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Unshrinking the baby lung to calm the VILI vortex

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Abstract

A hallmark of ARDS is progressive shrinking of the 'baby lung,' now referred to as the ventilator-induced lung injury (VILI) 'vortex'. Reducing the risk of the VILI vortex is the goal of current ventilation strategies; unfortunately, this goal has not been achieved nor has mortality been reduced. However, the temporal aspects of a mechanical breath have not been considered. A brief expiration prevents alveolar collapse, and an extended inspiration can recruit the atelectatic lung over hours. Time-controlled adaptive ventilation (TCAV) is a novel ventilator approach to achieve these goals, since it considers many of the temporal aspects of dynamic lung mechanics.

Keywords: Acute respiratory distress syndrome (ARDS), Ventilator-induced lung injury (VILI), Protective mechanical ventilation

Introduction

The acute respiratory distress syndrome (ARDS) remains a significant clinical problem with primary management being supportive use of mechanical ventilation (MV) [1]. However, inappropriate use of MV may result in ventilator-induced lung injury (VILI), which significantly increases ARDS mortality [2]. The use of MV for ARDS patients must balance its life-preserving attributes against its potential for harm. Strategies for optimizing this balance may vary substantially across patients, and even within the same patient over a given clinical course.

The shrinking baby lung

The ARDS lung has been conceptualized as being composed of two distinct, gravitationally separated compartments: (1) dependent regions consisting atelectatic and/or edematous airspaces and (2) normally inflated tissue in less dependent regions comprising the so-called baby

lung [3]. This conceptualization led to the hypothesis that ventilating patients with ARDS using a reduced tidal volume (V_T) would protect the baby lung from volutrauma caused by overdistension, while simultaneously allowing the atelectatic compartment to rest and [ideally] recover [4]. It was also assumed that an appropriate level of positive end-expiratory pressure (PEEP), based on oxygenation, would avoid atelectrauma [4, 5]. This ARDSNet method was studied in a NIH clinical trial in 2000 [4] and showed a significant reduction in ARDS mortality using volume control [assist-control] mode with a V_T of 6 mL kg⁻¹ compared to 12 mL kg⁻¹ of ideal body weight. The use of 6 mL kg⁻¹ soon became the standard of care for patients with ARDS.

Recent statistical analyses suggest, however, that this low V_T (LV_T) strategy has not lived up to its initial promise in reducing mortality in ARDS [6–9]. Deans et al. [10] analyzed data from 2587 patients that were screened but excluded from the ARDSNet Acute Respiratory Management Approach (ARMA) trial for technical reasons but were followed and treated with V_T of ~ 10 mL kg⁻¹, which was the standard of care for ventilation at the time. The group with V_T ~ 10 mL kg had the same mortality as the

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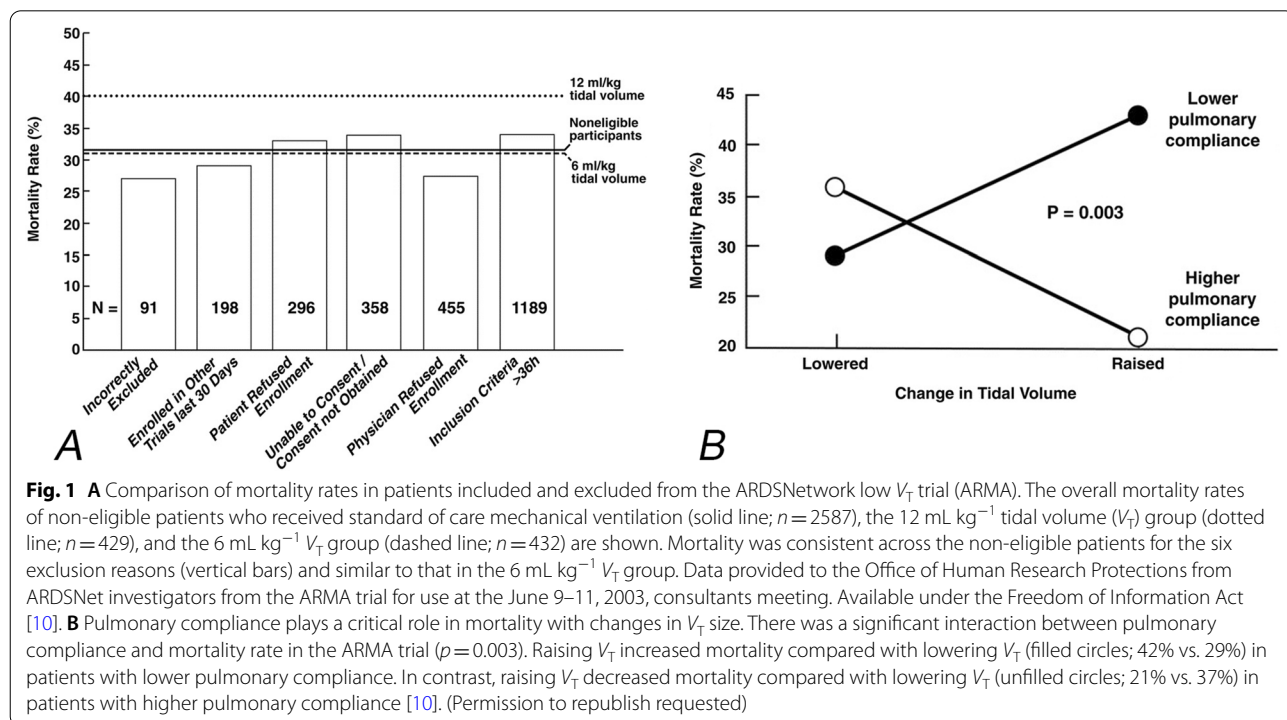
LV_T (6 mL kg⁻¹) group (Fig. 1A). Also, a V_T greater than 6 mL kg⁻¹ was not always associated with increased mortality, nor was LV_T always associated with reduced mortality. Rather, in patients with lower respiratory system compliance (C_{RS}), raising V_T increased mortality compared to LV_T (42% for LV_T vs. 29% for high V_T), while raising V_T in patients with higher C_{RS} reduced mortality (21% for high V_T vs. 37% for LV_T; *p* = 0.003; Fig. 1B) [10].

These findings demonstrate that a patient’s individual lung pathophysiology is critically important for clinical outcome. Thus, there cannot be a single weight-based value of V_T that is best for all patients either at the initiation of MV or as their clinical course evolves. Appreciation of this fact is evidenced by the recent interest in driving pressure (Δ*P*), calculated as the difference between plateau and end-expiratory pressures. Δ*P* can evolve over a patient’s clinical course and is approximated by the ratio V_T/C_{RS}, which explains why letting V_T be influenced by C_{RS} has proven to be better at stratifying ARDS-related mortality risk compared to weight-based V_T [7, 11–15].

