Review

# Ventilator-associated lung injury

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**Mechanical ventilation is indispensable in support of patients with respiratory failure who are critically ill. However, use of this technique has adverse effects, including increased risk of pneumonia, impaired cardiac performance, and difficulties associated with sedation and paralysis. Moreover, application of pressure to the lung, whether positive or negative, can cause damage known as ventilator-associated lung injury (VALI). Despite difficulties in distinguishing the effects of mechanical ventilation from those of the underlying disorder, VALI greatly assists patients with the most severe form of lung injury, acute respiratory distress syndrome (ARDS). Moreover, modification of mechanical ventilation so that VALI is kept to a minimum improves survival of patients with ARDS. Here, we outline the effects of mechanical ventilation on injured lungs and explore the underlying mechanisms.**

## Protective ventilation in patients with acute respiratory distress syndrome (ARDS)

Interest in the effects of mechanical stimuli on lung tissue has been generated by clinical studies that have clearly shown the importance of such effects, especially in patients with acute respiratory failure. Results of an international survey[1] showed that most patients with ARDS were ventilated with tidal volumes of at least 10 mL/kg. These large tidal volumes (compared with about 7 mL/kg when spontaneously breathing at rest) tend to maintain a normal partial pressure of carbon dioxide ($PaCO_2$) and prevent atelectasis in patients with lung injury. Conversely, limitation of pressure and volume leads to retention of carbon dioxide, with potentially harmful effects.[2] Although the advantages and disadvantages of hypercapnia are still debated, the permissive hypercapnia technique was associated with a low death rate in a non-randomised study[3] in patients with ARDS in 1990. In 1993, a consensus conference[4] while acknowledging the lack of convincing data for human beings, recommended that this approach should be adopted, by limiting tidal volume to 5–7 mL/kg and plateau pressure to 35 cm $H_2O$.

Subsequently, clinical studies[5–9] have been published in which protective and conventional ventilatory strategies were compared (table). Whether the conventional groups were ventilated in accordance with best practice in these trials is debatable since prescribed limits were exceeded. Apart from the ARDS Network study,[8] the other studies[5–7,9] were underpowered to show a difference in death rates between the two groups. Similarly, death rates of patients in the conventional treatment group of the Amato study[9] were much higher than would be predicted for this patient group, therefore we have not considered this study any further. Results from only one of the remaining four studies showed a benefit from protective ventilation, however the data perhaps more convincingly show the negative effect of high tidal volumes and pressures on outcome. The ARDS Network study[8] provides the most compelling data for benefits of low tidal volume ventilation in patients with lung injury, not only because the number of patients (n=861) was sufficient to show a survival advantage, but also because the protective ventilation group achieved the lowest tidal volume (6·2 mL/kg ideal bodyweight) and plateau pressure (<30 cm $H_2O$), and because results of this trial showed the greatest difference in tidal volume between the protective and conventional ventilation groups compared with the other studies.[8] Although features of the ARDS Network trial protocol provide less biologically plausible explanations for the survival difference (eg, management of respiratory acidosis in the protective ventilation group needed administration of bicarbonate), the need to limit tidal volume and inflation pressures has been established.

Aspects of the ARDS Network trial protocol raise issues that need further consideration. First, the required response to respiratory acidosis was initially to increase the respiratory rate and then to give sodium bicarbonate if necessary. The effects of hypercapnia and mild respiratory acidosis on the outcome of patients with ARDS are not known. The protocol also prescribed increased positive end-expiratory pressure as the concentration of oxygen was increased to meet targets for arterial oxygenation. The ARDS Network has recently reported on the Alveoli trial,[10] which confirmed the benefit of a strategy that lowers tidal volume and limits the plateau pressure in patients with ARDS. The death rate of patients ventilated with high and conventional positive end-expiratory pressure strategies was less than 30% and did not differ significantly between the two groups. Hence, the optimum positive end-expiratory pressure in patients with ARDS could not be

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### Search strategy and selection criteria

We selected references by searching English language articles published in the past 20 years in Pubmed under each subheading of the review. We have done a non-systematic review of the results of our searches and articles collected by the authors. Priority was given to articles published in journals with high impact factors.

| | Stewart[5] (n=120) | | Brower[6] (n=52) | | Brochard[7] (n=116) | | ARDS network[8] (n=861) | |
|---|---|---|---|---|---|---|---|---|
| | Protective | Conventional | Protective | Conventional | Protective | Conventional | Protective | Conventional |
| **Variables** | | | | | | | | |
| Target tidal volume (mL/kg) | <8 | 10–15 | 5–8 | 10–12 | 6–10 | 10–15 | 6 | 12 |
| Mean VT mL/kg (mL/kg of predicted bodyweight*) | 7·2 (8·1) | 10·8 (12·2) | 7·3 (7·3) | 10·2 (10·2) | 7·1 (7·8) | 10·3 (11·3) | 6·2 (6·2) | 11·8 (11·8) |
| Target pressure | <30 | 50 | <30 | 45–55 | <25 | <60 | <30 | <50 |
| Mean plateau pressure cm $H_2O$ | 20 | 28·6 | 24·9 | 30·6 | 24·5 | 30·5 | 26 | 37 |
| Positive end-expiratory pressure (cm $H_2O$) | 9·6 | 8·0 | .. | .. | 9·6 | 8·5 | 8·1 | 9·1 |
| Mortality | 50† | 47† | 50† | 46† | 46·6‡ | 37·9‡ | 31† | 39·8† |

*Male predicted bodyweight=(50+0·91) (height in cm–152·4); female predicted bodyweight=45·5+0·91 (height in cm–152·4). †Percentage in-hospital mortality or ‡mortality 60 days after trial entry was significantly less in the protective ventilation group than in the conventional ventilation strategy group in the ARDS network study only (p=0·007).

