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;■:■−■)**

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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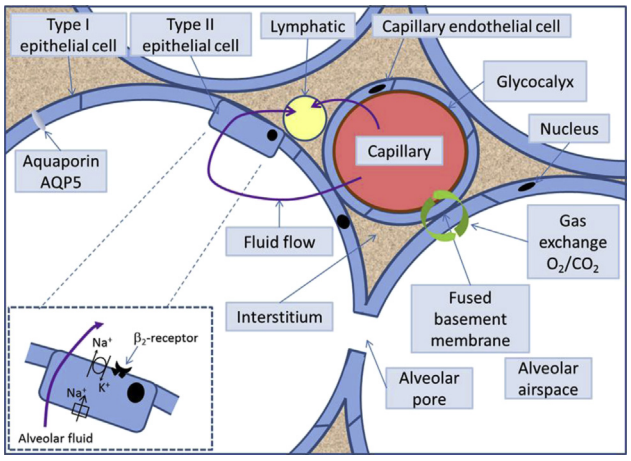

Figure 1. Anatomy of the alveoli and pulmonary microcirculation—schematic representation of the anatomy of the pulmonary capillaries and alveoli (not to scale). Type II alveolar cells act to clear fluid from the alveoli by removing Na^+ through epithelial amiloride-sensitive Na^+ channels (ENaC) and 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.

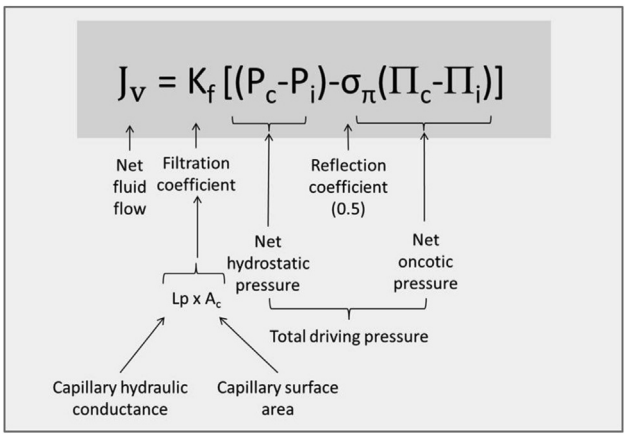

Figure 2. Starling equation. J_v represents the net fluid flow across alveolar capillary membrane (or flux). K_f is the filtration coefficient and measures the ease (conductance) of fluid (solvent or water) movement across the alveolar membrane. K_f is the product of capillary surface area (A) and capillary 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

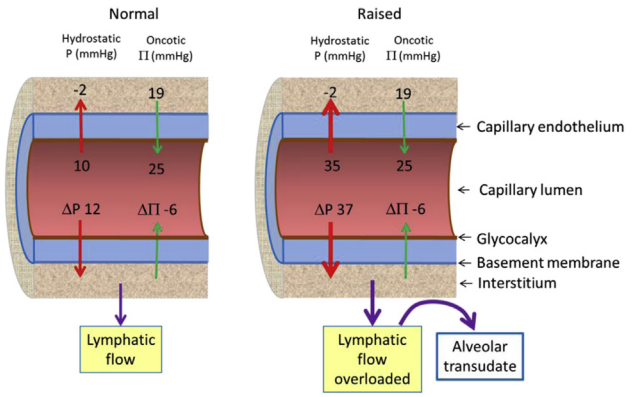

Figure 3. Pulmonary capillary pressures. In health, the hydrostatic pressure inside capillaries is ~10 mm Hg. Lymphatic flow returns the fluid to the circulation. Alveolar edema develops once the lymphatic flow is exceeded and interstitium reaches capacity. Net hydrostatic pressure is normally ~12 mm 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]