These observations beg the question as to whether Δ*P* should replace V_T as the key factor guiding protective ventilation strategies [7, 11–16]. Dramatic reductions in Δ*P* can be achieved with high-frequency oscillatory ventilation (HFOV), because it uses V_T that are less than the anatomic dead space volume. However, when tested in randomized controlled trials [17–19], HFOV failed to

reduce ARDS-related mortality below that in the ARMA study [4]. Such a disappointing result may be related to the heterogeneous way that ventilation is distributed throughout the lung when cycled at high frequencies [20, 21] and the resultant heterogeneous distributions of parenchymal strain [20, 21]. Moreover, studies have shown that normal lung tissue, which is presumed to comprise the baby lung, is resistant to tissue damage induced by overdistension [22–30]. Also, although some studies suggest VILI occurs when a threshold of mechanical power applied to the lung is exceeded, studies in animal models suggest that VILI in the normal lung is only initiated when atelectrauma is allowed to occur regardless of V_T [26, 31, 32].

The baby lung concept, which established the rationale for LV_T, was originally based on CT imaging [3]. However, more recent studies pairing CT with ³He or ¹²⁹Xe magnetic resonance imaging (MRI) have shown that pathologic airspaces develop heterogeneously throughout the ARDS lung [33–36], contrary to the notion of a normal baby lung compartment. Furthermore, it has recently been shown that the principle mechanism of VILI at the tissue level is regional alveolar instability [5], defined as cyclic alveolar collapse causing scattered micro-atelectasis to develop throughout the lung [33–38]. In addition, Broche et al. using high-resolution synchrotron phase-contrast computerized tomography (CT) showed that acute lung injury significantly increased



small airway (1.7–0.21 mm) closure and that this closure was time dependent. They suggest that the airway pressure release ventilation (APRV) mode, with a very short expiratory duration, may help to keep these small airways open [39]. Since micro-atelectasis cannot be seen in conventional chest radiographs or CT images [32, 40], its importance as a VILI mechanism may not have been fully appreciated until recently.

An assumption of the current protective ventilation approach is that the injured lung can be easily compartmentalized into simple opened and closed components. However, several studies have demonstrated that the injured lung has a far more heterogeneous distribution of parenchymal mechanical properties. Techniques that may be used to further assess such intraparenchymal heterogeneity include electrical impedance tomography [39,

41], computed tomographic image registration [42, 43] and oscillometric measurements of respiratory impedance [44]. How any of these approaches may be used to further refine the ventilation modality will of course require further investigation.

Unshrinking the baby lung

Marini and Gattinoni recently described the progression of VILI as a *shrinking of the baby lung* whereby tissue moves from the open to the atelectatic compartment, a process labeled the ‘VILI vortex’ (Fig. 2) [45]. They hypothesize that as the baby lung continues to lose normal tissue as a result of alveolar instability and collapse, increasing stress and strain from a fixed V_T will be placed on the remaining open tissue, amplify existing lung injury. The VILI vortex concept was recently supported

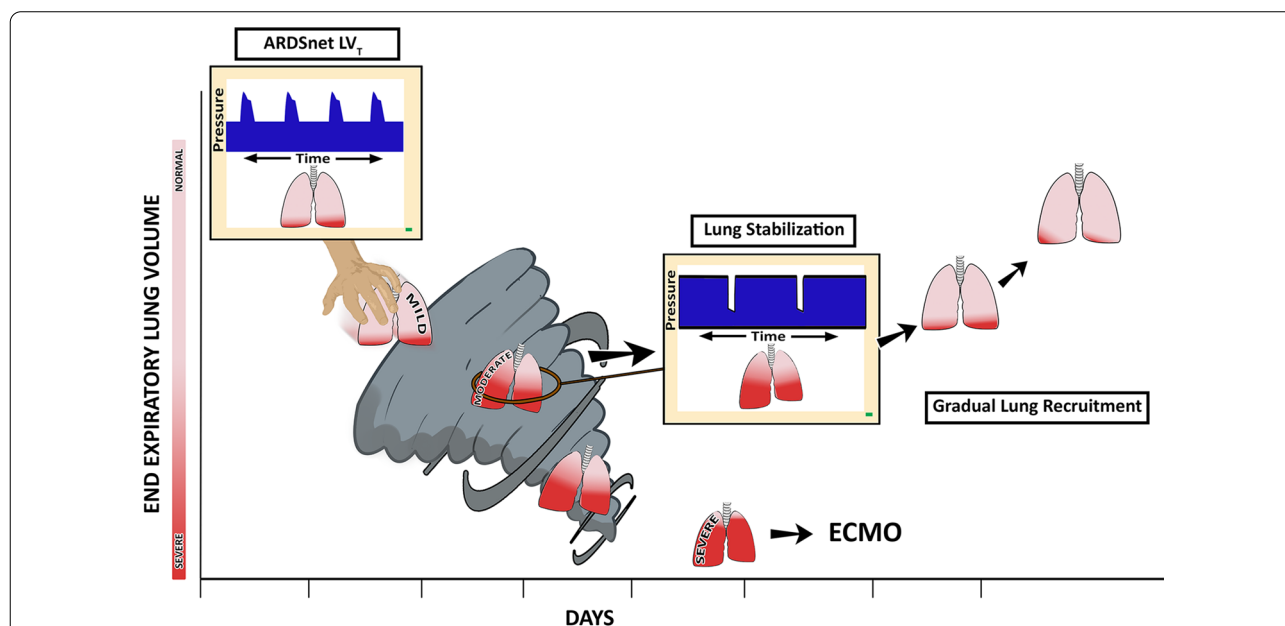


Fig. 2 The evolution of ventilator-induced lung injury (VILI) can be described as an ever-shrinking baby lung known as a VILI vortex [45]. The ‘patient’ with mild ARDS with mostly open lung tissue (pink) and a lesser amount of collapsed tissue (red) is placed on ARDSNet LV_T ventilation. The LV_T strategy is designed to shield the ‘baby lung’ from overdistension. However, this strategy using low V_T and low airway pressures allows acutely injured tissue to continually collapse pushing it into the VILI vortex. As normal tissue progressively shrinks (pink → red), lung pathogenesis moves from mild-to-moderate ARDS. If unchecked, lung injury will progress into severe ARDS, at which point rescue methods such as extracorporeal membrane oxygenation (ECMO) may be necessary. ARDS causes the lung to become *time* and *pressure* dependent. This means that it will take more time for alveoli to open and less time for them to collapse at any given airway pressure. Thus, inspiratory and expiratory time can be used to accelerate alveolar opening and to minimize alveolar collapse. Using the ARDSNet approach, the short *time* at inspiration is not adequate to open collapsed alveoli, while the extended *time* at expiration will not prevent alveolar collapse (upper left ARDSNet LV_T , Pressure/Time curve on the ventilator monitor). The open lung approach (OLA) using higher PEEP with and without recruitment maneuvers to rapidly (seconds or minutes) open the collapsed ARDS lung has not been successful at reducing ARDS-related mortality. Our group and others have shown the ability of inspiratory and expiratory duration to open and stabilize alveoli. Multiple studies using time-controlled ventilation strategies have confirmed that an extended inspiratory time will progressively recruit alveoli and a very brief expiratory time will prevent re-collapse [63, 66, 68, 71–83, 85, 86, 90]. An ventilator method to rapidly stabilize the lung (Center, Lung Stabilization, Pressure/Time curve on the ventilator monitor) using a very brief expiratory duration (Fig. 4B, Release Phase) has been shown to stabilize alveoli (Fig. 6, APRV 75%) and prevent progressive lung collapse pulling the lung from the Vortex. Once removed from the vortex, the collapsed tissue can be reopened slowly (gradual lung recruitment) over hours or day depending on the level of lung pathophysiology (Fig. 4B, CPAP Phase) [63, 66, 68, 71–83, 85, 86, 90]

in a clinical study showing COVID-19-induced ARDS (CARDS) resulted in progressive lung collapse over a 3-week period [46].

