Which is the most important strain in the pathogenesis of ventilator-induced lung injury: dynamic or static?

Alessandro Protti[a], *Emiliano Votta*[b], *and Luciano Gattinoni*[a,c]

Purpose of review
To discuss the relative role of dynamic and static tissue deformation (strain) generated by inflation of tidal volume and application of positive end-expiratory pressure in the pathogenesis of ventilator-induced lung injury.

Recent findings
Cellular, animal and human studies strongly suggest that dynamic strain is more injurious than static strain, at least when total lung capacity is not exceeded. One possible explanation for these findings is pulmonary viscoelasticity. Large and rapid dynamic deformations generate high and unevenly distributed tensions, internal frictions and energy dissipation in the form of heat, posing microstructure at risk for rupture.
The most important strategy to protect the lung may thus be limiting the tidal volume. Increasing static strain may add benefit by diminishing inhomogeneities (stress raisers), especially in the already severely injured lung. On the other side, however, it may adversely affect the haemodynamics.

Summary
Large lung dynamic strain is more harmful than equivalent static strain.

Keywords
hysteresis, lung strain and stress, positive end-expiratory pressure, tidal volume, viscoelasticity

INTRODUCTION

Values of lung deformation (or strain) that can be safely reached during mechanical ventilation are poorly defined, especially in humans. The aim of this work is to review the concepts of dynamic and static strain and to define their relative role in the pathogenesis of ventilator-induced lung injury (VILI). We will mainly analyse the data obtained in healthy cells and healthy animals to isolate the net effect of mechanical ventilation. We will then consider the clinical evidence derived from randomized controlled trials, mainly performed in patients with acute lung injury. Finally, we will interpret our findings in light of the biomechanical principles.

DYNAMIC AND STATIC STRAIN DURING MECHANICAL VENTILATION

Lung distension is commonly inferred from tidal volume (V_T) (ml/kg of ideal body weight) and end-inspiratory (plateau) airway pressure [1]. However, neither of these two variables reliably reflect tissue deformation, especially during acute lung injury, when relationships between body weight and functional residual capacity (FRC) and between airway and transpulmonary pressure become unpredictable [2].

Referring to strain and stress may help clinicians to better describe the effects of mechanical ventilation on whole lungs. In engineering, strain and stress are used to describe the microscopic responses

[a]Dipartimento di Anestesia, Rianimazione ed Emergenza-Urgenza, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, [b]Dipartimento di Bioingegneria, Politecnico di Milano and [c]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy

Correspondence to Luciano Gattinoni, Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Via F.sco Sforza 35, 20122 Milan, Italy. Tel: +39 2 55033232; fax: +39 2 55033230; e-mail: gattinon@policlinico.mi.it

KEY POINTS

- When lung volume does not exceed the total capacity, dynamic inflation (due to tidal ventilation) is more injurious than equivalent static inflation (due to the application of positive end-expiratory pressure).
- When lung volume exceeds the total capacity, pulmonary damage invariably occurs.
- Benefits for the lung of very high static inflation must be weighed against the risks for the heart.

of a body to external loading: strain is the relative change in size and shape and stress is the internal tension [3].

The exact measurement of lung strain and stress is unfeasible in clinical practice. More simplistically, we define lung strain as the ratio between the volume of gas inflated (change in volume) and FRC. Lung stress equals the corresponding change in transpulmonary (airway minus pleural) pressure [4]. Lung mechanics can then be described as:

$$\text{stress} = \text{specific lung elastance} \times \text{strain}$$

where specific elastance refers to the intrinsic elasticity of the lung open to gases. In quasi-static condition, specific lung elastance is reasonably constant (around 13 cm H_2O in humans) and lung stress–strain relationship is almost linear until the total capacity is approached [2]. Therefore, lung strain can be derived from stress and vice versa. At the bedside, lung strain can be computed from FRC, which several ventilators automatically measure, whereas over-imposed lung stress can be estimated from changes in the oesophageal pressure [2].