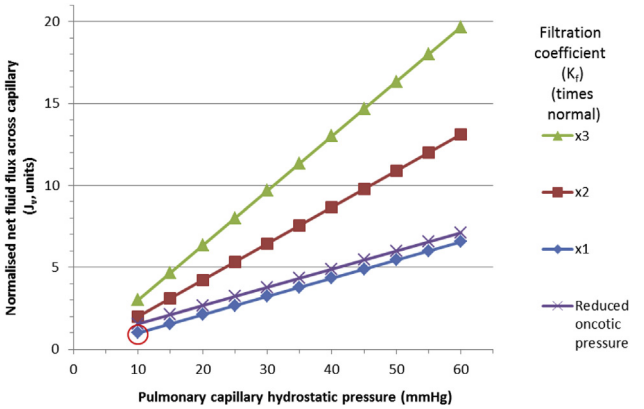

Figure 4. Relative importance of the variables in the Starling equation. Plots derived from the Starling equation showing the effect of increasing capillary hydrostatic pressure on fluid flux across the capillary membrane into the interstitium. Fluid flux increases linearly with hydrostatic pressure when filtration coefficient is normal *(diamonds)*. The effect on fluid flux by an increase in filtration coefficient is also shown (*squares*: twice normal and *triangles*: 3 times normal). A decrease in capillary oncotic pressure from 25 to 15 mm Hg with a normal filtration coefficient causes a small increase in fluid flux *(crosses)*. *Dashed line* shows a theoretical threshold that could result in APE assuming an upper limit of lymphatic clearance of 3 times normal at rest. J_v normalized to units of normal flux at rest. K_f is shown as multiples of normal *(circle)*.

For pulmonary edema to occur, excess fluid must first form in the interstitium before flowing into the alveoli. It is caused by an imbalance in Starling "forces". The 3 most common causes are an increase in capillary hydrostatic pressure (P_c), an increase in capillary permeability (K_f), and an inadequate clearance by the pulmonary lymphatic system. For example, when there is increased capillary hydrostatic pressure (P_c), more fluid is driven out of the circulation and into the interstitium (Figure 4). A decrease in hydrostatic pressure in the interstitium (P_i) from rapid evacuation of pleural fluid, pneumothorax, and acute upper airway obstruction results in a lowering of P_i (hence increasing ΔP) causing an increase in net fluid flux (J_v). Pure hydrostatic pulmonary edema is a transudate without inflammatory cells.

Physiological mechanisms have evolved to resist the development of pulmonary edema. These are (a) increased lymph flow, (b) decreased interstitial oncotic pressure, and (c) high interstitial compliance.

(a) An increased fluid filtration (F_v) causes an increase in interstitial hydrostatic pressure and lymph flow that tend to remove the fluid. However, because the lymphatic vessels drain into the systemic veins, the flow may be countered by an increase in venous pressure.[4]

(b) Increased lymph flow washes the albumen out of the interstitium lowering the interstitial oncotic pressure (oncotic buffering). The combination of increased lymph flow and decreased albumen concentration reduces interstitial oncotic pressure, thus increasing the oncotic pressure gradient favoring retention of fluid in the capillary.[4]

(c) A large volume of fluid (300 to 400 ml in an adult) can be accommodated in the gel of the interstitium without an increase in interstitial pressure because of the high interstitial tissue compliance.[11]

