35] The CPAP phase will gradually recruit alveoli with each breath, slowly "nudging" the lung open without injury. Therefore, the TCAV protocol fits the second criterion of a preemptive protective breath strategy by maintaining an open, homogeneously ventilated lung.

The third component of the optimal preemptive ventilation strategy is that the lung, once recruited, must be kept open. Although an appropriate level of PEEP can be effective at stabilizing the lung once it is open, the ability for PEEP to stabilize alveoli following an RM worsens with progressive ALI, and a recent clinical trial[81] combining an RM with titrated PEEP was shown to increase ARDS mortality.[62]

The TCAV protocol uses the slope of the expiratory flow curve to determine the duration of the release phase, or expiratory duration, necessary to maintain lung stability and prevent alveolar collapse (Fig. 3B).[49,50] The slope of the expiratory curve is a function of lung elastance, where a higher elastance correlates with a faster collapse time constant (thus requiring a briefer expiratory phase).[82,83] Mechanical compliance and resistance of the lung-thorax can be calculated from the flow recorded during passive expiration.[84] In addition, elastance is a better correlate of residual lung volume (i.e., baby lung) than is predicted body weight.[85] Using the slope of the expiratory curve personalizes the expiratory duration to the pathophysiology of each patient's lung without the need for any special maneuvers and is adaptive as the lung pathology changes (improves/worsens) (Fig. 3b).[49,50] The brief expiratory duration stabilizes the lung by two mechanisms: time and pressure (i.e., alveoli do not have time to collapse and TC-PEEP).[32] We have demonstrated that this dual mechanism of lung stabilization is more effective at stabilizing alveoli and preventing their collapse than is high-set PEEP with conventional ventilation.[23]

TABLE 1. Misconceptions of APRV as Set Using the TCAV Protocol

Comfort: When set properly for the patient's lung pathology, patients are typically comfortable on APRV. APRV provides increased comfort by: (1) an open exhalation system allows patients to exhale at any point during the respiratory cycle without pressure limiting and is not confined to the release phase; (2) allows inspiration at any time during the respiratory cycle eliminating inspiratory efforts during a fixed flow ventilation and high pleural pressure efforts; and (3) APRV provides CPAP for 90% of pressure-time profile, which allows for a protective form of spontaneous breathing during mechanical ventilation.[90]

APRV set according to the TCAV protocol is essentially CPAP with a brief release phase and no trigger to deliver a mechanical or assisted breath. Because APRV set according to the TCAV protocol is a comfortable ventilation strategy, it can be used preemptively as the primary mode as soon as the patient is intubated and, throughout their entire course of mechanical ventilation, from intubation to weaning.

TC-PEEP

In the TCAV method of APRV, the release phase is used to dynamically manage the evolving time constants of the respiratory system. This can be determined by the slope of the expiratory flow curve, which reflects [in real-time] the elastance and resistance of the respiratory system at any given time throughout the course of the patient's illness. Because of the viscoelastic behavior of the lung, set PEEP allows progressive airway closure at a given PEEP level over the prolonged end-expiratory period. TC-PEEP eliminates this weakness by controlling time and eliminating airway closure, thereby maintaining a stable static end-expiratory lung volume. Because 90% of the total cycle time in APRV is CPAP, dynamic hyperinflation is decreased.

Tidal Volume (Vt): Since APRV, set according to the TCAV protocol, is simply CPAP with a brief release, without any triggers to deliver a mechanical breath, Vt is not set but rather is dependent on the pathophysiology of the lung. If the patient has severe ARDS and is placed on the TCAV protocol, the initial Vt is typically <6 mL/kg as Vt is proportional to lung compliance and residual lung volume (i.e., lower compliance, lower Vt). As a result, Vt does not come at the cost of increased driving pressure (DP) since lung Cstat is increased (DP = Vt/Cstat). Thus, it is not only the magnitude of the Vt that is injurious but also the residual lung volume and Cstat of the lung to which the Vt is applied. The prolonged CPAP phase enhances time-dependent recruitment of lung tissue, and the T_{Low} prevents time-dependent derecruitment, limiting heterogeneous alveolar instability (HAI). Because the slope of the expiratory flow curve reflects the elastance and resistance changes in lung mechanics, the T_{Low} slope and termination function to provide a dynamic real-time adaptation to evolving lung mechanics.

