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Ventilator-Associated Lung Injury

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Introduction

The provision of ventilatory support as an intervention dates back to biblical times with passages from the bible stating "And the Lord God formed man of the dust of the ground and breathed into his nostrils the breath of life. (Genesis 2:7) And he [Elisha] went up, and lay upon the child, and put his mouth upon his mouth and the flesh of the child waxed warm. (II Kings 4:34)." Invasive mechanical ventilation dates to the 16th century from Vesalius who as Professor of Anatomy first described the possibility of tracheotomy and the rising of lungs. Fothergill reported in the *Phil. Trans.* in 1745 a case of a man revived by a surgeon, Mr. William Tossack, who "applied his mouth close to the patient's, and, by blowing strongly, holding the nostrils at the same time, raised his chest fully by his breath. The surgeon immediately felt six or seven very quick beats of the heart…" and the patient eventually recovered. Fothergill says, "It has been suggested to me, by some of my acquaintance, that a pair of bellows might possibly be applied with more advantage in these cases, than the blast of a man's mouth; but if any person be got to try the charitable experiment by blowing, it would seem preferable to the other. First, as the bellows may not be at hand: secondly, as the lungs of one man may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determined; Thirdly, the warmth and moisture of the breath would be more likely to promote circulation, than the chilling air forced out by a pair of bellows" (Fothergill, 1744). This key application of positive pressure ventilation during resuscitation is often the determinant for admission to modern day intensive care unit. Indeed, the wider use of invasive positive pressure ventilation was first introduced by anesthetist Bjorn Ibsen during the polio pandemic in Copenhagen. Ibsen saw the established methods (negative pressure body-cuirass respirator) were being overwhelmed in the pandemic and he established simple anesthetic methods of manual intermittent positive pressure ventilation outside of the regular operating theater environment to better ventilate the polio patient (Trubuhovich, 2004).

The "Baby" Lung

A full appreciation of the concept of ventilator-associated lung injury (VALI) cannot be obtained without a knowledge of the five decades of clinical management and research that has led to the current status of interventions. The lung during acute respiratory distress syndrome (ARDS) has been labeled as "stiff" and the distribution of ventilation was assumed to be similar across all areas of

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lungs. Indeed, the physiological targets for ARDS management during the 1960s and 1970s were $PaCO_2$ and PaO_2. The former being managed by higher minute ventilation through high pressure, high volume and high respiratory rate with resultant consequences such as pneumothoraces (Kumar et al., 1973). It was soon widely acknowledged that mechanical ventilation could cause harm. Oxygenation was managed through the application of PEEP which showed a linear relationship with PaO_2. The overarching approach of that era was the thought that PEEP led to hemodynamic compromise and high FiO_2 was detrimental. It was not until the advent of CT scans and the appreciation of the dependent nature of the ARDS lung that the functional and smaller 'baby' lung components came to the fore (Gattinoni et al., 1986; Maunder, 1986; Gattinoni and Pesenti, 2005). Indeed, it was only then appreciated that the ARDS lung was not stiff but small, with generally preserved specific tissue compliance (compliance/normally aerated tissue) (Gattinoni et al., 1987, 1993). These studies showed that respiratory compliance correlated well with the amount of normally aerated tissue and hence the compliance measured was a result of the dimension of the "baby" lung.

Further studies have attempted to dissect the mechanisms that drive ventilator associated lung injury (VALI) and distinguish them from the underlying cause of respiratory failure. However, the "magic bullet" for VALI reduction remains elusive. Indeed, the heterogeneity within and between patients with ARDS at a single time-point (e.g. admission versus over time) makes it difficult to implement a catch all strategy. Indeed, a precision medicine based strategy through the detection of and personalized application of interventions is the holy grail for reduction of VALI to minimal levels.

Pulmonary Physiology and VALI

Gas flow into the alveoli from the airways occurs when there is a sufficient pressure gradient to overcome the elastic properties of the lungs and resistance of the airways. At the end of inspiration, gas flow is zero, and the force needed to maintain the airspaces open is the transpulmonary pressure (Ptp = the alveolar pressure minus the pleural pressure). A positive Ptp accelerates flow into the airspaces (**Fig. 1**). The determinants of the transpulmonary pressure gradient change depending on the status of the patient's lungs and type of ventilation. For instance, the pressure gradient in healthy lungs is generated through the creation of a negative pleural pressure in comparison to an alveolar pressure which is equivalent to atmospheric pressure. Patients who are anesthetized and paralyzed on positive pressure ventilation have an increased airway pressure (above pleural pressure) that drives gas flow into the alveoli. Patients that have respiratory distress who are spontaneously breathing may create very negative pleural pressures and when positive pressure is applied in addition, generate extremely positive Ptp gradients. While the Ptp determines the extent to which the lung volume changes its direct measurement is very cumbersome. The pleural pressure changes with gravity and hence, there are regional variations in the Ptp. In the broader clinical and research context, esophageal pressure is used as a surrogate for pleural pressure such that the Ptp can be estimated (Akoumianaki et al., 2014).

Biophysical Concepts

The lungs extracellular matrix receives the forces applied during mechanical ventilation. This consists of a central 'axial' component anchored to the hilum, along the conducting airways down to the alveolar airsacs. Peripherally, the airways are anchored to the visceral pleura. This lung skeleton is linked at the alveolar level and forms a continuum. Two types of fibers underpin the architecture of this lung skeleton: (1) extensible elastin and (2) inextensible collagen. The latter determines the maximal distensibility of the lung as they unfold to achieve a maximal length. Further distension at whole lung and at regional levels is prevented once the lungs reach total lung capacity. After injury, the regional variation in distension of the lung leads to different maximal capacities in discrete lung areas. The alveolar parenchymal cells are anchored to this collagen and elastin skeleton through cell-matrix interactions (e.g.