During mechanical ventilation with no positive end-expiratory pressure (PEEP), lung deformation is due to tidal ventilation. This dynamic strain can be computed as:

$$\text{dynamic strain} = V_T : \text{FRC}$$

When PEEP (and the corresponding volume of gas, V_{PEEP}) is applied, lungs are also kept tonically inflated above their FRC and are exposed to an additional static strain:

$$\text{static strain} = V_{PEEP} : \text{FRC}$$

Global strain is the sum of these two components:

$$\text{global strain} = (V_T + V_{PEEP}) : \text{FRC}$$

DYNAMIC VERSUS STATIC STRAIN: CELLULAR STUDIES

Rat alveolar epithelial cell monolayers, mounted on stretching devices, underwent various deformation protocols. Injury was quantified as the final percentage of dead cells. Conclusions were similar for type I and type II cells [5,6].

First, injury was relevant only when cellular surface area increased by at least 37% as it does, *in vivo*, when lungs are inflated approximately at total capacity. Second, dynamic was more harmful than equivalent static strain. Third, diminishing dynamic strain whilst increasing static strain, so as to maintain global strain constant, resulted in fewer cell deaths. Fourth, increasing the cellular surface area by 50% (that is, inflating lungs above their total capacity) always caused large cell deaths.

DYNAMIC VERSUS STATIC STRAIN: ANIMAL STUDIES

Several (but not all) animal studies have shown that ventilation with large tidal volume and zero end-expiratory pressure is more injurious than ventilation with small tidal volume and some PEEP, for a given peak pressure [7].

Here, we summarize the results of our own observations in healthy pigs.

First, we evaluated the effects of dynamic lung deformation by ventilating animals with different tidal volumes and zero PEEP [8]. Dynamic strains below 1.5, resulting in stresses lower than 10 cm H_2O (pig specific lung elastance is around 6 cm H_2O), did not cause gross lung damage over 54 h. By contrast, dynamic strains above 2.0, resulting in stresses higher than 15 cm H_2O, always produced fatal pulmonary oedema. For intermediate values, lung outcome could not be reliably predicted.

Then, we investigated the effects of dynamic plus static lung deformation by ventilating animals with different combinations of tidal volume and PEEP [9▪]. Global strain was always 2.5 (end-inspiratory lung volume $\approx$ total lung capacity). If overall inflation had been the real cause of lung damage, all these pigs should have developed fatal pulmonary oedema, global strain being well above the threshold of 2.0 reported above. Animals ventilated with dynamic strain of 2.5 (static strain equal to 0) actually did so. By contrast, those ventilated with smallest dynamic (0.5) and largest static (2.0) strain ended the experiment with normal lungs, although they needed large amount of fluids and high dose of norepinephrine to maintain an adequate cardiac output. Intermediate settings usually produced nonfatal pulmonary

oedema. Therefore, in these medium-sized animals, harms of mechanical ventilation depend not only on overall lung inflation, but also on the way this is achieved: large cyclic deformations are more injurious than equivalent, but mainly static, ones.

Our results apparently contradict those of Dreyfuss and Saumon [10], who showed that healthy rats develop pulmonary oedema if ventilated with small tidal volume (7 ml/kg of body weight) and high PEEP (15 cm H_2O). However, the volume of gas globally inflated during these experiments was 11.4 ml (assuming 307 g of rat body weight). On average, FRC in rats of similar weight is 2.5 ml, inspiratory capacity 9.7 ml and total lung capacity 12.2 ml [11,12]. Accordingly, end-inspiratory lung volume (2.5 ml + 11.4 ml = 13.9 ml) ml) quite certainly exceeded the total lung capacity (on average, by 14%). End-inspiratory airway pressure was 45 cm H_2O and transpulmonary pressure was probably around 40 cm H_2O. In other words, lungs were inflated above their upper physiological limit [13].

The bulk of these data can be reconciled as follows. When end-inspiratory volume does not exceed the total capacity, healthy lungs better tolerate static, than dynamic, inflations. However, when end-inspiratory lung volume exceeds the total capacity, static or dynamic inflation invariably causes lung damage. Thus follows the importance of measuring lung volumes during mechanical ventilation [14].

