

The POOR Get POORer: A Hypothesis for the Pathogenesis of Ventilator-induced Lung Injury

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Abstract

Protective ventilation strategies for the injured lung currently revolve around the use of low V_T , ostensibly to avoid volutrauma, together with positive end-expiratory pressure to increase the fraction of open lung and reduce atelectrauma. Protective ventilation is currently applied in a one-size-fits-all manner, and although this practical approach has reduced acute respiratory distress syndrome deaths, mortality is still high and improvements are at a standstill. Furthermore, how to minimize ventilator-induced lung injury (VILI) for any given lung remains controversial and poorly understood. Here we present a hypothesis of VILI pathogenesis that potentially serves as a basis upon which minimally injurious ventilation strategies might be developed. This hypothesis is based on evidence demonstrating that VILI begins in isolated lung regions manifesting a Permeability-Originated Obstruction Response (POOR) in which

alveolar leak leads to surfactant dysfunction and increases local tissue stresses. VILI progresses topographically outward from these regions in a POOR-get-POORer fashion unless steps are taken to interrupt it. We propose that interrupting the POOR-get-POORer progression of lung injury relies on two principles: 1) open the lung to minimize the presence of heterogeneity-induced stress concentrators that are focused around the regions of atelectasis, and 2) ventilate in a patient-dependent manner that minimizes the number of lung units that close during each expiration so that they are not forced to rerecruit during the subsequent inspiration. These principles appear to be borne out in both patient and animal studies in which expiration is terminated before derecruitment of lung units has enough time to occur.

Keywords: volutrauma; atelectrauma; mechanical ventilation; acute respiratory distress syndrome; surfactant

Acute respiratory distress syndrome (ARDS) is an acute-onset form of noncardiogenic pulmonary edema that results from a variety of insults, including hemorrhage, systemic infection, and inhalation of noxious agents. These insults lead to widespread alveolar collapse and small airway closure, and ARDS has a mortality of 30–40%, with ~75,000 deaths annually in the United States alone (1, 2). The only treatment for ARDS is supportive care centered around mechanical ventilation (3, 4), but this itself can cause ventilator-induced lung injury (VILI).

Mechanical ventilation is thus a double-edged sword that may significantly increase the level of respiratory distress.

Current protective ventilation strategies use the ARDSnet Protocol (5), which attempts to minimize VILI by reducing V_T and plateau pressure while increasing positive end-expiratory pressure (PEEP). This strategy is based on the notion that the injured lung can be divided into two distinct compartments, one consisting of normal open lung tissue (usually in the nondependent region) and the other of collapsed injured tissue. When injury is severe, the collapsed compartment may

comprise a large fraction of the lung. The remaining open compartment is correspondingly small, being referred to by some as the “Baby Lung” (6). Ventilation with a V_T suitable for a normal lung then obviously runs the risk of overinflating the small open compartment. Overinflating lung tissue clearly has the potential to inflict serious mechanical damage and indeed is a well-accepted mechanism of VILI known as *volutrauma* (6, 7).

The ARDSnet protocol was designed to protect the open compartment from volutrauma by reducing V_T , and hence

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plateau pressure, while resting the severely injured tissue of the collapsed compartment by allowing it to remain collapsed throughout the ventilatory cycle. At the same time, the application of PEEP prevents moderately injured tissue from derecruiting at the end of expiration. This has the obvious benefit of preserving the tissue area available for gas exchange, thus improving oxygenation. Even more importantly, however, PEEP reduces the amount of lung that must be forcibly recruited during each inspiration by preventing it from becoming derecruited during the previous expiration. Repetitive recruitment of lung units is very damaging to the parenchymal tissue and leads to a form of injury known as *atelectrauma* (5, 8) because cyclic reopening and reclosing introduces substantial focused mechanical stress on the epithelium as described in detail below. A seemingly logical extension of this strategy would be to eliminate V_T altogether by replacing ventilation with extracorporeal membrane oxygenation (9) so that the lung is able to rest completely. Curiously, this strategy has not been demonstrated to reduce mortality in patients with ARDS (10). Similarly, using the tiny V_T of high-frequency oscillatory ventilation would seem to make eminent physiological sense in terms of protecting tissues from being stretched excessively. Again, however, this has not been borne out in clinical trials (11, 12) perhaps because atelectasis *per se* can cause vascular pathology (13).