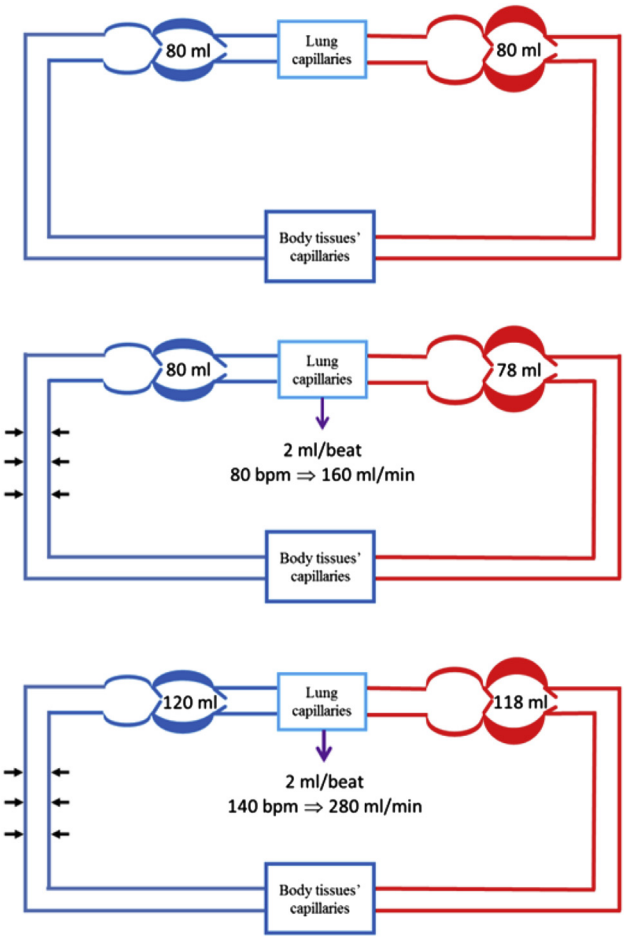

Figure 5. Hemodynamic mechanism of APE. The circulation consists of 2 double pumps (the right atria and ventricle and left atria and ventricle) in series. The right and left heart must maintain the same stroke volumes; any condition that results in an imbalance will cause serious abnormalities. *Top*, represents the normal balanced flows and assumes a normal stroke volume at rest of 80 ml and on exertion of 120 ml. *Middle*, indicates the situation in APE at rest when a small decrease in left ventricular stroke volume by 2 ml results in a stroke volume mismatch. Assuming a heart rate of 80 beats/min, excess fluid will accumulate at a rate of 160 ml/min. *Bottom*, shows that a similar discrepancy in stroke volumes may occur during exertion; fluid will accumulate even more rapidly because of the faster heart rate (140 beats/min, 280 ml/min). The schematic ignores lymphatic flow and bronchial and Thebesian venous flow. A reduction of the systemic intravascular volume occurs by venoconstriction (indicated by *arrows*). The lower systemic volume in the constricted systemic veins is transferred to the right heart. From here, the fluid is shifted to the pulmonary interstitium and alveoli resulting in a redistribution of fluid. Alveolar edema results from a discrepancy between right and left ventricular stroke volumes. An increase in capillary hydrostatic and, therefore, APE is predominantly caused by the driving pressure of the right ventricle. An increase in the left atrial pressure is a consequence of the elevated pulmonary capillary pressure.

Once the interstitium is full, fluid overflows into the alveoli. The capillary hydrostatic pressure must increase 3-fold before alveolar flooding occurs (equivalent to a pulmonary capillary wedge pressure of 25 to 30 mm Hg) in a dog model using aortic constriction (Figure 4).[12] The protective mechanisms are largely ineffective if the capillary

membrane is damaged through inflammatory, allergic, or septic conditions. However, secondary capillary damage is probably common with high hemodynamic pressures. The high pressure causes direct insult through increasing shear stress and by damaging both the glycocalyx lining and the endothelium (Figures 1 and 3).[1] Injury to the lung capillaries causes them to leak both solutes and protein so that the resulting edema fluid is an exudate.

When albumin levels in blood are low, as happens in nephrotic syndrome or liver disease, the lower capillary oncotic pressure increases the flux of fluid forced into the interstitial tissues. The protein content of the interstitium is low, and thus, the edema fluid is a transudate. An isolated very low capillary oncotic pressure has only a limited effect on fluid flux (Figure 4), but when a low albumin is combined with a modest increase in hydrostatic pressure, it can result in edema formation (Figure 4).[12] There is active reabsorption of fluid from the alveoli driven by sodium transport pumps (Figure 1).[13,14] AQP5 (aquaporin type 5) in the membrane of aquaporin water channels in type I epithelial cells contribute to water permeability although their role in pulmonary edema is uncertain.[14]

Mechanisms of an Increase in Capillary Hydrostatic Pressure

In cardiogenic pulmonary edema, the increase in capillary hydrostatic pressure is conventionally seen to be a consequence of an increase in left atrial pressure. There is a curvilinear relation between the filling pressure of each ventricle and its subsequent stroke work—the Frank-Starling relation. The primary function of the Frank-Starling mechanism is to deal with the small beat-to-beat variations in stroke volume between left and right ventricles. In the failing left ventricle, the relation is maintained but is shifted down and to the right, meaning that to maintain any given stroke volume, a higher left ventricular filling pressure is required. The end-diastolic pressure is often thought to determine the left atrial pressure that governs the pulmonary venous pressure and, ultimately, the pulmonary capillary pressure. This "backward failure" hypothesis was originally proposed in 1832 by James Hope.[15] He contended that when the ventricle fails to discharge its contents, blood accumulates and pressure increases in the atrium and the venous system emptying into it.[15]