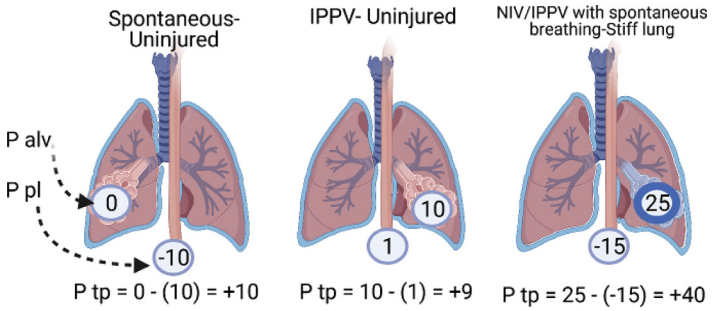

Fig. 1 Transpulmonary pressure (Ptp) is the difference between alveolar pressure (Palv) and pleural pressure (Ppl); i.e. Ptp = Palv – Ppl. During spontaneous ventilation, respiratory muscles (left panel) create a negative intrapleural pressure leading to a positive Ptp difference to enable flow of gas through an airway open to atmosphere. During anesthesia, intubated patients requiring invasive positive pressure ventilation (IPPV) (middle panel) creates a positive alveolar pressure which drives the Ptp difference and gas flow. Injured or stiff lungs lead to the creation of an extreme negative Ppl and often patients' gas exchange deteriorates leading to the requirement of further positive pressure ventilation (non-invasive or invasive). The total contribution could indeed create considerable Ptp gradient leading to high levels of stress and strain delivered to the lung.

integrins) and accommodate the shape as the skeleton deforms. Following the application of a force to the fibrous skeleton through mechanical ventilation, there is the development of an internal tension within the lung skeleton through spatial rearrangement of molecular structures, which is equal and opposite to the force applied on the fibers by the ventilator.

Stress and Strain

Stress and strain phenomena are bioengineering concepts that facilitate an understanding of how ventilatory forces can lead to injury at the microstructural level within the lung. Hooke's law states that the force (F) needed to extend or compress a spring by some distance (x) scales linearly with respect to that distance. That is, $F_s = kx$, where k is the spring constant which characterizes elastic properties of the spring's material (i.e., its stiffness), and x is small compared to the total possible deformation of the spring. Though this "law" was established for mechanical springs, it has since been related to all materials of known surface area. The relationship used most readily today is the direct proportionality between stress and strain, but the area these materials possess must be accounted for. Stress is the distribution over a unit area of a force ($\sigma = F/A$) that opposes a load and is equivalent to the tension applied to the fibers (the spring). The SI unit for stress is pascals (Pa) which is equal to 1 Newton per square meter. The application of stress leads to a change in the length of the fibers from a state of rest. Strain is a geometrical measure of deformation (change in size and shape) in relation to the initial composition prior to the force being applied. Hence, as per Hooke's Law, stress = k multiplied by strain where k is Young's modulus of elasticity (the tendency of an object to deform along an axis when opposing forces are applied along that axis). The higher the modulus, the more stress is needed to create the same amount of strain; an idealized rigid body would have an infinite Young's modulus. Conversely, a very soft material such as a fluid, would deform without force, and would have zero Young's Modulus. The clinical surrogate for strain is the ratio of volume change to the end-expiratory lung volume (EELV). Clinically, the surrogate of stress is the applied pressure, which is not the airway pressure, but the TPP (as discussed above). However, these surrogates are global indices of pulmonary state and do not consider the regional inhomogeneity of pulmonary mechanics and ventilation. Once the critical stress threshold is reached, the tensile properties of the non-elastic collagen are overcome leading to rupture (or 'barotrauma'). If this critical threshold is not reached, there may still be the application of unphysiological levels of strain depending firstly on the mechanical properties of the skeleton and secondly on how different regions respond to the forces delivered by the ventilator. This strain (or 'volutrauma') leads to the activation of mechanosensors which anchor the cells to the skeleton, while transduction of potential and kinetic energy to heat and chemical energy leads to the development of inflammation (or 'biotrauma').

Regional Inhomogeneity

It is a well-established concept that the high pressures and high volumes being delivered to the "baby" lung and the consequent "over distension" of this more compliant area leads to the injurious manifestation of mechanical ventilation even at low lung volumes (Terragni et al., 2007) (**Fig. 2**). Additionally, there is considerable lung inhomogeneity which is dependent on the distinct