It is thus clear that there is more to preventing VILI than simply avoiding overdistension of the lung tissues. This raises the question of the relative roles of volutrauma versus atelectrauma. Although generally considered independent processes, recent studies suggest that volutrauma and atelectrauma interact in important ways. Here we present our hypothesis of VILI pathogenesis that links volutrauma and atelectrauma together into a unified mechanistic framework. We also discuss the implications of this hypothesis for the design of minimally injurious personalized ventilation strategies.

Pathophysiology of Acute Lung Injury

Despite its structural complexity, the healthy lung is remarkably stable because of

two interacting biomechanical mechanisms. One involves pulmonary surfactant, which reduces and dynamically modifies the surface tension of the lining fluid and thus reduces the mechanical stresses applied to the lungs during respiration. The other mechanism is mechanical interdependency between the alveoli and airways, which allows the alveolar parenchyma to tether the compliant airways and help keep them patent (14). Likewise, patency of the large number of downstream alveoli is driven by inflation via the airways.

In the acutely injured lung, the blood–gas barrier becomes damaged as a result of either systemic factors such as sepsis, hemorrhagic shock, and inflammation or local factors such as aspiration, pneumonia, and trauma (15). This allows plasma-derived material to leak into the airspaces where they inactivate pulmonary surfactant, increasing surface tension and causing collapse of alveoli and small airways (16). At the same time, accumulations of plasma fluid flood the distal airspaces (17), eventually overwhelming the natural capacity of the lungs to clear fluid from the airspaces (18). These events conspire to increase the tissue stresses caused by mechanical ventilation, further compromising the epithelial and endothelial barriers (19). This sets up a vicious cycle involving an accelerating leak of fluid and proteins through the blood–gas barrier that progressively worsens lung injury.

A key hallmark of acute lung injury is reduced lung compliance, which occurs largely as a result of two distinct mechanisms that alter the local lung environment but that are both apparent in their effects on global lung function. One mechanism is the increase in surface tension that results from surfactant dysfunction (Figure 1). Curiously, although surfactant reduces cell damage *in vitro*, administering surfactant into the lung has not shown clinical benefit in patients with acute lung injury (20). This ineffectiveness is attributed to either deactivation of surfactant *in situ* by the presence of plasma proteins that enter the airspaces when blood–gas barrier function is disrupted (21) or delivery limitations (22).

The other mechanism behind the reduced compliance of the injured lung is derecruitment of lung units, which reduces the amount of parenchymal tissue available to receive ventilation. Application of PEEP

is seen as providing the means for countering this mechanism, yet PEEP has not been shown to reduce mortality in clinical trials (23), and even how to set the level of PEEP in any given situation remains controversial (24). These issues may stem in part from lack of appreciation of the fact that recruitment and derecruitment depend on time as well as pressure. That is, whereas a recruitment maneuver (deep inhalation) invariably brings about an immediate and often substantial increase in the compliance of the lung, during subsequent mechanical ventilation, compliance will decrease again in a quasi-exponential manner (25) as lung units close progressively over time (19). Furthermore, the rate of decrease of lung compliance following a recruitment maneuver depends on both the degree and nature of lung injury (26) as well as the local $\dot{V}/\dot{Q}$ ratio and inspired oxygen fraction (27).

These factors have obvious implications for how often recruitment maneuvers need to be applied to have a significant impact on the mean level of open lung while not imparting undue stress on the lung tissues. In fact, evidence from mouse models of VILI suggests that there may be an optimum frequency for recruitment maneuvers that balances their therapeutic and potentially damaging effects (28). This optimum rate is almost certainly patient-specific and could thus make up an important aspect of personalized treatment in ARDS. In any case, the dynamic nature of lung compliance following a recruitment maneuver can be readily measured and has been linked directly to injury biomarkers (29–31), so it provides a convenient and sensitive quantifier of lung injury that can be used follow how VILI develops over time (26, 31, 32).

