Ventilator-induced lung injury: The anatomical and physiological framework

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Since its introduction into the management of the acute respiratory distress syndrome, mechanical ventilation has been so strongly interwoven with its side effects that it came to be considered as invariably dangerous. Over the decades, attention has shifted from gross barotrauma to volutrauma and, more recently, to atelectrauma and biotrauma. In this article, we describe the anatomical and physiologic framework in which ventilator-induced lung injury may occur. We address the concept of lung stress/strain as applied to the whole lung or specific pulmonary regions. We challenge some common beliefs, such as separately studying the dangerous effects of different tidal volumes (end inspiration) and end-expiratory positive pressures. Based on available data, we suggest that stress at rupture is only rarely reached and that high tidal volume induces ventilator-induced lung injury by augmenting the pressure heterogeneity at the interface between open and constantly closed units. We believe that ventilator-induced lung injury occurs only when a given threshold is exceeded; below this limit, mechanical ventilation is likely to be safe. (Crit Care Med 2010; 38[Suppl.]: S539–S548)

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Since its introduction, the use of mechanical ventilation in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) has been interwoven with its side effects, mainly hemodynamic instability attributable to augmented intrathoracic pressures and mechanical trauma to the lung structure. At the beginning of the 1970s, the most feared side effects were circulatory impairment, first reported by Cournard et al in 1948 (1), and the potential development of pulmonary fibrosis attributable to the use of a high inspiratory fraction of oxygen (2). Surprisingly, alterations to the lung structure induced by mechanical ventilation were less considered and only noted as gross barotrauma. Pontoppidan, from Harvard Medical School, and coworkers reported in the *New England Journal of Medicine* in 1972, "We ventilated thousands of patients in this way (i.e., with tidal volume [TV] of 12–15 mL/kg of body weight and positive end-expiratory pressure of 5–10 cm H_2O) and the only side effect was hypocapnia" (3). At the same time, Kirby et al (4) in Miami were suggesting the use of so-called super-positive end-expiratory pressure (PEEP) with levels of 25-30 cm H_2O, whereas the French group of Tenaillon (5) proposed that PEEP should be increased until the right-to-left pulmonary shunt could be reduced to less than 15%. Not surprisingly, in this context, airway end-inspiratory (plateau) pressures reached during mechanical ventilation were far higher than what is today considered a safe threshold (≈30 cm H_2O) (6), at least in the most severe ARDS cases. As documented by the first randomized trial of extracorporeal membrane oxygenation, the mortality rate of patients with ARDS was close to 90% (7). These data, 40 yrs later, may be considered from two different, but not mutually exclusive, points of view. This high mortality rate may be attributed to ignorance of, and lack of concern for, the potential harms of high-volume/pressure mechanical ventilation. However, because the researchers cited were all highly experienced and competent, we may query whether the way mechanical ventilation was used at that time was the cause of such a high mortality rate rather than an epiphenomenon.

In this article, we critically review the current knowledge of ventilator-induced lung injury (VILI). We try to separate the evidence derived from experimental and clinical studies from common beliefs. It is our opinion that common beliefs, which have mainly originated from conferences and personal opinions rather than strong evidence, have led to claims that mechanical ventilation should be invariably considered harmful and that a safe limit for airway pressure may not even exist (8).

Potential Mechanisms of VILI

Barotrauma and volutrauma

The term *barotrauma* is used to indicate lung damage attributable to the application of high airway pressure (9). Different forms of barotrauma have been described, with the most common being pneumothorax. This can be easily detected on an anteroposterior chest radiograph when the lateral lung regions collapse, but a computed tomography scan is needed when it is strictly anterior or posterior (10). A less common form of barotrauma is pneumomediastinum, which may extend to the body surface (for example, to the neck, face or trunk, and

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scrotum). Finally, gaseous embolism also has been reported (11). These forms of barotrauma are collectively described as "gross" barotrauma.

Nobody questioned the term *barotraumas* until Dreyfuss et al (12), in the 1980s, proposed that the use of high TV, and not airway pressure, was the major factor responsible for mechanical damage to the lung structure. The new term *volutrauma* immediately achieved great popularity, possibly because of a common fascination with novelty rather than any particular insight into basic respiratory physiology. The experiments by Dreyfuss actually involved healthy rats subjected to mechanical ventilation with the use of high airway pressure, with their chest walls strapped and unable to expand. With this experimental setup, TVs were modest, airway pressures were extremely high, and lung lesions were absent. In a second group of animals with unstrapped chest walls, the corresponding TV was much higher for a given airway pressure and pulmonary lesions were dramatic. Based on these findings, the authors concluded that volutrauma, and not barotrauma, was responsible for VILI (12).

The animal model developed by Dreyfuss et al resembles the scenario of a diver at 10 m below the surface whose chest wall excursion is hampered by one extra atmosphere (1034 cm H_2O) around the thorax. The diver then requires a tank providing gas at a pressure of 2 atm (one extra atmosphere compared to water level) to breathe normally. Ventilation may occur with a physiologic TV, but the airway pressure would be abnormally high at approximately 1034 cm H_2O. Nonetheless, no lung damage is expected to occur, just as in the rats ventilated with a strapped thorax. Conversely, if the diver ventilates with similarly high airway pressures after immersion, when the pressure around the chest wall has returned to normal (unstrapped thorax), then impressive lung damage is likely to occur provided that the diver does not "explode," as did some of the animals in the aforementioned study.

This concept becomes clearer when one considers that the force really acting on the lung structure during ventilation, either artificial or spontaneous, is the transpulmonary pressure, the difference between airway pressure (Paw) and pleural pressure (P_{PL}). The airway pressure, instead, is the pressure required to distend to the same extent not only the lung but also the chest wall. Thus, $Paw = P_L + P_{PL}$.