**Clinical trials of protective versus conventional ventilation strategies in patients with acute lung injury and ARDS**

defined. We still cannot define the best pressure or the physiological criteria by which positive end-expiratory pressure should be adjusted.[11]

## Mechanisms of VALI (panel)

Results of clinical studies[13–15] have suggested that mechanical stress is important in determining the outcome of patients with ARDS. However, despite adoption of a strategy that maintains a low tidal volume, injured lungs continue to be damaged by mechanical ventilation (figure 1). Thus, to improve further the outcome of such patients, we need to understand how mechanical ventilation affects acutely injured lungs. In animals, mechanical ventilation at high volumes (volutrauma) and pressures (barotrauma) can cause a similar histological appearance to that associated with other types of lung injury.[15] The histological appearance is accompanied by high-permeability pulmonary oedema in the previously uninjured lung[16] and by exacerbated damage in lungs that have already been injured.[17] Ventilation of small animals with high end-inspiratory airway pressures but with expansion of the lungs independently limited by thoraco-abdominal strapping, suggests that alveolar over-distension rather than pressure itself causes lung injury. Lung injury is more severe in animals ventilated without positive end-expiratory pressure than in those ventilated with such pressure, suggesting that the forces generated by repeated opening of recruitable lung units (atelectotrauma) also damage the lung.[18,19]

### Components of ventilator-associated lung injury

**Volutrauma**
Damage caused by over-distension. Sometimes called high volume or high end-inspiratory volume injury

**Atelectotrauma**
Lung injury associated with repeated recruitment and collapse, theoretically prevented by using a level of positive end-expiratory pressure greater than the lower inflection point of the pressure volume curve.[12] Sometimes called low volume or low end-expiratory volume injury

**Biotrauma**
Pulmonary and systemic inflammation caused by the release of mediators from lungs subjected to injurious mechanical ventilation

**Oxygen toxic effects**
Damage caused by a high concentration of inspired oxygen. The oxygen concentration: toxic effect relationship for damaged lung is not known

**Barotrauma**
High pressure induced lung damage

Because adjacent alveoli and terminal bronchioles share walls, forces acting on one lung unit are transmitted to those around it and the size of the alveoli remain constant.[20] When the lung expands uniformly, all lung units have a similar transalveolar pressure, but if the lung is unevenly expanded (as in ARDS) such forces can vary greatly. When an alveolus collapses, the traction forces exerted on its walls by adjacent expanded lung units increase and these forces are applied to a smaller region. The forces will promote re-expansion at the expense of greatly increased and potentially harmful stress at the interface between collapsed and expanded lung units (figure 2). Expanded pseudocysts were concentrated around atelectatic lung regions of patients who died from ARDS, suggesting that these forces play a clinically important role in VALI.[21] In small airways occluded by exudate or apposition of their walls, the shear stress needed to reopen the airway can cause physical damage (atelectotrauma), especially if the cycle of recruitment and derecruitment is repeated with each breath. The pressure needed to reopen an occluded airway is inversely proportional to its diameter,[22] which is consistent with the observation that damage to the small airway in isolated lungs ventilated at zero positive end-expiratory pressure occurs more distally as such pressure is applied.[23]

When applying the protective strategy termed the open lung approach, positive end-expiratory pressure is set at 2 cm $H_2O$ above the lower inflection point of the pressure-volume curve (figure 3). If the lower inflection point cannot be determined, a positive end-expiratory pressure of 16 cm $H_2O$ is used.[9,12] The driving pressure, defined as plateau pressure minus positive end-expiratory pressure, is kept below 20 cm $H_2O$, peak pressure is restricted to 40 cm $H_2O$, and the respiratory rate is kept below 30 breaths/min. When the patient is disconnected from the ventilator, a recruitment procedure with use of continuous positive airway pressure of 35 cm $H_2O$ is applied for 40 s before reinstituting the previous postive end-expiratory pressure, since even a single breath without positive end-expiratory pressure can cause derecruitment. Production of a static pressure-volume curve for patients with ARDS is technically difficult, does not always provide clear inflection points, and is of unproven benefit.[24–26]

## Multiple organ failure associated with mechanical ventilation

In patients with ARDS, the severity of lung injury is not associated with outcome, which is mostly related to non-pulmonary factors such as systemic hypotension and non-pulmonary organ dysfunction.[27] So why does lung-protective ventilation improve survival of patients, and how does VALI increase death rates? Figure 4 summarises the possible ways that ventilation affects systemic inflammation and distal organs.

