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# Physical and biological triggers of ventilator-induced lung injury and its prevention

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*Physical and biological triggers of ventilator-induced lung injury and its prevention. L. Gattinoni, E. Carlesso, P. Cadringher, F. Valenza, F. Vagginelli, D. Chiumello. ©ERS Journals Ltd 2003.*

**ABSTRACT: Ventilator-induced lung injury is a side-effect of mechanical ventilation. Its prevention or attenuation implies knowledge of the sequence of events that lead from mechanical stress to lung inflammation and stress at rupture.**

**A literature review was undertaken which focused on the link between the mechanical forces in the diseased lung and the resulting inflammation/rupture.**

**The distending force of the lung is the transpulmonary pressure. This applied force, in a homogeneous lung, is shared equally by each fibre of the lung's fibrous skeleton. In a nonhomogeneous lung, the collapsed or consolidated regions do not strain, whereas the neighbouring fibres experience excessive strain. Indeed, if the global applied force is excessive, or the fibres near the diseased regions experience excessive stress/strain, biological activation and/or mechanical rupture are observed. Excessive strain activates macrophages and epithelial cells to produce interleukin-8. This cytokine recruits neutrophils, with consequent full-blown inflammation.**

**In order to prevent initiation of ventilator-induced lung injury, transpulmonary pressure must be kept within the physiological range. The prone position may attenuate ventilator-induced lung injury by increasing the homogeneity of transpulmonary pressure distribution. Positive end-expiratory pressure may prevent ventilator-induced lung injury by keeping open the lung, thus reducing the regional stress/strain maldistribution. If the transpulmonary pressure rather than the tidal volume per kilogram of body weight is taken into account, the contradictory results of the randomised trials dealing with different strategies of mechanical ventilation may be better understood.**

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In the 1970s, the typical setting for mechanical ventilation in acute respiratory distress syndrome (ARDS) was a tidal volume ($V$T) of 12–15 mL·kg body weight$^{-1}$ with a positive end-expiratory pressure (PEEP) of 5–10 $cmH_2O$.

"We ventilated thousands of patients in this way and the only side effect was hypocapnia" was a statement made by PONTOPPIDAN *et al.* [1] in the *The New England Journal of Medicine* in 1972. However, since the mid-1970s, there has been progressive recognition of the potential harm of mechanical ventilation. The recognition that the ventilatable lung in ARDS is small, and not stiff (the baby lung concept [2]), made obvious the possible mechanical harm of using a high $V$T in a little lung, and led to concepts such as permissive hypercapnia [3], *i.e.* to more gentle lung treatment. In parallel, it was recognised *ex vivo* [4] and *in vivo* [5] that, irrespective of mechanical rupture, mechanical ventilation may induce a complex biological response, with release of inflammatory and anti-inflammatory mediators. This led to the concept of biotrauma, which is widely, although not universally [6], accepted. In the present article, the authors present their understanding of the initial physical and biological events which trigger ventilator-induced lung injury (VILI) and its clinical consequences, without intending to either provide an exhaustive review of full-blown VILI or preclude or invalidate other interpretations.

## The distending force of the lung and its distribution in healthy and diseased lung parenchyma

The distending force of the lung per unit area, *i.e.* the pressure, is that applied to the visceral pleura. This is the transpulmonary pressure ($P$L), which is the difference between the pressure inside the alveoli and the pleural pressure ($P$pl). Unfortunately, in normal clinical practice, it is usual to consider the plateau or airway pressure ($P$aw) as the distending force of the lung. Under static conditions, $P$aw closely reflects the intra-alveolar pressure, which, in part, is spent to inflate the lung, and, in part, to inflate the chest wall. In a simple model that ignores blood shift, lung inflation is considered to be equivalent to chest wall inflation. The relationship between $P$aw and $P$pl, which determines the $P$L, depends on the relative mechanical characteristics of lung and chest wall, which is convenient to express as elastance (pressure/volume).

The elastance of the respiratory system ($E$rs) is the $P$aw required to inflate the respiratory system to 1 L above its resting position under static conditions. Indeed, $P$aw equals the sum of the pressure used to inflate the lung (PL) and the one used to inflate the chest wall ($P$pl):

$$P_{\mathrm{aw}} = P_{\mathrm{L}} + P_{\mathrm{pl}}, \tag{1}$$

and

$$E_{rs} = E_L + E_w, \quad (2)$$

where $E_L$ and $E_w$ are the elastances of the lung and chest wall. Accordingly,

$$P_L = P_{aw} E_L / E_{rs}. \quad (3)$$

Under normal static conditions, since $E_L$ is approximately the same as $E_w$, whatever pressure is applied to the alveoli, it results in a change in $P_L$ of ~50% ($E_L/E_{rs}$=0.5).

For many years, unfortunately, any change in $E_{rs}$ was attributed to $E_L$. However, there is now consistent evidence that $E_w$ may be altered in ARDS patients [7–10] due either to individual patients' anatomical characteristics (body size and weight) or the nature of the disease leading to ARDS. It has been shown that abdominal pressure, which directly increases $E_w$, is frequently altered in abdominal diseases associated with ARDS, such as peritonitis or bowel ischaemia [11, 12]. Indeed the $E_L/E_{rs}$ ratio, which determines the relationship between $P_{aw}$ and the resulting $P_L$ (Equation 3), may range in acute lung injury/ARDS from 0.3 to 0.8 or more, greatly different from the normal value of 0.5. Since VILI occurs due to distension of the lung, which depends on $P_L$, it follows that its measurement or estimation is a key issue, as, for the same applied $P_{aw}$, $P_L$ and its potential harm to the lung may vary greatly between patients.

### *Pressure transmission throughout the lung*

The $P_L$ is applied to the visceral pleura and has to be transmitted throughout all lung regions. The force-transmitting system is the lung's fibrous skeleton, which consists of two components, the axial fibres, anchored to the hilum, which run along the branching airways down to the level of alveolar ducts, and the peripheral fibre system, anchored to the visceral lung pleura, which penetrates centripetally into the lung down to the acini. The two systems are linked at the alveolar level by the alveolar septal fibres [13]. The lung's fibrous skeleton consists mainly of elastin and collagen fibres, which are intimately associated with each other. Other load-bearing force elements connecting to the pulmonary interstitium are actin and myosin microfilaments originating from myofibroblasts.