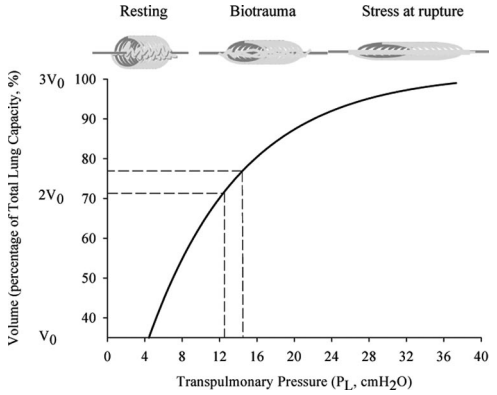

Figure 1. Relationship between lung volume (percentage of total lung capacity) and transpulmonary pressure (modified from reference 14). V_0 corresponds to the functional residual capacity. When the lung is inflated with a tidal volume equal to functional residual capacity, the transpulmonary pressure is approximately 13 cm H_2O (specific elastance). The maximum physiologic lung volume (total lung capacity) is reached when tidal volume is two times functional residual capacity and 2 and transpulmonary 2 and transpulmonary pressure is approximately 26 cm H_2O. The behavior of the lung fibrous skeleton, modeled as elastin fibers (extensible spring) and collagen tissue (inextensible string) set in parallel, is described at the top of the figure.

The same relationship holds true when elastance (i.e., pressure/volume) is considered: $E_{RS} = E_L + E_{CW}$, where E_{RS}, E_L, and E_{CW} refer to elastance of the respiratory system, lung, and chest wall, respectively.

Regarding the Dreyfuss experiment, bearing in mind that the distending force of the lung is represented by the transpulmonary, and not the airway, pressure, whenever the chest wall elastance is artificially increased, as in the case of the rats with a strapped thorax, then pleural pressure, for a given TV, must increase. Therefore, a higher airway pressure and a higher pleural pressure will be recorded, but the resulting transpulmonary pressure will be normal. Conversely, when the chest wall is free to expand, the pleural pressure is relatively low but high airway pressures are now associated with high transpulmonary pressures. Lung structural damage can then develop. In other words, for a given airway pressure, the development of VILI will depend on the resulting transpulmonary pressure.

The forces developing into the lung structure that react to the transpulmonary pressure are collectively defined as stress. Conversely, when we consider the lung deformation (relative to its resting position, V_0) attributable to tidal inflation (TV), we refer to a variable called *strain* ($\Delta V/V_0$). Within the physiologic limits, stress and strain are almost linearly related: stress = K * strain; therefore, $P_L = K * TV/V_0$.

It follows that K, known as *specific elastance*, is the transpulmonary pressure recorded when TV equals the resting volume or, in other words, when the lung doubles its volume. We have recently demonstrated that specific lung elastance is approximately 13 cm H_2O in subjects with healthy lungs as well as in patients with ALI/ARDS (13). This means that even during lung injury, barotrauma (stress) and volutrauma (strain) bear the same constant relationship observed in normal subjects, representing two sides of the same coin. The distinction between volutrauma and barotrauma then vanishes. Interestingly, a similar value of specific elastance may be derived from the *Handbook of Physiology*, which contains the original cartoon describing changes in lung volume as a function of changes in transpulmonary pressure (Fig. 1) (14). The clinical challenge is to clarify whether lung damage develops proportionally (in a sort of continuum) to the stress/strain applied or only when a critical threshold is exceeded.

Biotrauma and atelectrauma

The classic concept of gross barotrauma implies that damage occurs only when stress/strain is high enough to break the lung structure. Since the early 1990s, however, a series of experiments have suggested that even without causing tissue rupture, unphysiological stress/strain can still promote the release of proinflammatory cytokines and the recruitment of white cells, with lung inflammation occurring as a result. This

biological reaction to mechanical forces is known as *biotrauma* (15–18).

Finally, atelectrauma has been recently proposed as an additional possible form of lung injury attributable to mechanical ventilation. Muscedere et al (19) found that tidal ventilation at low airway pressure (starting from below and finishing above the lower inflection point determined from an inspiratory volume/pressure curve) can augment lung injury by cyclic opening and closing of airway and pulmonary units. The conceptual basis for atelectrauma was originally developed by Mead et al (20), who constructed a theoretical model to suggest that the forces effectively acting on the lung parenchyma can be much higher than those applied to the airway. According to a mathematical approximation, an airway pressure of 30 cm H_2O may result in a pressure as high as 140 cm H_2O acting locally at the interface between closed and open lung units (20). This model remained ignored for many years until Lachmann (21) popularized the concept of "open up the lung and keep the lung open." Since then, the theoretical model of Mead has been mistakenly considered as experimental evidence. Barotrauma, volutrauma, biotrauma, and atelectrauma are considered as undisputable truth and represent the background for the development and universal acceptance of the so-called lung-protective strategy.

Anatomical and Physiological Framework in Which VILI May Occur

We believe that a meaningful discussion on VILI requires knowledge of the anatomical and physiologic scenario in which the forces that eventually lead to lung injury act. Therefore, we discuss the composition and properties of the lung fibrous skeleton, the mechanical characteristics of alveolar epithelial cells, and the properties of the gas/liquid interface.

Lung fibrous skeleton

The lung fibrous skeleton is the structure that directly bears the forces applied by mechanical ventilation. It mainly consists of two fiber systems: an axial system anchored to the hilum and running along the branching airways, down to the alveolar ducts, and a peripheral system anchored to the visceral pleura going centripetally down into the lung. The two systems are linked at the level of the alveoli and form a continuum that is the lung skeleton (22).