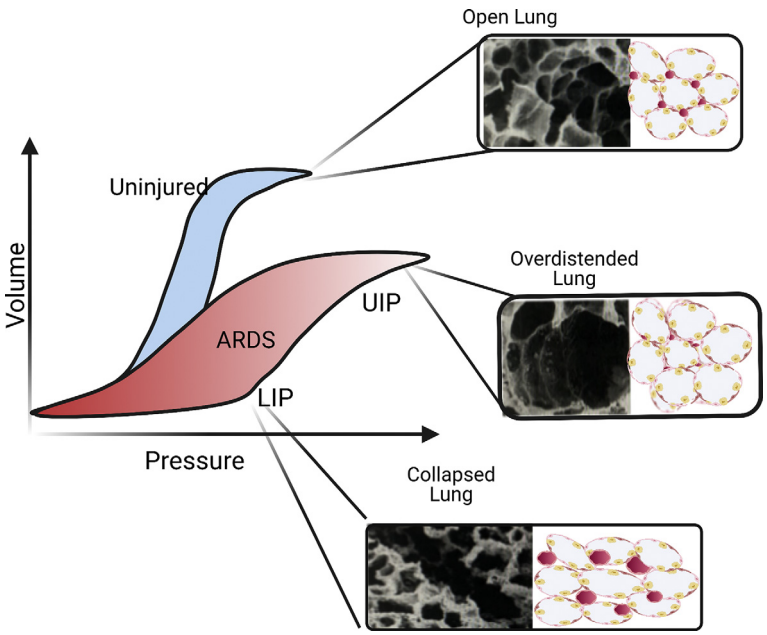

Fig. 2 The application of positive end-expiratory pressure (PEEP) induces the opening of alveolar units once above the lower inflection point of the pressure-volume curve. Overall, the ARDS lung has a worse compliance and higher PEEP levels can recruit collapsed lung units, modest levels of PEEP lead to overdistension of lung units within the already aerated but smaller "baby" lung.

pathological processes and host response to the insult (Cressoni et al., 2013; Terragni et al., 2007). This is physiologically demonstrated through the application of PEEP. PEEP effects are two-fold, the first is over distending the lung that is already open, i.e. the increased stress and strain with unfolded collagen fibers reaching their maximal length and an opposing force being placed on the elastic fibers; the second, the opening of new lung units and increasing resting lung volume (i.e. EELV). While the former leads to an increase in strain the latter reduces it, with the ultimate effect varying between patients and within the same patient at different times as disease progresses (Fig. 3).

Given strain is the change in size of the baby lung from its resting end-expiratory lung volume (EELV) (i.e. Vt/EELV) when Vt/EELV = 1 then the lung doubles in size in a single breath. In any patient at any given time, the volume of the baby lung may be highly variable. When the baby lung volume decreases, the potential for a set Vt to induce over distension becomes higher. Hence, PEEP response to EELV should theoretically enable a Vt/EELV of 0.8–1.0, considered to be optimal for lung protection. However, the dynamic measurement at the bedside of EELV due to the changes in parenchymal disease over time in ARDS remains elusive.

Spatial Heterogeneity and Cyclic Deformation

The distribution of stress and strain is heterogenous within the aerated baby lung. In particular, the flooding or collapse of a nearby alveolar unit inevitably leads to the deformation and elongation of collagen fibers of neighboring units. This is apparent in confocal studies examining alveolar dynamics in real time in preclinical models of ARDS (Perlman et al., 2011). The application of PEEP is a balance between ability to recruit collapsed tissue and the unavoidable damage in the "baby lung" as a result of overdistension. It is more established now that the mechanistic benefit of higher PEEP depends on severity of disease (Cressoni et al., 2017). Furthermore, the application of PEEP with low tidal volumes to reduce "cyclic" strain, in the context of the same peak strain, leads to a lower degree of lung injury. Clinically, this equates to (1) a sustained deformation at the end of expiration and maintaining as high as feasible EELV, (2) a reduced tidal volume and subsequently a lower cyclic deformation; and (3) an upper limit of inspiratory pressure to prevent the excessive stress and rupture of the skeleton. Overall, VALI occurs when tidal volume is increased at a given end-inspiratory pressure. PEEP can obviate this as when optimal levels of PEEP are added to reach the same end inspiratory pressure, although the occurrence of microvascular permeability alterations are not prevented, the development of edema and severity of