### *Pressure, stress/tension and strain*

The strict definition of stress and strain is beyond the purpose of the present article and may be found elsewhere [14]. However, in its simplest definition, in a monodimensional structure (such as a string/spring pair), stress (or tension) may be defined as the force per unit area which develops in a structure as a reaction to an applied external force of the same entity but opposite direction, *i.e.* $\sigma n=\Delta F/\Delta S$, where $\sigma n$ is stress, $\Delta F$ change in force and $\Delta S$ the reference surface to which the force is applied. This internal force, cutting the structure by an ideal surface, may be resolved into three components, one of which is normal to the plane (normal stress) and two of which are tangential (shear stresses). The deformation of the structure (if any) due to the applied force is called strain. In the simplest monodimensional structure under traction, strain is defined as the ratio of the change in length of the structure ($\Delta L$) to its length in the resting position ($L_0$), *i.e.* $\in=\Delta L/L_0$, where $\in$ is strain. Indeed, stress and strain are the natural response of a structure to an applied force. In the lung, during mechanical ventilation, stress and strain are periodically changing variables characterised by maximal and minimal values (end-inspiratory and end-expiratory PL for stress, and end-inspiratory and end-expiratory lung volume (EELV) for strain) at a given frequency and amplitude (difference between maximal and minimal value).

When $P_L$ is applied to the visceral pleura surface by the inspiratory muscles or ventilator, this applied force, under static conditions, is equal to the sum of the forces developed within the lung parenchyma. Part of these forces are borne by the alveolar air/liquid interface, which, in the presence of surfactant, are very low up to 80% of total lung capacity [15], whereas the remaining forces are shared by the fibre system of the lung's fibrous skeleton. With lack of surfactant, the liquid/air interface bears more force and conceptually works as an "added force-bearing fibre system". Indeed, each fibre experiences a stress/tension according to the force it has to bear. In a homogeneous lung, every fibre shares an equal proportion of the total force applied and develops an equal tension and equal strain. If some of the fibres are destroyed (as in emphysema), fewer fibres have to share the applied force and experience greater stress and strain. However, if part of the parenchyma remains collapsed during inflation or cannot expand, as in consolidated pneumonia, the interwoven fibres in the diseased region bear the force and are in tension but do not strain. The fibres connected to the not expandable region, however, have to carry a greater force load, with greater tension and distortion (fig. 1). These concepts have been developed, on a theoretical background, by MEAD *et al.* [16], who, in a simplified model in which the volume of the collapsed region was one tenth of the volume that this region would have occupied if not collapsed, computed that, for an applied pressure of 30 $cmH_2O$, the resulting tension in the neighbouring region would have been 140 $cmH_2O$. Independently of the precision of this computation, it is clear that, when the stress and strain are not homogeneously distributed, greater tension and distortion develop in some regions and the order of magnitude of fibre tension may be such to lead to stress at mechanical rupture.

## Targets of injury

As discussed above, it appears that the triggers of VILI are the mechanical forces which globally (excessive applied $P_L$) or locally (stress/strain maldistribution due to lung inhomogeneity) cause mechanical alterations of the lung parenchyma which range from excessive and nonphysiological strain up to stress at rupture. Indeed, the three main targets of injury are the fibre systems in the extracellular matrix, alveolar cells and lung capillaries. The small airways may also be affected [17, 18], but have scarcely been studied and so are not discussed further.

### *Fibre system*

As the most important components of the lung's fibrous skeleton are the collagen and elastin fibres, it is appropriate to briefly summarise their mechanical characteristics (fig. 2, table 1). The simplest approach to elastin/collagen interaction is to consider the elastin a spring in parallel with a folded string of collagen. The elastic behaviour of the simple unit is shown in figure 2a. When an external force is applied, the spring (elastin) is the force-bearing element and develops stress and strain according to its mechanical characteristics. The string (collagen) develops its stress when completely unfolded. Since the collagen is almost inelastic, it works as a stop-length fibre, preventing further strain of the elastin/collagen unit. However, different units may have different elastic constants