DYNAMIC VERSUS STATIC STRAIN: HUMAN STUDIES

Clinical research has mainly focussed on the survival benefits of limiting the tidal volume and increasing PEEP during acute respiratory insufficiency. Results of some of the most influential trials published so far [1,15–19] can be summarized as follows.

Limiting the tidal volume is beneficial either *per se* [1] or in conjunction with increasing PEEP [15,17]. By contrast, increasing PEEP does not generally diminish hospital mortality [16,18,19], unless tidal volume is concomitantly reduced [15,17].

Although the number of similar trials enrolling patients with 'healthy' lungs is minor, conclusions might be similar. One meta-analysis suggests that mechanical ventilation with smaller tidal volumes and higher PEEPs is associated with a lower incidence of pulmonary complications in patients without acute lung injury at enrolment [20]. Two subsequently published randomized controlled trials confirm these findings [21,22▪▪]. By contrast, increasing the PEEP without changing the tidal volume did not diminish the incidence of acute respiratory distress syndrome in mechanically ventilated patients with nonpulmonary disease [23].

SAFE MECHANICAL VENTILATION: SMALLER TIDAL VOLUME OR HIGHER POSITIVE END-EXPIRATORY PRESSURE?

In many experimental and clinical studies, including the very first seminal study by Webb and Tierney [24], lung protection was achieved by using smaller tidal volumes and higher PEEPs ('open-lung' ventilation). Therefore, it is hard to define the relative role of these two interventions to the final outcome.

According to Starling [25], inflammatory oedema develops when capillary transmural (internal minus external) pressure drives excessive fluid filtration through a disrupted, highly permeable barrier. Here, we discuss three, nonmutually exclusive explanations for why the 'open-lung' approach diminishes the incidence of VILI.

HIGHER POSITIVE END-EXPIRATORY PRESSURE LOWERS PULMONARY CAPILLARY TRANSMURAL PRESSURE

PEEP may merely act as a hydrostatic barrier against pulmonary oedema formation [26]. In fact, by increasing the mean airway pressure, it diminishes venous return, cardiac output and pulmonary capillary inflow (and pressure), while increasing extravascular pressure [27,28]. Oedema may not develop even if the blood–gas barrier actually loses its integrity.

To address this issue, we ventilated healthy pigs with small tidal volume and high PEEP, so that the end-inspiratory lung volume was equal to the total capacity. After 36 h, PEEP was suddenly zeroed. If the blood–gas barrier had been disrupted, fluid extravasation should have freely occurred, driven by normal (and occasionally supra-normal) haemodynamics. However, pulmonary oedema did not develop over the following 18 h [29]. This strongly suggests that mechanical ventilation with small tidal volume and high PEEP (with end-inspiratory lung volume not exceeding the total capacity) does not simply impede fluid extravasation from the pulmonary capillaries.

SMALLER TIDAL VOLUMES PRESERVE THE INTEGRITY OF THE BLOOD–GAS BARRIER

From a mechanical point of view, lungs behave as viscoelastic bodies: they combine the properties of elastic and viscous materials (Fig. 1).

