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Mechanotransduction in the Lung Ventilation-induced lung injury and mechanotransduction: stretching it too far?

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Uhlig, Stefan. Ventilation-induced lung injury and mechanotransduction: stretching it too far? *Am J Physiol Lung Cell Mol Physiol* 282: L892–L896, 2002; 10.1152/ajplung.00124.2001. The Acute Respiratory Distress Syndrome Network clinical trial on ventilation of critically ill patients has drawn attention to the potential side effects of mechanical ventilation. Both clinical and basic research have demonstrated that injurious ventilation strategies can initiate or perpetuate local and systemic inflammatory responses. There are four principal mechanisms that can produce such a response. 1) Ventilation, especially with high ventilation pressures and zero positive end-expiratory pressure, can cause stress failure of the plasma membrane and of epithelial and endothelial barriers. Stress failure of the plasma membrane causes necrosis, which leads to liberation of both preformed inflammatory mediators and agents that stimulate other cells that are still intact to produce such mediators. 2) Stress failure of the barriers causes loss of compartmentalization with spread of mediators and bacteria throughout the body as a consequence. 3) Less injurious ventilation strategies that do not cause tissue destruction can elicit release of mediators by more specific mechanisms, presumably through activation of stretch-activated signaling cascades (mechanotransduction). 4) Ventilation with increasing positive pressures raises the pressure in the pulmonary circulation and thus vascular shear stress, both of which are known stimuli for endothelial cells. These different mechanisms should be taken into account in the design and the interpretation of studies on molecular mechanisms of ventilation-induced lung injury.

inflammation; proinflammatory cytokines

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK study has cogently demonstrated the importance of protective ventilation strategies to prevent ventilator-associated lung injury (28). A remarkable finding of this and another clinical study (21) was the fact that protective ventilation strategies were associated with reduced

markers of inflammation, among them proinflammatory cytokines. In accordance with experimental data (e.g., Refs. 29, 38, and 39), these findings resulted in the biotrauma hypothesis, stating that the lung injury caused by injurious ventilation strategies results from excessive release of proinflammatory mediators and overactivation of the immune system (30). Not surprisingly, this has elicited a vivid interest in the mechanisms by which ventilation activates the immune system, most notably in mechanotransduction (recently reviewed in Refs. 6, 32, 36, and 42). The term mechanotransduction describes intracellular signaling processes in response to external forces such as stretch. Obviously, such signaling processes can occur only if the cells remain intact. If cells are stretched too far, the plasma membrane breaks, and mechanotransduction becomes impossible. Also under these conditions, proinflammatory mediators are liberated, but in this case by mechanisms different from mechanotransduction. Therefore, whenever mechanotransduction is studied, it is important to exclude alternative mechanisms that may lead to superficially similar results. For that reason, it is the aim of this communication to discuss the principal physical forces by which ventilation can cause the release of proinflammatory mediators and to identify potential pitfalls in studies aimed at understanding the signaling processes involved in ventilation-induced mediator release. As summarized in Table 1, ventilation-induced release of proinflammatory mediators may result from stress failure of the plasma membrane, from stress failure of endothelial and epithelial barriers, from stretch-induced mechanotransduction, or from effects on the pulmonary vasculature.

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Table 1. *Ventilation can cause release of proinflammatory mediators*

<i>Principal Ways by Which Ventilation Can Cause Release of Proinflammatory Mediators</i>
<i>Stress failure of plasma membrane (necrosis)</i>
Release of preformed mediators
Proinflammatory effects of cytosol released from damaged cells
<i>Stress failure of endothelial and epithelial barriers</i>
Loss of compartmentalization
Hemorrhage and accumulation of leukocytes in the lungs
<i>Overdistension without tissue destruction</i>
<i>Effects on the vasculature independent from stretch and rupture</i>
Increased intraluminal pressure
Increased shear stress