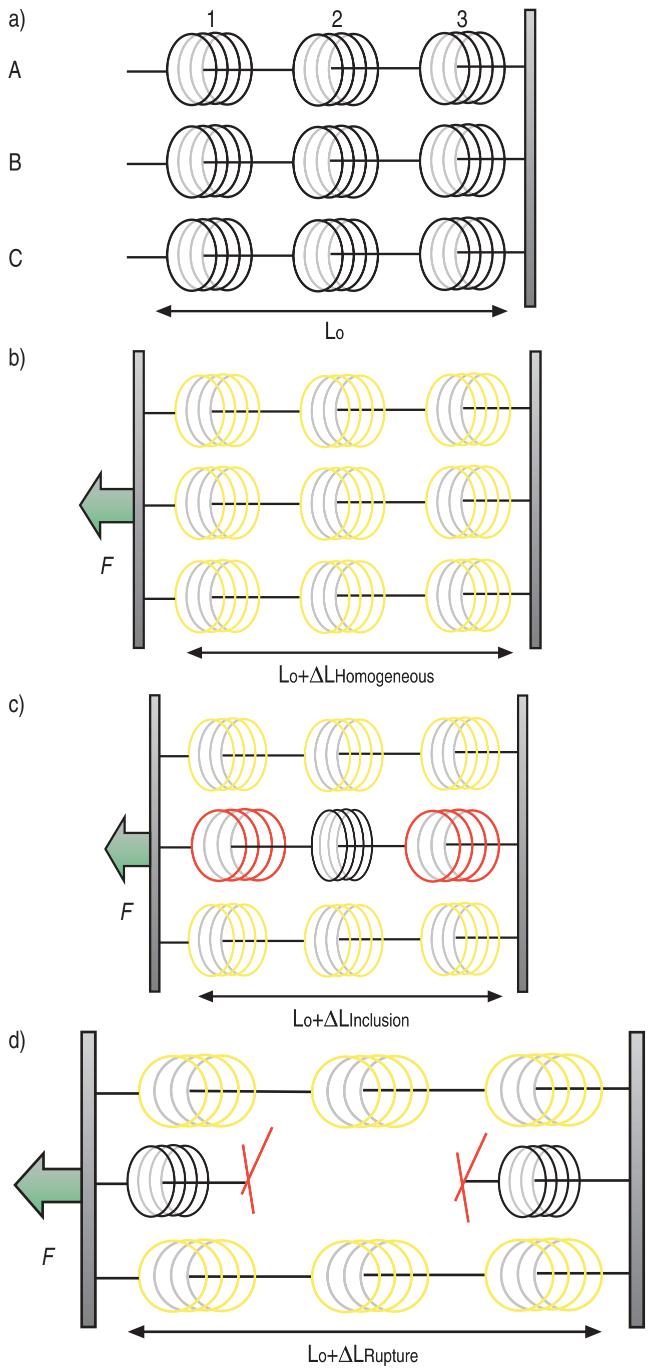


Fig. 1. – Model of fibrous network showing three fibre lines in parallel (A–C), with each line containing three springs (1–3). a) Resting position. b) When a force ($F$) is applied and the system is homogeneous, each line bears a third of the force (0.33$F$) and each spring in each line carries the same force (0.33$F$). Thus the strain is equally distributed within the lines and the springs. c) If one element is consolidated (inclusion), it carries the force but does not strain. The connected springs experience greater strain. d) In the case of rupture (of line B), the line does not carry any stress/strain; however, the lines in parallel undergo greater stress and strain. In mathematical terms, each spring has stiffness $K$, except spring B2, whose stiffness is $MK$ and which determines the different behaviours of the model. When $F$ is applied, the model behaves according to the following equations: $\Delta L=F(6M+3)/(K(7M+2))$; $\Delta L_{A1}=\Delta L_{A2}=\Delta L_{A3}=\Delta L_{C1}=\Delta L_{C2}=\Delta L_{C3}=\Delta L/3$; $\Delta L_{B1}=\Delta L_{B3}=M\Delta L/(2M+1)$; $\Delta L_{B2}=\Delta L/(2M+1)$; $F_A=F_C=F(6M+3)/(21M+6)$; and $F_B=3MF/(7M+2)$. If $M$=1 the system is homogeneous; if $M$=0, line B is broken; and, finally, if $M\rightarrow\infty$, B2 behaves as an inclusion. $\Delta L$: change in length of structure; $L_0$: total length in resting position.

and different stop lengths. When connecting different units with different characteristics in series, the overall behaviour results from the contribution of the simple elements (fig. 2b and c). The situation is more complex when considering the network of spring/string units connected in series and parallel. Assuming a statistical density distribution of elastin/collagen mechanical characteristics, models have been developed, which describe the mechanical behaviour of the system as tested *ex vivo* (fig. 2d) [19, 20]. Considering the mechanical behaviour of the whole fibre system and its tissue/air ratio, it appears that the order of magnitude of the stress at rupture is ~100 $cmH_2O$.

## *Alveolar cells*

Three-quarters of all lung cells (by volume) are located in gas exchange regions. Although type II epithelial cells are located in the alveolar corners, type I epithelial cells (about ~90% of the alveolar surface) are flat and wide, and the same cell may encompass, in a sandwich-like fashion, approximately four endothelial cells. It is worth emphasising that, in most of the alveolar structure, type I epithelial cells share a common basal membrane with endothelial cells, suggesting mechanical coupling. The fibre system and associated fibroblasts as well as filaments of actin and myosin, which all contribute to mechanical support [21], are located in the basal membrane (extracellular matrix) to which both the epithelial and endothelial cells are anchored *via* integrins.

When a distending force is applied to the fibre system, which primarily bears the load, all of the anchored cells have to accommodate their shape to the new surface. Obviously, there is a continuum from physiological deformation up to plasma cell break (stress failure). The interaction between the mechanical deformation and the biological reaction has been extensively investigated in cell culture (excellently reviewed in [22–28]). However, it is unlikely that the stress/strain relationship in cell culture is equivalent to that *in vivo* due to the complex architecture of the alveolar wall as well as phenomena such as alveolar cell unfolding at high volume [29]. Therefore, it is hard to translate lung volume changes into cell strain changes. However, despite these limitations, the present authors believe that the available data, obtained in cultures of different alveolar cells, may be considered as offering a unique perspective, which is internally consistent.

As summarised in figure 3, the cells react to deformation, first reinforcing the plasma membrane by recruiting intracellular lipids to the cell surface, a phenomenon called deformation-induced lipid trafficking [30, 31]. In the meantime, the "mechanosensors", *i.e.* the integrins, the cytoskeleton and ion channels, transduce the mechanical signal in biochemical events, *via* a complicated network of signalling molecules [26–28]. The final result of an "intermediate" nonphysiological strain, not such as to produce physical rupture of the alveolar wall, is the reinforcement/sealing of the plasma cell membrane [32], as well as, *via* mechanosensors, upregulation of inflammatory cytokines and, possibly, $Ca^{2+}$-mediated cell contraction [33].

The results of various experiments in different cell cultures are summarised below. At a strain causing a 12% increase in surface area, it has been shown that human macrophages, *via* nuclear factor-κB, produce interleukin (IL)-8 [34], a cytokine of the CXC chemokine family, which is the most powerful chemoattractant for neutrophils. At the same level of strain, macrophages produce metalloproteins, which remodel the extracellular matrix. Interestingly, no alveolar cells tested at this level of strain produced any other cytokine, including tumour necrosis factor-α. At 17–18% linear strain change