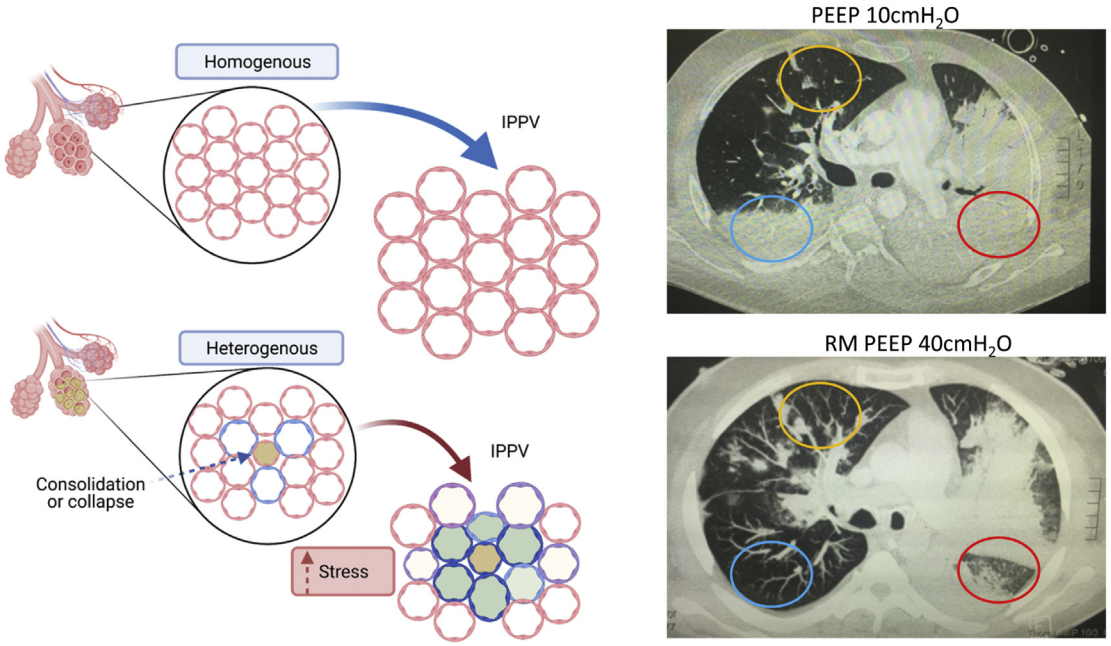

Fig. 3 The application of positive end-expiratory pressure (PEEP) induces the opening of alveolar units to enable them to contribute to gas exchange. The CT scans are of the same patient supported on extracorporeal membrane oxygenation at a PEEP of 10 cmH_2O and 40 cmH_2O. In the ARDS lung (CT images), there is a dependent consolidation (top CT: blue circle) which with higher levels of PEEP (e.g. during a recruitment maneuver) can open basal lung units (bottom CT: blue circle). However, this also leads to the over distension of already open units (orange circles). Depending on the state of the alveolar unit and the dependency of nearby units, the application of a pressure or volume can have quite distinct effects. An alveolar unit with relatively normal compliance (e.g. in the "baby" lung) will lead to a homogenous increase in lung volume causing homogenously increased stress and strain to these units (orange circles on CT scans). In contrast, application of pressure and volume to consolidated and collapsed areas can open up some areas (blue circles on CT scans) but can also in the same patient leads to greater stress in those units surrounding consolidated areas whilst achieving no alveolar recruitment. Indeed, this inhomogeneous lung architecture and inhomogeneous delivery of force of ventilation (red circles on CT scans) makes completely mitigating VALI almost impossible and showcases the balance of goals versus penalties required from any ventilation strategy.

tissue injury is reduced, (Dreyfuss et al., 1988). However, PEEP can be detrimental when it results in overdistension, as the extent of edema actually increases (Dreyfuss and Saumon, 1993).

Mechanical Power

Most traditional surrogate measures of ventilator associated lung injury only use static measures of respiratory physiology, for instance, plateau pressure and tidal volume. However, the dynamic exposure of the lung to these variables, including flow and frequency at which they are applied, has only recently been implicated through the mechanical power equation (Gattinoni et al., 2016). As discussed, ventilator pressure, volume, flow and respiratory rate can cumulatively and synergistically induce VALI. Each of these modalities contributes to the delivery of energy to the lung parenchyma and the variability in lung architecture that accepts this energy determines the injurious response. Mechanical power potentially presents a single conceptual variable to incorporate each of these component ventilation settings to better estimate what forces the lung is exposed to such that it can be clinically better understood. However, there are considerable assumptions that are made in this approach that utilizes the classic equation of motion to determine the energy delivered per breath based on the ventilatory settings. For instance, it assumes a linear relationship between pressure and volume of the lung, but most importantly, it does not take into account the volume of the baby lung to which the energy is delivered. Hence, any change in lung dimensions and specific lung elastance will lead to a lower mechanical power required to induce VILI. Furthermore, an equation cannot account for the regional and spatial heterogeneity encountered during the application of each breath. Additional details about the concept of mechanical power are discussed by Gattinoni et al. (2016).

Progression of ARDS

The vulnerability of the lung to VALI occurs through mechanisms arising from both internal pulmonary and external ventilatory factors, and how they interact with one another. Current targets of lung protective ventilation (e.g. tidal volume) only consider the settings delivered by the ventilator, with no specific targeting of progression of lung disease and changes in baby lung volume. 'Baby lung' volume reduces as lung injury worsens and hence, the alveolar ventilation must increase to clear the same amount of carbon dioxide. Over time, this is unattainable, and a critical threshold of disease severity is reached. Ultimately, a lung protective tidal volume and increasing respiratory rate to achieve a given expired minute volume (in an attempt to attain a normal arterial pH) will lead to an increased anatomic component of dead space per breath. Indeed, worse dead space fraction on admission and over the first few days is associated with worse outcome (Nuckton et al., 2002; Morales-Quinteros et al., 2019). Furthermore, a higher respiratory frequency also promotes VALI through repetitive opening and closing of injured lung units with subsequent inflammatory edema production, loss of surfactant production and increased strain within microstructural elements (known as 'atelectrauma') (Hotchkiss et al., 2000).

The kinetics of progression and resolution of individuals with ARDS remains uncertain. The Berlin definition taskforce assessed progression of ARDS over 7 days and found 29% of patients progressing from mild to moderate, and 17% from both mild or moderate to severe (The ARDS Definition Task Force, 2012). The Lung SAFE study showed 26% of patients progressing from mild to moderate, and 17% from both mild or moderate to severe (Bellani et al., 2016). A secondary analysis of the Lung SAFE study shows that only 24% of ARDS patients resolved within 48 h whereas 76% persisted to fulfill ARDS diagnostic Berlin criteria after 48 h of initial ARDS diagnosis (Madotto et al., 2018). Those which resolved, had a higher PaO_2/FiO_2 ratio, reduced multiorgan failure (with a lower Sequential Organ Failure Assessment (SOFA) score) and a mortality of 31%. In comparison, those patients which had persistent ARDS at day 2 had an overall hospital mortality of 41% but this mortality increased with severity of disease, from 36% with mild, to 39% with moderate and 57% with severe ARDS. In a multivariate analysis, pneumonia was a risk factor for persisting ARDS. Other factors measured on day 1 significantly associated with persistent ARDS were lower PaO_2/FiO_2 ratio, higher peak inspiratory pressure (PIP), higher non-respiratory SOFA score, and higher tidal volume (Madotto et al., 2018).