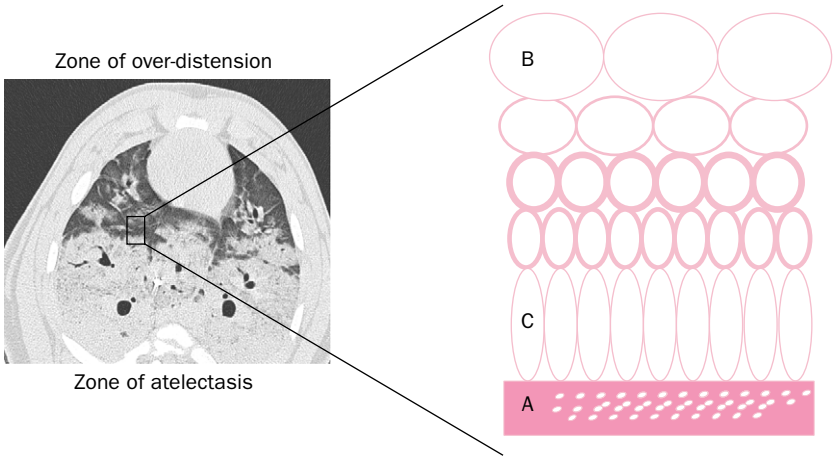



Figure 1: **Atelectotrauma**
The interface between collapsed and consolidated lung (A) and over-distended lung units (B) is heterogeneous and unstable. Depending on ambient conditions this region is prone to cyclic recruitment and derecruitment and localised asymmetrical stretch of lung units (C) immediately apposed to regions of collapsed lung.

Results of studies[28] suggest a mechanism by which ventilation contributes to systemic inflammation and multiple organ failure. Injurious ventilation of rats is associated with a 50-fold increase in recovery of proinflammatory cytokines from broncho-alveolar lavage[29] and a significant increase in serum concentrations.[30] Ranieri and coworkers[31,32] assessed this proposed mechanism in patients with ARDS by investigating the effect of ventilatory strategies on systemic plasma cytokine concentrations. They randomly allocated 44 patients to either a protective strategy, in which the positive end-expiratory pressure and tidal volume were set such that tidal ventilation was between the lower and upper inflection points of the pressure-volume curve (figure 3), or a control strategy in which tidal volume was set to obtain normal values of arterial carbon dioxide and the positive end-expiratory pressure was set to produce the greatest improvement in arterial oxygen saturation without worsening haemodynamics. The protective group had significantly lower concentrations of cytokines in plasma and bronchoalveolar lavage and significantly less organ failure than did the control group.[31,32] Results of the ARDS Network study[8] also showed that plasma concentrations of interleukin 6 were lower in the protective ventilation group than in the control group. Pulmonary production of inflammatory mediators is likely to exacerbate lung injury, and overspill of these agents into the systemic circulation of patients can contribute to multiple organ failure. However, which factor or factors are responsible for mediating this detrimental effect and how they exert a toxic effect on distal organs is not clear. The term biotrauma has been coined to describe this potentially injurious local and systemic inflammatory response to physical stress.

Finally, ventilation can cause systemic inflammation through translocation of bacteria or their products from the airspaces into the circulation. In animals, bacteraemia is more likely to develop when lungs that have been inoculated with bacteria are ventilated with high tidal volume and zero positive end-expiratory pressure, than when ventilated with less injurious strategies.[33] A similar effect has been identified in rabbits that have been ventilated after administration of intratracheal lipopolysaccharide.[34]

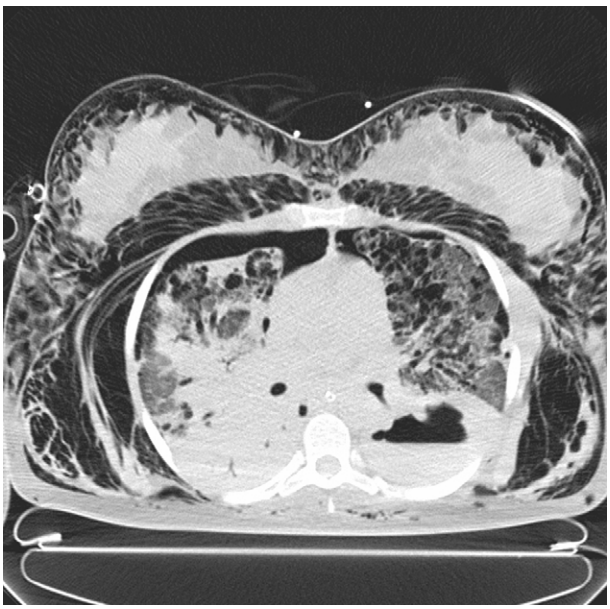
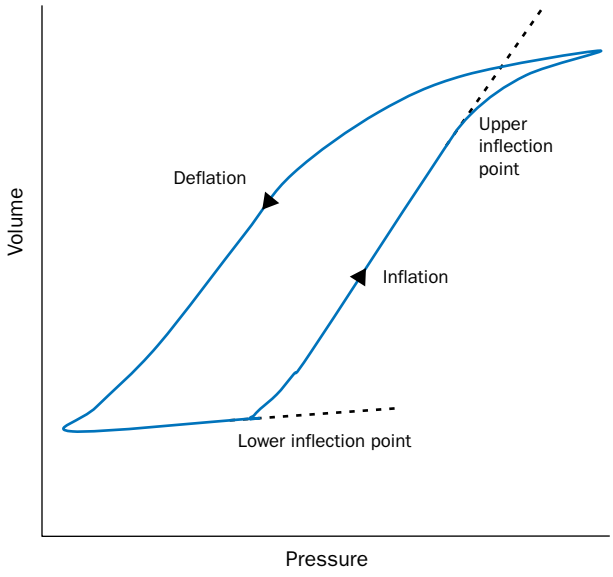


Figure 2: **CT thorax of ARDS complicated by substantial air leaks**
The patient developed massive surgical emphysema of the thorax and abdomen while having a CT scan. There are anterior pneumothoraces bilaterally despite presence of bilateral intercostal drains. ARDS in this case was associated with pneumococcal pneumonia and an abscess in the left lower lobe. There is extensive cystic change in the lung parenchyma consistent with VALI.