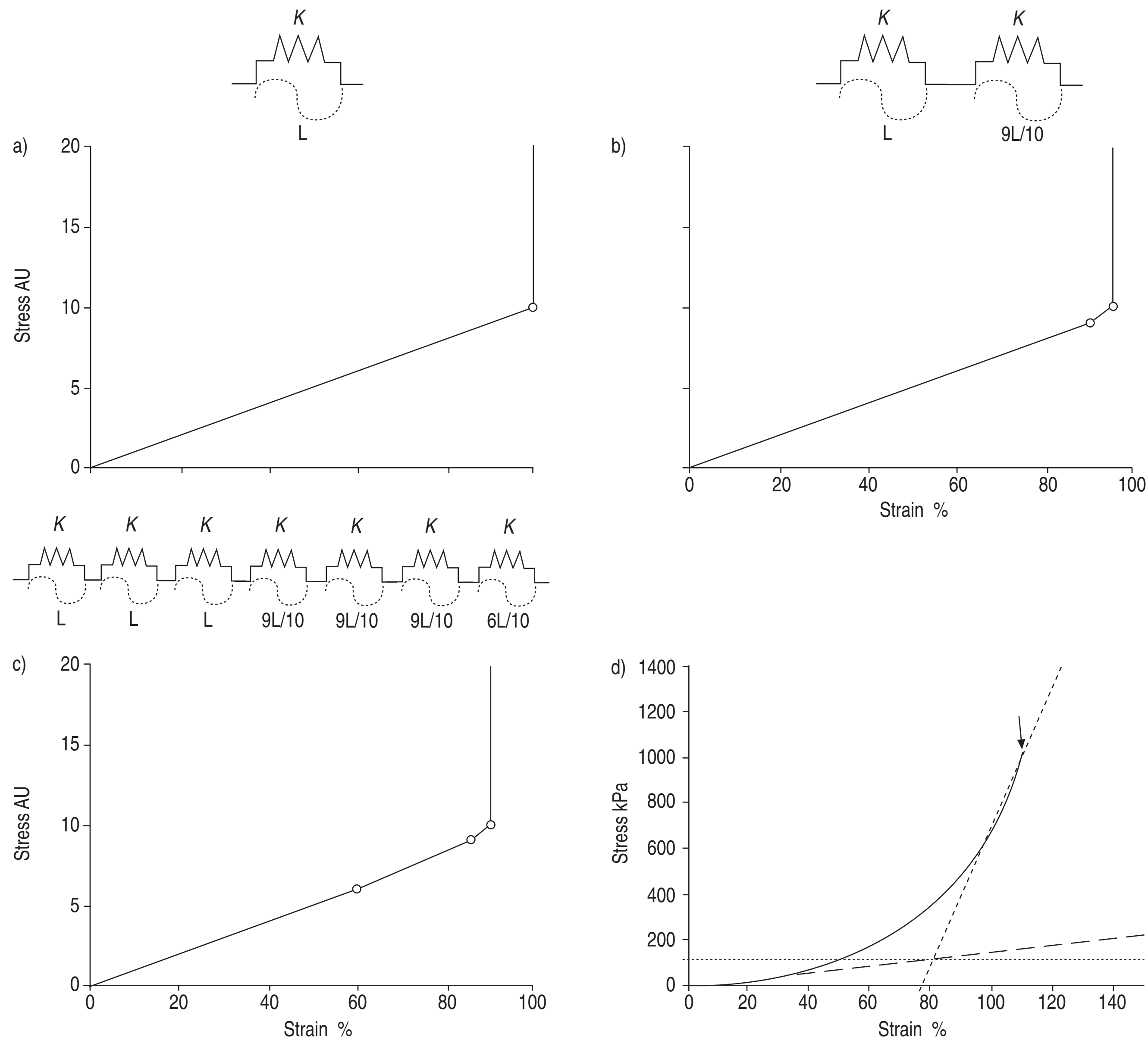


Fig. 2. – Mechanical characteristics of elastin and collagen: Young module (stress/strain) (see table 1). Stress/strain relationship of: a) one; b) two; and c) seven elastin/collagen pairs of elasticity *K* (——) and maximal length L (……). The elastin/collagen pairs have the same *K* but different L and are connected in series (○: stress/strain at which the various collagen fibres become unfolded and reach their stop length). d) Stress/strain relationship obtained in tissue strips (——: behaviour of whole system; – – – –: elastic behaviour of elastin fibres; - - - - -: elastic behaviour of collagen fibres; ·········: elastin stress at rupture limit). It appears that the stress at rupture (indicated by vertical arrow) is 1,000 kPa. As the ratio between tissue and air is ~1:100, the stress at rupture in the lung should be ~1,000/100 kPa, *i.e.* 100 $cmH_2O$. AU: arbitrary units. (d) adapted from [19].

Table 1. – Mechanical properties of collagen and elastin fibres

| | Young module MPa | Stress at rupture MPa | Strain at rupture % | Elastic limit % | Content % |
|---|---|---|---|---|---|
| Collagen | 1000 | 50–100 | 10 | 1–2 | 2 |
| Elastin | 0.6 | 1 | 100 | 60 | 10 |

(which should correspond to ~37% surface change), it has been shown that human endothelial cells produce metalloproteins [35]. At 30 and 40% strain, A549 epithelial cells produce IL-8 [36, 37], whereas, at 50% surface strain, which should correspond, in that experimental set-up with rat epithelial cells, to a volume change greater than total lung capacity *in vivo*, 70% cell death has been reported [38]. These data refer to the magnitude of strain (a rough equivalent of end-inspiratory lung volume). However, it has been shown, both *in vitro* and *in vivo*, that the duration of strain, as well as its amplitude and frequency, may increase the injury [39–42]. Interestingly, for the same magnitude of strain, reducing its

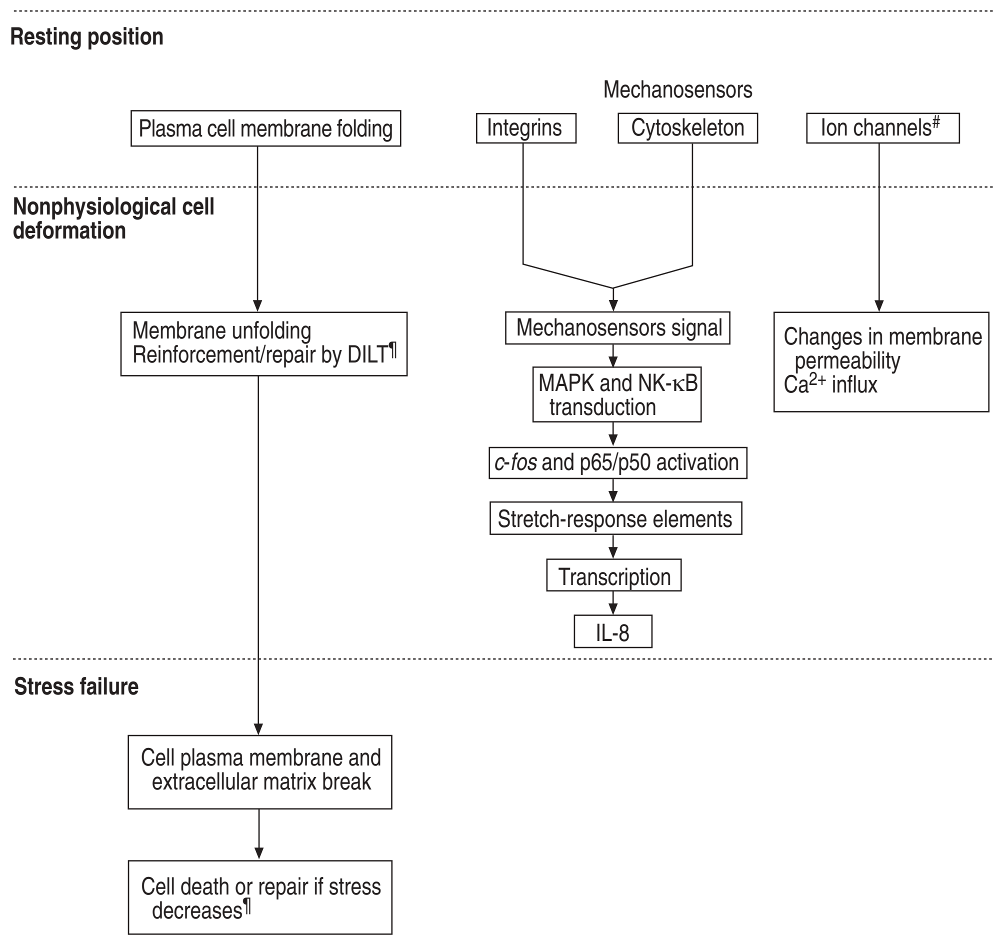


Fig. 3. – Simplified scheme showing cell reaction to mechanical stress (------: separates different stages in reaction). DILT: deformation-induced lipid trafficking; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; IL: interleukin. (Data from [25, 28#, 30, 31¶]).

amplitude (by increasing baseline strain) reduces epithelial cell injury [40]. Indeed, from the bulk of data, it appears that cyclic nonphysiological strain on alveolar cells induces release of IL-8 and metalloproteins, whereas cell death occurs when the strain exceeds the total volume capacity. It is tempting to speculate that the possible first trigger of the biological reaction is IL-8, the most powerful chemokine for neutrophil activation.

