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# Pulmonary vascular heterogeneity and the Starling hypothesis

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ABSTRACT

It has generally been assumed that movement of fluid between the pulmonary microvasculature and surrounding tissues is governed by a "Starling" balance of hydrostatic and protein osmotic forces similar to that which prevails in the extremities. However, both recent and older observations suggest that the lungs are more resistant to edema formation than most other organs. Several structural aspects of the lung may account for protection of the airspaces from edema formation. The pulmonary microvasculature, which comprises >70% of the pulmonary circulatory bed, appears to be less permeable to fluid and electrolytes than the endothelium of the pulmonary arteries and veins and other microvascular exchange areas. This arrangement may help explain why early edema is confined to the perivascular and peribronchial regions and why lymphatics do not reach the alveoli. Unlike the peripheral vasculature, which is compressed by edema formation, the extra-alveolar vessels remain tethered open by airway distention, even when interstitial pressures rise above those in the vessels. This may also facilitate return of proteins to the circulation. Ultrafiltration of plasma may lower local protein concentrations in the interstitium, thereby slowing further edema formation. Transendothelial reabsorption of fluid may also be altered by vesicular transport.


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## Introduction

Gas exchange in the lungs is enhanced by the large surface area of the alveoli and the extreme attenuation of the endothelial and epithelial membranes that separate the blood and gas compartments. However, these same factors also predispose the lungs to edema formation, thereby imperiling transfer of oxygen and carbon dioxide and survival of the organism. Recent studies suggest that the pulmonary circulation is protected from edema formation by several mechanisms that distinguish the pulmonary vasculature from systemic vessels such as those of the legs, which were used by Starling to characterize fluid exchange between capillaries and surrounding tissues. Because the bronchial vessels represent a relatively small fraction of the vessels in normal lungs, this review will be confined to the pulmonary vasculature.

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## Starling hypothesis in systemic vascular beds

In February of 1896, Starling presented a series of 3 lectures at the Royal College of Surgeons in which he summarized his investigations on the pathogenesis of "dropsy," the former term used for edema (Starling, 1896b). Though more than a century has passed, these studies remain a fundamental cornerstone for our understanding of fluid balance in patients with congestive heart failure and various forms of hypoalbuminemia. Starling argued that reabsorption of fluid from tissues is a passive osmotic process that is attributable to the fact that vascular protein concentrations exceed those in the interstitium.

Prior to the publication of Starling's analysis of exchange in the legs, it was generally assumed that much of the fluid and protein that leaked from the capillaries in the legs returned directly to the venous vessels because interstitial pressures exceed those in the veins. Arguing against this hypothesis, Starling showed that when saline is injected subcutaneously into canine legs, increases in tissue pressures compressed the venous circulation, thereby obstructing flow and accelerating edema formation (Fig. 1A) (Starling 1896a). Although his experiments dealt with compression of the femoral vein, the same conclusions can be drawn regarding all of the vessels in the leg, including the capillaries. Unless hydrostatic pressures within these vessels remain above those in the surrounding tissues, they will tend to collapse. Starling also showed that fluid reabsorption from the legs is possible when they are perfused with proteinaceous fluid, but not when they are perfused with protein-free, electrolyte solutions. He went on to demonstrate that although the effective molar concentrations of proteins in the plasma are considerably below those of the electrolytes, differences in vascular and interstitial protein concentrations are sufficient to generate osmotic forces that can overcome hydrostatic pressure gradients that are responsible for promoting edema formation (Starling, 1896a). It must be understood, that although reducing vascular hydrostatic pressures slows edema formation, vascular pressures must remain above tissue pressures to avoid vascular compression. It can therefore be concluded that *all* fluid reabsorption by much of the systemic vasculature depends upon the fact that protein concentrations are higher in the vessels than the interstitium. Perfusion of the extremity with protein solutions can cause a fall in the interstitial pressure by promoting the loss of fluid from the interstitium to the vasculature, thereby reducing the possibility of vascular compression.