The main stress-bearing constituents of lung tissue are elastin fibers and collagen tissue. Elastin fibers represent 10% of total lung tissue and can be easily deformed and stretched, by up to 100%. Collagen tissue represents 2% of total lung tissue, is much stiffer than elastin, and tolerates elongation poorly (strain at rupture is only 10%) (23). The simplest approach to elastin/collagen interaction is to consider the elastin as an elastic spring set in parallel with a flaccid, inextensible string of collagen that impedes any further elongation of the unit when unfolded. According to this simplified model, as long as lungs are inflated at low strain and collagen fibers are not tensed, the force applied to the fibrous skeleton is borne by the elastin fibers. As strain increases, collagen fibers progressively unfold and finally become tensed, acting as a stop-length system. Stress then abruptly increases. Gradual recruitment of collagen fibers is believed to account for the nonlinear stress/strain characteristics of the lung tissue (24, 25). When collagen fibers are maximally unfolded, lungs reach their maximal volume, i.e., total lung capacity (TLC) (Fig. 1). If stress/strain increases further, exceeding the tensile properties of the collagen (stress/strain at rupture), then lungs experience classic barotrauma. When the stress/strain is unphysiological (barotrauma/volutrauma), although without reaching the levels needed for physical rupture, the cells anchored to the lung skeleton are abnormally stretched. Cellular mechanosensors may then be activated, cytokines are released, and full-blown inflammation may develop (biotrauma) (23).

According to the model described, lung units with similar mechanical properties, lying in parallel, grossly bear an equal fraction of any externally applied and homogeneously distributed force (such as that applied by mechanical ventilation). This may not hold true in case of unevenly diseased lung parenchyma. In fact, when pulmonary units are consolidated, they become stiff and variably fail to elongate. The spring–string pairs connected in series then experience greater deformation for a given force (atelectrauma). When pulmonary units get ruptured, they do not even carry the force. Spring–string pairs in series are unloaded; however, the adjacent intact ones that bear a proportionally increased force and experience a similarly high stress/strain are at increased risk of rupture (23). This situation becomes even more complex when one considers that elastin and collagen fibers vary in length, width, orientation, and curvature, and their arrangement in lung tissue is not only serial and parallel but also interwoven.

Alveolar epithelial cells

Both alveolar cells, types I and II, and endothelial cells do not directly bear the force applied during mechanical ventilation, but instead they rearrange their shape when the lung fibrous skeleton expands. The cytoskeleton of alveolar and endothelial cells is connected to the extracellular matrix via the integrin system. Putatively, spatial changes occurring in either the lung fibrous skeleton or the anchored alveolar epithelial cells can be sensed by the cytoskeleton, the integrins, and the ion channels (collectively acting as mechanosensors), and they are then transduced in a biochemical signal through the activation of specific intracellular pathways (mechanotransduction). As a result, extracellular matrix may undergo remodeling, cytokines may be released, white cells may be recruited, and full-blown inflammation may eventually develop (15–17). Once again, the clinically relevant question is whether there exists a critical threshold above which the force applied to the lung actually triggers this inflammatory response. It is difficult to believe that inflammation can develop when the lung expands up to 25% above its resting position, as occurs during normal breathing.

Although the inflammatory reaction induced by unphysiological stress/strain has been fairly well-documented in both *in vitro* and *ex vivo* experiments, its occurrence does not necessarily exclude the possibility of direct damage to the lung structure that is not mediated by any mechanotransduction. For example, variable degrees of capillary stress failure have been clearly shown during mechanical ventilation in animal experiments and can possibly lead to the development of lung edema in the absence of any macroscopic structural damage (26). Of note, the development of stress failure depends not only on the level of stress acting on a body but also on, even more importantly, the rate and total length of time during which a given stress acts. The clinical problem remains the same: what is the magnitude of

distortion, and how many times does it have to be applied to the lung structure before stress failure develops?

We believe that the following questions are the most clinically relevant issues regarding the pathogenesis of VILI that still need to be addressed. First, is there any end-inspiratory stress (transpulmonary pressure or plateau pressure as an approximation) or strain (TV) threshold above which VILI develops? Second, what is the role, if any, of the ventilatory rate (application of stress/strain over time) in VILI? Third, does it make any difference in terms of biological response whether a given stress/strain is applied intermittently (as during tidal ventilation) or continuously (for example, in the form of PEEP)?

The gas/liquid interface

Temperature in the lung is normally approximately 37°C, air is saturated with water, and the gas/liquid interface is evenly distributed on the alveolar surface. The mechanical properties of the lung depend, at least in part, on the physical characteristics of this gas/liquid interface. In fact, the molecules of water on the alveolar surface interact with each other, generating a cohesive force known as *surface tension*. When the lung is inflated, alveoli expand and their (liquid) surface increases. Part of the distending force is then used to overcome the surface tension that tends to maintain the interaction between neighboring molecules of water. In normal lungs, the surface tension is kept at a low level by the presence of natural surfactant. This is a mixture of molecules secreted by type II alveolar epithelial cells and is maximally concentrated in the proximity of the gas/liquid interface. It facilitates alveolar expansion by decreasing the cohesive force between molecules of water. When surfactant is lacking (and surface tension is no longer counterbalanced), greater inspiratory forces are needed to reach the same alveolar expansion. Similarly, at end expiration, greater pressure is required to keep the alveolar units open. Therefore, collapse can easily occur in the absence of surfactant.

The force needed to expand a pulmonary unit can then be split into three components: the first is used to overcome surface tension ($P_{SURFACE\ TENSION}$), the second distends the lung fibrous skeleton, and the third expands the chest wall. The first two forces define the transpulmonary pressure. The following equation can be derived:

$$Paw = P_L + P_{PL} = (P_{SURFACE\ TENSION} + P_{LUNG\ FIBROUS\ SKELETON}) + P_{PL}$$

Accordingly, any increase in surface tension (such as surfactant deficit) or decrease in pulmonary deformability (for example, during early fibrosis in ALI/ARDS) can increase lung elastance.