The role of IL-8 as a first cytokine responsible for the further sequence of events that leads to inflammation, through neutrophil recruitment, has been recently underlined in a mouse model. Belperio *et al.* [43] showed, in mice ventilated at a *V*T of 6 (low-strain group) and 12 (high-strain group) mL·kg body weight$^{-1}$, that neutrophil activation was increased compared to the spontaneously breathing control group and that neutrophil activation was proportional to the strain. The strain/injury was associated with an increase in levels of CXC2 chemokine (a murine equivalent of IL-8) and its receptors. Blocking CXC2 or its receptors with specific antibodies, or using knockout mice for CXC2 receptors, did not induce neutrophil activation and attenuated VILI. The bulk of data strongly support a cause/effect relationship between strain, IL-8 production, neutrophil activation and VILI.

## *Lung capillaries*

The fibre system provides mechanical support for the pulmonary blood vessels. In the alveolar septum, where the axial and peripheral fibre systems are interconnected, the alveolar capillary network is interwoven with the meshwork of septal fibres. It has been known for a long time that excessive strain of the lung structures, for minutes or days, depending on animal species, causes pulmonary oedema of varying degree (the closed chest approach results in less oedema than the open chest approach when applying the same *P*aw), associated with gas exchange impairment, hyaline membrane formation and neutrophil infiltration [44–49]. The key issue is understanding how the excessive mechanical strain causes oedema. When the alveolar fibre network experiences a nonphysiological excessive strain, the capillary meshwork of the alveolar septum flattens, whereas the corner vessels maintain or increase their patency. The final result is increased resistance to blood flow, which leads to increased pulmonary artery pressure. This, in turn, causes an increased filtration rate in excess of the increased lymph flow, with fluid accumulation in the interstitial spaces. Indeed, part of the oedema due to high pressure/volume ventilation is "hydrostatic" in nature [50].

However, the excessive strain also causes increased permeability of the capillary network [45, 46]. This was initially attributed to a "stretched pore phenomenon", a passive process due to the increased hydrostatic pressure forcing the loose connections between the endothelial cells. However, it has also been shown that intercellular gaps may occur at high transmural capillary pressure despite the intact extracellular matrix [51–53]. This active process, probably involving cell contraction [54], is possibly due to $Ca^{2+}$ influx through mechanically gated calcium channels. The increase in intracellular $Ca^{2+}$ level has multiple effects that may influence permeability, including increased actin/myosin filament tension. Blocking the $Ca^{2+}$ influx using gadolinium, an inhibitor of stretch-activated cation channels [55], or preventing actin/myosin filament contraction [56] significantly reduces endothelial permeability. Indeed, opening of intracellular/intercellular gaps, remodelling of the cytoskeleton and active cell contraction may all contribute to increased permeability. Moreover, full-blown inflammation, in which neutrophils are recruited, may very well induce, through a variety of mediators, increased endothelial permeability [54]. At intermediate degrees of strain, such mechanosignalling may be the trigger of VILI. When the applied mechanical stress is very high, however, the extracellular matrix may break, the inflammatory process being a consequence rather than the initiator/associated trigger of the observed damage. Indeed, it is quite clear that, depending on the applied stress/strain, pulmonary oedema may occur with or without inflammation.

It is worth underlining, however, the harmful interaction between excessive alveolar strain, pulmonary artery pressure and lung capillary blood volume. First, high capillary pressure may induce stress failure with increased permeability [53] and any increase in pressure increases oedema formation [57]. Moreover, it has been shown that cyclic changes in perivascular pressure surrounding extra-alveolar vessels due to mechanical ventilation cause greater oedema than isolated phasic elevation of pulmonary artery pressure without mechanical ventilation [41]. Finally, not only elevated but also low capillary pressure may damage the lung. Indeed, low capillary pressure may facilitate collapse and decollapse of the alveolar capillaries, with possible stress failure, whereas, in the meantime, it may increase transmural pressure in extra-alveolar capillaries, with increased oedema formation [58].

## Ventilator-induced lung injury and species

As most of the studies on VILI have been performed in animals, it is worth discussing some of the important differences between the various animal species. In some experiments, VILI was induced by using different *V*T normalised to body weight (in kilograms) (table 2) [43, 48, 49, 59, 60]. Unfortunately, lung volume, alveolar size and body weight are not linearly related across the various species. In figure 4, based on anatomical data reported by MERCER *et al.* [64], alveolar diameter changes, which reflect the tension to which the fibres of the lung's fibrous skeleton are subjected, are shown relative to *V*T per kilogram of body weight. As shown, a *V*T of 10 mL·kg body weight$^{-1}$ in normal humans induces an increase in alveolar diameter of ~10%. In mice, the same normalised *V*T induces an alveolar diameter increase of ~40%, which, in humans, would correspond to a *V*T of ~45 mL·kg body weight$^{-1}$. In other experimental studies on VILI, the injurious strategy was applied using high *P*aw rather than high *V*T. However, the relationship between *P*aw and *P*L, the real trigger of VILI, depends on the ratio between *E*L and *E*rs (Equation 3). This ratio (EL/*E*rs) varies widely across species, from near 1 in mice to ~0.5 in normal humans (table 2).

If *P*L is taken into account, the distinction between volutrauma and barotrauma vanishes. In the experiments of DREYFUSS *et al.* [65], which led to the volutrauma concept, the high *P*aw/low *V*T was obtained by increasing the *E*w by strapping the rat thorax with rubber bands. In this case, the *P*L, despite the high *P*aw, was greatly decreased, and, obviously, the lung damage was lesser than in rats ventilated at the same *P*aw with normal *E*w.

Indeed, from the bulk of the data, it appears that, to produce VILI in normal lung, high *P*L need to be used, irrespective of whether volume control or pressure control ventilation are used.

However, in clinical practice, the great concern is VILI in an already diseased lung. Interestingly, the few experimental data available suggest that VILI may be induced in diseased lung at lower *V*T/*P*aw than in normal lung [66, 67]. This is quite understandable if the relationship between *E*rs and EELV is taken into account. In ARDS, the lung is "small" rather than "stiff" [2], and *E*rs is a function of ventilatable EELV [68], specific *E*rs (*E*rs/EELV) being near normal [69]. Indeed, the tension throughout the lung parenchyma depends on the ratio between the *V*T and EELV to which the *V*T is delivered. For example, in a human with severe ARDS with an EELV of 500 mL (the baby lung [2]), a *V*T of 500 mL induces approximately the same tension as a *V*T of 2,500 mL in a human with a normal EELV of 2,500 mL.