## The injured lung: set up for VALI?

The injured lung is predisposed to VALI at several levels, although differentiation of cause and effect is difficult. Compared with that of controls, the surfactant obtained by bronchoalveolar lavage from patients with ARDS showed increased minimum surface tension and decreased hysteresis of the relation of surface tension to surface area, two critical indices of surfactant dysfunction in vivo.[35] Surfactant deficiency and dysfunction, in part caused by plasma proteins in the airspace, might contribute to the pathophysiology of ARDS and VALI via several mechanisms, including exacerbation of atelectasis,[36,37] increased formation of oedema, and impairment of local host defence.[38] Thoracic CT images of patients with ARDS showed that a large volume of dependent lung is typically collapsed or consolidated and therefore inaccessible for gas exchange (figure 1). The corollary is that the ventilator delivers a set tidal volume calculated according to the patient's weight to a disproportionately small lung volume—the so-called baby lung of ARDS.[39]

The cellular constituents of the lung change greatly during lung injury, as does the phenotype of the predominant resident—the alveolar epithelial cell. The alveolar epithelium usually has extensive necrosis of type-1 cells, which slough from the alveolar surface to be replaced by proteinaceous deposits (hyaline membranes). Type-2 cells, in addition to secreting surfactant, provide a population of cells capable of replication and differentiation to replace type-1 cells.[40] Epithelial regeneration manifests as rows of cuboidal cells extending along alveolar walls to cover previously denuded basement membrane. Type-2 cells are more vulnerable to the effects



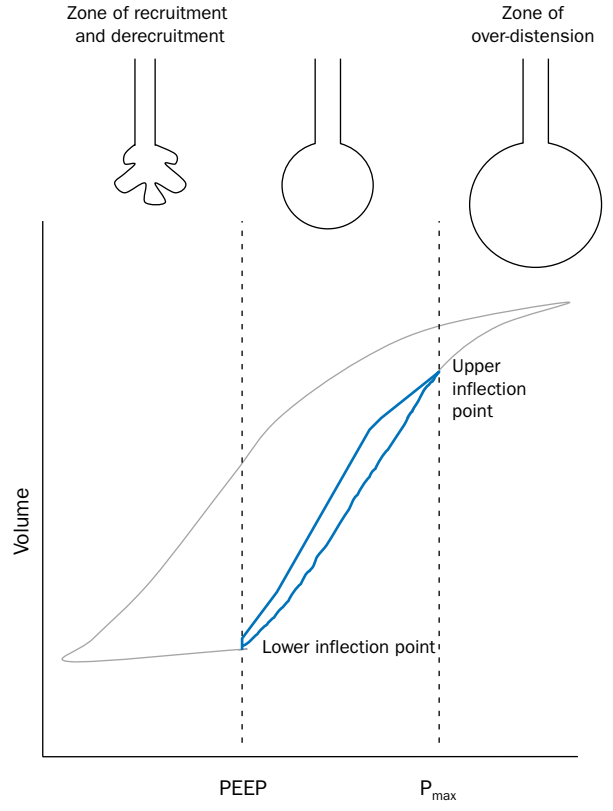




Figure 3: **Pulmonary pressure-volume relation of a patient with acute lung injury**

(Upper) the lower inflection point is typically 12–18 cm $H_2O$ and the upper inflection point 26–32 cm $H_2O$. (Lower) specific protective ventilation strategies require that positive end-expiratory pressure is set just above the lower inflection point and the pressure limit ($P_{max}$) just below the upper inflection point. Hence the lung is ventilated in the safe zone between the zone of recruitment and derecruitment and the zone of overdistension, and both high and low volume injury are avoided.

of stretch at day 1 of culture than at day 5.[41] This observation is consistent with the phenotype of type-1 cells being more resistant to stretch and could contribute to the adverse effects of over-distension of the injured lung when the alveolar epithelium is regenerating.

