The Vital Role of the Right Ventricle in the Pathogenesis of Acute Pulmonary Edema

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The development of acute pulmonary edema involves a complex interplay between the capillary hydrostatic, interstitial hydrostatic, and oncotic pressures and the capillary permeability. We review the pathophysiological processes involved and illustrate the concepts in a number of common clinical situations including heart failure with normal and reduced ejection fractions, mitral regurgitation, and arrhythmias. We also describe other rarer causes including exercise, swimming, and diving-induced acute pulmonary edema. We suggest a unifying framework in which the critical abnormality is a mismatch or imbalance between the right and left ventricular stroke volumes. In conclusion, we hypothesize that increased right ventricular contraction is an important contributor to the sudden increase in capillary hydrostatic pressure, and therefore, a central mechanism involved in the development of alveolar edema. **(Am J Cardiol 2015;115:992−1000)**

The purpose of this review is to consider new insights into the mechanisms involved in the development of acute pulmonary (alveolar) edema secondary to hemodynamic abnormalities and describe the possible pathophysiological processes involved in both common and rare causes. Pulmonary edema because of adult respiratory distress syndrome and sepsis is beyond the scope of this review.[1] Acute pulmonary edema (APE) is a dramatic medical emergency. The pulmonary airspaces fill with liquid, and the patients start to drown in their own fluids. The pathophysiology is usually described in terms of a failing left ventricle requiring an ever-higher filling pressure to function: the consequent increase in pulmonary capillary hydrostatic pressure because of backward pressure causes transudation of fluid from the capillaries into the airspaces. However, as de Bono eloquently wrote "it is salutary to be reminded that patients with disease are often the most appropriate model for studying human pathophysiology, and when clinical observations do not tally with theories, it is usually the latter that are wrong."[2] One such observation is that pulmonary edema may occur in subjects with an apparently normal heart given the right circumstances.

Pulmonary Microcirculation Anatomy and Physiology

The walls of the alveoli consist of type I and type II epithelial cells (pneumocytes; Figure 1). Type I cells form 90% of the alveolar cell surface area and are fragile. Type II cells are more robust, produce surfactant, transport ions, and regulate fluid flow out of the alveoli. Type II cells can also proliferate and differentiate into type I cells. Fluid and solute filtration occur across the pulmonary capillary endothelium into the adjacent interstitial space. Gas exchange takes place in the thin segment between the capillary and the alveolar wall (Figure 1). At this point, the endothelial and epithelial cells' basement membranes (basal lamina) become tightly fused into a single layer. The total capillary blood volume in the lungs is ∼70 ml (∼10% of the pulmonary circulation volume) and is similar to the right ventricular stroke volume.[3,4] Approximately 1/3 of the pulmonary vascular resistance is because of the pulmonary capillaries.[5] Capillary hydrostatic pressure (Although the term hydrostatic pressure is widely used in clinical practice and physiology literature, the term should strictly only be applied to stationary fluids. A more accurate term is the hydrodynamic lateral pressure and differs from the pressure measured along the direction of travel of the fluid.) is usually closely determined by pulmonary artery pressure because of the relatively low pulmonary vascular resistance.[4]

The interstitial fluid moves toward the hilum along the spaces beside the vessels and the airways. The excess filtrate is removed by the pulmonary lymphatic system. Lymphatic flow arises because the interstitial hydrostatic pressure is more negative closer to the hilum; flow is assisted by the cyclic external compression that occurs during the breathing cycle coupled with the presence of 1-way valves in the lymphatic vessels and intrinsic lymphatic peristaltic contraction.[4] The lymphatic vessels drain into the systemic venous system through the thoracic duct. The lymphatic channels can dilate in chronic situations, such as mitral stenosis, suggesting that an adaptive increase in flow at rest can occur.[6]

Starling's Hypothesis Revisited

In 1896, Starling described the relation between the fluid flow across the capillary membrane (flux) and the

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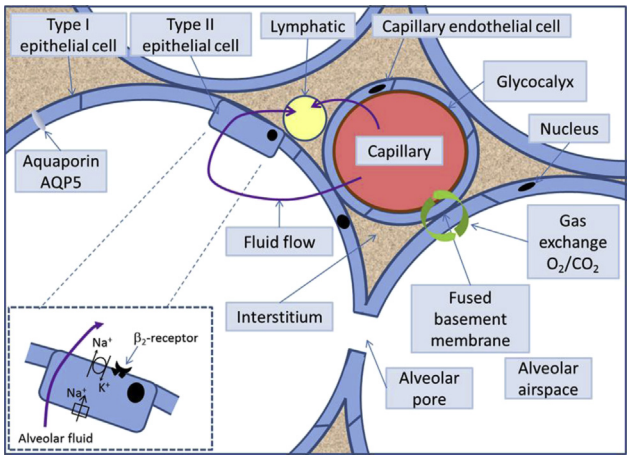

Figure 1. Anatomy of the alveoli and pulmonary microcirculation—schematic representation of the anatomy of the pulmonary capillaries and alveoli (not to scale). Type II alveolar cells act to clear fluid from the alveoli by removing Na^+ through epithelial amiloride-sensitive Na^+ channels (ENaC) and Na^+/K^+ exchange pumps into the interstitium. Catecholamine-dependent (mediated by β_2-adrenergic receptors) and independent regulatory mechanisms modulate the Na/K-ATPase pump (inset). Water follows the movement of Na^+ by osmosis. The tightly fused basement membrane of the capillaries and alveoli allow rapid gas transfer. Proteogylcans in the interstitium prevent collapse of the capillary.