The limited capacity of the baby lung, especially as severe disease worsens, when associated with injurious ventilation, leads to an accelerating progressive deterioration in pulmonary function as a result of biomechanical forces, which eventually lead to hyperinflation and changes in pulmonary vascular flow with consequent cor pulmonale and eventually right heart failure (**Fig. 4**) (Vieillard-Baron et al., 2013; Boissier et al., 2013; Chiumello and Pesenti, 2013). This coupling between the pulmonary vasculature and the right ventricle was particularly important in ARDS induced by more vascular inflammation as experienced globally during the coronavirus pandemic (Patel et al., 2020; Ridge et al., 2020; Tavazzi et al., 2019; Bleakley et al., 2020).

Self-Inflicted Lung Injury

While clearly having some advantages, including the reduction in ventilator associated pneumonia, an increase in rehabilitation potential and reduction in ventilator induced diaphragm dysfunction, spontaneous breathing in patients with ARDS is emerging as a potential major contributor to lung injury through a process known as P-SILI (patient self-induced lung injury) (Grieco et al., 2019). The process is thought to also occur in patients who breath spontaneously with non-invasive ventilation and in

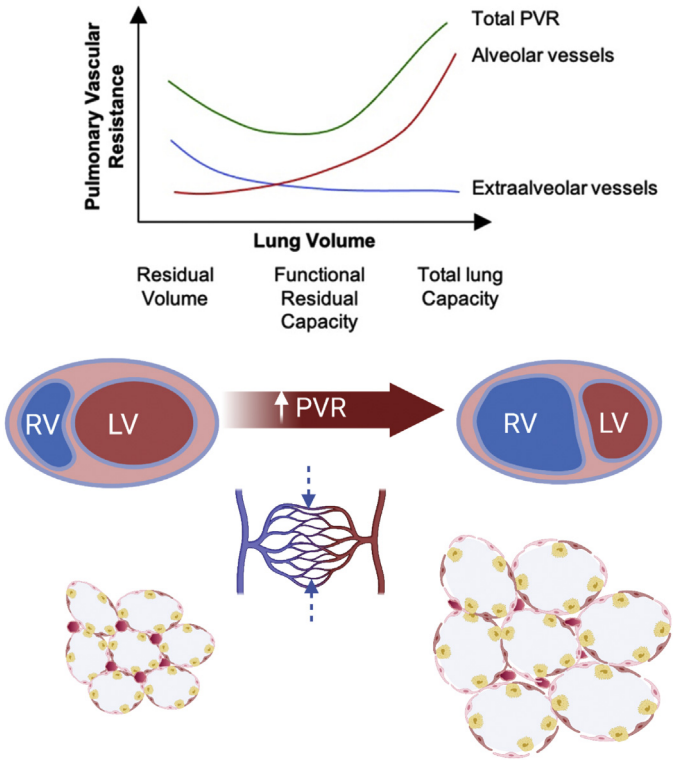

Fig. 4 The pulmonary vascular resistance (PVR) is dependent on the volume of the alveolar units. PVR is lowest at functional residual capacity (FRC) and increases as the (1) the lungs collapse (as a result of compression of extra-alveolar vessels) and (2) the lungs over distend at total lung capacity (as a result of compression of alveolar capillaries). The increase in PVR as a result of overzealous application of higher pressures in non-recruitable lung compounds the established vascular lung injury seen in ARDS, leading to high pulmonary arterial pressures and significant right ventricular dilatation and failure, the latter known as acute cor pulmonale.

patients with respiratory failure even without any form of ventilatory support. Hence, the term ventilation-associated lung injury would seem more appropriate (Gattinoni and Quintel, 2016).

Unlike in mandatory invasive ventilation where peak airway pressure may be a useful surrogate, the major determinant of TPP in spontaneously breathing patients is the inspiratory effort, which can be measured by the negative deflection in esophageal pressure during breathing. If high, the TPP generated by the respiratory muscles can result in regional variation in lung stress accompanied by large uncontrolled tidal volumes affecting the 'baby lung' and contributing to both barotrauma and volutrauma. In some cases, the low levels or complete lack of PEEP in these patients leads to cyclical opening and closing of alveoli resulting in 'atelectrauma,' which may be exacerbated by high respiratory rates. Furthermore pendelluft, the process by which gas transfers between alveolar units during the same breath, is exacerbated by spontaneous breathing trials (Yoshida et al., 2013; Coppadoro et al., 2020). In ARDS this leads to a time dependent increase in distribution of gas and therefore stress from non-dependent to dependent areas, potentially worsening lung injury. Finally increased work of breathing can result in high vascular transmural pressures leading to an increase in permeability causing pathophysiological changes similar to those seen in negative pressure pulmonary edema (Grieco et al., 2019).

Evidence for P-SILI comes directly from animal studies (Mascheroni et al., 1988; Yoshida et al., 2012) and is supported by clinical data showing neuro-muscular blockade improves clinical outcomes and reduces bio-inflammation (Mascheroni et al., 1988; Yoshida et al., 2017). It is not yet clear which patients are at risk of P-SILI and why some patients can tolerate a high TPP and why some cannot. Certainly, in controlled experiments in marathon runners tidal volumes up to 3 L did not induce significant injury (Guenette et al., 2007). This is likely as a result of physiological increases in both alveolar and pleural pressures creating relatively modest changes in TPP and increases in PEEP from upper airway maneuvers. Some authors have suggested that those most at risk are patients with a PaO_2/FiO_2 ratio of <200 mmHg. While others have suggested that the increase risk of P-SILI can be ameliorated with application of adequate PEEP which reduces the work of breathing. This may go some way to explain the benefits of helmet vs mask NIV in improving outcomes from respiratory failure (Patel et al., 2016).