Unfortunately, fixing the VILI vortex is unlikely to be achieved solely with the use of a LV_T strategy because the parenchymal tissues at the interfaces between normal and atelectatic regions experience particularly high distortional forces. These forces predispose the interfacial tissues to being the site of VILI pathogenesis through a permeability-originated obstruction response (POOR) that is self-reinforcing (Fig. 3) [37]. This means that VILI will continue to progress at the interfacial regions even if the baby lung as a whole is not over-inflated. It also leads to the conjecture that the only way of preventing VILI progression is through a substantial reduction in the

total burden of POOR regions, something that requires the immediate mitigation of alveolar instability followed by steps to progressively and safely reopen densely atelectatic lung tissue (Fig. 2) [38].

The above supposition is not new, and indeed, it motivated the open lung approach (OLA) to protective MV. The OLA attempts to open the majority of collapsed lung by applying high levels of PEEP, either with or without periodic recruitment maneuvers (RM) [47–50]. Several large clinical trials using the OLA, however, failed to show a reduction in ARDS-related mortality [47–50] despite preliminary data suggesting that opening the ARDS lung reduces VILI. While this might seem puzzling given that the OLA has an apparently well-founded physiologic rationale, there are two critical factors that

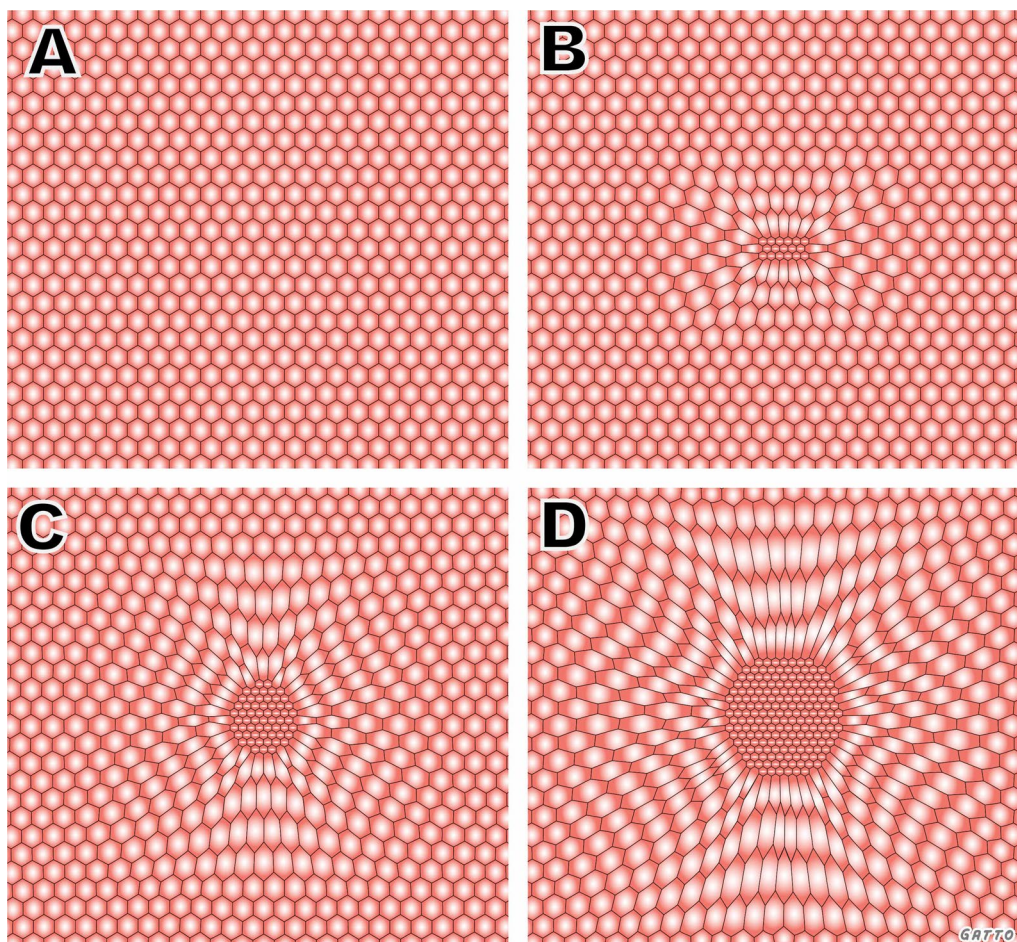


Fig. 3 Ventilator-induced lung injury (VILI) in the microenvironment arises through a permeability-originated obstruction response (POOR) that is self-reinforcing (POOR-becomes-POORer). **A** In normal homogeneously ventilated lung, alveoli (hexagons) are uniformly open and stress is evenly distributed. **B** Isolated POOR areas of edema-filled or collapsed alveoli (center) that occur in early lung injury concentrate stress in adjacent patent alveoli, causing overdistension and instability. **C** The size of the POOR area expands due to collapse and flooding of surrounding alveoli, leading to the POOR region becoming POORer. **D** As the size of the POORer region expands, the stress applied to the surrounding alveoli is amplified and, unless this pathogenesis is interrupted, tissue damage secondary to VILI will continue to spread rapidly. (Permission to republish requested)

potentially account for its lack of success. First, while recruitment/derecruitment (R/D) is a process normally associated with excursions in lung volume over the lower end of its functional range, these processes can manifest at increasingly elevated volumes as the lung becomes progressively more injured and may eventually even extend over the entire lung volume range [51, 52]. Thus, in some ARDS cases there may be no safe level of PEEP at which R/D is eliminated during MV.

The second factor not addressed by the OLA is that recruitment is not solely determined by the amount of airway pressure applied but also depends on inspiratory and expiratory time. Indeed, lung reopening may take a long time, sometimes hours or days, to occur [53]. The OLA uses RMs that rely on high inspiratory pressure applied transiently (seconds to minutes) to achieve rapid reopening, but lung recruitment can be challenging to achieve quickly even with very high pressures due to accumulation of surfactant deactivation and edema in the airspaces [38, 54]. Also, the nondurable recruitment produced by the OLA has the potential for increasing the number of unstable airspaces if adequate PEEP is not applied.

Similarly, reducing airway pressure may not cause immediate derecruitment because collapse also takes time to occur. The timescale for alveolar collapse is typically much faster than the timescale for alveolar reopening, and the delay before collapse begins may be <0.5 s [55]. If PEEP is set too low and/or expiratory time too long, the resulting progressive lung collapse is reflected in transient increases in lung elastance (i.e., reductions in C_{RS}) observed immediately following a RM [56]. Furthermore, the rates at which both alveolar opening and collapse occur are functions of the nature and severity of lung injury [57], as well as the level of airway pressure applied [58]. In general, the more severe the lung injury, the more rapid and extensive derecruitment will be at a given pressure [59]. As conventionally practiced, the administration of a RM does not consider how rapidly the lung derecruits following each maneuver. If atelectatic regions are recruited but not stabilized, then cyclic R/D will continue to cause atelectrauma [60].