We have previously considered the transpulmonary pressure as being equal to the stress developed in the lung structure. This is true only when surfactant is present and surface tension is kept to a minimum. Otherwise, the real stress acting on the lung fibrous skeleton becomes lower than the transpulmonary pressure. This is attributable to the fact that part of the latter pressure is actually used to overcome the increased surface tension. Paradoxically, a lack of surfactant (if any) could partly protect the lung from excessive stress/strain by lowering, for a given transpulmonary pressure, the tension truly acting on the lung structure and the deformation experienced by the alveolar surface.

Pathophysiology of VILI

The role of end-inspiratory stress/strain

It must be clearly kept in mind that VILI can only occur in ventilated regions. For example, during lobar bacterial pneumonia the consolidated region is excluded from ventilation and therefore VILI cannot develop there. Conversely, the healthy lung can be ventilated and VILI can potentially develop in virtually every region.

Let us now consider the role of the end-inspiratory stress/strain in the pathogenesis of VILI. Inflammatory lung edema resembling clinical ARDS consistently has been induced in animals with healthy lungs using extremely high TV (usually ≈20–40 mL/kg body weight) and airway pressure (as high as 35–45 cm H_2O) (Table 1). In our opinion, however, the safety (or harm) of a particular TV or airway pressure cannot be judged *per se* without considering the size of the ventilated lung and the mechanical properties of the chest wall (13). This becomes even more important during lung disease.

The TLC of a normal 70-kg adult male is usually considered to be approximately 7.5 L, with a resting lung volume (functional residual capacity [FRC]) of approximately 2.5 L; however, inter-individual variability can be great. According to these values, the upper limit for physiologic strain is normally reached when the lung volume is increased two-fold relative to end expiration. In other words, maximal strain should be equal to 2, considering the strain as the ratio between the volume of gas inflated (7.5–2.5 L) and FRC (2.5 L) (Fig. 1). At this level of strain, the collagen fibers of the lung fibrous skeleton are likely to be completely unfolded. Any attempt to further expand the lung (above TLC) will probably result in tissue rupture. What is the stress corresponding to these degrees of strain? As long as we consider the quasi-linear part of the lung volume/transpulmonary pressure curve, the relationship between the two variables (in other words, the relationship between strain and stress) is described by the following equation:

$$Stress = K * strain$$

where K is the lung-specific elastance (≈13 cm H_2O in either healthy or acutely injured lungs) (13). Accordingly, if strain is equal to 2, transpulmonary pressure will be approximately 26 cm H_2O. The airway pressure corresponding to these values of transpulmonary pressure strictly depends on the relationship between lung and chest wall elastances. Thus, $P_L/Paw = E_L/E_{RS}$. Even if E_L/E_{RS} is normally considered to be 0.5 (meaning that lung and chest wall elastances are equal), it can greatly vary among ALI/ARDS patients as well as in sedated, supine, individuals with healthy lungs. In these cases, the value is usually approximately 0.7 (13). If so, then the airway pressure corresponding to a transpulmonary pressure of 26 cm H_2O would be approximately 37 cm H_2O.

Summarizing, we may expect lung injury to occur whenever the upper limit of physiologic strain is exceeded, i.e., when a TV of at least 5 L is used to ventilate a 70-kg man with healthy lungs and an FRC equal to 2.5 L. Strain would then be equal to 2, transpulmonary pressure would be approximately 26 cm H_2O, and airway pressure would be approximately 37 cm H_2O. These values may appear unrealistic at first sight. However, it is worth recalling that TV of up to 70 mL/kg and similarly high airway pressures were originally used in animals with healthy lungs to document the harm of mechan-

Table 1. Seminal experimental evidence of end-inspiratory stress/strain

Author	Year	Setting	Species	Lung Status	Tidal Volume, mL/kg	Peak Pressure, cm H_2O	Positive End-Expiratory Pressure, cm H_2O	Injury Measurements	Importance
Greenfield et al	1964	*In vivo*	Dogs	Healthy	—	≈29	0	Surfactant alteration	Surfactant
Webb et al	1974	*In vivo*	Rats	Healthy	≈44	45	0	Outcome, histology	First report on outcome
Dreyfuss et al	1985	*In vivo*	Rats	Healthy	≈40	45	0	Lung edema and permeability, histology	High-permeability edema
Kolobow et al	1987	*In vivo*	Sheep	Healthy	≈59	50	7	Outcome, respiratory mechanics	Large animal models
Dreyfuss et al	1988	*In vivo*	Rats	Healthy	≈40	45	0	Lung edema and permeability, histology	Barotrauma/volutrauma
Tremblay et al	1997	*Ex vivo*	Rats	Healthy/ Injured	40	≈41	0	Respiratory mechanics, cytokines	Biotrauma
Imai et al	1999	*In vivo*	Rabbits	Injured	≈14	25	5	Oxygenation, cytokines	Tumor necrosis factor-α
Chiumello et al	1999	*In vivo*	Rats	Injured	16	≈35	0	Respiratory mechanics, oxygenation, cytokines	Systemic release of cytokines
Ranieri et al	2000	*Ex vivo*	Rats	Injured	≈16	≈72	≈21	Respiratory mechanics, cytokines	Stress index
Sibilla et al	2002	*In vivo*	Rats	Healthy	≈35	≈56	≈4	Time, histology, respiratory mechanics	Equal injury (% of total lung capacity)
Belperio et al	2002	*In vivo*	Mice	Healthy	≈24	40	0	Histology, cytokines	Interleukin-8
Gajic et al	2003	*Ex vivo*	Rats	Healthy	40	≈38	0	Cell injury and resealing, histology	Plasma membrane stress failure repair
Imai et al	2003	*In vivo*	Rabbits	Injured	≈16	—	≈2	Histology, apoptosis	Systemic apoptosis
Wilson et al	2005	*In vivo*	Mice	Healthy	≈44	≈49	0	Cytokines	Tumor necrosis factor-α
Caironi et al	2005	*In vivo*	Mice	Healthy	≈30	≈22	≈2	Outcome, oxygenation, inflammatory mediators	Leukotrienes