Indeed, whereas *P*L may be considered the rough clinical equivalent of stress, the *V*T/EELV ratio may be viewed as the rough clinical equivalent of strain. Stress (*P*L) and strain (*V*T/EELV) are linked by specific *E*L (*E*L,sp) according to the formula

$$E_{L,sp} = (\Delta P_L / \Delta V_T)\mathrm{EELV}. \tag{4}$$

It, therefore, follows that

$$\Delta P_L = E_{L,sp} \Delta V_T / \mathrm{EELV}. \tag{5}$$

This indicates that considering the *P*L or the *V*T/EELV ratio (*i.e.* the ratio between the inflation of the whole lung, or any given region, and its resting volume) are two ways of looking at the same reality, thus reunifying the concepts of barotrauma (not *P*aw alone but *P*L) and volutrauma (not *V*T alone but *V*T/EELV), according to basic physiology. It may also be useful to point out that *E*L,sp is a kind of "Young module" for the lung (*i.e.* stress/strain) and stress is the independent variable in pressure control ventilation, whereas strain is the independent variable in volume control ventilation.

Table 2. – Experimental ventilator-induced lung injury in normal lungs

| First author [Ref.] | Species | *P*aw cmH$_2$O | *V*T mL·kg body weight$^{-1}$ | Alveolar diameter deformation % | *E*rs$^{\#}$ cmH$_2$O·mL$^{-1}$ | *E*w cmH$_2$O·mL$^{-1}$ | *E*L cmH$_2$O·mL$^{-1}$ |
|---|---|---|---|---|---|---|---|
| KOLOBOW [48] | Sheep | 50 | 50–70 | – | 0.050 [61] | 0.020 | 0.030 |
| BROCCARD [59] | Dog | 44 | 77 | – | 0.027 | 0.004 | 0.023 |
| NISHIMURA [60] | Rabbit | 24$^{¶}$ | 31 | >100 | 0.230 [18] | 0.030 | 0.200 |
| WEBB [49] | Rat | 40 | 40 | 70 | 3.400 [62] | 0.400 | 3.000 |
| BELPERIO [43] | Mouse | 40 | 24 | 72 | 13.70 [63] | Near 0.00 | 13.70 |

*P*aw: airway pressure; *V*T: tidal volume; *E*rs: elastance of the respiratory system; *E*w: elastance of the chest wall; *E*L: elastance of the lung. #: additional references provided as data not given in articles cited; ¶: transpulmonary pressure.

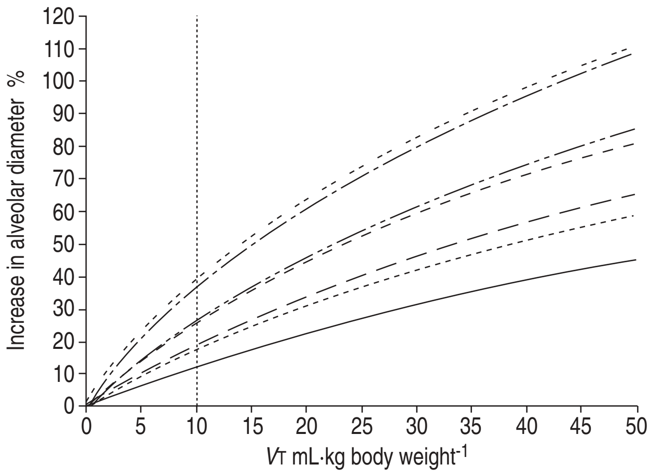


Fig. 4. – Relative increase in alveolar diameter as a function of tidal volume ($V_T$) normalised to body weight in different species (——: human (1.00); ------: monkey (1.40); – – – –: baboon (1.58); - - - -: rat (2.13); – -- –: hamster (2.23); – - –: rabbit (3.08); -- -- --: mouse (3.18)). Alveolar diameter changes were computed on the assumption that the relationship existed in a sphere, *i.e.* $\%\Delta\text{diameter}=-1+(1+\%\Delta\text{volume})^{0.33}$. The strain index, *i.e.* the alveolar diameter change relative to that expected in humans, at a $V_T$ of 10 mL·kg body weight$^{-1}$ (·········) is indicated above in parenthesis for each species. (Baseline data were derived from [64]).

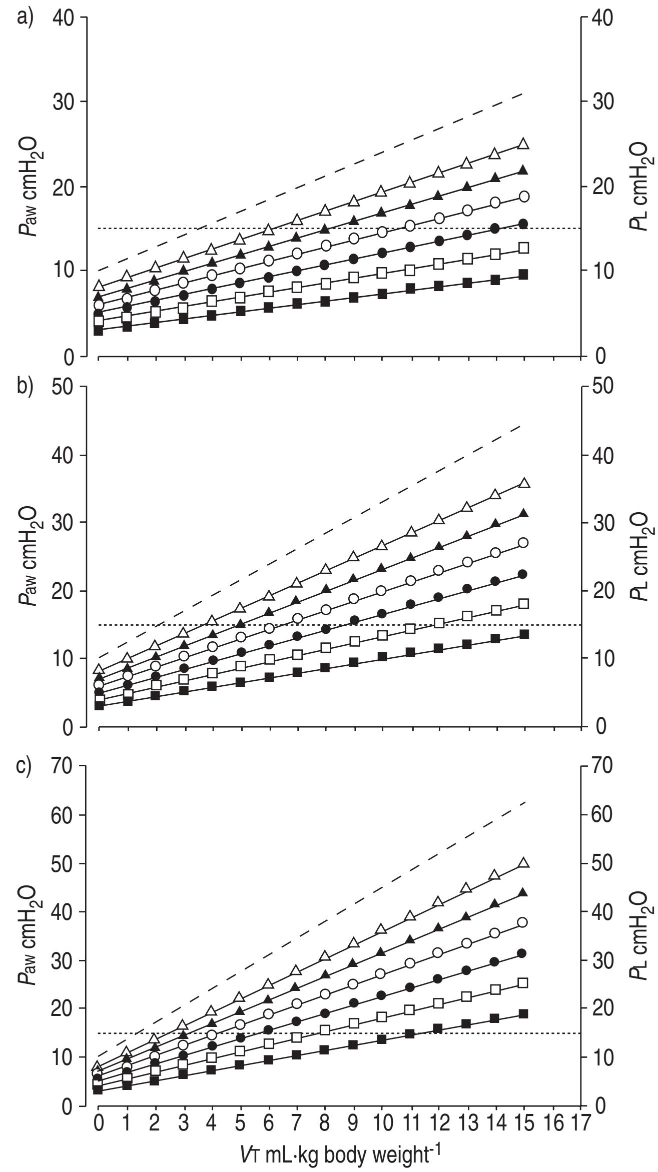


Fig. 5. – Relationships between tidal volume ($V_T$), plateau pressure ($P_{aw}$; - - - - -) and transpulmonary pressure ($P_L$; ——) in a model of a 70-kg human at 10 $cmH_2O$ positive end-expiratory pressure with constant compliance of the respiratory system of: a) 50; b) 30; and c) 20 mL·$cmH_2O^{-1}$, *i.e.* elastances of the respiratory system ($E_{rs}$) of 0.02, 0.033 and 0.05 $cmH_2O$·mL$^{-1}$ respectively. $P_{aw}$ were computed using $P_{aw}=V_T E_{rs}$. At each $P_{aw}$, the $P_L$ resulting from elastances of the lung ($E_L$)/$E_{rs}$ ranging 0.3–0.8 (■: 0.3; □: 0.4; ●: 0.5; ○: 0.6; ▲: 0.7; △: 0.8), *i.e.* $P_L=P_{aw}E_L/E_{rs}$, were computed. The dangerous $P_L$ was arbitrarily set at 15 $cmH_2O$ (·········), which correspond to ~70–75% of total lung capacity in normal humans; the area below this represents the "safe zone". Depending on $E_{rs}$ and $E_L/E_{rs}$, a $V_T$ of 6 or 12 mL·kg body weight$^{-1}$ could be either harmful or safe.