The above considerations suggest that a non-injurious ventilation strategy for the ARDS lung must first be able to halt ongoing derecruitment and then progressively pull the lung out of the VILI vortex by gradually opening atelectatic lung (Fig. 2). To do this, such a strategy must have the following two key attributes:

- a. It must *rapidly stabilize alveoli* that are actively undergoing atelectrauma, such that susceptible airspaces do not have enough time to close during expiration and thus are prevented from having to reopen

again during the subsequent inspiration. This prevents the accumulation of breath-to-breath atelectrauma and so pulls the lung from the VILI vortex.

- b. It must *progressively recruit atelectatic lung tissue* in a sustained manner over a period of hours or even days. This minimizes the amount of excessively distorted parenchyma at the interfaces between patent and atelectatic regions of the lung that are frequently the sites of VILI initiation [61]. Once gradual airspace opening begins, it can spread to adjacent collapsed regions via the forces of parenchymal tethering and interdependence [62].

Neither attribute is likely to be realized in the injured lung during conventional MV because expiration is usually long enough to allow rapidly closing lung units sufficient time to derecruit unless very high PEEP is applied, and inspiration is too brief to recruit collapsed alveoli that open slowly over time (Figs. 4A, 5A). The above two attributes can be realized, however, if the pattern of ventilation is allowed to depart from traditional mechanical ventilation in the following two ways (Figs. 4B, 5B):

- (1) Expiration must be sufficiently brief that derecruitment does not have enough time to occur prior to the beginning of the next inspiration (Fig. 4B, Release Phase).
- (2) Inspiratory duration and pressure must be sufficient to progressively recruit atelectatic lung over an extended period of time, but not so high as to be injurious to the parenchyma or have adverse hemodynamic consequences (Fig. 4B, CPAP Phase). Pressure must be sustained in a manner that is capable of recruiting lung units gradually, and this pressure must be applied for hours or days until the lung is fully open and stable (Fig. 5B–D).

A mode of MV that potentially meets the above two requirements is APRV, although it must be administered in a very particular manner (Fig. 4B). The most critical APRV parameter is the duration of the expiratory Release Phase (T_{Low}), which must be brief enough to prevent collapse of even the most rapidly closing alveoli, thereby attending to the first requirement. It is important to realize, however, that extending T_{Low} from its optimal value by even a fraction of a second can increase expiratory derecruitment dramatically, with potentially disastrous results for the lung (Fig. 6A, B—APRV 10%) [63].

The second requirement can be met by an appropriate level of inspiratory airway pressure (P_{High}) applied for an extended duration (T_{High}) (Fig. 4B, CPAP Phase). This

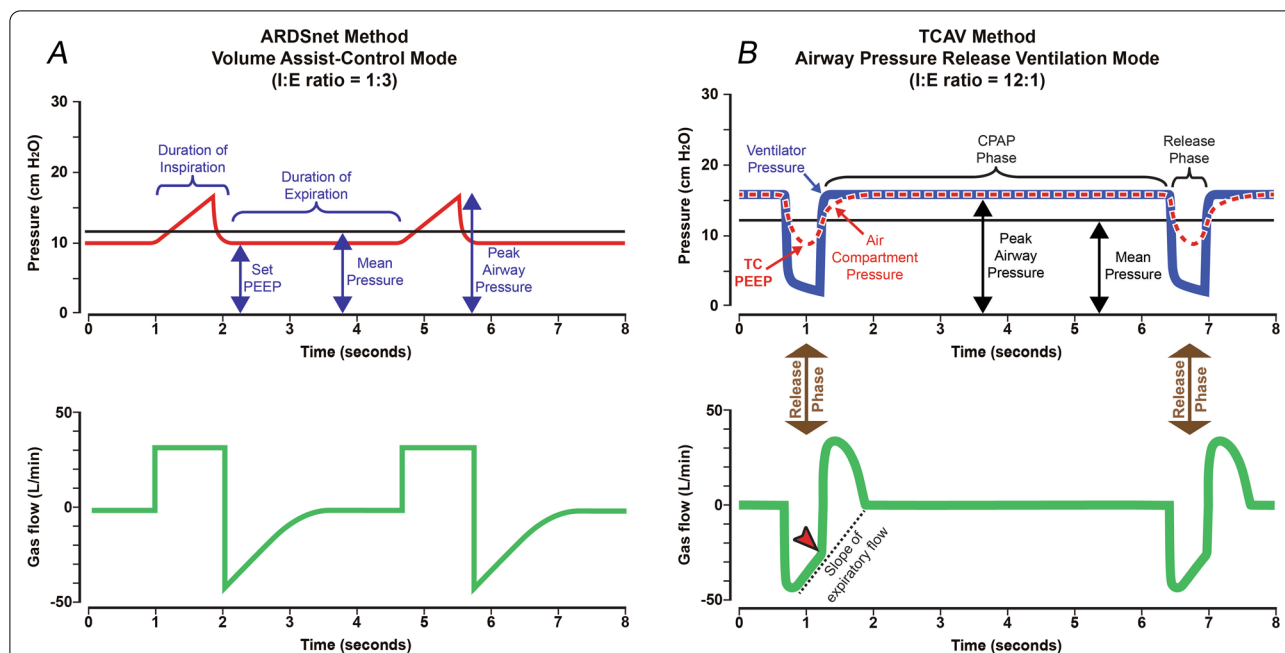
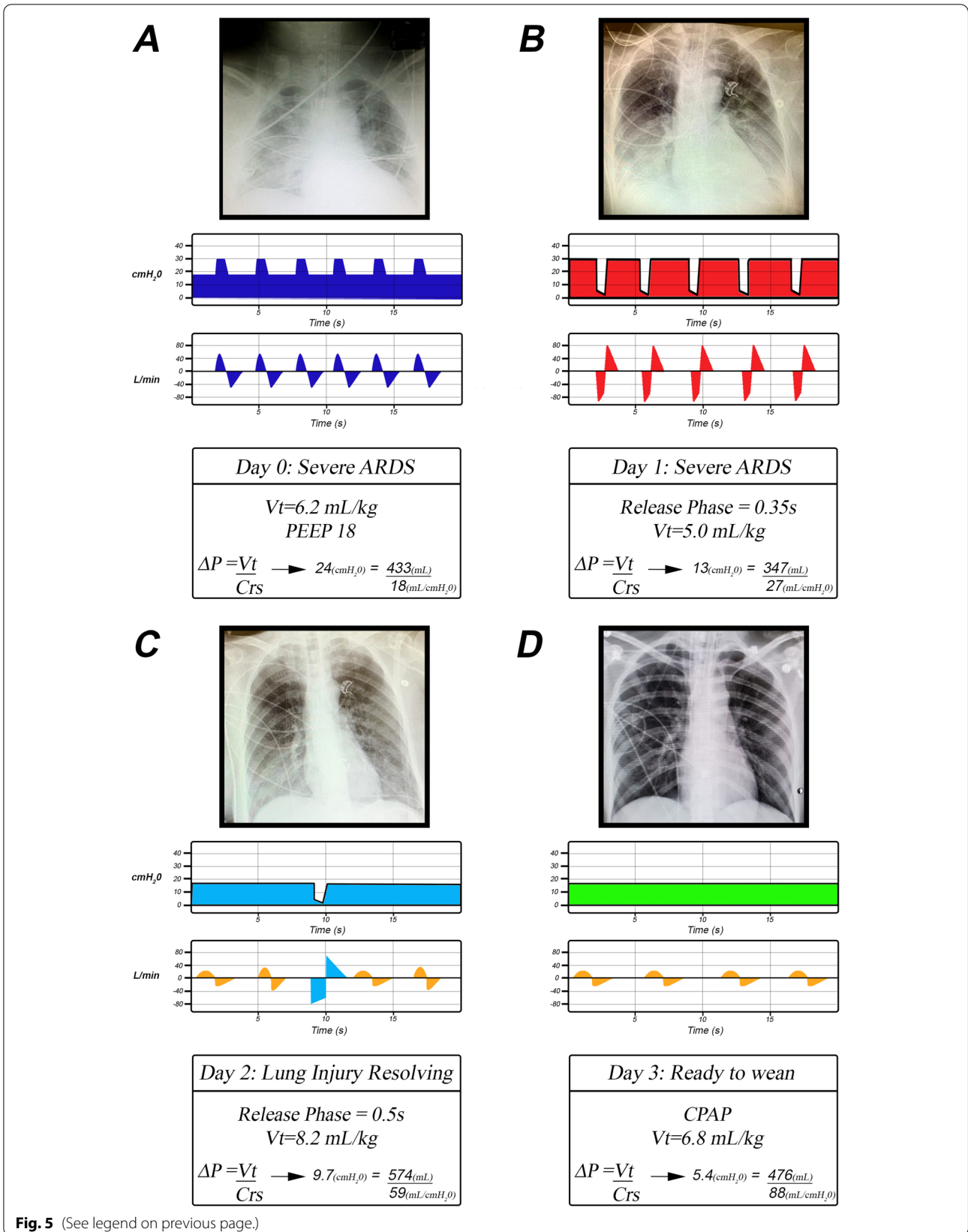


