Capillary Pressure-induced Lung Injury: Fact or Fiction?

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Yesterday nobody knew about it.
Today, everybody is talking about it.
And tomorrow, we shall have therapy for it.

I am referring to the whole new concept of capillary pressure-induced lung injury. I shall try to highlight this concept.

The alveolar wall can be regarded as a mesh of pulmonary capillaries. Increased tension in the alveolar wall caused by high inflation pressures, is transmitted to the capillary wall. This can be seen during ventilator-induced lung injury (Figure 1).[1,2,3,4,5]

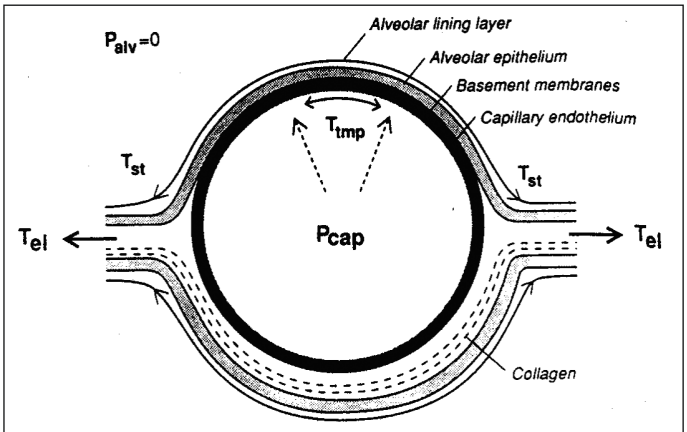


Fig. 1. Three forces act on the blood-gas barrier (BGB). T_{tmp} is the circumferential or hoop tension caused by the capillary transmural pressure. T_{el} is the longitudinal tension in the alveolar wall elements associated with lung inflation; part of this is transmitted to the BGB. T_{st} is the surface tension of the alveolar lining layer; this apparently exerts an inward-acting force to support the capillary when the latter bulges into the alveolar space at high capillary transmural pressures. P_{alv}, alveolar pressure; P_{cap}, capillary pressure. [From West et al. (57).]

Another method of increasing the wall stress of the pulmonary capillaries, is by increased trans-mural pressures. This is the mechanism around which capillary pressure-induced lung injury revolves.

Why is this important to the anaesthetist? The lung microvascular pressure profile shows a major pressure drop, in particular across the alveolar septal capillary network. This capillary pressure drop accounts for 33-50% of the total vascular pressure drop across the lung.

Looking at the pathogenesis of lung capillary hypertension, we see that an increase in vascular pressure may be transmitted to the lung capillaries from either the pulmonary arterial, or the pulmonary venous compartment.

By far the most common cause of pulmonary capillary hypertension is pulmonary congestion due to left heart disease. It is important to keep in mind that even in healthy subjects, pulmonary arterial wedge pressure may rise above 20mmHg during severe exercise, thus causing significant capillary hypertension. Pulmonary capillary hypertension can also result from severe pulmonary arterial hypertension or pulmonary venoconstriction. This may be of particular relevance in two clinical conditions, namely congenital cardiac disease with high left to right shunting, and neurogenic pulmonary oedema.

Up to now, pulmonary capillary hypertension has been regarded as the main mechanism of hydrostatic lung oedema; the underlying mechanisms and functional consequences were assumed to be related to passive fluid dynamics and to be rapidly reversible.

Recent studies, however suggest that the micro-vascular response to lung capillary hypertension is more complex with respect to both mechanical forces involved in the formation of hydrostatic pulmonary oedema as well as active cellular responses evoked by high-pressure stress.

To clarify the significance of lung capillary pressure and its consequences, it is important to review the basic mechanisms of fluid dynamics in the lung. As early as 1970, consensus had been reached on two issues of hydrostatic pulmonary oedema formation: Firstly, that lung oedema formation is attributable to passive fluid micro-vascular filtration across endothelial junctions. Secondly, that pulmonary oedema results from an imbalance between micro-vascular filtration and removal of interstitial and alveolar fluid by lung lymphatics.[6] Clinically hydrostatic pulmonary oedema reaches its critical stage when liquid finally enters the alveoli. The precise site of liquid entry remains unknown.