## Prevention of ventilator-induced lung injury

VILI is the result of a sequence of events, which begins with mechanical alteration of the lung parenchyma, due to excessive global and/or regional stress/strain. If the resulting tension in the structure reaches the limits of stress at rupture, the structures are destroyed (alveolar wall and capillaries). If the tension is lower than these limits, but nonphysiological, a biological reaction occurs, probably involving, first, the macrophages, with IL-8 production, from which the inflammatory cascade, through neutrophil recruitment, fully develops. Patients with VILI present with typical lung inflammation, with all its biochemical, histological and pathological characteristics. Indeed, VILI may be prevented or attenuated by interfering with the sequence of biological reactions leading to the inflammatory response (chemokine antibodies [43], steroids [70], *etc.*). However, since nonphysiological stress and strain appear to be the first trigger of VILI, the possibilities available for limiting/preventing the excessive regional and global stress and strain of the ARDS lung, *i.e.* prone position, PEEP and low $V_T$, are discussed.

### *Prone positioning*

Thus far, $P_L$ has been considered as being uniformly distributed; however, it is well known that, in both humans and experimental animals, there is a gradient of $P_L$ along the vertical axis, with the nondependent lung regions experiencing greater $P_L$ and greater tension of the fibres of the lung's fibrous skeleton than dependent lung regions. This phenomenon is enhanced in a nonhomogeneous lung. It was found, for example, that, in an oleic acid model in the supine position, the difference in $P_L$ between nondependent and dependent regions was as great as 10 $cmH_2O$ [71]. In the prone position, in both humans [72] and experimental settings [73], regional inflation is more uniformly distributed along the vertical axis, indicating a significant reduction in the $P_L$ gradient. This suggests that the stress and strain are more homogeneously distributed within the lung parenchyma, and this is the rational basis for the possible effectiveness of prone positioning in attenuating VILI, as shown experimentally in dogs [59] and rabbits [60]. Unfortunately proof is still lacking in patients that prone positioning affects outcome. However, in a subgroup of acute lung injury/ARDS patients treated with high-volume ventilation ($V_T$ of $\geqslant$12 mL·kg body weight$^{-1}$), the mortality rate of patients ventilated in the supine position was significantly greater (almost double) than that observed in patients ventilated while prone [74].

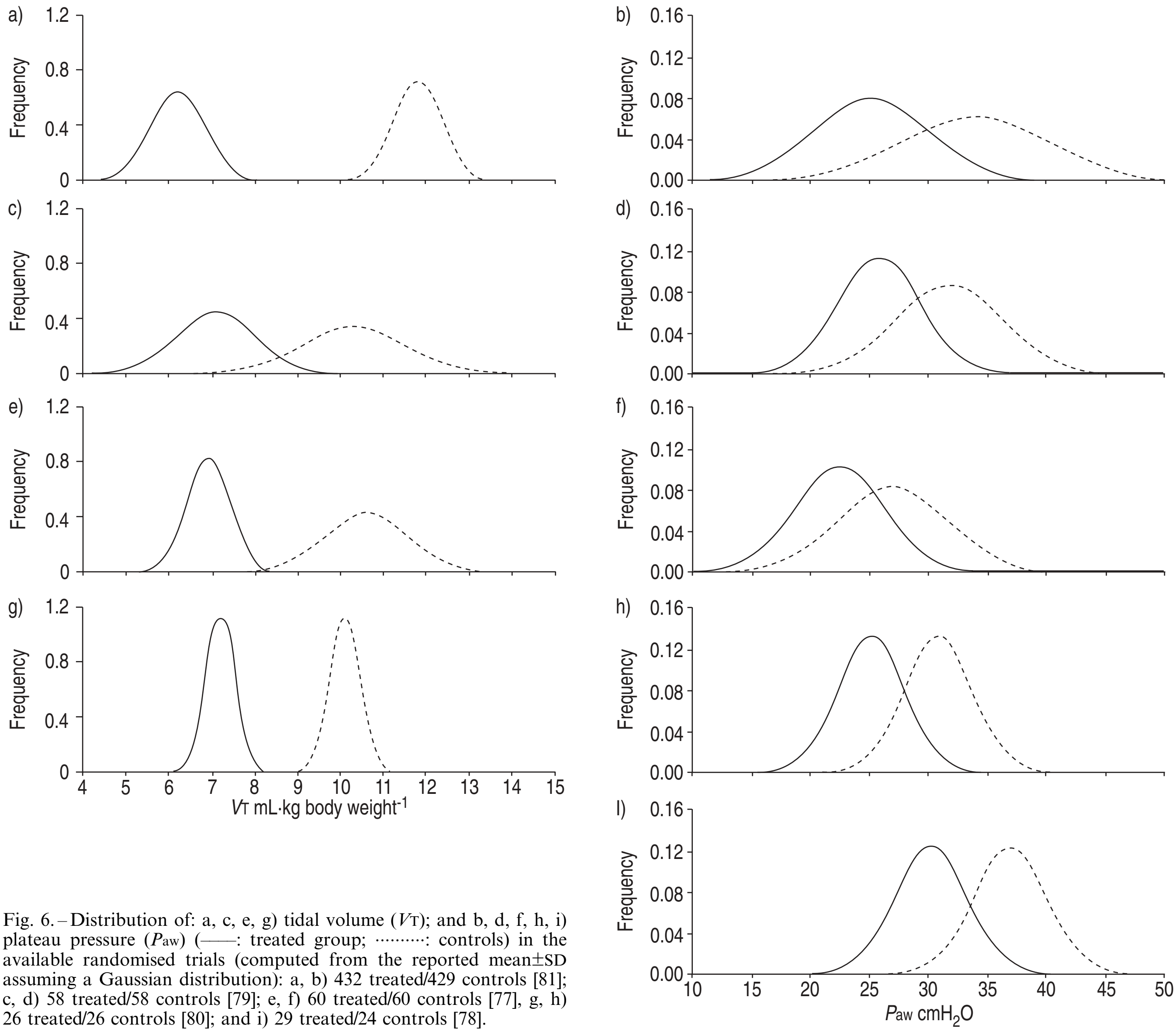


Fig. 6. – Distribution of: a, c, e, g) tidal volume ($V_T$); and b, d, f, h, i) plateau pressure ($P_{aw}$) (——: treated group; ··········: controls) in the available randomised trials (computed from the reported mean±SD assuming a Gaussian distribution): a, b) 432 treated/429 controls [81]; c, d) 58 treated/58 controls [79]; e, f) 60 treated/60 controls [77], g, h) 26 treated/26 controls [80]; and i) 29 treated/24 controls [78].