Fig. 4 **A** Pressure/Time and Gas Flow/Time curves for Volume Assist-Control mode set and adjusted using the ARDSNet method. Key features include an inspiratory/expiratory ratio of 1:3. Plateau pressure is not extended, so peak inspiratory pressure is brief. Positive end-expiratory pressure (set-PEEP) and FiO_2 are adjusted using oxygenation as the trigger for change [4]. **B** Pressure/Time and Gas Flow/Time curves for the airway pressure release ventilation (APRV) mode that is set and adjusted using the time-controlled adaptive ventilation (TCAV) method. Key features include an inspiratory/expiratory ratio as high as ~ 12:1, generating a prolonged inspiratory and short expiratory time. The continuous positive airway pressure (CPAP) phase is often ~90% of each breath. A tidal volume (V_T) is not set, rather it is influenced by changes in (i) respiratory system compliance (C_{RS}), (ii) the CPAP Phase pressure, and (iii) the duration of the Release Phase. The Release Phase is set as a percentage (75%) of the peak expiratory gas flow, which creates a very brief expiratory duration (Flow/Time curve, red arrowhead). Although this percentage is the same for most patients, the duration of the Release Phase can vary substantially in response to changes in C_{RS} . The slope of the expiratory flow curve in the Gas Flow/Time curve provides a breath-to-breath measure of C_{RS} . The lower the C_{RS} , the steeper the slope of the expiratory flow curve, and the shorter the Release Phase. The slope of the expiratory flow curve becomes less steep as the patient's C_{RS} improves, which causes the Release Phase to lengthen (Fig. 7). The short Release Phase does not allow the lung time to depressurize fully, maintaining a time-controlled positive end-expiratory pressure (TC-PEEP, red dotted line). TC-PEEP is ~ 50% of the CPAP Phase pressure [91]. (Permission to republish requested)

(See figure on next page.)

Fig. 5 A representative illustration of the sequence of events typically seen during the progressive 'Unshrinking the Baby Lung' using the TCAV method to set and adjust the APRV mode. Using this method, the lung is first stabilized using a brief expiratory duration (**B**) and then gradually recruits collapsed lung tissue over hours or days using an extended inspiratory duration (**B**). **A** Patient with severe ARDS with extensive lung collapse and edema (X-ray) ventilated using the ARDSNet low V_T method showing typical Pressure/Time and Flow/Time curves (blue) as seen on a ventilator monitor. Even with a low V_T (6.2 mL kg^{-1}), the driving pressure (ΔP) is elevated ($24 \text{ cmH}_2\text{O}$) because the C_{RS} is very low ($18 \text{ mL/cmH}_2\text{O}$). **B** The first day after the patient has been switched to the TCAV method, and the lung has begun to reopen showing typical Pressure/Time and Flow/Time curves as seen on a ventilator monitor (red). Although the lung has partially opened, it is still unstable and would rapidly re-collapse at lower airway pressures or if expiratory time was greater than the 0.35 s Release Phase. The C_{RS} has improved ($27 \text{ mL cmH}_2\text{O}^{-1}$) because of the recruited lung tissue (X-ray). Nevertheless, the C_{RS} is low and lung recoil remains high, so the Release Phase is brief. The brief Release Phase generates a small V_T (5.0 mL kg^{-1}), which maintains the ΔP ($13 \text{ cmH}_2\text{O}$) within the safe range. At this time, there are no spontaneous breathing efforts. **C** On Day 2, the lung is nearing full recruitment, as evidenced by a markedly improved chest X-ray. The patient is breathing spontaneously (Flow/Time curve gold waves) and is contributing to the total minute ventilation (MVe). Although the T_{Low} is still set to 75%, the release time is now 0.5 s and V_T have increased (8.2 mL kg^{-1}) with a more fully recruited lung. The ΔP has decreased to $9.7 \text{ cmH}_2\text{O}$, even with a V_T of 8.2 mL kg^{-1} because of an increase in C_{RS} ($59 \text{ mL cmH}_2\text{O}^{-1}$). Only an occasional Release Phase is needed to facilitate CO_2 removal (Flow/Time curve light blue wave), since most of the MVe is generated by the patient's spontaneous breathing (Flow/Time curve gold waves). Spontaneous V_T average 6.0 mL kg^{-1} . **D** On Day 3, the patient is ready to be weaned with restored lung volume. The Release Phase has been eliminated and the patient is generating all of their MVe with spontaneous breathing (Flow/Time curve gold waves). As a result, V_T has increased further (6.8 mL kg^{-1}), and ΔP ($5.4 \text{ cmH}_2\text{O}$) and C_{RS} ($88 \text{ mL cmH}_2\text{O}^{-1}$) are within their normal ranges. Note that a V_T greater than 6 mL kg^{-1} is not harmful (i.e., normal ΔP) when delivered into a fully inflated lung with high C_{RS} [10]. Also, note V_T remains proportional to C_{RS} . $V_T = \text{tidal volume}$, $PEEP = \text{positive end-expiratory pressure}$, $C_{RS} = \text{respiratory system compliance}$, $MVe = \text{minute ventilation}$, and $\Delta P = \text{Driving Pressure } (V_T/C_{RS})$.