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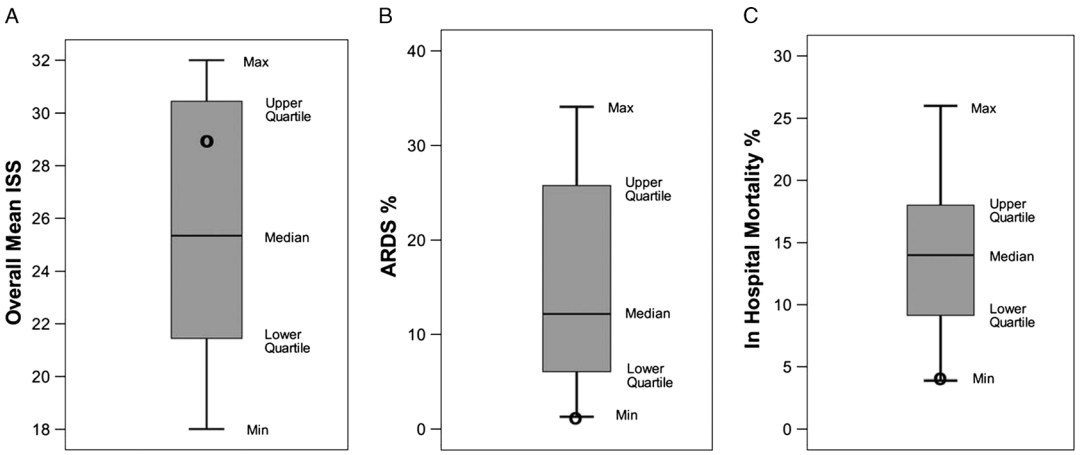

Figure 5. (*A*) Injury Severity Score (ISS), (*B*) ARDS incidence (%), (*C*) in-hospital mortality (%) from 16 surgical ICUs using standard-of-care ventilation (bar and whisker) and from R. Adams Cowley Shock Trauma Center using the preemptive TCAV protocol (bold circles).[87]

We have found that APRV set using the TCAV protocol generates a TC-PEEP with the dual stabilizing action of pressure and time that will prevent alveolar collapse, thus fulfilling the third criterion of a preemptive protective breath strategy of not allowing the open lung to collapse. A recent study has shown that the TCAV protocol reduces ALI and inflammation in a primary and secondary rat endotoxin-induced ARDS models as compared with volume-controlled ventilation.[86] Due to the sometimes counterintuitive components of APRV, set according to the TCAV protocol and based on assumptions made in the ARDSnet protocol and many misconceptions have been generated on level of comfort, use of TC-PEEP, how to set TC-PEEP, and the size of the Vt. We have discussed these misconceptions in Table 1.

CLINICAL STUDIES USING A PROTOCOL WITH APRV AS THE MODE

To date, there have been no RCTs using the TCAV protocol in patients with or at high risk of developing ALI. The TCAV protocol is used as a primary mode of ventilation (i.e., criterion for applying the TCAV protocol is intubation) at the R. Adams Cowley Shock Trauma Center in Baltimore, MD, and thus thousands of patient have been successfully treated with this ventilation strategy. A meta-analysis compared patients using the TCAV protocol as the primary ventilation strategy at R. Adams Cowley Shock Trauma Center with patients in 15 other surgical ICUs for incidence of ARDS and mortality. There was a significant decrease in both ARDS incidence and mortality in the patients on the preemptive TCAV protocol (Fig. 5).[87] A recent RCT used APRV in a protocol similar, but not identical, to the TCAV protocol.[88] In 138 patients, this study compared the ARDSnet protocol with that of protocol similar to TCAV. The study showed the protocol using APRV improved oxygenation, respiratory system compliance, and Pplat, with a shorter duration of both mechanical ventilation and ICU stay (Fig. 6). A recent review of both animal and clinical studies using APRV in the ventilation protocol has been published.[89] Table 2 overviews the basic TCAV protocol APRV settings and weaning strategy.

CONCLUSIONS

Study of dynamic alveolar physiology during inflation and deflation has revealed alveoli function as a viscoelastic system with a fast and slow phase during both recruitment and collapse in response to the application or removal of the applied force (i.e., Vt). This suggests that the mechanical breath component of time during both inspiration and expiration is critical in both maximizing alveolar recruitment and minimizing derecruitment. The TCAV protocol takes advantage of this knowledge by extending the time at inspiration to gradually