Mechanisms of VILI

The atelectasis, edema, alveolar instability, and subsequent hypoxemia occurring in a severely injured lung may lead to respiratory failure, necessitating mechanical ventilation (1, 33) that itself can induce damage if applied inappropriately (33). The stakes are high because those who survive ARDS frequently go on to lead normal lives. Accordingly, successful ARDS management may be contingent upon simultaneously avoiding the volutrauma and atelectrauma that cause VILI.

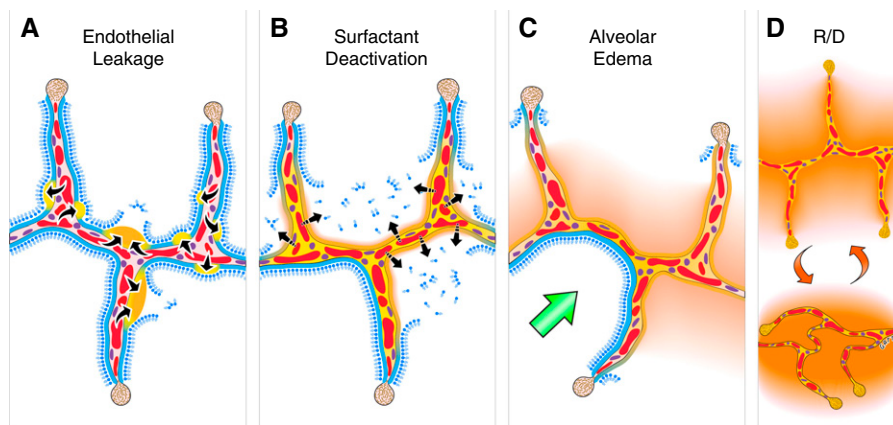


Figure 1. The hypothesis of the pathologic tetrad of acute respiratory distress syndrome at the microscale. (A) Systemic or local inflammation causes an increase in permeability (endothelial leakage), which leads to (B) alveolar flooding with edema fluid (alveolar edema) inhibiting surfactant function (surfactant deactivation). (C) Alveolar edema causes a heterogeneous challenge generating stress concentrators (green arrow) on neighboring alveoli. Loss of surfactant function destabilizes alveoli in this region, (D) predisposing them to cyclic recruitment and derecruitment that initiates and exacerbates damage due to atelectrauma and regionally decreases the compliance. Adapted from Reference 65 under the terms of the Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>). R/D=recruitment and derecruitment.

Volutrauma is presumed to arise as a result of tissues being stretched by overinflation to the point of mechanical failure. This hypothesis was founded on early studies using computed tomography in ARDS and has been supported more recently by positron emission tomography showing strain-dependent neutrophil activity in ventilated regions of human ARDS lungs (34). It is easy to imagine that mechanical damage to the tissues will occur if excessive inspiratory volume is forced into the small open compartment, and indeed this has been linked to inflammatory responses in the lung (35). These factors helped motivate the adoption of low V_T ventilation (5). Nevertheless, the early work of Webb and Tierney showed that consistent overdistention alone is not enough to cause VILI in normal animals (36). In fact, Seah and colleagues (32) found that normal mice can tolerate mechanical ventilation for up to 4 hours with a V_T equal to TLC provided this is accompanied by a modest level of PEEP. Likewise, Gattinoni and colleagues report that it is very difficult to induce VILI in a normal lung unless extremely high pressures are imposed (37). The normal lung thus appears to be surprisingly resilient to persistent overinflation alone.

The lung's resilience is lost, however, when overdistention is accompanied by repetitive recruitment and derecruitment events. This can lead to cyclic

hyperinflation as the volume of the ventilated portion of the lung decreases with time, and the initially normal lung develops progressive VILI that is eventually fatal (32). As we explain below, this response may not be due to volutrauma to the open regions of the lung *per se* but instead could imply that the initiation of VILI is due to the opening and closing of airways and alveoli, introducing atelectrauma as the instigating damage mechanism.