The theoretical basis of trans-capillary fluid dynamics is given by the Starling equation that classifies pulmonary oedema as being either due to increased hydrostatic pressure or increased permeability.

With hydrostatic pulmonary oedema, we mean an increased fluid filtration due to altered hydrostatic or oncotic pressure gradients across an intact capillary wall. On the other hand, increased permeability occurs when the endothelial barrier is in-

terrupted at constant hydrostatic or oncotic pressure gradients.

At the onset of hydrostatic pulmonary oedema, there is an initial safety factor, the low interstitial compliance, which counteracts the further progression of pulmonary oedema.[7] The rapid onset of matrix (interstitial) remodelling subsequently increases tissue compliance that promotes oedema progression.

Under physiological conditions, the alveolar fluid is reabsorbed rapidly secondary to active Na^+ transport by the alveolar type II cells.[8] At elevated lung micro-vascular pressures, active Na^+ transport is impaired, which may play a role in the pathogenesis of hydrostatic lung oedema.[9]

Interestingly, catecholamines increase this active Na^+ transport and accelerate alveolar fluid re-absorption, presumably by recruitment of epithelial Na^+-K^+ pumps and may thus offer an interesting therapeutic modality.[10]

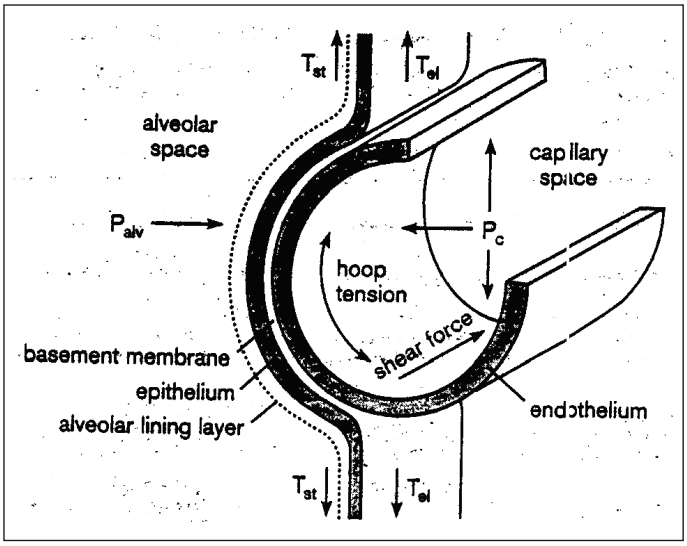
The classical view of hydrostatic pulmonary oedema was that the endothelial cell of the lung capillaries was only passively involved. Hydrostatic lung oedema appeared to be rapidly reversible by alveolar fluid absorption and lymphatic drainage, once the triggering pathological event was eliminated. Accordingly, we have considered capillary transmural pressures (P_c) less than 40 mmHg as being relatively benign.[11] Now, by fluorescence imaging it is shown that pressure changes as small as 4mmHg, induce a second messenger response.[12]

Recent advances in endothelial biology challenged this classical view and raised an entirely new set of questions concerning the endothelial role in lung micro-vascular barrier regulation. The response of lung capillary pressure to high pressure appears to be more complex; active signal transduction processes that are capable of modifying barrier properties, are identifiable in the epithelium.[13]

It has therefore been become clear that a capillary transmural pressures of greater than 40 mmHg should not be tolerated as it may cause ultrastructural disruptions of both the capillary endothelial and the alveolar epithelial layer.[14]

Why, is the effect of hydrostatic pressure in the lung capillaries, more than just a compression effect? The answer lies in mechano-transduction, the term used to describe the mechanisms by which physical forces are converted to biological signals.[15] [16]