A selection of what we consider seminal experimental works investigating the role of excessive end-inspiratory alveolar stress/strain in the pathogenesis of ventilator-induced lung injury (12, 18, 27, 55–66). Setting denotes whether the experiments have been performed *ex vivo* or *in vivo*, and lung status is whether the study has been designed in healthy or injured animals. Tidal volume is the injurious tidal volume applied; peak pressure is the end-inspiratory peak airway pressure applied. Injury measurements are the type of measurements used to document the development of lung injury, and importance denotes the reason why we arbitrarily consider it as a seminal study from among the available literature on ventilator-induced lung injury. When not directly reported, numerical data have been obtained from a careful visual inspection of the graphs included in the original articles.

ical ventilation (27, 28). If we cautiously move this threshold down to the point where the relationship between strain and stress becomes curvilinear (≈75% of TLC) (Fig. 1), then TV of at least 3 L (45 mL/kg) would be required to induce VILI. The corresponding strain would then be equal to 1.2 and transpulmonary pressure would be 14 cm H_2O. The corresponding airway pressure would be approximately 20 cm H_2O. A TV of this order of magnitude (45 mL/kg) has been shown to produce VILI in rabbits, rats, and mice (Table 1).

According to the model we propose, the end-expiratory lung volume and the TLC represent the two extremes in which VILI may occur. Unfortunately, the quantification of these two volumes is far from being easy. When we consider values usually reported in classic physiology textbooks (quoted previously), the maximal physiologic strain should be approximately 2. We may then conclude that a strain more than 2 cannot be reached without rupturing the lung fibrous skeleton. However, it does appear to be more complicated. As an example, TLC and FRC are predicted by the algorithm proposed by the American Thoracic Society (29) to be 6 L and 3 L, respectively, in a healthy, 180-cm-tall man. The maximal strain (at TLC) would consequently be 1 instead of 2. Furthermore, the FRC values reported so far refer to awake subjects in either a standing or a sitting position, whereas critically ill patients are usually sedated, sometimes paralyzed, and in a supine position. According to Ibanez and Raurich (30), FRC values in critically ill patients may markedly differ from those of healthy subjects. We recently observed that in adult surgical patients with healthy lungs, FRC measured by helium dilution is on average 1.7 L, which is a value lower than predicted by any of the previously cited formulae (13). Accordingly, any given TV will correspond to different strain levels depending on whether (and how) FRC is estimated or directly measured. Height, age, body position, sedation and paralysis, and changes in abdominal pressure may all significantly impact on the lung volume at rest, even in the absence of pulmonary disease.

Because the maximal physiologic strain occurs at TLC, it would seem logical to define the strain as the ratio between end-inspiratory lung volume and TLC rather than FRC. In this case, the maximal physiologic strain would be 1 (end-inspiratory lung volume = TLC). Unfortunately, estimation and measurement of TLC can be as tricky as those of FRC. Therefore, although the concept of strain either referenced to FRC or TLC is based on a strong physiologic premise, the (real or artifactual) variability of gas volume for any given amount of lung tissue can be so large that its definition and clinical utility may be not straightforward.

Another possible approach to the definition and computation of strain could be to refer it to the amount of ventilated lung tissue. Inflation strains the lung fibrous skeleton and not the gas volume. Because lung tissue density is approximately 1, pulmonary tissue weight and volume are virtually the same. The weight of the lung tissue in contact with gas (i.e., open to ventilation) can be easily measured by a computed tomography scan. We may then

arbitrarily say that strain is 1 whenever the gas volume is equal to the weight (or volume) of the aerated lung tissue. Any further increase in gas volume, relative to lung tissue weight, would indicate a strain higher than 1. If, for example, aerated tissue weighs 800 g and FRC is 1000 mL, then the strain at baseline will be 1000/800 = 1.25, i.e., 0.25 above the reference value, arbitrarily set at 1. A TV of 1000 mL will then result in a global strain of (200 + 1000)/800 = 1.5. This approach may allow the standardization of the definition of strain, avoiding the pitfalls that are intrinsic to the measurement of gas volumes. Applying this method in preliminary experiments on healthy pigs ventilated for at least 48 hrs at an end-expiratory pressure equal to zero, we consistently found that VILI starts to develop when the strain is approximately 2.5 to 3. Translating these findings to healthy human subjects with an estimated aerated lung tissue weight equal to 800 g and FRC equal to 1.6 L, a TV of at least 1.2 to 1.6 L (17–22 mL/kg in a 70-kg man) would be required to produce VILI.