### *Positive end-expiratory pressure*

As PEEP unavoidably results in an increase in mean $P_L$, leading to greater stress of the lung parenchyma, it is quite surprising, at first sight, that it is so effective in many (but not all) circumstances in attenuating VILI, as reviewed extensively by DREYFUSS and SAUMON [75].

A possible explanation is that, if a lung region is collapsed/consolidated and does not expand during inspiration, the fibres of the neighbouring open regions show increased tension and strain. Indeed, if PEEP is effective in keeping open the collapsed region, the applied force is shared by more fibres with more uniform distribution of stress and strain. Interestingly, the positive effect of PEEP in protecting against VILI have been described in animal models with great potential for lung recruitment, in which PEEP is effective in keeping open most of the lung, thus attenuating the stress/strain maldistribution. It may be wondered, however, whether VILI can be prevented by PEEP when most of the lung is consolidated and the potential for lung recruitment is very low, as in diffuse pneumonia [11]. Although not proved, it is possible that, in this setting, PEEP simply increases total stress without affecting stress/strain maldistribution. Interestingly, there are no reports showing positive effects of PEEP on outcome in patients, and the PEEP/outcome relationship is still a controversial issue. However, this is not surprising since PEEP was tested in patients with varying probable potentials for lung recruitment. It is possible that the positive effect of PEEP in the patient subgroup with a high potential for lung recruitment was obscured by its negative or zero effects in the subgroup of patients with a low potential for lung recruitment.

### *Low tidal volume*

Following consensus conference suggestions [76], since the late 1990s, several studies [77–81] have been performed in order to investigate the effects on outcome of low *versus* high $V_T$. These studies, although based on the same rationale (gentle lung treatment), were of different power and design. Three studies compared $V_T$ of 7 and 10–10.5 mL·kg ideal body weight$^{-1}$ and were not able to show any difference in outcome [77, 79, 80]. The study of AMATO *et al.* [78] compared two ventilatory strategies, high PEEP/low $V_T$ and low PEEP/high $V_T$. This study showed an impressive difference in mortality between the two strategies but was criticised, mainly because of the high (70%) mortality in the high $V_T$/low PEEP group. The last study of the series was performed by the National Institutes of Health (NIH) network and tested, in an adequately powered trial, the mortality differences between patients treated with $V_T$ of 6 and 12 mL·kg body weight$^{-1}$ [81]. The results showed a significantly different outcome, with ~9% decrease in absolute mortality in the 6 mL·kg body weight$^{-1}$ group. In most of these studies, with the exception of the study of AMATO *et al.* [78], the "safety limit" for $P_{aw}$ was set at 35 cm$H_2O$. The contradictory results generated a lot of controversy, to the point that a recent meta-analysis claimed that the NIH network ventilation at a $V_T$ of 6 mL·kg body weight$^{-1}$ was unsafe, suggesting that the relationship between $V_T$ and outcome is U-shaped, with greater risk of mortality associated with low as well as high $V_T$ [82].

Before discussing the results of the available clinical studies, it is worth recognising that, if two different kinds of ventilation produce different outcomes, as in the NIH network ARDS trial, this probably means that the "amount of VILI" associated with the two different kind of ventilation is also different. However, since the real cause of VILI is the $P_L$, it is evident that measuring $V_T$ is associated with a great deal of confounding variables. A given $V_T$ causes different $P_{aw}$ depending on the $E_{rs}$ ($P_{aw}=E_{rs}V_T$). A given $P_{aw}$, in turn, produces different $P_L$ according to the ratio of $E_L$ to $E_{rs}$ ($P_L=P_{aw}E_L/E_{rs}$). This indicates that the relationship between $V_T$ and the resulting $P_L$ may be highly variable. Indeed, it is quite obvious that, in a relatively small population, randomisation may be unable to distribute equally between groups of different $E_L$ and $E_w$ present in the population under study. This bias should be attenuated in a large population. However, even in this case, the linkage between $V_T$ and $P_L$ is weak. This is underlined in figure 5, where $P_L$ is plotted as a function of $V_T$ normalised to body weight, for an ideal 70-kg human at 10 cm$H_2O$ PEEP, for a range of $E_{rs}$ and $E_L/E_{rs}$. Despite the obvious oversimplification of assuming, in this model, a linear volume/pressure curve, and setting the "dangerous $P_L$" arbitrarily at 15 cm$H_2O$ (~70–75% of total lung capacity in normal humans), it is quite evident that potentially dangerous $P_L$ may be associated with a great variety of $V_T$ normalised to body weight as well as with $P_{aw}$ well below the suggested "safety limit of 32 cm$H_2O$" [83].

The $V_T$ distributions in the available randomised trials are depicted in figure 6. The distributions of $P_{aw}$, which is related to $P_L$ more than to $V_T$ (Equation 3), are also shown in figure 6. A huge overlap in the $P_{aw}$ observed in the different studies is evident. However, the discussion between supporters of the importance of $V_T$ *versus* supporters of the importance of $P_{aw}$ as VILI determinant does not seem to have a sound physiological basis as $P_L$ is the main determinant of VILI, and it has never been controlled in any randomised trial.

## Conclusions

On the basis of the available experimental and clinical data, the following conclusions may be drawn. Ventilator-induced lung injury is due to excessive global/regional stress/strain and affects the relatively healthier regions of the lung, since consolidated lung regions are not distended. The excessive stress/strain appears to activate first macrophages and subsequently neutrophils *via* interleukin-8. The neutrophils amplify the tissue inflammation. If stress and strain reach the limit of rupture of the fibre system, mechanical failure may occur with direct rupture of alveolar walls and pulmonary capillaries. The excessive regional stress/strain may be limited by prone positioning and positive end-expiratory pressure (in a recruitable lung) which both allow a more uniform distribution of the stress and strain. A low global transpulmonary pressure decreases stress and strain and the available clinical evidence suggests that a low tidal volume is associated with less ventilator-induced lung injury than a high tidal volume. It would have been better, however, to test different plateau pressures, which are linked to the transpulmonary pressure more than to the tidal volume. The best solution, however, would be to directly test different transpulmonary pressures.

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