In this context, capillary pressure not only exerts a pressure effect on the capillary endothelium, but also causes an increase in the trans-mural pressure. This results in the passive bulging of the capillaries into the alveolar space (Figure 2).[17]



The capillary distension secondary to the increased transmural pressure, has two important consequences.(Figure2) Firstly, according to the Laplace equation, the high transmural pressure causes an increased circumferential hoop tension in the thin-walled capillaries.[18] This stretch effect on the vascular endothelium, rather than compression, plays an important role in the endothelial dysfunction. Stretching of the endothelium triggers stretch-activated cation channels to open, which cause a rise in intracellular calcium.[19] [20]

Secondly, capillary distension has a direct effect on capillary hemodynamics and thus alters the shear forces acting on the endothelial layer. As the micro-vascular endothelial cells form the front line is exposed to these hemodynamic alternations, it is not surprising that the endothelial cells plays a important role in pressure-induced cellular responses.[21]

The endothelial dysfunction is mediated by active second messenger responses and is characterized by an imbalanced release of vaso-active mediators,[22] namely vasodilatory parastaglansins (prostacyclin)[23] and nitric oxide.[24] The effects of diminished endothelial vasodilator production are amplified by an increased release of the vasoconstrictor endothelin-1 and thromboxane A_2. The production of endothelin-1 is enhanced in congestive heart failure and pulmonary expression.[25] [26] [27]

The increased release of endothelin-1 leads to vaso-constriction in both the arterial and venous sides of the pulmonary circulation, aggravating the already existing hypertensive state in the lung capillaries.[28] Acute endothelin-1 receptor A blockade with sitaxsentan, significantly reduced the mean pulmonary artery pressure and pulmonary, but not systemic vascular resistance. Therefore, endothelin-1 is the major cause of pulmonary hypertension secondary to chronic heart failure. Endothelin-1 induced pulmonary vasoconstriction is probably amplified by the release thromboxane A_2 and by alveolar hypoxia following hydrostatic oedema. Promising clinical approaches in this context include the blockade of endothelin-1 receptors[29,34] or pulmonary gene transfer of endothelial or inducible nitric oxide synthase.

The rise in intra-cellular calcium also leads to the expression of P-selectin and Von Willebrand factor on the endothelial cell, causing platelet adhesion and aggregation. This worsens the vasoconstriction by releasing potent vasoactive mediators like serotonin and thromboxane A_2.[30] P-selectin mediates the interaction between leukocytes and pulmonary endothelium. Their extravasation of leucocytes into the alveolar space was long considered a feature confined to inflammatory lung disorders.[31] [32] [33] [34] [35] The increased intra-cellular calcium, also activates myosin light chain kinase, that causes an increased micro-vascular permeability.[36]

The proliferative effect of endothelin-1 as well as the deficient production of anti-proliferative mediators nitric oxide and prostacyclin causes endothelial remodelling.[37] This structural remodelling is reversible over a period of months, but is not rapidly responsive to reversal with pharmacological interventions. It is thus referred to as a chronic fixation of the hypertensive state.

In summary, pulmonary endothelial dysfunction arises in the endothelial cell, which is characterized by an increase in intracellular calcium concentration causing an imbalanced in the release of vasoactive mediators. Furthermore, the endothelial dysfunction initiates a multi-cellular response that compromises

features of vascular leakage, thrombosis, inflammation, vasospasm and vascular remodelling. A vicious cycle develops between capillary hypertension and endothelial dysfunction.

The clinical implication of the concept of pulmonary endothelial dysfunction is that increased pulmonary vascular pressures should be taken cognisance of and treated timeously. As the dysfunction is initiated by mechanical factors and perpetuated by biochemical mechanisms, therapy should address both aspects.

In conclusion, until recently, increased hydrostatic pressure in the lung capillaries was considered a pure mechanical problem, which affected the micro-vascular fluid balance and capillary barrier properties in the lung by passive mechanisms. The principle of mechano-transduction has explained a complex and highly sensitive cellular response, triggered by high lung capillary pressures.

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