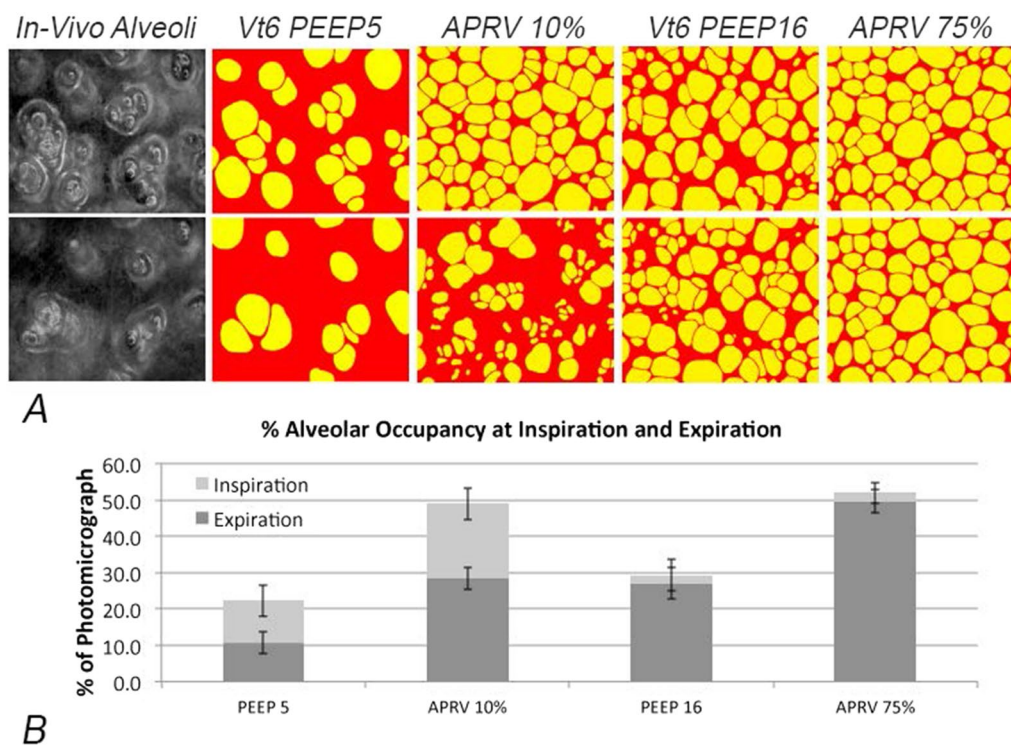
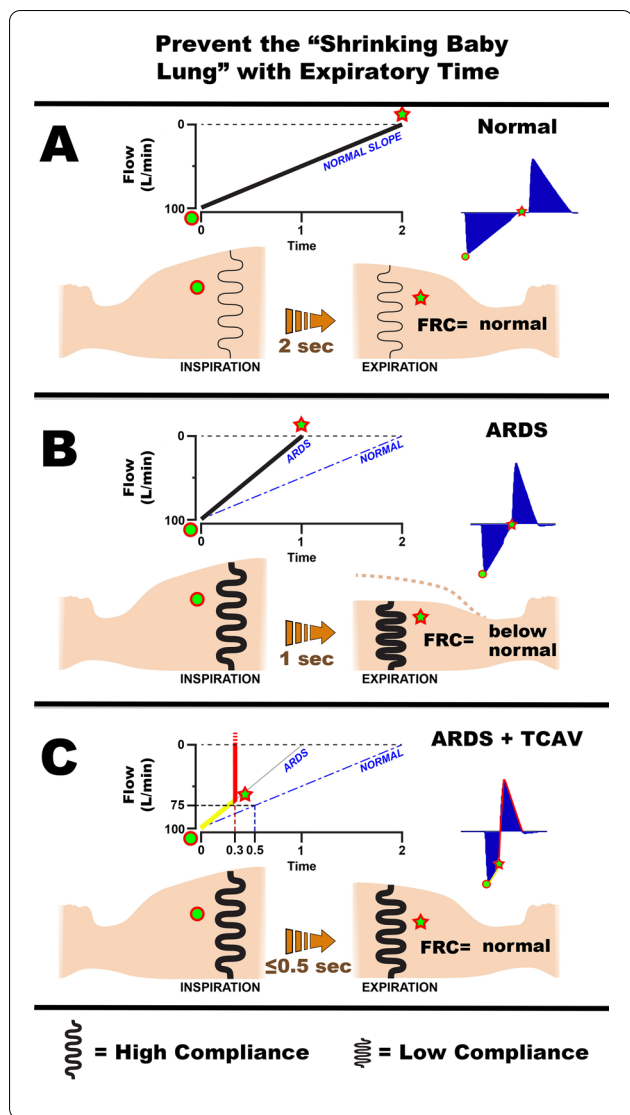


Fig. 6 **A** Photomicrograph of in vivo subpleural alveoli (in vivo alveoli) at inspiration (top panel) and expiration (bottom panel) following lung injury in rats. Alveoli in the four ventilation treatment groups are depicted in yellow, while collapsed alveoli are in red. The images show the impact of ventilation strategies on alveolar recruitment and collapse using a conventional ventilation strategy with a low tidal volume (LV_T) of 6 mL kg^{-1} (Vt_6) combined with either PEEP $5\text{ cmH}_2\text{O}$ (Vt_6 PEEP5) or $16\text{ cmH}_2\text{O}$ (Vt_6 PEEP 16). Also shown for comparison are the results of using APRV with an extended P_{High} (CPAP Phase, Fig. 4B) combined with two expiratory durations set at either 75% of peak expiratory flow (APRV 75%) or 10% of peak expiratory flow (APRV 10%). APRV 75% has a very short expiratory duration, while APRV 10% has a much longer expiratory duration (Fig. 4B, Release Phase). **B** The impact of each ventilation strategy on alveolar recruitment at inspiration (light gray bar) and derecruitment at expiration (dark gray bar) expressed as the percent (%) of the microscopic field. Conventional ventilation using LV_T did not effectively recruit alveoli (PEEP5 and PEEP16). Increasing to PEEP16 reduced the number of alveoli that collapsed during expiration (difference between the light and dark gray bars), but did not recruit as many alveoli as APRV with an extended CPAP Phase. However, using APRV with an extended expiratory duration (APRV 10%) caused many of the newly recruited alveoli to re-collapse. Alveolar collapse at expiration was prevented with the use of a brief expiratory duration (APRV 75%) [58]. (Permission to republish requested)

effectively applies CPAP to the lung, initiating a gradual and sustained alveolar reopening over a prolonged period of time (Fig. 5B–D). Since the time required to recruit some regions of the lung can be extremely long, the benefits of opening the lung in this manner may not be evident for hours or even days (Fig. 5B–D) [32–35]. The level of pressure applied during expiration (P_{Low}) is less critical to the derecruitment process because the brief T_{Low} prevents the lungs from completely emptying by the end of expiration, resulting in a degree of time-controlled PEEP (Fig. 4B, TC-PEEP). Setting P_{Low} to $0\text{ cmH}_2\text{O}$ maximizes expiratory flow and facilitates CO_2 elimination with each breath, thus helping to maintain normocarbia. At the exhalation termination point (T_{Low}), the lung is rapidly re-inflated to the CPAP Phase (Fig. 4B, Gas Flow/Time curve, red arrowhead).