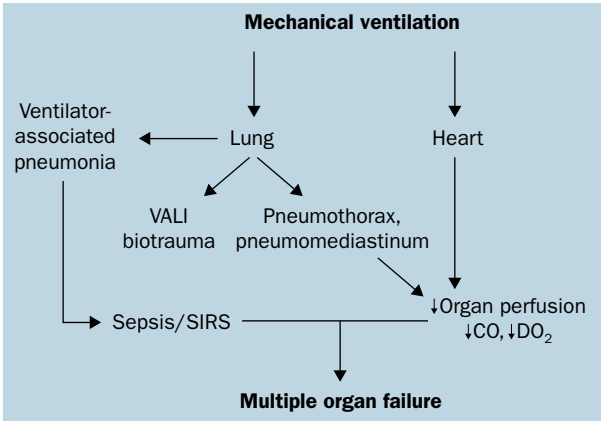



Figure 4: **Mechanical ventilation as a cause of multiple organ failure**

The ventilated patient is susceptible to pneumonia and lung injury (VALI). Inflammatory mediators generated in the lung can spill over into the systemic circulation causing generalised inflammation (SIRS). Patients with ARDS who are mechanically ventilated are at high risk of air leaks manifesting as pneumothorax or pneumomediastinum. High intrathoracic pressure can contribute to poor organ perfusion and oxygen delivery ($DO_2$) by decreasing cardiac output (CO).

The resident lung cells not only change their appearance in response to injury, but the response to further ventilator induced injury is probably also affected by the many inflammatory and reparative cells that have been recruited. In the initial phases of lung injury an acute neutrophilic inflammatory exudate predominates. Subsequently, other leucocytes are recruited as the acute alveolar exudate is converted to granulation tissue. Under profibrotic conditions, the exudate is transformed so that the thicker and more resistant type-1 collagen predominates;[42] healing by fibrosis is associated with a poor outcome and can manifest clinically as non-compliant lungs.

## Cellular pathology of VALI

The mechanical forces applied during ventilation can injure the lung in two inter-related and overlapping ways: through physical disruption of the tissues and cells, and through activation of cytotoxic or proinflammatory responses. Although which mechanism is more important clinically is not clear, we discuss only the second mechanism in greater detail because of the possibility that these processes could be targets for therapeutic intervention.

### *Physical disruption: stress failure*

The extremely thin (0·2–0·4 μm) alveolar-capillary membrane exposes the capillaries to high wall stress, determined by the ratio of wall tension to thickness.[43] In rabbits, stress failure occurs at capillary transmural pressures of at least 40 mm Hg and the microscopic lesions of endothelial and epithelial disruption are similar to those caused by high-volume ventilation.[44] The blood-gas barrier is more prone to stress failure at higher lung volumes, probably because of increased longitudinal forces acting on pulmonary capillaries.[45] Similarly, isolated rabbit lungs ventilated with a peak pressure of 30 cm $H_2O$ have greater oedema and haemorrhage when perfused at high pulmonary artery pressures than when perfused at low pressures.[46]

### *Mechanical activation of cellular pathways*

Physical forces, such as stretch, play an important part in physiological processes in the lung. Hence, breathing is

essential for development of the fetal lung and in the mature lung, ventilation stimulates surfactant production by type-2 cells.[47,48] Central to this mechanism is mechanotransduction, whereby physical forces are detected by cells and converted into biochemical signals. There is now good evidence that signalling events activated by injurious ventilation causing pathological mechanical strain have a role in VALI.

Results of several studies[29,30,49–52] of isolated lungs or animals with injured lungs have shown that injurious ventilatory strategies are associated with release of proinflammatory mediators, including thromboxane $B_2$, platelet activating factor, and several cytokines. This humoral inflammatory response precedes overt histological damage and seems to be mediated by stretch-activated pathways rather than being a non-specific inflammatory reaction to injury. VALI can be attenuated in rabbits by administration of antibodies to tumour necrosis factor α or of interleukin-1 receptor antagonists.[53,54]

Leucocytes are recruited to the lungs[55] and activated[56,57] in animals with VALI. Surfactant depletion enhances recovery of granulocytes[49,56] and recruitment tends to be more marked in studies of longer duration.[58] As with other lung injury models, depletion of leucocytes before the insult confers protection.[59] Cyclic strain of endothelial cells in vitro increases expression of intercellular adhesion molecule ICAM-1 and adhesion of monocytes,[60] providing a further mechanism by which lung stretch could cause local inflammation. Apart from the proinflammatory effects of injurious ventilation, raising intra-alveolar pressure increases the transit time of leucocytes through the pulmonary circulation and thus increases the likelihood of interaction with the endothelium.[61]

Not all findings have supported the model of release of inflammatory mediators by the lung that is induced by mechanical ventilation. In particular, the role of tumour necrosis factor α that was supported by the ex-vivo rat model of Tremblay and colleagues,[29] has been challenged by studies in which rat lungs were subjected to VALI.[57,62,63] Thus, the role of individual inflammatory mediators in initiation and propagation of VALI has not been resolved. Similarly the results of ex-vivo experiments must be viewed with caution since in some cases pulmonary perfusion is not maintained and the ventilation variables used would rapidly kill an animal.