The proximal cause of atelectrauma is commonly ascribed to damaging mechanical stresses that are presumed to be applied to the epithelial surfaces of the airways and alveoli as they are peeled apart during lung inflation (38). This applies stresses to the epithelium that are both frictional (shear) and compressive (normal), the latter pushing across the surface much like a rolling pin. Biomechanical studies demonstrate that the compressive stress components are primarily associated with atelectrauma (39, 40). The propensity for derecruitment during expiration increases markedly with increases in surface tension (41). In ARDS, the capacity of surfactant to lower surface tension is reduced by the presence of plasma proteins (21). Surfactant dysfunction also makes the airway surface film unstable and prone to the formation of liquid plugs that occlude the lumen (42).

Liquid plugs, or the motion of compliantly collapsed regions in airways, have been related to clinical observations of lung sounds for centuries (43), but their direct observation is difficult. Recent evidence for the motion of these compliantly collapsed regions is provided by Broche and colleagues (44). Recruitment maneuvers can drive the obstructions distally along the airways until they break apart, but recruitment pressures can be large (45), and both the movement and disintegration of these obstructions can apply potentially damaging microscale stresses to the airway epithelium (46). These stresses may be large enough to cause direct membrane damage by the plug motion (39, 40) and are amplified significantly when alveolar walls held in apposition by the lining fluid are peeled apart by a finger of air propagating axially along the airway (38), as in compliant collapse. As such, the stresses involved in restoring patency to an occluded small airway can induce damage that compromises epithelial barrier function by puncturing cell membranes (39, 40) and/or by disrupting tight junction proteins ZO-1 and claudin 4 (47).

Liquid plugs can obstruct airways, resulting in heterogeneous ventilation and reducing the volume of the ventilated lung. When pressures are large enough, the liquid plug moves along an airway and tends to deposit some of its fluid content on the airway walls, progressively reducing the axial dimension of the plug to the point where it suddenly ruptures and distributes its remaining fluid onto the airway wall. This is a high-speed explosive event that opens the airway lumen, creating an audible crackle that can be detected via auscultation (48, 49). Plug rupture can damage the cell layer directly beneath the plug (48), so crackle-like lung sounds may be indicative of microscale damaging events that can eventually lead to large-scale lung damage (49). Nevertheless, atelectrauma alone is not usually sufficient to cause VILI in a normal lung (32). Indeed, it seems that atelectrauma and volutrauma act synergistically.

One potential explanation for the synergy between atelectrauma and volutrauma is that the mechanical stresses of parenchymal interdependence at interfaces between open and atelectatic regions become enhanced to the point of mechanical failure when the atelectatic

regions fail to expand as the lung is inflated. In other words, atelectatic regions concentrate stress on bordering regions of the open lung. Mechanical stress induces a high level of strain-induced tissue damage during mechanical ventilation (50).

In support of this idea, computed tomographic images from patients with ARDS and animal models show that inflation heterogeneity is prominent at interfaces between aerated and nonaerated tissue (51), and VILI propagates concentrically from preexisting lesions (52). Stress concentrators near atelectatic regions thus act as *foci* from which VILI propagates to previously normal lung regions, in much the same way as cracks fracture solid materials, thereby acting as a key mechanism by which VILI worsens.

Another explanation for the genesis of VILI is offered by the findings of Hamlington and colleagues (29) indicating that the size distribution of holes in the blood–gas barrier resulting from VILI follow a power law. It is not clear whether this barrier disruption was created predominately between the epithelial and endothelial cells (53) or through the cell membranes (30), but their power-law distribution provides evidence that barrier disruption is generated by a “rich-get-richer” mechanism in which atelectrauma causes initial barrier disruption while concomitant volutrauma causes the holes to increase in size (54). The rich-get-richer theory thus suggests that the key to avoiding the initiation of VILI is avoidance of atelectrauma.

The POOR-Get-POORer Hypothesis

As described above, the synergy between volutrauma and atelectrauma appears to arise through a combination of focused damage at sites of stress and/or strain multipliers, together with diffuse damage arising through a rich-get-richer mechanism in which overdistension builds on initial cell injury caused by repetitive recruitment/derecruitment. The lung itself, however, is more appropriately viewed as becoming “poorer” rather than “richer,” because it increasingly manifests a Permeability-Originated Obstructive Response (POOR) as illustrated at the microscale in Figure 1 with

1. Initiation by increased endothelial permeability;
2. Local surfactant deactivation;
3. Edema; and
4. Recruitment/derecruitment events that expand the original damage regions by decreasing compliance and imposing atelectrauma-inducing deleterious mechanical stresses.