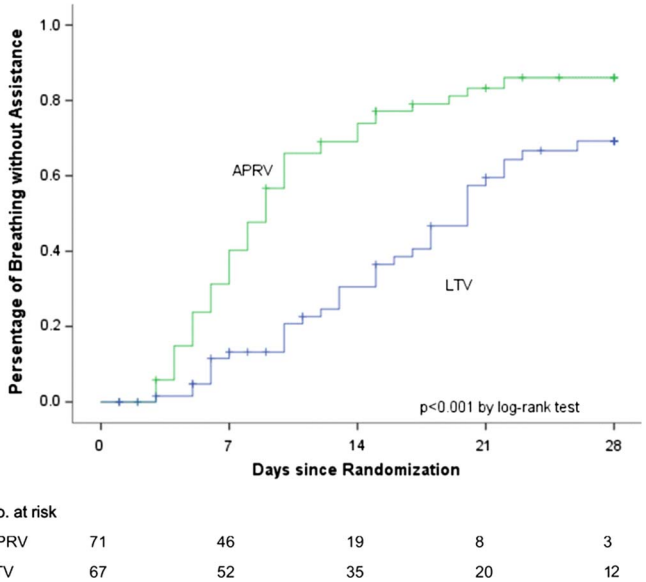

Figure 6. Patients breathing without assistance (%) in the APRV group and the low tidal volume (LVT) group for 28 days from the time of enrollment.[88]

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TABLE 2. Time-Controlled Adaptive Ventilation Protocol Clinical Guide

- **Goals**
  - Increase (recruit) and maintain lung volume (P_{High} and T_{High})
  - Decrease elastic work of breathing (WOB) with CPAP (P_{High} and T_{High})
  - Minimize number of releases to supplement ventilation from spontaneous breathing (SB)
  - Limit derecruitment by setting T_{Low} to terminate at 75% of the peak expiratory flow rate (PEFR)
  - Allow SB (25%–50% of total minute ventilation [MVe]) within 24 h of TCAV protocol application to limit ventilator-induced diaphragm dysfunction (VIDD)
- **Setup**
  - Newly intubated with acute restrictive lung disease
    - P_{High}—set typically 20–35 cmH_2O. P_{High} >35 cmH_2O may be required in patients with decreased chest wall compliance
    - P_{Low}—0 cmH_2O (Note: pressure during the release phase never reaches 0 cmH_2O when the T_{Low} is set appropriately at 75% of the PEFR)
    - T_{High}h—4–6 s
    - T_{Low}—0.2–0.8 s (set based on 75% of the PEFR)
- **Weaning**
  - Determine capability to maintain autonomic rhythmic breathing, which indicates an intact pre-Botzinger complex
  - Increase T_{High} to ensure patient's ability to spontaneously breathe. Stretch T_{High} to 20 s as tolerates so the patient is contributing 50%–80% to total MVe while assessing for increased WOB
  - Simultaneously reduce P_{High} and continue to increase T_{High} for a gradual reduction of mean airway pressure and simultaneously increase the contribution of MVe from SB to total mVe. This evolves CPAP with release (i.e., APRV) to CPAP
  - Wean CPAP and consider extubation when CPAP 10–15 cmH_2O.

EEF indicates end-expiratory flow; P_{High}, high airway pressure; P_{Low}, set low pressure; T_{High}, the time at P_{High}; T_{Low}, the time at P_{Low}.
Table modified from Habashi.[50]

recruit alveoli with each breath and setting a very brief expiratory duration to minimize alveolar collapse by a dual mechanism of time and pressure (TC-PEEP). A recent RCT demonstrated that early application of a protocol similar to TCAV improved oxygenation and respiratory system compliance, decreased plateau pressure, and reduced mechanical ventilation and ICU time.

AUTHORSHIP

G.F.N. performed inception, drafting, editing, and final approval of the manuscript. J.S., M.K.S., P.A., and N.M.H. performed drafting, editing, and final approval of the manuscript. K.W., M.M., SB, LAG and H.A. performed editing and final approval of the manuscript.

DISCLOSURE

P.A., G.F.N., M.K.S., and N.M.H. have presented and received honoraria and/or travel reimbursement at event(s) sponsored by Dräger Medical Systems, Inc., outside the published work. P.A., G.F.N., and N.M.H. have lectured for Intensive Care Online Network, Inc. (ICON). N.M.H. is the founder of ICON, of which P.A. is an employee. N.M.H. holds patents on a method of initiating, managing, and/or weaning APRV, as well as controlling a ventilator in accordance with the same, but these patents are not commercialized, licensed, or royalty producing. The authors maintain that industry had no role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript. Funding: Salary support for G.F.N., J.S., and S.B. from NIH R01 HL131143.

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