The "backward failure" hypothesis cannot be the whole explanation. Energy has to be added to the left-sided system to increase filling pressure—a direct consequence of the law of conservation of energy. One potential source of the energy is the right ventricle.[16] In health, there is a steady state where right and left ventricular stroke volumes are matched by the Frank-Starling mechanism (Figure 5, top). The total energy of flowing blood is the sum of the dynamic (kinetic) and lateral pressure energy (Bernoulli's principle—flowing blood has mass and velocity [v] and, therefore, kinetic energy. The kinetic energy density is defined by $^1/_2\ \rho v^2$. As the blood flows inside a vessel, pressure is exerted laterally against the walls of the vessel; this pressure represents the pressure energy density (P). The total energy density (E) of the blood flowing within the vessel is the sum of the kinetic, pressure, and gravitational energy densities, $E = {}^1/_2\ \rho v^2 + P + \rho gh$.

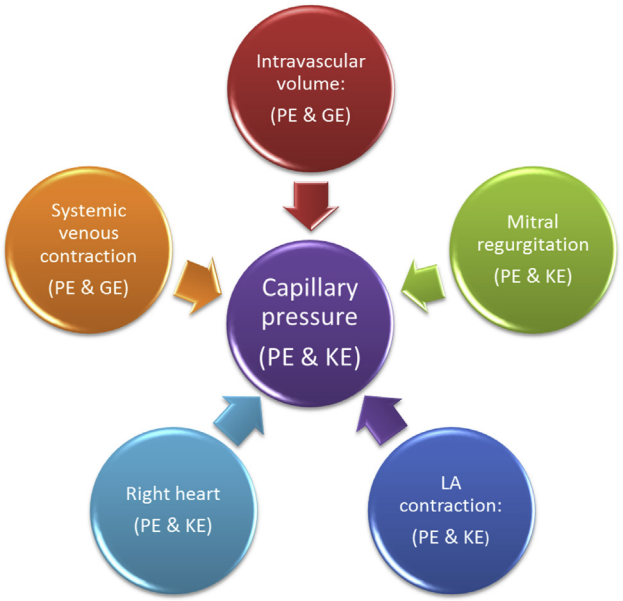

Figure 6. Potential determinants of the capillary hydrostatic pressure. Capillary hydrostatic pressure is predominantly maintained by the pressure generated by the right heart. The capillary pressure will increase if there is a decrease in left ventricular stroke volume at the same time as right ventricular stroke volume is maintained. An increase in intravascular volume (because of renal fluid retention) can modestly elevate the intravascular pressure. Sympathetic activation may also cause systemic venous contraction and elevate pressure (demonstrated by an elevated jugular venous pressure). Mitral regurgitation adds kinetic and pressure energy as a consequence of left ventricular contraction. Finally, there is a small contribution from left atrial contraction (as seen in the A wave). GE = gravitational energy; KE = kinetic energy; PE = pressure energy.

Total energy change is obtained from the sum of the products of volume difference (ΔV) and individual energy densities. Blood flows from a higher to a lower energy density.). Accordingly, rather than the left atrial pressure determining capillary hydrostatic pressure, it is the capillary pressure that determines left atrial pressure (before atrial contraction). An acute increase in pulmonary capillary pressure can only arise if there is an additional input of pressure energy originating from right ventricular contraction. For APE to occur, there must inevitably be a mismatch between the right and left ventricular stroke volumes as fluid is lost from the circulation into the airspaces (Figure 5).[17] Consider the example of a patient having an acute and extensive anterior myocardial infarct. Left ventricular stroke volume decreases, but right ventricular function is largely unaffected or may, indeed, increase because of the catecholamine drive (Figure 5, middle). The greater right ventricular stroke volume relative to the left must cause an increase in capillary hydrostatic pressure with 2 consequences: (a) transudation of fluid into the interstitium of the lung and (b) an increase in left atrial pressure. The left atrial pressure may increase to a point where left ventricular stroke volume returns toward normal through the Frank-Starling mechanism. Capillary hydrostatic pressure might also increase if there is a transient increase in right ventricular stroke volume that exceeds the left ventricular stroke volume during effort. Catecholamine-dependent systemic venoconstriction causes an increase in