## Effects of stretch on lung cells

Resident lung cells and their basement membranes form the skeleton of the lung parenchyma, hence allowing these cells to sense stretch through their attachments to neighbouring cells and underlying matrix. Alveolar epithelial and pulmonary microvascular endothelial cells produce an arsenal of inflammatory mediators with direct effects, as well as chemokines that recruit leucocytes. Both cell types probably modulate VALI. Leucocytes and alveolar macrophages also contribute to VALI, although the ability of cells dependent on anchorage to sense and respond to stretch directly is questionable. However, in the absence of other cell types, cyclic stretch alveolar

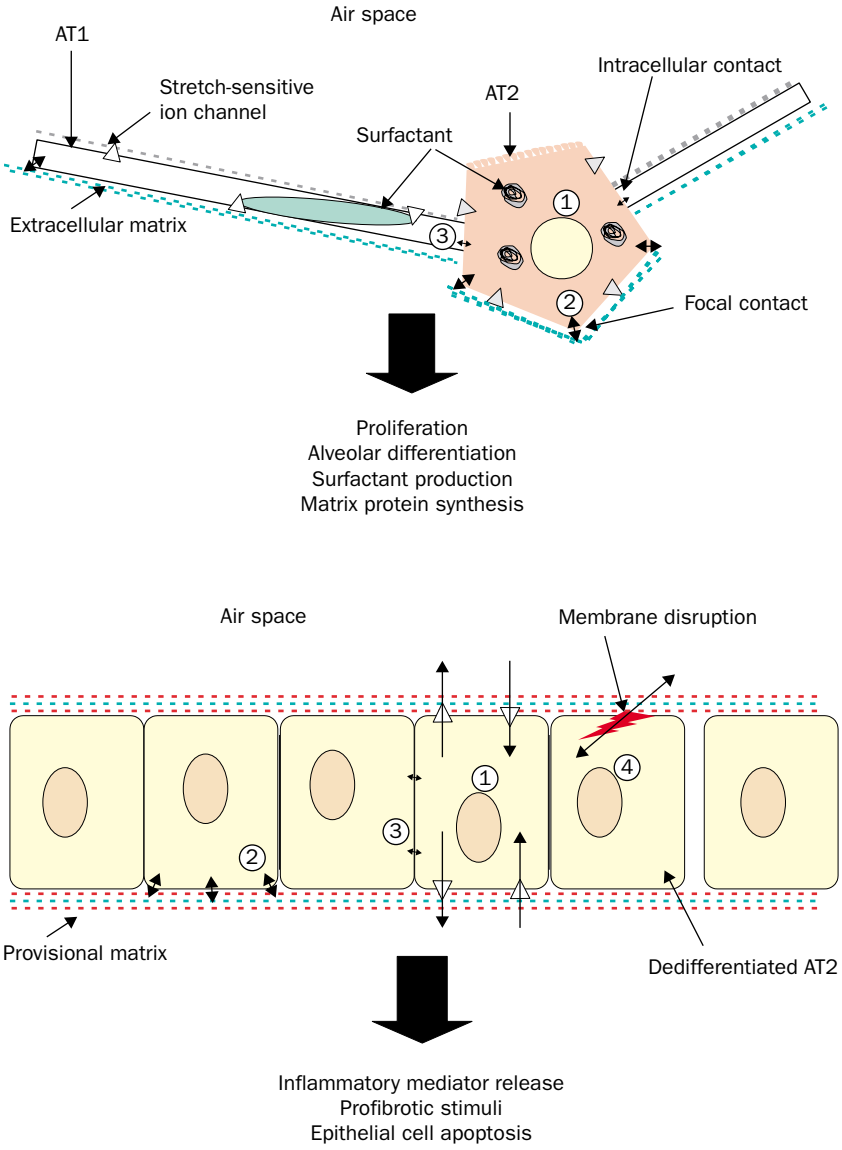



Figure 5: **Physiological distension of healthy alveolar epithelium (upper) and pathological over-distension of injured alveolar epithelium (lower)**
AT1=alveolar type-1 epithelial cell; AT2=alveolar type-2 epithelial cell; 1=signalling dependent on stretch (and gadolinium)-sensitive ion channels. 2=extracellular signalling pathway between the matrix, integrin, and cytoskeleton signalling pathway. 3=signalling and intercellular solute transport through intercellular contacts. 4=non-specific fluxes caused by sublethal temporary cell membrane disruption. (Upper) type-1 and 2 cells constitute the normal adult alveolar epithelium. Focal contacts or adhesions occur at sites of cell adhesion to underlying matrix from highly organised aggregates of integrins, other adhesion molecules and their connections to signalling molecules and the cytoskeleton. Stretch-sensitive ion channels may occur on AT1 as well as AT2 and facilitate fluxes in either direction. Intercellular adhesions (and their functions) include: gap junctions (intercellular solute transfer), adherens junctions (cadherin mediated signalling) and desmosomes (bonding cells in a sheet with the help of intermediate filaments). (Lower) The alveolar epithelium that is recovering from injury is constituted by proliferating dedifferentiated AT2 that may express a distinct repertoire of adhesion molecules. The provisional matrix formed after injury is rich in plasma-derived proteins and proteins produced in response to injury.

macrophages respond to stretch by releasing interleukin 8 and a metalloprotease (MMP9[64]); both interleukin 8 and MMP9 are increased in the lung lining fluid of patients with ARDS.[65]

Mechanical strain of lung cells in fetal rats encouraged proliferation through increased expression of the platelet-derived growth factor β receptor.[66] Because of technical difficulties, it has not been possible to show directly that stretch affects proliferation of adult type-2 cells. Observations in whole animals and cultured type-2 cells suggested that lung expansion stimulates secretion of surfactant.[67] Cyclic stretch is associated with increased expression of mRNA for surfactant proteins B and C.[68] The relevance of these observations to VALI is uncertain. Since the effects of over-distension are overwhelmingly negative, the net effect of pathological stretch probably does not encourage proliferation of type-2 cells or production of surfactant—both of which would be expected to promote recovery and could be responses to physiological mechanical stimulation.