We have so far discussed the damage induced by mechanical ventilation to otherwise healthy lungs in either animals or humans. Can these results be applied and, if so, to what extent to the already injured lung? Ignoring any eventual damage to the airways, VILI can develop only in the pulmonary units that are actually ventilated. Are the regions that remain open to ventilation during ALI/ARDS similar to the healthy ones? Do they respond differently to any given stress/strain? Based on radiologic criteria, different regions can be arbitrarily defined in the ALI/ARDS lung at end expiration. One region is characterized by a normal gas-to-tissue ratio, i.e., a density between −500 and −900 Hounsfield units (HU). A second region includes units with densities between −100 and −500 HU: the aeration is definitely lower than normal but at least partly preserved. The third region is gasless (where functional shunt occurs) and includes units with a density higher than −100 HU (31). When TV is delivered into the lung, density globally decreases; some regions become overinflated (density <−900 HU) and some poorly aerated regions become well-aerated, whereas some of the gasless regions regain aeration (recruitment). Despite great variability, lung recruitability is usually low in the majority of ARDS patients; the regions that are always open to ventilation represent 30% to 70% of lung weight (32). For any given TV, strain will be obviously greater when delivered into an ARDS lung than into a healthy one, simply because the lung open to ventilation is smaller during acute lung injury; this concept has been described as the metaphor of the "baby lung" (33). The relevant issue here is whether the baby lung is more fragile *per se* and susceptible to VILI. Regional analysis by computed tomography scanning has shown that the baby lung is heavier than normal, relative to its size, mainly because of interstitial edema (being the intra-alveolar space open to ventilation). The scanty data obtained with positron emission tomography suggest that the baby lung may be overall inflamed (34). At a microscopic level, the structure of the baby lung may be profoundly altered by interstitial edema, inflammation, and, possibly, early fibrosis and surfactant alteration. However, at a macroscopic level, the mechanical properties of the baby lung seem to be normal. The specific elastance of the baby lung, for example, is very similar to that of the healthy lung (13). Therefore, the anatomical changes that occur during acute lung injury apparently do not alter the mechanical characteristics of the regions open to ventilation. Because the extracellular matrix is, at the same time, the main determinant of lung mechanics and bears most of the stress/strain attributable to mechanical ventilation, it seems to us that the available evidence is not sufficient to conclude that the baby lung is more prone to VILI compared to the healthy lung. On the contrary, we are tempted to believe that the baby lung actually behaves normally, provided its actual size is taken into account. For example, if the aerated (baby) lung is 400 g and the gas volume at end expiration is 500 mL, then a potentially injurious tissue strain of 2.5 would be reached with a TV of 500 mL (≈7 mL/kg in a 70-kg man). In the case of a smaller baby lung (as rarely observed in the most severe ARDS patients), even TV 6 mL/kg or less may exceed the potentially critical strain threshold of 2.5 to 3.

The role of end-expiratory stress/strain

Several decades ago, Mead et al (20) suggested that any lung damage attributable to mechanical ventilation is amplified whenever lung units collapse at end expiration and reopen at the next inspiration (atelectrauma). They provided a theoretical model that can be oversimplified as follows: the forces acting on a collapsed lung structure are far greater than those acting on an already expanded region because the surface bearing the force is diminished (stress = force/area). The alveolar surface expands according to the power of two-thirds of any volume increase. If a collapsed region (V_0) expands its volume 10-fold (V), then the increase in alveolar surface will be $(V/V_0)^{2/3} = 10^{2/3} = 4.6$. If the force at full expansion is 30 cm H_2O, then the force acting at V_0 (when the unit is still closed) will be as high as 30 * 4.6 = 140 cm H_2O (20). This model is based on many theoretical assumptions and, as such, represents the fascinating hypothesis of a beautiful mind. Despite its limitations, it has progressively become dogma. It has even been reported as experimental evidence and is advocated as the rational basis for the use of end-expiratory pressures high enough to prevent airway collapse and atelectrauma (21). Truly experimental works investigating the role of end-expiratory stress/strain in the pathogenesis of VILI are summarized in Table 2.

Even if we separately considered the end-inspiratory (TV) and end-expiratory (PEEP) phenomena, in reality they are likely to be strictly interwoven. The amount of tissue that remains open at end expiration or that may undergo intra-tidal opening and closing depends on the TV previously delivered and the corresponding inspiratory pressure (35, 36). The potential dangerous effect of high TV may then be not only attributable to high TV *per se* (end-inspiratory phenomenon) but also may depend on the increased amount of tissue undergoing cyclic opening and closing (end-expiratory phenomenon). According to the model proposed by Mead (20), the major amplification of distorting forces occurs at the interface between open and constantly closed pulmonary units. If recruitment occurs during inflation, then the alveolar surface bearing the applied force will augment and the local amplification of force will decrease accordingly.

Strategies to Prevent VILI During ALI/ARDS: Clinical Evidence

Reduction of both end-inspiratory and end-expiratory stress/strain

As mentioned, it was not until the 1990s that the occurrence of gross baro-

Table 2. Seminal experimental evidence of end-expiratory stress/strain

Authors	Year	Setting	Species	Lung Status	Tidal Volume, mL/kg	Peak Pressure, cm H_2O	PEEP, cm H_2O	Injury Measurements	Importance
Webb et al	1974	*In vivo*	Rats	Healthy	≈44	45	0	Outcome, histology	First report on PEEP
Dreyfuss et al	1988	*In vivo*	Rats	Healthy	≈40	45	0	Lung edema and permeability, histology	High-permeability edema
Dreyfuss et al	1993	*In vivo*	Rats	Healthy	≈39	45	0	Lung edema and permeability	Protection of PEEP on lung edema
Muscedere et al	1994	*Ex vivo*	Rats	Injured	6	≈26	0	Respiratory mechanics, histology	Atelectrauma
Tremblay et al	1997	*Ex vivo*	Rats	Healthy/ injured	15	≈24	0	Respiratory mechanics, cytokines	Atelectrauma, biotrauma
Chiumello et al	1999	*In vivo*	Rats	Injured	16	≈35	0	Respiratory mechanics, oxygenation, cytokines	Systemic release of cytokines
Ranieri et al	2000	*Ex vivo*	Rats	Injured	7	≈21	4	Respiratory mechanics, cytokines	Stress index
Valenza et al	2003	*In vivo*	Rats	Healthy	42	≈43	0	Time	PEEP buys time

PEEP, positive end-expiratory pressure.