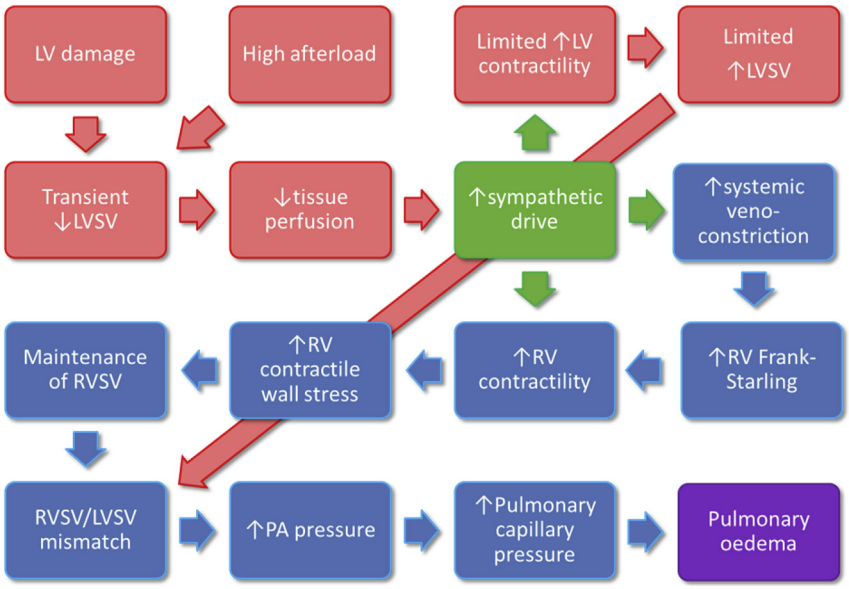

Figure 7. Schematic representation of mechanisms of elevated pulmonary artery pressure. Left ventricular SV may decrease after acute damage to the left ventricle and/or an increase in afterload. Reduced tissue perfusion results in an increase in sympathetic drive. When there is a combination of limited improvement in left ventricular stroke volume and no such limit to the right ventricle's response, an imbalance in stroke volumes occurs and is accompanied by an increase in PA pressures. The increase in pulmonary pressure arises from the extra work performed by the RV. The elevated left heart filling pressure is a consequence of an increased work performed by the right heart. LV = left ventricular; PA = pulmonary artery; RV = right ventricle; SV = stroke volume.

right-sided filling pressures as energy is converted by contraction of the venous smooth muscle cell (Figure 6). The right ventricle's response is to maintain its stroke volume output through the combination of its Frank-Starling mechanism and by a direct catecholamine-dependent myocardial stimulation.

An increase in interstitial pressure can be sufficient to compress the capillaries (the Starling resistor effect). The patency of capillaries is critically dependent on the integrity of the extravascular proteoglycan molecules linking the matrix to the endothelial cells. Once the interstitial hydrostatic pressure increases significantly, the extravascular proteoglycan molecules can rupture and the capillaries will collapse. The process further impairs capillary blood flow and increases pulmonary vascular resistance. The increased pulmonary vascular resistance brought about by the Starling resistor effect and collapsed capillaries predispose to a further transient decrease in left ventricular stroke volume and lead to an increasing sympathetic drive. This follows Darcy's law of flow that states $\Delta P = \dot{Q}R$, so if $\dot{Q}$ (flow) is maintained and R (resistance) increases, then ΔP (pressure difference) must also increase. In effect, the catecholamine-dependent increase in right ventricular contractility and systemic venoconstriction (through the Frank-Starling mechanism) leads to an even greater increase in pulmonary artery pressure (Figure 7). There is redistribution of flow from blocked to patent capillaries as a consequence of the capillary damage. Because the total pulmonary flow now goes through the remaining capillaries, resistance increases with a corresponding further increase in right ventricular contraction and capillary hydrostatic pressure. Additional pressure injury to the residual patent capillaries may then occur and cause a greater hemodynamic deterioration (Figure 5, bottom).