Mechanical stretch of monolayers of A549 cells (a human type-2 cell-like adenocarcinoma cell line) increased secretion of proinflammatory agents recoverable from the lungs of patients with ARDS, such as the chemokine interleukin 8.[69] Fetal rat lung cells in organotypic culture released macrophage inflammatory protein (MIP2) in response to stretch, which also caused cell damage measured by lactate dehydrogenase release.[70] Only after lipopolysaccharide pretreatment did stretch cause an increase in MIP2 mRNA; this synergistic effect leads to production of tumour necrosis factor α by type-2 rat cells[71] and might underlie the exaggerated response of injured and inflamed lungs to over-distension.

## Mechanotransduction

The means by which mechanical stimuli are converted into chemical signals that affect cellular function are not well understood, but stretch-activated ion channels and the matrix-integrin-cytoskeleton pathway have received the most attention. Few experiments have been done on cells that constitute the adult lung parenchyma and caution must be applied in generalising results from studies using cell lines, cells from tissues not usually subjected to mechanical strain, and from mechanical models that do not mimic cyclic over-distension. Figure 5 shows a model of possible pathways involved in mechanotransduction in the lung parenchyma. Stress failure of the cell membrane can occur at low levels of stretch,[70,72] which might have a proinflammatory effect without invoking a recognised pathway of mechanotransduction if preformed mediators are released or if there is an inflammatory response to the released cytoplasm.

### *Stretch-activated ion channels*

Mechanical forces can affect the permeability of the cell membrane to various ions, reflecting the activity of stretch-responsive ion channels. In isolated rat lungs the increase in vascular permeability induced by high-pressure ventilation can be blocked by gadolinium, an inhibitor of stretch-activated cation channels,[73] and cyclic stretch of fetal rat lung cells in vitro induced calcium ion influx via gadolinium-sensitive channels with activation of protein kinase C, which is associated with increased DNA synthesis.[74]

### *Extracellular pathways between the matrix, integrin, and cytoskeleton*

The tensegrity model proposed by Ingber[75] is based on observations of realignment of the cytoskeleton and organelles after application of mechanical stress. Mechanical signals could be integrated and transduced into biochemical effectors through force-dependent changes in the cell's scaffolding, which is constituted by adhesion molecules (eg, integrins), the cytoskeleton (organised at the cell surface at focal adhesions), and their intracellular connections. Many signalling intermediates induced to bind to the cytoskeleton by stretch continue to do so after the cell membrane is removed.[76]

Results of early studies,[77] in which matrix-coated magnetic beads ligated to integrin cell surface receptors were twisted, showed that integrins initiate signalling pathways induced by strain that regulate morphology and gene expression. Stretching of fetal rat lung cells increased total protein tyrosine kinase activity in cell lysates within 5 min and induced an association of the activated signalling intermediate pp60$^{src}$ with the cytoskeleton.[78] In A549 cells, mechanical stretch activated c-Jun $NH_2$-terminal kinase, a mitogen activated protein kinase known to mediate expression of cytokine genes.[79] Results of more recent studies[80,81] have shown that for mechano-transduction to take place, integrins have to be bound to their specific ligands rather than being initiated by distortion of the receptors alone. Thus, integrins act as mechanotransducers by aggregating at sites of focal adhesion, by physically connecting the extracellular matrix to the cytoskeleton, and through their signal transduction pathways.

### *Intercellular junctions*

Intercellular adhesions in the alveolar epithelium include gap junctions, adherens junctions, and desmosomes, which transmit force by bonding epithelial cells in a sheet with the help of intermediate filaments. Adherens junctions probably act as mechanosensors in the alveolar epithelium and secondary messengers are probably transmitted across epithelial cell gap junctions and perhaps between different cell types.[82] For example, mechanical stimulation of n-cadherin in intercellular adherens junctions in fibroblasts caused gadolinium-sensitive calcium influx and induced actin polymerisation at the sites where force was applied.[83] Expression of connexin proteins, the constituents of gap junctions in rat type-2 cells is modulated by the matrix protein fibronectin, which is abundant in the airspace after alveolar injury.[84] This expression is another mechanism by which the healthy and injured alveolar epithelium could respond differently to over-distension.

### *Transcriptional and post-transcriptional regulation*

Many of these signalling pathways affect gene expression by modulating the activity of transcription factors that bind to regulatory elements on promoter sites of target genes. Mechanical strain can thus change expression of immediate early response genes (eg, c-*fos* and *Erg-1*), which encode proteins related to transcription factors and signal transduction. Injurious ventilation of isolated rat lungs up-regulated c-*fos* mRNA,[29] and plasma membrane disruption of fibroblasts and endothelial cells in vitro directly induced production of the fos protein.[85] This response was associated with a rise in intracellular calcium, but was not mediated by calcium channels sensitive to stretch. Grembowicz and colleagues[84] propose that breaching the cell membrane allows either influx of agents (eg, calcium) that induce c-*fos* or efflux of inhibitors or ligands for cell surface receptors (eg, fibroblast growth factor). This new model of mechanotransduction lies between mechanical damage of tissues and stimulation of physiological pathways. Finally, mechanical force could

affect gene expression directly by allowing restricted DNA molecules to unfold[86] or by modulating nuclear pore size,[87] although these effects would probably not be specific or reproducible.