A repetitive cycle of these events results in increasing VILI, with the POOR becoming POORer, unless definitive steps are taken to interrupt it.

The POOR-becoming-POORer cycle is described at the macroscale in Figure 2 and begins with normal homogeneous parenchyma (Figure 2A) that then experiences its first injurious insult. This increases local endothelial and epithelial permeability, allowing leakage of surfactant-deactivating proteinaceous fluid into the airspaces to create a POOR region of the lung (Figure 2B). The proteins within the POOR region deactivate surfactant, which increases surface tension and the pressure necessary to rerecruit closed lung units. If the POOR region is not recruited, gas trapped downstream of obstructed airways then becomes absorbed, leading to distal atelectasis. Recent studies have indicated that high FiO_2 to regions with low $\dot{V}/\dot{Q}$ ratios can suffer from increased rates of adsorption atelectasis (27).

Recruitment/derecruitment events applied to this expanding region subsequently create stress and/or strain concentrators in the adjacent open parenchyma as the separation of the walls held in apposition by an air–liquid interface exposes the tissue to damaging mechanical stresses resulting from large focal strains. As such, ongoing mechanical ventilation has the potential to stretch the adjacent alveolar walls as it repetitively recruits the surrounding alveoli, creating further damage and expanding the POOR regions to make them POORer by increasing the degree of damage and extending the atelectatic regions from the site of the original insult (Figure 2D).

Clinical Implications

The fact that mechanical ventilation can be both therapeutic and harmful, depending on how it is applied, leads directly to the notion that there ought to exist an optimal ventilation strategy for the injured lung.

Indeed, the motivation for evidence-based management of ARDS is based on this notion. Despite a great deal of research, however, there remains remarkably little in terms of specific recommendations; the current standard of care in ARDS is limited to the use of a low V_T ventilation together with empirical recommendations about PEEP (5), plus the recent addition of prone positioning (55), which has been demonstrated to induce more homogeneous airflow by reducing the gravitational effects from organs (56). Observational studies have indicated that prone positioning may improve recruitment in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated ARDS (57).

Part of the reason for this paucity of options is that the clinical trials on which evidence-based medicine rests are invariably designed to test what is best for the patient population on average, such as the ARDSnet trial that showed ARDS mortality to be reduced by a V_T of 6 versus 12 ml/kg ideal body weight (5). Although pragmatic, this general approach has two key problems. First, refining the prescription further, such as determining whether a V_T of 5 or 7 is better than 6 ml/kg, rapidly becomes impossible owing to lack of statistical power. Second, in a highly heterogeneous disease such as ARDS, what is best on average may be very far from best for an individual patient. Both of these issues can potentially be mitigated by clinical trials that test personalized approaches to management. The challenge here, however, lies in deciding what personalized approach to test because of the vastness of the potential search space. It is therefore vital to focus on personalized prescriptions that are based on an understanding of underlying pathophysiology.

Our POOR-get-POORer hypothesis is based upon a biomechanical understanding of the underlying pathophysiology and implies that mitigating VILI may be achieved by meeting two fundamental requirements:

1. Open the lung to minimize the presence of heterogeneity-induced stress concentrators on the lung parenchyma that are focused on the regions of atelectasis, and
2. Ventilate in a manner that minimizes the number of lung units that close during each expiration so that they are