True "backward failure" can occur but is unusual. For example, significant mitral regurgitation, particularly if it is of sudden onset, because of papillary muscle or chordal rupture, can cause pulmonary edema. In this situation, pressure and kinetic energy are added to the left atrium by the left ventricle—as can be seen on a pulmonary wedge pressure tracing. Although many patients with APE have no increase in intravascular volume before or during its development, some do. Acute on chronic heart failure usually occurs when there has been a gradual increase in intravascular and extravascular volume over some weeks. A typical example is in heart failure with a reduced ejection fraction where there is a generalized increase in intravascular pressures independent of the heart. In 1940, Starr showed that immediately after circulatory arrest, the "static" intravascular pressure remained high in patients with heart failure and peripheral edema (20.3 vs 7.6 cmH_2O).[18] At least in some patients with fluid retention, the high pressure in the pulmonary circulation is a consequence of a greater intravascular volume resulting from renal fluid retention and a positive fluid balance (Figure 6). The baseline or "static" pressure energy, unrelated to any cardiac chamber contraction, is stored as elastic energy in the vessels. A similar increase in venous pressure is seen after infusion of fluids or during sympathetic activation where systemic venoconstriction occurs (Figure 6).

In chronic disease, such as mitral stenosis, an increase in capillary hydrostatic pressure because of an increase in systolic right ventricular pressure may be prevented (at least in part) by hypertrophy and/or constriction of the capillary arterioles. In this instance, some of the increased driving pressure from the right ventricle is lost through energy transfer to heat (entropy) secondary to a higher shear stress and friction between the layers of blood. Furthermore, there

Table 1
Theoretical mechanism predisposing to pulmonary edema based on the variables in the Starling equation

Process or variable	Magnitude of effect
Increased filtration coefficient (K_f)	Large
Increased capillary hydrostatic pressure (P_c)	Large
Reduced interstitial hydrostatic pressure (P_i)	Small
Decreased reflection coefficient (σ_π)	Small
Reduced capillary oncotic pressure (Π_c)	Medium
Increased interstitial oncotic pressure (Π_i)	Medium

is evidence of reduced capillary permeability in chronic heart failure and mitral stenosis that may protect the patient from the development of pulmonary edema.[19]

Clinical Scenarios Associated With Pulmonary Edema

The causes and treatment of edema in heart failure have recently been reviewed.[20] Table 1 summarizes the possible mechanism and relative importance of the processes in the development of pulmonary edema based on the Starling equation. An understanding of the physiology of the microcirculation allows a better comprehension of the pathophysiological process involved in the development of pulmonary edema. Often there is >1 mechanism operating with the combination resulting in APE.

Acute Myocardial Infarction and Heart Failure With a Reduced Ejection Fraction

Acute myocardial infarction can cause 1 of 2 distinct clinical syndromes, namely (1) hypotension with or without shock or (2) APE. The 2 conditions can occur either separately or together. Shock is characterized by a low cardiac output. Causes of cardiogenic shock include an inferior myocardial infarct where both the right and left ventricles are injured. When the infarcted right ventricle is sufficiently damaged to be unable to generate a significant increase in pulmonary artery and capillary hydrostatic pressure, pulmonary edema will not occur. This contrasts with an acute anterior wall infarct where the right ventricle is relatively preserved and APE is more likely (Figure 5, middle). The concept of an imbalance between the right and left ventricles' stroke volumes causing APE differentiates it from the separate condition of shock.[16]

There is some debate as to the changes in intravascular volume during the development of APE. Most studies suggest that there is redistribution of fluid from the systemic to the pulmonary circulation.[20] There may even be a reduction in intravascular volume as blood plasma transfers into the pulmonary interstitium and alveoli.[17] A gradual increase in the intravascular volume in patients with chronic heart failure before an admission with an acute exacerbation can also occur.[21] A similar mechanism may explain orthopnea and paroxysmal nocturnal dyspnea (PND), conditions that conventional theories struggle to explain.[16] We suggest that orthopnea and PND may be readily described as follows: venous return from the lower half of the body increases in the supine position because of gravitational effects (with additional fluid reabsorption in PND). A greater right ventricular stroke volume results from activation of the right ventricular Frank-Starling mechanism. Lying flat is known to elevate pulmonary artery pressures in chronic heart failure.[22] If the left ventricle is damaged by myocardial disease, the left-sided Frank-Starling mechanism is impaired and so is unable to respond to balance the output from the right heart.[23] If the left ventricular end-diastolic pressure is already chronically raised, it will additionally limit left ventricular filling and inhibit the appropriate increase in stroke volume to match the right heart. The consequence of the left ventricular stroke volume not increasing to the same extent as the right ventricle stroke volume is pulmonary hypertension, an increase in capillary hydrostatic pressure, extravasation of fluid, and pulmonary congestion (Figure 7).