## Prospects for pharmacotherapy

Can elucidation of the cellular mechanisms underlying VALI and design of effective treatments to block mechanotransduction and its downstream consequences further reduce deaths in patients with ARDS who are optimally ventilated? Apart from stretch-sensitive ion channels, mechanosensors are likely to also attach cells to matrix or each other. After injury the extracellular matrix changes and inducible adhesion molecules might be expressed, which could be viable targets for blockage of antibodies or peptides. Hence, an ideal target for intervention is a cell surface receptor that is induced during lung injury and that is an initiator of mechanotransduction signalling pathways. For example, expression of the integrin αvβ6 and its ligand fibronectin on the surface of the alveolar epithelium are increased by lung injury,[88] and mice who do not have the β6 subunit are protected against acute lung injury[89] and fibrosis.[90]

Interference with downstream components of the mechanotransduction signalling pathways could attenuate VALI if specific agents are delivered to the lung parenchyma. Antagonism of key humoral mediators of inflammation and tissue damage might have similar effects. For example, an inhibitor of p38 mitogen activated protein kinase (FR-167653) attenuated pulmonary fibrosis and cachexia induced by bleomycin in mice.[91] Administration of the drug was associated with decreased whole lung expression of mRNA for tumour necrosis factor α and connective tissue growth factor, but not transforming growth factor β, suggesting that specific mitogen activated protein kinase inhibitors could be useful treatments for acute lung injury and could down-regulate expression of likely mediators of VALI such as tumour necrosis factor α.

Finally, agents that attenuate lung injury might affect the processes of VALI indirectly, by dampening the inflammatory response to over-distension, hastening the resolution of air space oedema, and decreasing profibrotic stimuli.

## Recommendations

Inflammatory mediators produced as a result of pathological mechanical stimulation of lung cells could contribute to VALI and spill over into the systemic circulation, causing multiple organ failure and death. The low accessible alveolar volume, the tendency for recruitment and derecruitment, and the need for high-inspired oxygen concentrations set up the injured lung for VALI. At the cellular level, the regenerating alveolar epithelium is probably more easily damaged by stretch and the milieu in the air space could be primed for an exaggerated response to an inflammatory stimulus.

Protective ventilation is the only treatment or supportive modality that affects outcome in patients with ARDS. With few exceptions, for example patients with underlying disorders that would be exacerbated by hypercapnia (eg, raised intra-cranial pressure), low tidal volume ventilation should be used routinely for patients with injured lungs. Thus, there is a new gold standard of lung protective ventilation against which new supportive modalities, including high frequency ventilation, partial liquid ventilation, and extracorporeal membrane oxygenation must be tested. Similarly, interventions designed to improve gas exchange in the injured lung that have failed to improve survival in clinical studies, including inhaled nitric oxide, prone positioning, and surfactant replacement, could confer benefit if used in conjunction with a low tidal volume ventilation strategy.

The result of this huge advance is that we can now fix the tidal volume and limit the airway pressure of patients with ARDS knowing that this will give them the best chance of survival. However, even if such a protective ventilation strategy is followed, VALI still occurs in this patient group. The mechanisms that sense and convert excessive mechanical strain into cytotoxic and proinflammatory mediators are beginning to be understood. The identification of key players at the cellular and molecular level might identify targets for treatment that will enable us to prevent VALI and improve outcome further.

*Conflict of interest statement*

None declared.

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# Uses of error

## Clinical and research

*Patrick Vallance*

When I was a house officer, I took care of an elderly lady with a stroke affecting her non-dominant side who had been in hospital for many months. The day before she was due to go home, she fell out of bed in the middle of the night. I thought there was nothing wrong and sent her home as planned the following day. She was back within 24 h to have her fractured neck of femur sorted out. I learnt that non-dominant strokes cause sensory inattention and lack of pain does not mean there is not a fracture; and also to listen to the nurses. They suspected that the patient had fractured her hip, but I ignored them because I wanted to get the patient home. Another lesson was to follow; I assumed that I was about to be struck off before I was fully registered but my consultant took me to one side and said "just tell the patient and her family exactly what happened, admit that you made a mistake and say sorry". I did and that was the end of it.

As a consultant I discharged a young man who had been admitted from prison complaining of chest pain. He had not had an infarct and his exercise test was reported as negative. I told him that he probably did not have coronary artery disease and that his chest pain was likely to be due to something else. He returned 5 days later with a myocardial infarction. I learnt to take into account the full ramifications of a social history. I should not have sent him back to prison with the message that the chest pain was not due to coronary artery disease. His chances of being allowed back to hospital if the pain recurred were very low indeed. Indeed, he was only brought back when he collapsed.

In research, one learns from mistakes almost on a daily basis. One mistake I still keep making is assuming that I know more than I do. A few years ago a researcher elsewhere did an experiment that many of us in the nitric oxide research field would never have done—he gave arginine to boost nitric oxide production. We had detailed knowledge of the biochemical pathway and thought that his experiment made no sense in view of the enzyme involved and the amount of arginine already present in cells. However it turned out he was right and we were all wrong. As John Hunter said many years ago "why not try the experiment?". I keep learning to be humble in the face of nature.

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