STRESS FAILURE OF THE PLASMA MEMBRANE

Cells can die in two fundamentally different ways, by necrosis or by apoptosis (10). Apoptotic cell death represents a well-organized cellular suicide without release of the cellular content, whereas during necrotic cell death, the cytosol with all its ingredients [e.g., lactate dehydrogenase (LDH) or purines] is liberated. It is well known that necrosis is frequently associated with inflammation, whereas prevention and resolution of inflammation are viewed as major teleological justifications for apoptosis. A frequent cause of necrotic cell death is disruption of the plasma membrane by toxic agents or by stress failure of the plasma membrane. Recently, Vlahakis and Hubmayr (36) have calculated that "a typical plasma membrane can sustain strains between only 2 and 3% (in the plane of the membrane) before it breaks." In line with this, it was found that stretching of organotypical cultured fetal rat lung cells by 5% for 1 h liberated LDH into the supernatant (16). The supernatant of such overstretched cells contains not only cytosolic enzymes such as LDH but also preformed mediators such as the α -chemokine macrophage inflammatory protein-2 (16). In addition to the presence of such preformed proinflammatory mediators, the cytosol appears to contain further factors that stimulate other intact cells to produce proinflammatory mediators. For instance, it has been shown that the lysate of human fibroblasts elicits chemokine release from whole human blood (22). Thus direct (preformed mediators) and indirect mechanisms account for the increase in proinflammatory mediators in necrotic tissue. Obviously, such a condition's mediator release does not depend on mechanotransduction.

However, this does not imply that these phenomena are biologically or clinically irrelevant. For instance, many patients are ventilated with very low or even zero positive end-expiratory pressure (PEEP) (8). Data from animal experiments, however, clearly demonstrate that ventilation with high distending pressures in the absence of PEEP causes tissue destruction (7, 33, 34, 40). In this situation, tissue destruction (necrosis) probably occurs as a result of the high shear stress generated during repeated opening and reopening of atelectatic areas (atelectotrauma) (26) and as a result of deformation of the alveolar epithelium (31). As an

example, if rats are ventilated with 45 cmH₂O of distending pressure, alveolar levels of purines (as a marker of necrosis) are much higher in those lungs ventilated without PEEP (34). Consequentially, we (9) and others (29) have found high levels of mediators in animal lungs that have been ventilated with high pressures and zero PEEP.

STRESS FAILURE OF ENDOTHELIAL AND EPITHELIAL BARRIERS

Not only can the plasma membrane break, but so can the contact between cells (36, 41). If such a disruption happens to the pulmonary endothelial and epithelial barrier, this will lead to hemorrhage and loss of compartmentalization. The concept of compartmentalization comprises the fact that the inflammatory response remains compartmentalized in the area of the body where it is produced, e.g., in the alveolar space or in the systemic circulation. One consequence of the tissue destruction that occurs in lungs ventilated with high pressures and no PEEP is destruction of the barriers and decompartmentalization. As a result, local proinflammatory mediators, endotoxin, and bacteria are spread in the systemic circulation, and systemic factors enter the lung (12, 17, 35). In addition, loss of the barriers will also allow red (hemorrhage) and white blood cells to enter the lungs and to promote inflammation.

Thus if the forces generated during ventilation exceed certain limits, tissue destruction occurs. It is important to realize that the increased pulmonary and systemic levels of proinflammatory mediators that are observed under these conditions are the sum of both tissue destruction and mechanotransduction and can at least partly be prevented by applying PEEP (4, 9, 12).

MEDIATOR RELEASE IN RESPONSE TO VENTILATION WITHOUT TISSUE DESTRUCTION

Experiments on mechanotransduction can be properly interpreted only if necrosis can be excluded. Several authors have been successful in stretching lung cells without causing necrosis. In these studies, cell viability was checked by measurement of LDH, trypan blue exclusion, or the chromium release assay. For example, Vlahakis and colleagues (37) found increased interleukin(IL)-8 release from stretched alveolar epithelial type II cells, and Pugin and colleagues (20) made similar observations with alveolar macrophages. In intact organs, we have shown that ventilation of mouse lungs with a 2.5 \times increased end-inspiratory pressure (25 cmH₂O, 3 cmH₂O PEEP) does not cause lung damage according to light microscopy and LDH release (38, 39) but causes release of a variety of proinflammatory chemokines and cytokines (13, 38, 39). Collectively, these and other findings suggest that mechanotransduction can induce the production of proinflammatory mediators in intact lung cells. The usefulness of such models for studying the mechanotransduction triggered by ventilation is illustrated by

experiments with isolated mouse lungs and stretched cells, with both showing that activation of the transcription factor nuclear factor (NF)- κ B is an important step in mediator release in response to overdistension (13, 20). The current concepts concerning mechanotransduction in the lungs have recently been reviewed (6, 15, 32, 42).