Biological Consequences of VALI

The injured lung already has a physiological and biological pre-disposition to further insults induced by VALI. As discussed previously, the injurious mechanisms of VALI have been attributed to excessive pressure (barotrauma), excess volume or overdistension

(volutrauma), and shear forces applied as a result of cyclical opening and closing of lung units (atelectrauma). Each of these induce biophysical cellular and inflammatory responses within the lung (or biotrauma). Firstly, direct physical disruption or stress failure occurs easily in the thin alveolar capillary membrane where already fragile capillaries are exposed to excessive longitudinal forces and high transmural pressures (West et al., 1991; Fu et al., 1992). Secondly, at a cellular level the potential and kinetic energy delivered into the lung by positive pressure ventilation, is transduced to heat and chemical energy through mechanotransduction. The mechanisms through which stress and strain are propagated at a cellular and molecular level are poorly understood but may include stretch activated ion channels, changes in the cytoskeletal matrix, and actual physical deformation and breaks in cellular architecture (lung parenchymal cells and marginated leukocytes). Finally, further de-compartmentalization through translocation of alveolar inflammatory mediators (e.g. cytokines, bacterial products, damage-associated molecular patterns etc.) occurs as a result of injury to the pulmonary endothelium subsequently leading to the systemic propagation of extrapulmonary inflammation and multi-organ injury (Ranieri et al., 1999; Imai et al., 2003). Given the surface area within the lung and the number of breaths a patient can acquire over the course of an ICU stay, the accumulation of cellular biological responses can equate to a significant cumulative burden of injury and inflammation. In particular, the progressive application of stress and strain can lead to maladaptive reparative responses such as epithelial-mesenchymal transition implicated in the development of fibrosis (Cabrera-Benítez et al., 2012). It has been shown that volutrauma as opposed to atelectrauma is associated with higher cytokine release suggesting that low tidal volumes with an optimal PEEP approach may induce lower levels of inflammation as a result of mechanical ventilation (Wakabayashi et al., 2014). Indeed, blockade of numerous inflammatory pathways has been shown to attenuate the injurious response to mechanical ventilation, however, none have been translated to the bedside (Wilson et al., 2003; Bertok et al., 2012).

Clinical Management

As detailed above, ARDS is a heterogenous entity which not only differs between patients but also within patients as disease progresses. Indeed, ARDS can evolve rapidly from focal areas of edema and consolidation to complete obliteration of airspaces with fluid within hours. Given the short course of injury this is likely secondary to the natural progression of disease. In contrast, some patients do not deteriorate rapidly and the clinical management of ventilation in ICU requires the focused repetitive analysis of not only disease progression but also the mitigation of VALI. This requires constant attention at the bedside which is currently not immediately deliverable due to the lack of specific clinical or biological markers of VALI. Indeed, all interventions currently for ARDS are aimed at reduction in actual regional heterogeneity and edema or promoting more homogenous delivery of lung protective ventilation (Griffiths et al., 2019). As disease worsens the setting of the ventilator requires difficult decisions about the approach of the lesser evil: application of lung protective ventilation and permissive hypercapnia, versus the application of higher tidal volumes to mitigate respiratory acidosis. This needs to be aligned to the prediction for disease progression such that application of extracorporeal support, which can provide true lung rest while maintaining optimal gas exchange.

Ventilatory Management

The application of low tidal volume is mainstay of protection of the baby lung from further VALI. The seminal ARMA study by the ARDSNet investigators showed that a 6 mls/kg versus 12 mls/kg ventilation strategy in ARDS led to a 9% absolute reduction in mortality (39.8% versus 31.0%) (The ARDSNet Investigators, 2000). However, the use of 6mls/kg tidal volume is based on ideal predicted body weight using the ARDSNet formula (http://www.ardsnet.org/tools.shtml). This volume does not take into account the actual volume of the baby lung or the progression of disease. Hence, it is likely that even lower tidal volumes could be of even more benefit. However, this ultra-low tidal volume strategy e.g. 3mls/kg, would require additional support for gas exchange i.e. CO_2 removal devices (Bein et al., 2013; McNamee et al., 2017).

The "open lung" approach is crucial to optimize the end-expiratory alveolar collapse such that there are improvements in gas exchange but also to prevent the repetitive opening and collapse of alveoli that induce the atelectrauma component of VALI. An increase in the number of alveolar units involved in gas exchange can be achieved through the application of recruitment maneuvers to open collapsed units and the subsequent setting of PEEP to maintain them in an open state above the lower inflection point on the static pressure-volume curve (Amato et al., 1998). However, the optimal PEEP required changes constantly given the instability of these units during lung injury. As a result of the regional inhomogeneity in ARDS, a certain PEEP setting may allow some units to be recruited to reduce shunt by taking part in gas exchange, while concurrently leading to overdistension of another region of lung with subsequent increases in pulmonary vascular resistance, the latter leading to a compromise in venous return and inducing right heart dysfunction. Briel et al. conducted a metanalysis of three trials examining high and low PEEP strategies in ARDS (Brower et al., 2004; Meade et al., 2008; Mercat et al., 2008) and concluded that a higher PEEP could lead to a 5% absolute risk reduction in mortality in those with moderate/severe ARDS (Briel et al., 2010). In addition, it has been shown that a ventilator driving pressure of $>16cmH_20$ is associated with a significant increase in mortality (Amato et al., 2015). In a large cohort study, Amato and colleagues showed a strong negative association between driving pressure and survival even though all the ventilator settings that were used were lung protective. Importantly, the protective effects of higher PEEP were noted only when there were associated with decreases in driving pressure. Hence, the pressures set on the ventilator should be determined by the diseased lung's pressure-volume relationship which is often unknown or difficult to determine. This personalized ventilator management demands the

application of mechanical ventilation according to the physiological state of the diseased lung at that time. For instance, accurate measurement of the degree of recruitable lung could improve the ventilator driving pressure.