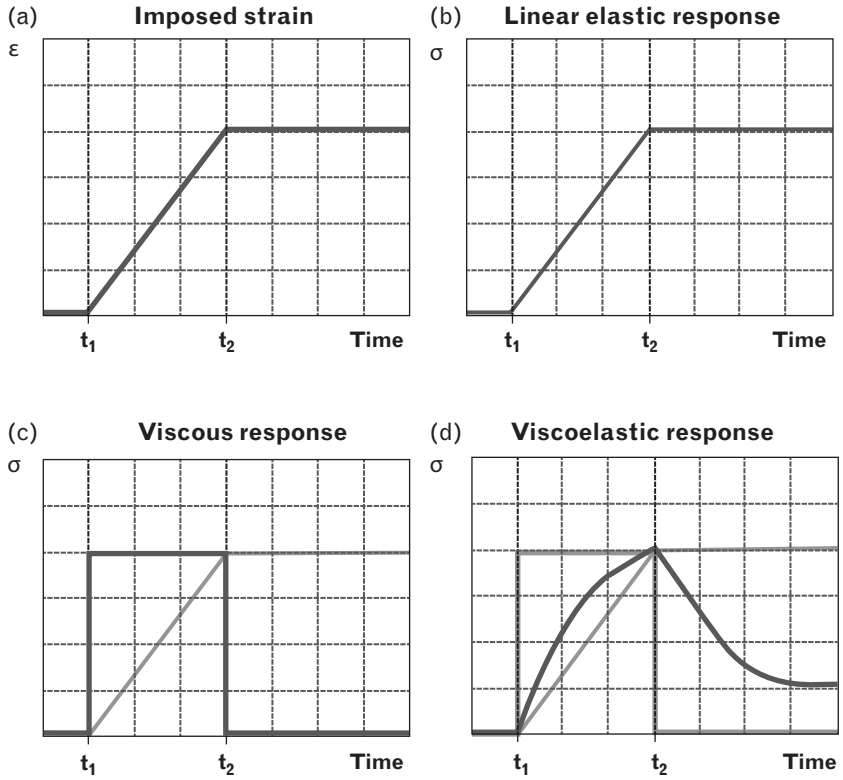

FIGURE 1. Stress–strain relationship for linear elastic, viscous and viscoelastic materials. Deformation (strain, ε) is progressively increased at a constant rate (dynamic phase) and then kept constant over time (static phase) (panel a). In a linear elastic body, internal tension (stress, σ) is proportional to strain: it increases during the dynamic phase and remains constantly high during the static phase (panel b). In a viscous body, stress is proportional to the velocity of deformation: it is high during the dynamic phase, but returns to zero when elongation ceases, irrespectively of the residual static deformation (panel c). In a viscoelastic body, which combines the properties of linear elastic and viscous materials, stress (and thus risk for rupture) is higher during dynamic than static strain (panel d).

Elastic materials accumulate energy when loaded (whilst deforming) and return it entirely when unloaded (whilst going back to their initial configuration). The stress–strain plots are exactly the same during loading and unloading, and the stress–strain relationship can be reasonably considered linear, at least below or beyond a critical threshold, in which the slope of the diagram markedly changes:

$$\text{stress} = k \times \text{strain}$$

where k is the proportionality constant.

Viscous materials are different. They only partly return energy during unloading, because internal frictions lead to energy dissipation in the form of heat. As a result, the stress–strain plots describing loading and unloading differ from each other, with stress being lower during unloading at any given strain. This property of dissipating energy is called 'hysteresis' and can be quantified as the area between loading and unloading stress–strain curves. The stress–strain relationship of viscous materials is:

$$\text{stress} = \eta * \text{strain rate}$$

where η is the proportionality constant and strain rate is the velocity of deformation.

Lung hysteresis is due to airway flow resistance, alveolar recruitment and de-recruitment, forces acting at the alveolar liquid–air interface and tissue viscoelasticity. This latter property mainly depends on the parenchymal microstructure and the internal frictions that develop during deformation [30,31]. The lung fibrous skeleton is a 'spaghetti-like' network of elastin and collagen fibres, embedded in a hydrated gel formed by proteoglycans and other extracellular matrix proteins. Elastin fibres act as extensible springs, whereas collagen fibres work as stiffer strings, limiting the tissue elongation when lung volume approaches total capacity [4]. Water and extracellular matrix proteins interact with these fibres and influence their orientation,

unfolding, stretching and reciprocal sliding. In response to external loading, lung fibrous skeleton constituents rearrange their configuration and interactions whilst transferring energy to each other [30,31]. As a result, heat is locally generated.

According to Bachofen and Hildebrand [32], lung hysteresis can be defined as:

$$\text{lung hysteresis} = k \times \text{volume} \times \text{pressure}$$

where k is the hysteresis constant of lung tissue. Energy dissipation is proportional to strain (volume inflated), as for elastic bodies, and strain rate, as for viscous materials. In fact, for any given strain, pressure amplitude is proportional to the velocity of deformation.