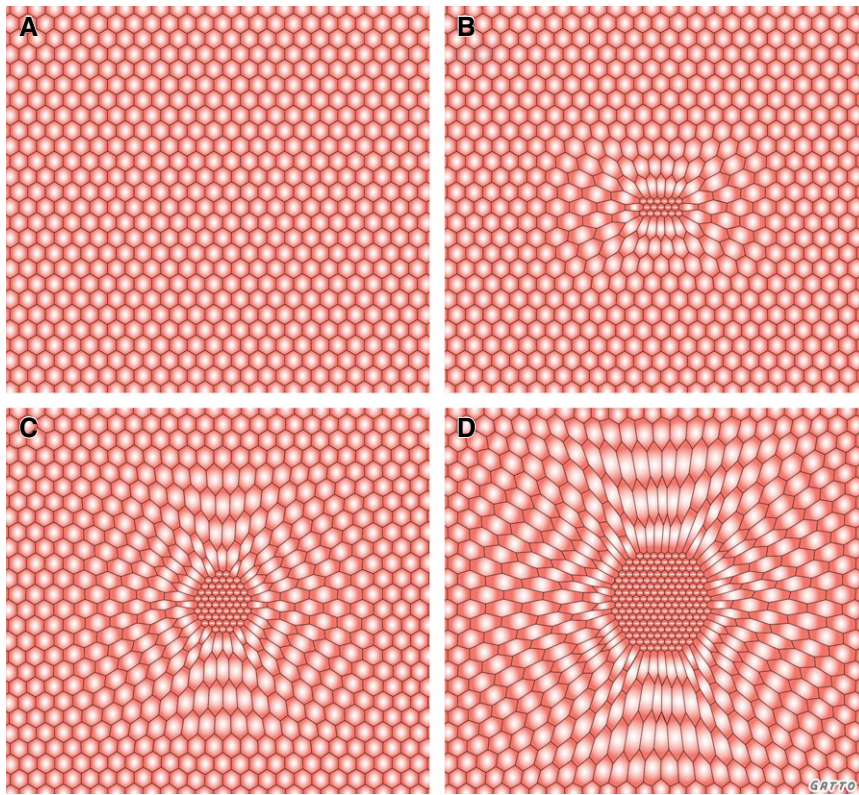


Figure 2. The macroscale view of the POOR-becomes-POORer interpretation of ventilator-induced lung injury progression. (A) Normal lung tissue consists of relatively uniformly expanded alveoli represented by hexagons. (B) Early lung injury consists of isolated POOR areas of edema-filled or collapsed alveoli (center) that concentrate stress, causing overdistension and instability in adjacent open alveoli. (C) These adjacent areas are at risk of sustaining injury themselves during mechanical ventilation, causing the POOR regions to become POORer. (D) The injury progresses to overwhelming ventilator-induced lung injury unless definitive steps are taken to interrupt it. POOR=Permeability-Originated Obstructive Response.

not forced to rerecruit during the subsequent inspiration.

Importantly, neither of these requirements makes specific reference to global overdistension. Instead, the POOR-get-POORer hypothesis suggests that the adverse consequences of overdistension can be avoided by focusing on the above two requirements. Critical to the implementation of this strategy, however, is that it must be adaptive because the likelihood of producing

atelectrauma depends on the mechanical state of the lungs, and this state changes with time depending on how the lung is ventilated. As such, the strategy suggested by the POOR-get-POORer hypothesis is neither a conventional open-lung nor a rested-lung approach.

Although clinical studies have yet to be done that test the POOR-get-POORer hypothesis, we have recently obtained promising results in both trauma patients

(58) and animal models of ARDS (59–61) using a form of airway pressure release ventilation in which the duration of expiration is adjusted so that the magnitude of expiration flow at the end of expiration is a fixed fraction of peak expiratory flow in a patient-specific manner. This adaptive approach adjusts the expiration duration to deal with the changing expiratory flow rates that arise as the mechanical properties of the lung change over time (62). Importantly, it appears to be crucial that end-expiratory flow is prevented from descending too far below peak expiratory flow, which in the absence of dynamic flow limitation (63) typically requires expirations that are extremely brief (often 0.5 s or less). If expiratory duration is extended much beyond this point, then this approach to ventilation quickly becomes extremely injurious (64). This can be explained on the basis of meeting the two requirements of preventing the POOR-get-POORer cycle described above; the vast majority of the time, the lungs are held at a pressure sufficient to recruit the lung tissue and minimize stress and/or strain concentrators. Conversely, expiration is too brief to allow significant derecruitment to occur, thus avoiding repetitive recruitment and its concomitant atelectrauma and the formation of new stress and/or strain concentrators. This does not mean, of course, that this form of airway pressure release ventilation implements the requirement of this hypothesis in an optimal manner. There may be approaches to mechanical ventilation, as yet unknown, that achieve these requirements more effectively. In any case, the POOR-get-POORer hypothesis provides us with a conceptual map of where to look in our search for reducing VILI. ■

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