PEEP titration does not take into account the true transpulmonary pressure. Talmor et al. considered the measurement of a surrogate of pleural pressure (by measuring esophageal pressure) to target an end-expiratory Ptp of 0–10 cmH_2O and an end-inspiratory Ptp of up to 25 cmH_2O. This study aimed to apply a more homogenous PEEP application targeted to lung protective transpulmonary pressure targets and showed an improvement in oxygenation with a tendency towards improved 28-day survival (Talmor et al., 2008). A recent study also showed that non-personalized recruitment of the lung utilizing high pressures can lead to harm (ART Investigators, 2017), while, a machine learning analysis of the data from this study showed that the negative impact was greater in a proportion of patients with pneumonia induced consolidated lung, which is more likely to be non-recruitable (Zampieri et al., 2019). Hence, pulmonary recruitment and its maintenance needs to be tailored to the state of the lung and an assessment of recruitability is key to avoid further VALI.

Adjunctive Management

As discussed above, self-inflicted lung injury occurs when trans-pulmonary pressures exceed a threshold at which damage starts to occur. Emerging evidence suggests that patients can exacerbate their own lung injury whether breathing with or without non-invasive support. Hence, the application of neuromuscular blocking agents (NMBA) to "take over" the delivery of lung protective ventilation to avoid excessive generation of Ptp gradients and patient-ventilator asynchrony has gained common application in the ICU. Papazian et al. tested the administration of NMBAs within 48 h of ARDS diagnosis for 48 h (Papazian et al., 2010). This study showed that 90-day mortality after adjustment for both the baseline PaO2:FIO2 and plateau pressure and the Simplified Acute Physiology II score, was improved from 33.3% to 23.7%. Interestingly the separation between groups with respect to mortality occurred after 16 days suggesting that the mechanism for this could have been the higher number of organ failure free days in the cis-atracurium group. In essence, a potential reduction in biotrauma. A more recent study by the PETAL clinical trials network examined the administration of a 48-h continuous infusion of cisatracurium with deep sedation versus a standard care approach without routine neuromuscular blockade and with lighter sedation targets (The NHLBI PETAL Clinical Trials Network, 2019). This study was stopped early in view of futility for showing no benefit. The use of non-invasive ventilation and HFNC to manage severe acute respiratory failure has gathered much interest in recent years. Both non-invasive ventilation and HFNC can improve oxygenation, reduce dyspnoea and recruit more alveolar sub-units through the application of PEEP (Grieco et al., 2019). This has led to some studies showing up to two-thirds of those patients with ARDS treated with NIV can potentially avoid intubation (Antonelli et al., 1998). NIV has been particularly effective when delivered by hood where PEEP can be applied more consistently and P-SILI prevented by off-loading the respiratory muscles (Patel et al., 2016). However, patients who failed NIV, who subsequently required intubation were burdened with worse outcomes likely as a direct result of high levels of stress and strain caused by high work of breathing (Bellani et al., 2017). The ideal timing for intubation and what constitutes failure of NIV therefore remains controversial and is an especially hotly debated topic in patients with COVID-19, with proponents of both early intubation (Gattinoni et al., 2020) and those who believe a trial of NIV prior to intubation is warranted (Yoshida et al., 2012) putting forward convincing arguments. Further studies are required to help delineate a population who may benefit from NIV and who should be managed with early intubation and neuro-muscular blockade with the aim of avoiding self-induced lung injury and improving outcomes in both groups.

The application of prone position is key in the management of respiratory failure and mitigation of VALI. Approximately 70% of prone patients respond with respect to oxygenation (Slutsky and Ranieri, 2013). However, the mortality benefit from prone position is likely to be a result of a reduction in VALI through a variety of mechanisms including increased EELV, improved ventilation-perfusion matching, better homogenous distribution of lung stress and strain, as well as a reduction in resultant loading of the right ventricle (Guérin et al., 2020). Indeed, Guerin and colleagues found that the application of 16 h per day of prone position in a cohort of patients with ARDS (PF ratio < 150 mmHg; and $FiO2 > 0.6$) showed a reduction in mortality from 37.7% to 20.1%. There were improvements in not only PaO_2/FiO_2 in the prone group but also reductions in PEEP and plateau pressure (Vieillard-Baron et al., 2007).