A selection of what we consider seminal experimental works investigating the role of excessive end-expiratory alveolar stress/strain in the pathogenesis of ventilator-induced lung injury (12, 18, 19, 56, 59, 60, 67, 68). Setting denotes whether the experiments have been performed *ex vivo* or *in vivo*, and lung status indicates whether the study has been designed in healthy or injured animals. Tidal volume is the injurious tidal volume applied; peak pressure is the end-inspiratory peak airway pressure applied; PEEP indicates the insufficient level of positive end-expiratory pressure applied; injury measurements indicates the type of measurements used to document the development of lung injury; and importance denotes the reason why we arbitrarily consider it as a seminal study from among the available literature on ventilator-induced lung injury. When not directly reported, numerical data have been obtained from a careful visual inspection of the graphs included in the original articles.

trauma became a major concern and clinical studies aimed at its prevention were performed. We may reasonably consider as the starting point of this area of research the article from Amato et al (37) who randomized two (small) groups of ALI/ARDS patients to either high TV and low PEEP or low TV and high PEEP. Regardless of any methodological limitation, this article marked the beginning of the "lung-protective" strategy era. As discussed, VILI may develop as a consequence of unphysiological end-inspiratory stress/strain and amplification of stress at end-expiration when lung units cyclically collapse. Amato addressed both of these issues, with an impressive outcome advantage in patients ventilated with a lung-protective strategy.

These findings were replicated in a similarly designed study performed by Villar et al (38). In this case, however, only patients with the most severe ARDS were enrolled. A third study tested the benefits of the lung-protective strategy (low TV and high PEEP) and also demonstrated improved survival (although this was not the primary outcome) and less lung inflammation in treated patients (39).

In summary, all three major studies that investigated the lung-protective strategy as a whole (both low TV and high PEEP) consistently reported clinical benefit as compared to "control" mechanical ventilation (Table 3).

Reduction of end-inspiratory stress/strain alone

Apart from these three studies, the lung-protective strategy generally was not tested as a whole but in its separate components: different TVs for a given PEEP level (end-inspiratory stress/strain adjustment) or different PEEP levels for a given TV (end-expiratory stress/strain adjustment) (Table 3). The most influential work was performed by the National Institutes of Health network and showed that the use of TV equal to 6 mL/kg ideal body weight was associated with lower mortality compared to those receiving 12 mL/kg (40). However, other studies comparing smaller differences in TV (for example, 6 vs. 8–10 mL/kg) failed to demonstrate any similar outcome benefit (41, 42). Patients enrolled in the National Institutes of Health study had ARDS of different severity. Accordingly, their baby lungs likely had markedly different sizes; extremely variable plateau pressures were reported, with some as low as 10 cm H_2O. It is possible that in the subgroup of more severe cases, the use of TV equal to 12 mL/kg resulted in a lung damage far greater than that observed, on average, in the whole study population. In other words, the signal against the use of high TV was so strong that it proved valid even when diluted by a large subgroup of patients with relatively mild disease who possibly did not experience any injurious strain even with TV as high as 12 mL/kg.

However, the use of inappropriately low TV has its own risks, including overuse of sedative drugs and possible formation of atelectasis, especially when applied to patients who could otherwise tolerate a higher TV. Because of the heterogeneity of the ALI/ARDS population, we consider mandatory to tailor TV to the specific characteristics of each individual patient. Knowledge of the actual size of the individual baby lung would suit this aim. Of note, in the aforementioned study, PEEP selection was not a major issue and was only performed based on the gas exchange response. This indicates that part of the lung-protective strategy was basically ignored.

Reduction of end-expiratory stress/strain alone

Three large randomized trials have recently investigated the value of the "keeping the lung open" approach, comparing the use of high vs. low PEEP (43–45) (Table 3). PEEP was selected according to different criteria but, in all the studies, this turned out to be 10 cm H_2O or less in the lower PEEP arm and 15 cm H_2O or more in the higher arm. None of these studies was able to show any survival advantage with the use of higher PEEP. It must be stressed, however, that in at least two of these studies the use of higher

Table 3. Seminal clinical studies of end-inspiratory and end-expiratory stress/strain

Authors	Year	Study Population	Type of Injury (Stress/Strain) Investigated	Lung Strategies	Tidal Volume, mL/kg	Plateau Pressure, cm H_2O	Positive End-Expiratory Pressure, cm H_2O	Mortality
Stewart et al	1998	ALI/ARDS	End-inspiratory	Injurious	11 ± 1	27 ± 7	7 ± 3	47
				Protective	7 ± 1	22 ± 5	9 ± 3	50
Amato et al	1998	ALI/ARDS	End-inspiratory and end-expiratory	Injurious	763 ± 26[a]	34 ± 2	7 ± 1	71
				Protective	362 ± 11[a]	32 ± 1	16 ± 1	38[b]
Brochard et al	1998	ALI/ARDS	End-inspiratory	Injurious	10 ± 2	32 ± 7	11 ± 2	38
				Protective	7 ± 1	26 ± 5	11 ± 3	47
Brower et al	1999	ALI/ARDS	End-inspiratory	Injurious	10 ± 0	31 ± 1	9 ± 1	46
				Protective	7 ± 0	25 ± 1	10 ± 1	50
Ranieri et al	1999	ALI/ARDS	End-inspiratory and end-expiratory	Injurious	11 ± 2	31 ± 5	7 ± 2	58
				Protective	8 ± 1	25 ± 2	15 ± 1	38
ARDS Network	2000	ALI/ARDS	End-inspiratory	Injurious	12 ± 1	33 ± 9	9 ± 4	40
				Protective	6 ± 1	25 ± 7	9 ± 4	31[b]
Brower et al	2004	ALI/ARDS	End-expiratory	Injurious	6 ± 1	24 ± 7	9 ± 4	25
				Protective	6 ± 1	27 ± 6	15 ± 4	28
Villar et al	2006	ALI/ARDS	End-inspiratory and end-expiratory	Injurious	10 ± 1	33 ± 6	9 ± 3	53
				Protective	7 ± 1	31 ± 6	14 ± 3	32[b]
Meade et al	2008	ALI/ARDS	End-expiratory	Injurious	7 ± 1	25 ± 5	10 ± 3	40
				Protective	7 ± 1	30 ± 6	16 ± 4	36
Mercat et al	2008	ALI/ARDS	End-expiratory	Injurious	6 ± 0	21 ± 5	7 ± 2	39
				Protective	6 ± 0	28 ± 2	15 ± 3	35