MEDIATOR RELEASE DUE TO INCREASED VASCULAR PRESSURE AND SHEAR STRESS

Interpretation of studies in intact organs is complicated by the interaction between ventilation and perfusion (2). Besides changes in circumferential stretch forces, different ventilation strategies may also cause changes in perfusion pressure and vascular shear stress. Given that fluid viscosity and perfusion rate remain constant, vascular shear stress (τ) will change with intraluminal pressure because τ is proportional to perfusion pressure, or more formally $\tau \sim (\Delta P/L)^{0.75}$, where P is the pressure drop over the vessel and L is the vessel length (24). The magnitude of pressure and shear stress during ventilation is expected to affect mediator production in the vascular bed independently from stretch, although as of now there is, except for prostacyclin as discussed below, little experimental evidence. However, the abundant evidence from other systems makes it very likely that such mechanisms will also become important in the pulmonary circulation when ventilatory settings are changed. For instance, it was shown that high shear stress combined with physiological pressure upregulated tissue plasminogen activator (t-PA) expression, whereas high intraluminal pressure with normal shear stress downregulated the t-PA protein and gene expression in endothelial cells (23, 24). A differential regulation by shear stress and intraluminal pressure was also observed for the transcription factors c-Jun and c-Fos (11). Particularly, shear stress is known to increase the activities of multiple transcription factors such as AP-1, NF- κ B, Sp-1, and Egr-1. The actions of these transcription factors on the corresponding *cis*-elements result in the induction of genes encoding for vasoactivators (prostacyclin, nitric oxide), adhesion molecules, monocyte chemoattractant protein-1, cytokines (IL-1, IL-6), and growth factors (platelet-derived growth factor, transforming growth factor- β) in endothelial cells (1, 3, 18, 25, 27).

An experimental setup that allows separation of the effects of stretch from those of increased vascular pressure and shear stress is to compare mediator production during positive pressure ventilation (PPV) and negative pressure ventilation (NPV). If lungs are perfused with the same constant flow and ventilated with the same transpulmonary pressures (and hence tidal volumes), the larger compression of pulmonary vessels during PPV will lead to a much greater pulmonary resistance than during NPV (5, 19). During NPV, the mean alveolar pressure remains unchanged, and expanding the lungs increases the transmural pressure on extraalveolar and corner vessels, which finally re-

sults in diminished vascular resistance (14). Therefore, with the same perfusion rate, pulmonary artery pressure is higher during PPV than NPV. This is illustrated by experiments with isolated mouse lungs perfused at constant flow (39). Switching from NPV to PPV (end-expiratory pressure/end-inspiratory pressure was switched from $-3/-10$ to $3/10$ cmH₂O) caused an instantaneous rise in vascular resistance that was accompanied by increased prostacyclin secretion. At higher *trans*-pulmonary pressures ($3/25$ cmH₂O), both vascular resistance and prostacyclin release were further enhanced during PPV, whereas during NPV ($-3/-25$ cmH₂O) vascular resistance decreased and only a small change in prostacyclin secretion was observed (39). Because in these experiments tidal volume, transpulmonary pressure, and perfusate flow rate were all similar, the elevated prostacyclin production during PPV must have been the result of either increased vascular pressure or shear stress. Importantly, there was no difference in the secretion of the cytokine tumor necrosis factor (TNF) and IL-6 during PPV and NPV (39), showing that two distinct mechanisms are responsible for the release of prostacyclin on one hand and TNF and IL-6 on the other.

Therefore, in experimental studies aimed at elucidating the pulmonary mechanotransduction in response to ventilation by increased volumes or pressure, it may be advantageous to ventilate the lungs by negative pressure. Under these conditions, any increase in ventilation pressure will reduce rather than increase pulmonary vascular pressure and shear stress. Another alternative, to ventilate lungs without perfusion, appears problematic, because the lung physiology of nonperfused lungs is only poorly defined. From experiments with isolated perfused rat lungs, we know that switching off the perfusion causes a rapid change in lung mechanics as indicated by a dramatic drop in tidal volume, pulmonary compliance, and airway conductance (unpublished observations).

CONCLUSIONS

Before the hypothesis of biotrauma emerged, barotrauma/volutrauma and atelectotrauma were considered the principal causes of ventilation-induced lung injury (7). However, these concepts are not mutually exclusive because by causing stress failure, both barotrauma/volutrauma and atelectotrauma can cause biotrauma. Thus ventilation with high volumes or pressures can cause release of proinflammatory mediators by a number of different mechanisms, all of which appear to be clinically relevant. Whereas in a clinical situation different mechanisms may coexist, when mechanistic studies are performed it appears important to distinguish between these different mechanisms by checking cell or tissue integrity and by choosing systems that allow differentiation between responses of the lung parenchyma and those related to changes in pulmonary perfusion.

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