Hypertension and Heart Failure With a Normal or Near-Normal Ejection Fraction

The left ventricular ejection fraction is modified by changes in the end-diastolic wall thickness and longitudinal and midwall circumferential strain.[24,25] Systemic hypertension typically leads to left ventricular hypertrophy and abnormalities of myocardial systolic strain but spares the right ventricle.[26] Importantly, left ventricular ejection fraction can be maintained despite abnormal myocardial shortening by the presence of a greater end-diastolic wall thickness.[27–29] The thicker the wall of the ventricle, the greater the ejection fraction becomes for a given myocardial strain.[29] In effect, a thick-walled ventricle can have both a normal ejection fraction and reduced myocardial contraction.[27,28] A thick-walled ventricle has a lower wall stress (Laplace's law) and, thus, needs a higher end-diastolic pressure to cause the stretch-activated Frank-Starling mechanisms.[30]

APE is particularly likely to occur in the presence of hypertension and concentric left ventricular hypertrophy.[31] A combination of high systemic vascular resistance (increasing the left ventricular power requirement)[32] and reduced myocardial strain (reflecting reduced contractility) predispose to a decrease in stroke volume given any additional minor myocardial insult. Long-standing systemic hypertension with concomitant concentric left ventricular hypertrophy and associated contractile abnormalities also results in an inability to increase left ventricular stroke volume appropriately.[26] In bilateral renal artery stenosis, there is defective pressure natriuresis resulting in intravascular volume expansion. Reduced arterial compliance increases the velocity of the reflected pulsewave and causes it to return during systole instead of during diastole, thereby further increasing the demand on the left ventricle. The right ventricle is relatively spared from all these abnormalities. The combination of problems can lead to the development of mismatch between right and left ventricular stroke volume. The right ventricle maintains its stroke volume, but the diseased left ventricle is unable to overcome its increased hemodynamic load (Figure 7). Rapid onset of (flash) pulmonary edema can arise in the presence of a significant acute stroke volume mismatch.

Acute severe mitral regurgitation can present with pulmonary edema before remodeling[33]; APE may be unilateral or even segmental if the jet is directed toward a single pulmonary vein[34] because of a difference in the end-on pressure of a jet compared with the lateral pressure (Bernoulli's principle).[4] The result is that the capillary

hydrostatic pressure may be elevated in 1 lung segment, whereas sparing the others.

APE is often precipitated by an acute arrhythmia, such as atrial fibrillation. This normally occurs when there is already a structural abnormality of the left ventricle. During sinus rhythm, the diseased left ventricle is working near its functional limit with the Frank-Starling mechanism activated, whereas the right heart has additional functional capacity. The onset of an arrhythmia tips the balance so that the right heart is able to maintain its stroke volume, whereas the contractile reserve in the left heart is insufficient.

Swimming-Induced Pulmonary Edema and Related Conditions

The development of acute exercise-induced pulmonary edema has been extensively investigated in racehorses[35] but only more recently described in humans.[10,36] APE has been seen in elite cyclists, marathon, and ultramarathon runners and during cross-country skiing in the cold.[10] Subclinical pulmonary edema may be quite common.[10] There is usually no evidence of a cardiac abnormality in these situations. We suggest that APE occurs when the Frank-Starling mechanism becomes exhausted during extreme and prolonged periods of exercise; the lymphatic system becomes overloaded because of a difference in ventricular stroke volumes during exertion (Figure 5, bottom). APE may be noticeably more frequent during swimming. One study showed that 1.4% of the participants had symptoms suggestive of pulmonary edema in endurance events with a swimming component.[10] Of soldiers performing a 2.4-km open water time trial, 27% developed frothy sputum, dyspnea, and hemoptysis consistent with APE.[10] The reported cases of swimming-induced pulmonary edema (SIPE) tend to occur in young and fit subjects performing intense exercise.[37] SIPE appears to be brought about by a specific combination of circumstances that individually would not normally cause a problem.[38,39] A high peripheral vascular resistance, because of arteriolar constriction (cold peripheries) or vascular compression (wet suit), may inhibit an appropriate increase in left ventricular stroke volume. External compression of the systemic veins may also increase right-sided cardiac filling pressures and pulmonary blood flow. If the pulmonary vascular resistance remains normal, and the right heart is unhindered, the right ventricular stroke volume may exceed the left. SIPE is more likely to occur if the subject is unable or unwilling to rest as extravascular alveolar fluid will continue to accumulate.