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

[a]Values of tidal volume reported as absolute values not available as mL/kg of predicted body weight; [b]$p < .05$ vs. injurious ventilation. A selection of what we consider seminal clinical works investigating potential strategies to protect the lung from the development of ventilator-induced lung injury, resulting from either excessive end-inspiratory and/or end-expiratory stress/strain (37–45, 69). Type of injury investigated denotes whether the clinical study investigated the end-inspiratory and/or end-expiratory stress/strain, whereas lung strategies represents the ventilator strategy applied. Tidal volume is the tidal volume applied; plateau pressure indicates the plateau airway pressure resulting from the ventilator strategy applied; and mortality indicates the hospital discharge mortality. For the studies from Amato et al and Ranieri et al, mortality refers to data at 28 days after study enrollment, whereas for the study by Brochard et al mortality refers to data at 60 days after enrollment.

PEEP was associated with a reduction in the number of patients with deteriorating conditions to such an extent as to require predefined rescue therapies (46). Similarly, the two most recent meta-analyses addressing this issue have suggested that the use of high PEEP may be of benefit, at least in patients with the most severe ARDS (47, 48). These latter patients are usually characterized by heavier lungs, greater recruitability, worse gas exchange, and a high rate of mortality (32).

VILI in the Healthy Lung: Clinical Evidence

Two clinical reports describe a possible association between mechanical ventilation and the development of lung injury in previously healthy lungs (49, 50). However, all patients included in these reports were characterized by profound hypoxemia at enrollment. The transition from healthy to ALI/ARDS lung was based only on radiologic findings (chest radiograph). Had hypoxemia been considered as a diagnostic tool, all of the patients would have been classified as having ALI/ARDS (rather than healthy) at randomization. Patients in whom ALI/ARDS (based on radiologic findings) developed were those ventilated with higher TV and lower PEEP. Any potential role of low PEEP in the pathogenesis of VILI was ignored and attention was only addressed to the use of high TV. In our opinion, data provided by these two articles may suggest, at best, a loose association between the use of high TV and the development of ALI/ARDS in previously "healthy" lungs and are absolutely insufficient to claim any cause–effect relationship. Of note, other studies have not shown any association between the use of TV as high as 12 mL/kg and other major end points relative to a 6-mL/kg strategy (51, 52). Choi et al (53) reported that the use of high TV for at least 5 hrs in surgical patients with no lung injury can result in some degree of intrapulmonary coagulation activation compared to patients ventilated with lower TV and greater PEEP. A slightly slower rate of normalization of plasma interleukin-6 with the use of higher TV was recently claimed as proof of a "second-hit" ventilatory injury in patients with apparently normal lungs, despite no change in any of several cytokines measured in bronchoalveolar lavage fluid (54).

The common belief that mechanical ventilation may harm acutely injured and healthy lungs to a similar extent seems to be based more on weak opinion rather than on solid experimental or clinical evidence. In the absence of any conclusive data, we might suspect that what Caesar stated at the Alesia battle, "*Putant quod cupiunt*," i.e., "to consider as truth what one desires to be true," applies perfectly to this particular issue. Therefore, although it is clear and well-documented that mechanical ventilation can damage the healthy lung, the extent of stress/strain required may be far greater than what is described in the literature. It is still possible that in some patients the presence of atelectasis or parenchymal alterations other than inflammatory edema may reduce the size of the lung really open to ventilation, thus augmenting the susceptibility to VILI. Our point is that neither mechanical ventilation *per se* nor the presence of lung lesions *per se* can be invariably considered injurious.

Damage only develops when mechanical ventilation is used in such a way that excessive stress/strain is reached.

Conclusions

There is no doubt that mechanical ventilation can harm the lung. However, the TV required must be high enough to expand the baby lung to its own total capacity. This may occur even at TV as low as 6 mL/kg, but only in a very small subgroup of ARDS patients. Putatively, PEEP may be protective against VILI, as long as it keeps open the lung regions that would otherwise collapse at end expiration. Once again, this concept might be valid only in a minority of ARDS patients. In the absence of consistent lung recruitability, the use of PEEP may solely increase end-inspiratory stress/strain with no benefit. The use of PEEP 15 cm H_2O or higher seems to be justified only in the presence of high lung recruitability. Unsafe limits of end-inspiratory and end-expiratory stress/strain are rarely reached in the overall ALI/ARDS population. However, unexpectedly high stress may develop locally, even at end-inspiratory levels that are globally lower than the threshold observed in the healthy lung, when lung is unevenly aerated and units open to ventilation are in contact with persistently closed ones. We do not know if unphysiological stress/strain is equally dangerous when applied continuously rather than intermittently. Similarly, we do not clearly understand the role (if any) of the respiratory rate. However, what we know for certain is that when mechanical ventilation occurs within the physiologic limits of the baby lung, not exceeding its own total capacity, it is likely to be safe.

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