The values of P_{High} , T_{High} , P_{Low} , and T_{Low} thus collectively define how APRV is administered. Using appropriate values for these parameters will mitigate some of the adverse effects of ventilating a baby lung. The question remains, however, as to how these values should be chosen, particularly T_{Low} . Figure 7 shows: (A) normal expiratory flow/time curve, (B) the changes caused by ARDS, and (C) how this information can be used to set T_{Low} necessary to stabilize alveoli and maintain a normal functional residual capacity (FRC). Passive exhalation in the normal lung is slow ($\sim 2\text{ s}$) due a high C_{RS} and low lung recoil (Fig. 7A—thin springs). A functioning pulmonary surfactant system maintains a normal FRC at atmospheric pressure. ARDS-induced surfactant deactivation reduces lung C_{RS} and increases recoil (thick springs) causing a rapid exhalation ($\sim 1\text{ s}$) of gas during expiration (Fig. 7B—ARDS). The FRC can decrease by up to 45% in



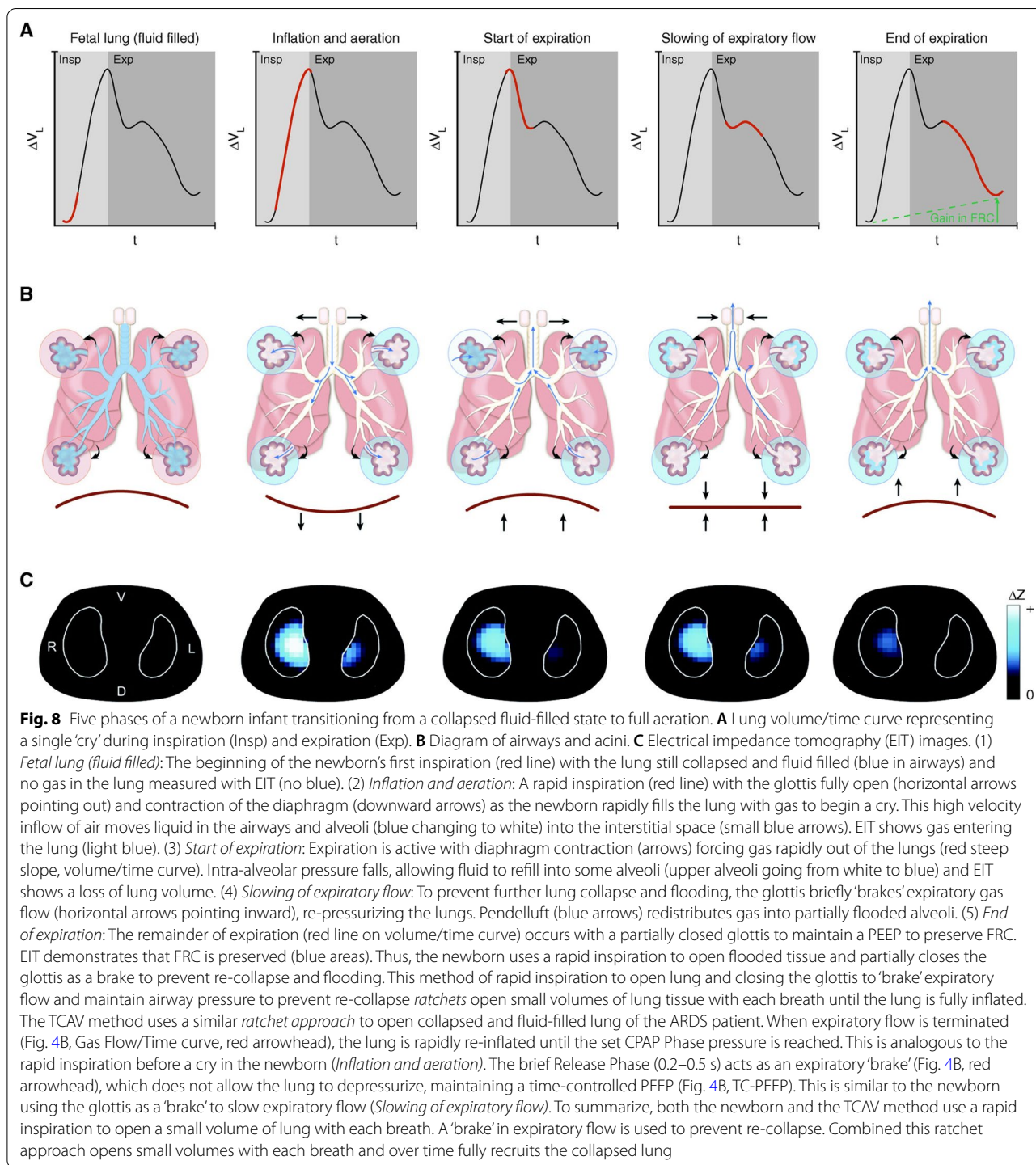
lungs with severe ARDS [64]. Thus, allowing the injured lung to collapse to atmospheric pressure will result in a much lower FRC than in the normal lung. Experience in both the animal laboratory and the intensive care unit (ICU) has demonstrated that the expiratory gas flow curve using the APRV mode can be used in a patient-targeted and adaptable approach to predict the T_{Low} duration necessary to stabilize alveoli.

Using this approach, T_{Low} is set such that expiration terminates when the magnitude of expiratory flow has fallen to a fixed percentage (75%) of its peak value at the start of expiration (Fig. 5C) [65, 66]. This results in T_{Low} values that vary across patients and disease states. For example, patients with severe ARDS typically have less compliant lungs that empty quickly, thus reaching their expiratory termination points (Fig. 7C, 0.3 s) earlier than patients with more compliant lungs (Fig. 7C, 0.5 s).