SIPE is more likely to occur in triathletes during the open water swimming phase,[37] presumably because of cold-induced peripheral vasoconstriction. Peripheral vascular resistance is lower during the cycling and running phases. Additional contributors to increased peripheral vascular resistance in some subjects with SIPE include systemic hypertension and concentric left ventricular hypertrophy.[37] The higher vascular resistance in hypertension accompanied by any subtle myocardial strain abnormalities may predispose a subject to SIPE (Figure 7). The lymphatic pump may also be reduced by the need to time breathing to swimming strokes and reduced ventilation in the supine position. APE has also been described in healthy subjects whilst aqua jogging,[40] during competitive breath-hold diving,[41] and in SCUBA divers.[42,43] There is a risk of recurrence in both SIPE and SCUBA divers.[44] In these settings, APE is a serious matter as it can be fatal.[44,45] Death because of pulmonary edema in swimmers may go unrecognized as it is likely to be reported as drowning. During deeper dives, the intrathoracic blood volume increases because of hydrostatic compression of the whole body. A cold environment augments the thoracic pooling of blood because of peripheral vasoconstriction, and the vessels may be compressed with a consequent increase in capillary hydrostatic pressure.[45] The respiratory effort needed to overcome the SCUBA regulator's resistance, a regulator malfunction, breathing against an involuntarily closed glottis or laryngospasm may generate large negative intrathoracic pressures thereby potentiating fluid formation (see negative pressure pulmonary edema described subsequently). Secondary capillary basement membrane damage follows aggravating pulmonary edema. In each of these swimming-related conditions, the primary abnormality is ventricular stroke volume imbalance (Figure 5).

Negative Pressure Pulmonary Edema and Re-expansion Pulmonary Edema

Negative pressure and re-expansion are rare causes of APE.[46] Typical precipitants include extubation,[46] rapid removal of pleural fluid, and treatment of a pneumothorax.[47,48] APE is more likely to occur with larger effusions or pneumothoraces and often occurs unilaterally. APE arises when a large negative intrathoracic pressure results in a significant reduction in alveolar pressure and, hence, interstitial hydrostatic pressure.[46] The resulting increase in the gradient of pressure from capillary to interstitium promotes fluid transudation. Additional mechanical damage to the pulmonary vasculature could cause increased permeability of the capillaries, thus, exacerbating pulmonary edema.[47]

Conditions Where Acute Pulmonary Edema Is Unlikely

As with right ventricular infarction described earlier, it is also worth considering conditions where APE is unlikely. In single-ventricle circulations (e.g., Fontan/total cavopulmonary connection), the pulmonary flow is maintained by the only remaining pump—the systemic ventricle. In the absence of a pulmonary ventricle, an acute increase in pulmonary (and capillary hydrostatic) pressure is not possible. Rarely, the systemic venous pressures might become sufficiently high, because of substantial fluid retention by the kidneys, to raise capillary hydrostatic pressure enough to generate chronic pulmonary edema.

It is also worth emphasizing that conditions that affect the right ventricle to a similar extent as the left ventricle, such as cardiac amyloid, also tend not to cause APE; a low output state and elevated intravascular volume are more common. APE is also unusual in hypertrophic cardiomyopathy despite contractile abnormalities in the absence of acute severe mitral regurgitation.[49] Two other situations where APE rarely occurs are in patients with either a pericardial effusion or constrictive pericarditis.[50] In these conditions, both right and left ventricular stroke volumes are reduced because end-diastolic volume is constrained. Intravascular volume increases because of renal hypoperfusion and consequent fluid retention, resulting in high

filling pressures throughout the circulation but associated with a low systemic pressure. Nevertheless, pulmonary edema does not occur because the stroke volumes of the 2 ventricles remain similar.

Conclusions

Acute cardiogenic pulmonary edema is usually described as being the inevitable consequence of the rise in left ventricular filling pressure required to maintain the output of a failing left ventricle. However, the main source of energy required to raise the capillary hydrostatic pressure acutely is the right ventricle and the cause of the edema fluid is a mismatch between left and right ventricular stroke volumes. The right ventricle is centrally involved in the development of APE.

Disclosures

The authors have no conflicts of interest to disclose.

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