Lung viscoelasticity might be one plausible explanation for the benefits of limiting the tidal volume (and inspiratory flow, if respiratory rate is kept constant). In fact, small and slow cyclic strain causes smooth sliding of lung skeleton fibres, whereas large and rapid strain creates entanglements or 'nodes', where stress accumulates and rupture possibly occurs. Slow deformation generates low stress (tissue gets less stiff), so that the risk of rupture is reduced. In addition, limiting the cyclic deformation diminishes the amount of energy converted into heat. According to the kinetic molecular theory, heating a material increases the amount of kinetic energy of its constituents [33]. Molecular vibrations become ample and fast, so that the intermolecular distance increases. In addition, heat changes the protein conformation, so that the weak bonds between molecules may fail. Fragmentation of lung extracellular matrix stimulates inflammation [34] and acutely amplifies tissue damage. For all these reasons, lowering the dynamic deformation possibly preserves lung microstructure.

HIGHER POSITIVE END-EXPIRATORY PRESSURE PRESERVES THE INTEGRITY OF THE BLOOD–GAS BARRIER

According to the model described above, higher PEEP appears beneficial only because it leads to the use of smaller tidal volumes (if overall lung inflation is kept constant). However, we believe it may have its own protective effects on the lung, especially during most severe disease [35].

Materials usually start to fail in correspondence with geometric discontinuities, where tensions concentrate so as to exceed the threshold for rupture. Ventilated healthy lungs do have inhomogeneities, owing to uneven alveolar geometry, local tissue mechanical properties, transpulmonary pressure and, thus, gas inflation [36]. Atelectasis and consolidation further augment them.

In a perfectly homogeneous (ideal) lung, strain and stress equally distribute within the fibrous skeleton. By contrast, in the presence of inhomogeneities, they concentrate on neighbouring fibres, which thus get exposed to unpredictably high strain and stress [4]. In other words, inhomogeneities act as 'stress amplifiers', as originally theorized by Mead *et al.* [37]. Perlman *et al.* [38] have shown that liquid filling of one single alveolus (to simulate oedema) is associated with overdistension of adjacent air-filled regions.

High PEEP may favour more homogeneous ventilation by reducing the intratidal opening and closing phenomenon (lower extent of 'stress raisers'), especially in patients with higher lung recruitability [39].

CONCLUSION

Growing experimental and clinical evidence suggests that lung damage during ventilation mainly depends on the amplitude and velocity of dynamic tissue deformation. Large static strain is better tolerated than equivalent dynamic strain and may even beneficially reduce the lung inhomogeneities. Tissue viscoelasticity may be a plausible explanation for these observations, although some of the concepts described above still need to be prospectively validated. In particular, whether heat produced by the internal frictions can change the conformation of molecules forming lung parenchyma, which is rich in water, is uncertain.

On the basis of the data reported above, we advocate the strategies that minimize tidal ventilation, including 'apnoea' with extracorporeal carbon dioxide removal [40]. High static inflation (up to total lung capacity) may be then required to keep the lung open, as suggested by animal studies [41] and by failure of high-frequency jet ventilation (at low PEEP) [42]. In fact, during 'apnoea', bronchial secretions are not efficiently cleared, distal airways get obstructed and re-absorption atelectasis leads to progressive alveolar de-recruitment.

However, two recent clinical trials embracing the same idea by using high-frequency oscillatory ventilation reported no outcome benefit in patients with acute respiratory distress syndrome [43▪,44]. We strongly suspect that this is explained by the right heart dysfunction because of very high mean airway pressure (close to or even above 30 cm H_2O), with higher need for fluids and vasoactive drugs in the study population [45▪]. Interventions designed to protect the lung will hardly improve survival if they concomitantly harm the heart.

Acknowledgements

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Conflicts of interest

The authors declare no conflicts of interest.

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This work clearly describes the incidence, pathogenesis and impact of a frequently misdiagnosed complication of high airway pressure ventilation during acute respiratory insufficiency: right ventricular failure.