## Solute reflection coefficients across capillary walls

Starling was careful to distinguish between the effects of high molecular weight solutes (hmw, mainly serum proteins) and low molecular weight solutes (lmw, primarily electrolytes) and assumed that the former tended to remain within the vasculature, whereas the latter freely diffused across the vessel walls. In modern terms this concept can be conceptualized with a simple equation:

$$J_v = L_p S\left(\Delta p - \sigma_{d,lmw}\Delta\pi_{lmw} - \sigma_{d,hmw}\Delta\pi_{hmw}\right) \quad (1)$$

where $J_v$ represents the rate of transudation from the vessel to the interstitium, $L_p$ and $S$ are the filtration coefficient and surface area of the capillary wall, and $\Delta p$ and $\Delta\pi$ are the hydrostatic and osmotic pressure differences between the plasma and interstitial fluids. $\sigma_d$ designates the solute reflection coefficients of the lmw and hmw solutes, and is used to gauge the relative effectiveness of these solutes in inducing fluid movement of water across specific membranes, e.g., the capillary wall. If the solute induces a flow from the tissues equal to that across a "semipermeable" membrane, which allows water but not solute movement, then $\sigma_d = 1.0$. If the solute does not induce an osmotic flow of fluid, then $\sigma_d = 0$. In effect, Starling implicitly assumed that $\sigma_{d,hmw} = 1.0$, $\sigma_{d,lmw} = 0$ and $\Delta\pi_{lmw} = 0$ (Fig. 2A).Eq. (1) may be simplified to (Ware and Matthay, 2005):

$$J_v = L_p S\left(\Delta p - \sigma_{d,hmw}\Delta\pi_{hmw}\right). \quad (2)$$

It should be emphasized that even Starling recognized that protein osmotic forces cannot play a significant role in the reabsorption of edema across some circulatory beds (Starling, 1896a). For example, gaps in the hepatic sinusoids make it unlikely that this endothelial

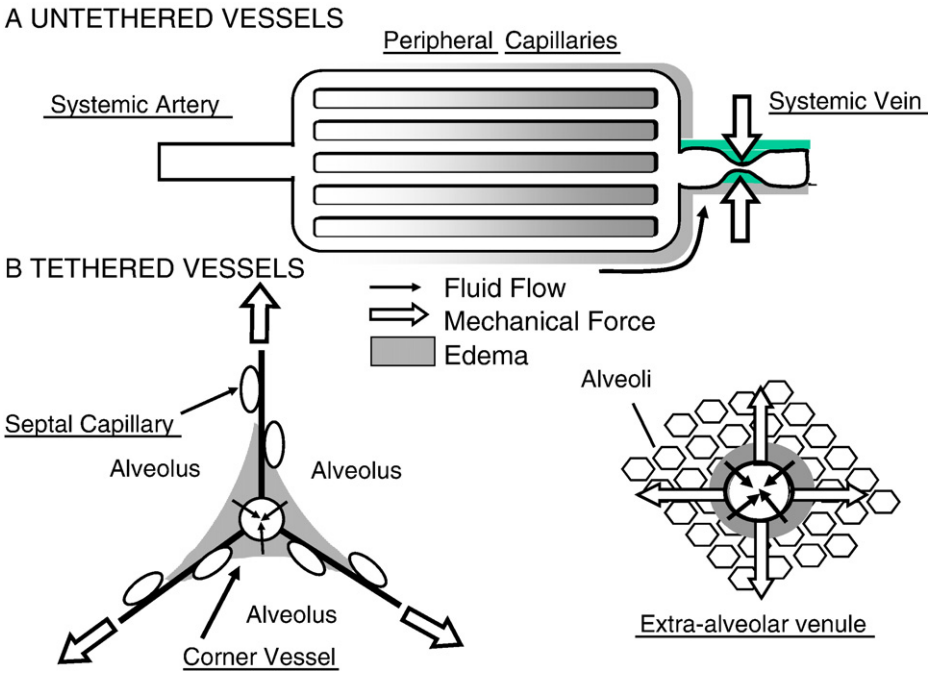


**Fig. 1.** (A) Increases in tissue pressure result in compression of femoral vein, thereby enhancing edema formation. (B) Pulmonary vessels (corner and extra-alveolar vessels) are tethered open by surrounding tissue and are kept open even when interstitial pressures exceed those in the vessels. In contrast, increases in airway pressure tend to compress alveolar septal capillaries.