The ultimate intervention for lung rest is the application of partial or full support with extracorporeal membrane oxygenation (ECMO). This avoids the excess injury caused by mechanical ventilation but brings its own challenges and risks. Veno-venous ECMO is the mainstay of therapy for severe ARDS refractory to adjunctive ARDS therapies (such as prone position and high PEEP) but where VALI to the baby lung is occurring. Numerous studies have shown conflicting results. Most recently, the EOLIA study showed no significant benefit of mortality at day 60 as compared with a strategy of conventional mechanical ventilation, which included crossover to ECMO. However, with 249 patients randomized, the observed mortality rate was 11% lower in the ECMO group (35% in the ECMO group vs 46% in the control group) but not statistically significant ($P = 0.09$). Furthermore, 28% of patients in the control group received ECMO. While the study was inconclusive as it was underpowered and stopped due to futility, it showed that ECMO was safe to apply in severe ARDS. Goligher et al. performed a rigorous Bayesian analysis of the EOLIA trial and showed that ECMO lowers mortality but it likely does not equate to a large benefit. Nonetheless, ECMO is a complex intervention and patients enter the ECMO "window" dependent on the progression of their disease and also their responsiveness over time to adjunctive interventions. It is now well established that the duration of mechanical ventilation prior to initiation of ECMO leads to longer ECMO duration and worse mortality (Schmidt et al., 2013). While ECMO mitigates the severe damage done with increasing ventilation settings within a deteriorating baby lung, the risk of VALI remains even on ECMO. The

international LIFEGARDS study prospectively examined the ventilatory management of patients on ECMO and found that implementation of ultraprotective lung ventilation strategies was high with most patients placed on pressure-controlled ventilation, presumably with an aim of controlling driving pressure (Schmidt et al., 2014, 2019). There was no association between ventilator settings over 48 h and outcome. However, a time-dependent analysis showed that higher tidal volume and lower driving pressure (both suggesting resolution of pulmonary mechanics and function) was associated with survival. More recently, it has been shown that even on ECMO there are reductions in surrogate systemic biomarkers of VALI when the ventilation strategy is modified (Sorbo et al., 2020). Sorbo et al. showed linear reductions in the plasma concentrations of interleukin(IL)-6, soluble receptor for advanced glycation end products, IL-1ra, tumor necrosis factor alpha, surfactant protein D, and IL-10 with changes in driving pressure on ECMO.

The Clinical Implementation Gap

Despite 20 years of clinical trial data showing significant improvements in ARDS mortality through lung protective ventilation via low tidal volume ventilation, limitation of inspiratory pressures, conservative fluid management, open lung ventilation, and prone position, there remains a gap in the personalized application at the bedside. Needham et al. showed 69% of ventilator settings are non-adherent to lung protective ventilation strategies (Needham et al., 2012). Indeed, the APRONET study examining application of prone positioning and showed its application in only 33% of patients with severe ARDS (Guérin et al., 2018). The most common reason for not proning was the clinician's judgment that hypoxemia was not severe enough to justify prone position in that patient. Furthermore, significant variations exist between countries with the trigger and application of prone position. A more contentious issue is the duration of which each prone intervention is applied but also when a prone period is terminated. The coronavirus pandemic has seen a surge in the need for optimal management of the ventilator through more sophisticated data science approaches to understand these gaps such that they can be improved through better bedside measurements and algorithms (Patel et al., 2021). Hence, there is significant rationale for the development of point-of-care clinical decision support systems which help personalize ventilatory strategy according to the current physiology (Rees et al., 2006a; Nieman et al., 2017; Karbing et al., 2018, 2020).

Personalized Approaches to Mitigate VALI

Mathematical models of pulmonary gas exchange can accurately describe lung states of patients during and following surgery (Kjærgaard et al., 2001; Spadaro et al., 2016, 2018a), in the ICU (Kjaergaard et al., 2003; Karbing et al., 2007, 2011), and have been validated against the experimental reference technique for measuring gas exchange (Rees et al., 2006c, 2010a). Similar models of acid-base accurately simulate changes in CO_2, O_2 and strong acid in blood (Rees and Andreassen, 2005), as well as the mixing of blood from different sources (Rees et al., 2010b). Finally, models of respiratory drive can simulate the effects of changes in support ventilation (Larraza et al., 2015). One example could be a model-based bedside decision support system tuned to the individual patient's physiology to advise on appropriate ventilator settings (Rees et al., 2006b). Personalized approaches using individualized descriptions may be particularly advantageous in complex patients at various stages of their lung injury, including those who are in the acute phases of ARDS and those who are difficult to wean from mechanical ventilation. The core of these systems is a set of physiological models including pulmonary gas exchange, acid-base chemistry, lung mechanics, and respiratory drive (Rees and Karbing, 2017). Such as system could tune these models to the individual patient such that they describe accurately current measurements of lung physiology to base further clinical decisions and monitor lung health in critical care in real time (Allerød et al., 2008; Karbing et al., 2007, 2018, 2020). Once tuned, the models can potentially be used by the system to simulate the effects of changing ventilator settings. The results of these simulations are then used to calculate the clinical benefit of changing ventilator settings by balancing the complex competing goals of mechanical ventilation (Karbing et al., 2010; Rees et al., 2006a). For example, an increased inspiratory volume will reduce an acidosis of the blood while detrimentally increasing lung pressure. Appropriate ventilator settings therefore imply a balance between the clinically preferred value of pH weighted against the preferred value of lung pressure. A number of these balances exist, and such any system would need to weigh up the penalties for each component, calculating a total score for the patient for any possible ventilation strategy. Systems taking these novel approaches are currently being examined in clinical trials and have been shown over 4 to 8 h periods to reduce levels of inspired oxygen, tidal volume, and pressure support, without detrimental effects on outcomes (Karbing et al., 2018) and while protecting the respiratory muscles (Spadaro et al., 2018b).

Conclusion

Over 50 years of research has informed us that ventilation, while a lifesaving intervention, can be just as harmful preventing resolution of inflammation and repair. There are many bedside interventions that mitigate VALI, however, further research is required to understand the mechanisms that lead to a survival benefit and how they can be personalized for different lung states. This

personalization will likely occur through a multimodal approach which includes the frequent physiological, biological, and radiological characterization of the lung at the bedside to understand how ventilation can be delivered in the least injurious manner.

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