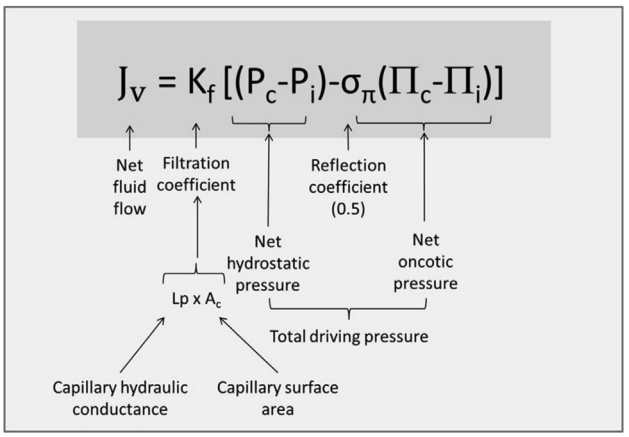

Figure 2. Starling equation. J_v represents the net fluid flow across alveolar capillary membrane (or flux). K_f is the filtration coefficient and measures the ease (conductance) of fluid (solvent or water) movement across the alveolar membrane. K_f is the product of capillary surface area (A) and capillary hydraulic conductance (Lp). A high value indicates a highly water-permeable capillary and a low value indicates low capillary permeability. The oncotic reflection coefficient (σ_π) is an indication of the alveolar capillary membrane resistance to protein (solute) movement across the membrane; it has a value close to 1 in the renal glomerulus, indicating a high resistance, and is nearly 0 in the hepatic sinusoids, indicating little resistance to transmembrane protein flux, and measures the alveolar capillary membrane resistance to protein (solute) movement across the alveolar capillary membrane. Total driving pressure is the combined effect of both oncotic (adjusted by the reflection coefficient, σ_π) and hydrostatic pressures. P_c = alveolar capillary hydrostatic pressure; P_i = interstitial hydrostatic pressure; Π_c = capillary oncotic pressure; Π_I = interstitial oncotic pressure.

hydrostatic and oncotic pressures (Figure 2). The Starling equation states that the net filtration (J_v) is proportional to the net sum of hydrostatic and oncotic pressures. Levick and

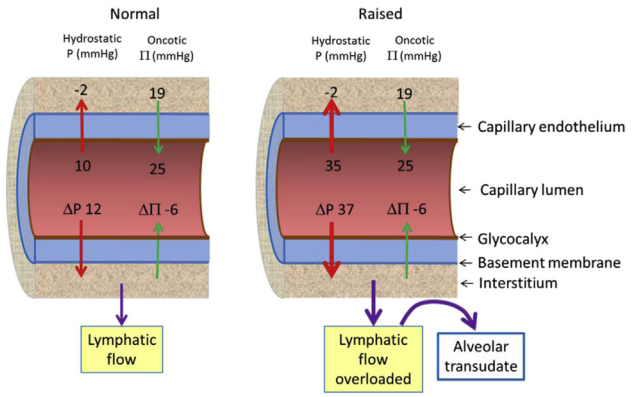

Figure 3. Pulmonary capillary pressures. In health, the hydrostatic pressure inside capillaries is ~10 mm Hg. Lymphatic flow returns the fluid to the circulation. Alveolar edema develops once the lymphatic flow is exceeded and interstitium reaches capacity. Net hydrostatic pressure is normally ~12 mm Hg *(outward)*, and net oncotic pressure is ~6 mm Hg *(inward)*. Pulmonary capillary oncotic pressure is ~25 mm Hg, and the interstitial oncotic pressure is ~19 mm Hg. Albumin generates most of the oncotic pressure of blood. In pulmonary edema, the capillary hydrostatic pressure increases resulting in a much higher net pressure gradient driving fluid into the interstitium.

Michel have recommended some modifications to the basic equation, where Π_g (oncotic pressure immediately beneath the glycocalyx) replaces Π_c.[7] By convention, an outward "force" (or, more correctly, pressure) is positive and an inward one is negative. Capillary hydrostatic pressure drives the fluid out of the vasculature and is opposed by the interstitial hydrostatic pressure.

Hydrostatic pressures (P) are usually measured in millimeter of mercury. The filtration coefficient (K_f) is a measure of ease of fluid (solvent or water) movement across the alveolar membrane. In humans, the lungs' total K_f is estimated to be 10 ml/min/cmH_2O and is lower than most other organs.[7,8] The capillary hydrostatic pressure (P_c) is normally ~13 mm Hg at arteriolar end and 6 mm Hg at venous end. The interstitial hydrostatic pressure (P_i) is approximately −2 mm Hg relative to atmospheric pressure. The net hydrostatic pressure (ΔP) is the difference between capillary and interstitial pressures and varies between the upper and lower lungs because of the difference in height and the effect of gravity (determined by ρgh, where ρ, g, and h denotes fluid density, gravitational constant, and height, respectively). A difference in height between the apex and base of the lung is ~25 cm. There is, thus, a pressure difference of 25 cmH_2O (18 mm Hg) between the apex and base of the lungs while standing. A typical pulmonary artery pressure is 25/8 mm Hg, sufficient for perfusion of the highest part of the lung while upright.

Oncotic pressure is the colloid osmotic pressure generated by colloidal solute components and is an inward pressure (Figure 3). The interstitial oncotic pressure is high because of a leak of protein (mostly albumin) across the thin capillary membrane.[4] The pulmonary capillaries have a reflection coefficient (σ_π) of ~0.5.[4,9] Normally, the hydrostatic pressure exceeds the opposing oncotic pressure along the capillary's full length, and so capillaries are continuously filtering (Figure 3).[4] The small net outward movement of fluid from the pulmonary capillaries is estimated to be 0.3 ml/min in a 70-kg human.[10]