Fig. 7 Using expiratory time and the airway pressure release ventilation (APRV) mode to maintain a normal functional residual capacity (FRC) and prevent progressive collapse of the ARDS lung (VILI vortex). **A** The Flow/Time curve (Fig. 4B) at the beginning of expiration (green dot) and at end expiration (Release Phase, red star). The normal lung is allowed to fully empty (Flow 0 L/min) to atmospheric pressure (0 cmH₂O). The respiratory system compliance (C_{RS}) in the normal lung is high, and therefore, the lung recoil is low (thin black spring). The slope of the expiratory flow curve (Slope_{EF}) is shallow (NORMAL SLOPE) taking ~2 s for the lung to fully empty. A functioning pulmonary surfactant system prevents lung collapse at atmospheric pressure, and FRC remains normal. The Flow/Time curve that would be seen on the ventilator monitor in blue (Fig. 4B, Gas Flow/Time). **B** ARDS diminishes surfactant function and dramatically decreases C_{RS} , leading to increased lung recoil (thick black spring). This results in a steep Slope_{EF} (ARDS, solid black line) compared with a normal slope (NORMAL, dashed blue line). As a result, the lung empties rapidly (~1 s), and there is a marked reduction in FRC seen as large reduction in chest volume (green star). The Flow/Time curve that would be seen on the ventilator monitor in blue (Fig. 4B, Gas Flow/Time). **C** The TCAV method uses a fraction (75%) of the peak expiratory flow (100 L/min) to set the expiratory duration. Changes in the Slope_{EF} with decreasing C_{RS} will modify the expiratory duration using this method (ARDS = 0.3 s; Normal = 0.5 s at the same 75% fraction). Note that in the ARDS lung the Slope_{EF} (yellow line) is steep and 75% is reached very rapidly (0.3 s) at which point the lung is rapidly re-inflated to the CPAP Phase (red line). In the normal lung, the Slope_{EF} is shallower and takes 0.5 s to reach 75% of the peak expiratory flow. The brief expiratory duration does not give the lung time to depressurize (Fig. 4B, TC-PEEP) or alveoli time to collapse (Fig. 6A, B, APRV 75%) maintaining a near normal FRC and preventing progressive lung collapse (VILI vortex). The Flow/Time curve that would be seen on the ventilator monitor in blue (Fig. 4B, Gas Flow/Time)

This effect can be appreciated by examining the slope of the expiratory gas flow/time curve (Slope_{EF}) from lungs with differing C_{RS} (Fig. 7C—ARDS and NORMAL) [67]. As lung health improves and C_{RS} increases, T_{Low} may be increased accordingly (Fig. 5C—ARDS = 0.3 s; NORMAL = 0.5 s). Thus, setting T_{Low} according to the Slope_{EF} affords a personalized approach to ventilating the injured lung that adapts to a patient's changing physiology. Finally, similar to normalizing V_T to C_{RS} (i.e., driving pressure) to reduce mortality (Fig. 1B), T_{Low} adjusted to 75% of peak expiratory flow produces V_T s (Fig. 5B 6.2 mL/kg and Fig. 5C 9.2 mL/kg) that is proportional to C_{RS} (Fig. 5B = C_{RS} low; 5D = C_{RS} high).

Applying APRV in the above manner requires continuous monitoring of intra-breath expiratory flow as well as the ability to control the termination of expiration. This precise method of setting the APRV mode using the Slope_{EF} is termed the *time-controlled adaptive ventilation* (TCAV) method (Fig. 7C). The TCAV method has been shown to enhance lung protection [63, 66, 68–83] by stabilizing alveoli [63] (Fig. 6A, B—APRV 75%) and progressively reopening recalcitrant regions



of atelectasis (Fig. 5 B–D). TCAV rapidly pulls the lung out of the VILI vortex and then gradually reopens collapsed tissue (Fig. 2) [63, 70, 84].

The TCAV method has been extensively studied by several groups [63, 66, 68, 71–83, 85, 86]. It has been shown to recruit subpleural alveoli in a rat model of ARDS

(Fig. 6, APRV 75%) [63, 71, 86] and reduce tissue damage compared to ARDSNet LV_T strategy in a clinically applicable porcine sepsis and gut ischemia/reperfusion-induced ARDS model [72, 79]. The TCAV method has also been shown to reduce ARDS incidence and mortality in trauma patients [60]. These findings suggest the

physiologic principles upon which TCAV is based represent a successful method to balancing the benefits of positive pressure ventilation against the harm it may cause to an already injured lung.

It must be noted that in patients with expiratory flow limitations (EFL) the TCAV method must be modified. Since flow/time is an integral of volume, airflow limitations are easily depicted with changes in peak expiratory flow rates and can be readily seen at the bedside with flow graphics using the TCAV method. The pattern of airflow limitations results in the following characteristics: (a) The peak expiratory flow rate decreases as expected in diseases with obstructed airways and (b) an uneven pattern of incomplete and sequential gas emptying that greatly increases the deceleration angle of the expiratory flow curve, which is a hallmark of obstructive lung disease. Once EFL is identified, the TCAV protocol is modified to increase the expiratory duration, since more time is needed for the same volume of gas to be exhaled. The TCAV protocol for patients with EFL is beyond the scope of this paper.

Insight into the mechanism by which the TCAV method opens collapsed lung tissue can be gained by analyzing the method the newborn infant uses to open their collapsed lung at birth (Fig. 8) [87]. Spontaneously breathing newborns recruit collapsed lung with a rapid inspiration (Fig. 8—*Inflation and aeration*) and prevent re-collapse of the newly opened tissue by partially closing the glottis to act as a ‘brake’ on expiratory flow (Fig. 8—*Slowing of expiratory flow*). Thus, the method by which nature opens the lung at birth is to inflate a small amount of tissue with each breath and then apply a ‘brake’ to prevent the newly opened tissue from re-collapsing. When a force causes a strain in one direction and some type of ‘brake’ prevents strain in the opposite direction it is termed a *ratchet*. Therefore, nature’s strategy is to ratchet open lung tissue with each breath until the lung is fully inflated.

We postulate that the TCAV method uses the ratchet mechanism to open collapsed lung in the ARDS patient. There is a rapid lung inflation from the termination point of expiration (Fig. 4B, Gas Flow/Time curve) that recruits a small portion of collapsed lung, combined with a brief Release Phase to ‘brake’ expiratory flow preventing derecruitment during expiration. In addition, the prolonged CPAP Phase accelerates recruitment of alveoli with long opening time constants (Fig. 4B, CPAP Phase). Addition of CPAP has been shown to significantly increase FRC in premature infants [88].

If our hypothesis is correct, the *ratchet approach* is a novel and innovative method of lung recruitment. Unlike

the OLA, which attempts to open the entire lung in a seconds or minutes [89], the TCAV method ratchets open small volumes of lung with each breath that will progressively open the entire lung over hours or days. As described above a ratchet is a device (ventilator) that causes an object to strain in one direction (alveolar recruitment during inspiration), while applying a ‘brake’ (very short expiratory duration) necessary to prevent strain in the opposite direction (prevent alveolar collapse during exhalation). An example of the ratcheting approach on progressive lung recruitment is shown in Fig. 5.

Conclusions

Low tidal volumes and airway pressures using the ARD-Net method can push the lung with mild ARDS into the VILI vortex. To prevent progressive lung collapse, the time-dependent nature of alveolar opening and collapse must be taken into account. The TCAV method to set APRV uses: (i) the ratchet approach combined with an extended inspiratory duration necessary to recruit alveoli and (ii) a brief expiratory duration to ‘brake’ the derecruitment of rapidly collapsing alveoli. The TCAV method is personalized and adaptable and has shown promising results in animal models of ARDS and has yielded positive clinical outcomes in the ICU. Whether TCAV, or a similar strategy, can significantly reduce ARDS-related mortality when implemented in a large-scale clinical trial remains to be seen, but it is clear that a new approach to MV in ARDS is needed. We propose that ventilating patients with ARDS in a manner that specifically addresses the time dependence of R/D is a logical strategy for interrupting and reversing the VILI vortex. Accordingly, we believe consideration should be given to the design of a clinical trial comparing the TCAV method to the current standard of care in ARDS patients.

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Competing interests

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