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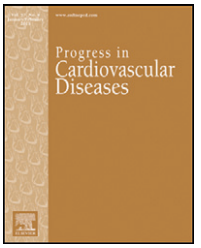

Endothelial Dysfunction and Lung Capillary Injury in Cardiovascular Diseases

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ABSTRACT

Cardiac dysfunction of both systolic and diastolic origins leads to increased left atrial pressure, lung capillary injury and increased resistance to gas transfer. Acutely, pressure-induced trauma disrupts the endothelial and alveolar anatomical configuration and definitively causes an impairment of cellular pathways involved in fluid-flux regulation and gas exchange efficiency, a process well identified as stress failure of the alveolar–capillary membrane. In chronic heart failure (HF), additional stimuli other than pressure may trigger the true remodeling process of capillaries and small arteries characterized by endothelial dysfunction, proliferation of myofibroblasts, fibrosis and extracellular matrix deposition. In parallel there is a loss of alveolar gas diffusion properties due to the increased path from air to blood (thickening of extracellular matrix) and loss of fine molecular mechanism involved in fluid reabsorption and clearance. Deleterious changes in gas transfer not only reflect the underlying lung tissue damage but also portend independent prognostic information and may play a role in the pathogenesis of exercise limitation and ventilatory abnormalities observed in these patients. Few currently approved treatments for chronic HF have the potential to positively affect structural remodeling of the lung capillary network; angiotensin-converting enzyme inhibitors are one of the few currently established options. Recently, more attention has been paid to novel therapies specifically targeting the nitric oxide pathway as a suitable target to improve endothelial function and permeability as well as alveolar gas exchange properties.

A typical feature of the failing left ventricle (LV) is the loss of its ability to relax and fill at normal pressures irrespective of the definition of heart failure (HF) based on preserved or reduced ejection fraction.[1] The pathophysiology of high end-diastolic pressures and its consequences on the lungs are complex and meaningful in clinical conditions involving both acute or chronic filling pressure elevation.[2] The most remarkable manifestation of an acute pressure challenge on lung capillaries is pulmonary edema, while pulmonary hypertension (PH) and right ventricular failure are the late consequences.[3]

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Abbreviations and Acronyms

ACE = angiotensin converting enzyme

AV = alveolar volume

ATPase = adenosine triphosphatase

CAV = caveolin

cGMP = cyclic guanosine monophosphate

CO_2 = carbon dioxide

DLco = diffusing capacity for carbon monoxide

DLNO = diffusing capacity for nitric oxide

EMT = epithelial-mesenchymal transition

ET1 = endothelin-1

GC = guanylate cyclase

HF = heart failure

HFpEF = heart failure-preserved ejection fraction

HFrEF = heart failure-reduced ejection fraction

L-NMMA = NG-monomethyl-L-arginine

LA = left atrial

LAP = left atrial pressure

LV = left ventricular

MCP-1 = monocyte chemoattractant protein 1

mPAP = mean pulmonary artery pressure

NO = nitric oxide

O_2 = oxygen

PH = pulmonary hypertension

PDE5 = phosphodiesterase 5

Q = pulmonary perfusion

sGC = soluble guanylate cyclase

TGF-α1 = transforming growth factor

TNF-α = tumor necrosis factor alpha

V/Q = ventilation/perfusion

Despite the fact that these unfavorable conditions are highly prevalent and portend a negative outcome[4,5] the pathophysiology of left-sided heart disease associated with lung capillary injury is not completely understood and is infrequently considered as potential therapeutic target.[6] In this article we review the pathophysiological bases and clinical implications of lung capillary injury and its consequences in patients with left-sided heart disease.

Lung capillary injury: pathophysiological bases

There is strong preclinical evidence that lung microcirculation impairment warrants attention as a determinant of unfavorable clinical outcome.[7] When lung capillaries are exposed to an excessive hydrostatic pressure a stress failure phenomenon occurs, initially described by West and co-workers in a series of experimental preparations in different animal models.[8] Stress failure challenges the anatomical integrity of the alveolar–capillary unit, alters endothelial permeability, fluid filtration and reabsorption and definitively leads to gas exchange impairment. Interstitial edema or alveolar flooding are the most impressive consequences of stress failure.[8] Alternatively, when left atrial (LA) pressure elevation is less striking and is long-lasting, a true remodeling of capillaries and small arteries takes place. A cascade of hormonal and cytotoxic activation is involved in the remodeling process that unequivocally leads to abnormalities in gas exchange (Fig 1).[9]

Tsukimoto et al.[10] studied the sequential disruption of the capillary endothelial and alveolar epithelial layers during a stepwise increase in hydrostatic pressure, reproducing the transition from interstitial leakage of protein (low permeability stage) to alveolar lumen leakage of protein and erythrocytes (high-permeability stage of pulmonary edema). A number of animal studies that have focused on the biological features of alveolar stress failure have shown that mechanisms other than mechanical injury may contribute to capillary stress.[11,12] Induction of volume overload through 0.5 ml/min/kg saline solution infusion for 180 min in the rabbit pulmonary artery was associated with a 44% portion of fluid accumulating in the interstitial space, ultrastructural changes, and impairment of gas transfer.[11] Development of hydraulic edema leads to activation of metalloproteinases, which degrades matrix proteoglycans thereby altering the composition of the plasma membrane and contributing to increased endothelial membrane fluidity. The weakened tensile strength of the membrane potentiates endothelial stress failure.[12] These findings might explain the acute rise in pulmonary hydrostatic pressure and pulmonary edema seen in humans, even if the pathophysiological correlates of alveolar–capillary stress failure in patients with cardiac disease have not been extensively investigated. In a study of 53 patients with acute cardiogenic pulmonary edema, injury of the alveolar–capillary barrier was associated with increased levels of plasma pulmonary surfactant associated proteins A and B and tumor necrosis factor (TNF)-α.[13] Persistence of elevated levels of TNF-α after pulmonary edema resolution may reflect pulmonary inflammation and explains why fluid accumulation can persist despite resolution of hydrostatic stress failure.

When pressure injury is sustained a true remodeling process takes place that might not be reversible. Several experimental models of PH due to cardiac dysfunction have brought important insights into this area. In a descending coronary artery ligation post MI model, abnormalities in the lung microcirculation consisted of increased oxidative stress and diffuse inflammation.[14]

Pacing-induced cardiomyopathy has been shown to produce alveolar–capillary membrane thickening as a result of excessive deposition of type IV collagen (the main component of the membrane lamina densa).[15] Similar findings were reported in a guinea pig model where an increased lamina was not accompanied by an increased lung water content,[16] suggesting that chronic proliferation rather than fluid accumulation predominates. In a mouse model of PH-HF-preserved ejection fraction (HFpEF) with LV hypertrophy, the LA pressure rise induced by aortic banding promoted impressive arteriolar remodeling, increased vascular oxidative stress, leucocyte infiltration and lung fibrosis after 4 weeks.[17] In addition, lung weight changes were due to tissue and vascular changes rather than extravascular lung water.[17] These features are reminiscent of the extracellular matrix thickening reported in patients with mitral stenosis