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Review Article

Cardiogenic pulmonary edema - is it lone cardiogenic? "Missing link" between hemodynamic and other existing mechanisms

Hamayak S Sisakian[1], Ani R Tavaratsyan[2]

[1]*Department of Cardiology and Clinic of General and Invasive Cardiology, University Hospital 1, Yerevan State Medical University, Yerevan, Armenia;* [2]*Erebouni Medical Centre, Yerevan State Medical University, Yerevan, Armenia*

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Abstract: The current traditional pathophysiologic concept of pulmonary edema of cardiogenic origin explains its development by a hydrostatic effect due to increased pulmonary capillary pressure resulting in fluid flux to alveolar and interstitial areas from capillaries. However, several experimental studies and clinical data of poor response to hemodynamic and diuretic treatment in many scenarios provide further evidence of the involvement of several other contributing factors to the development of cardiogenic pulmonary edema. Several experimental and clinical studies have found that sympathetic overactivity with elevated plasma catecholamine concentrations may play an important role in the development of cardiovascular-associated pulmonary edema. Catecholamine-induced pulmonary injury may be one of the key mechanisms in acute cardiogenic pulmonary edema triggering proinflammatory cytokine overactivation, oxidative stress and myocardial injury. In the everyday treatment of acute heart failure, physicians should consider the possibility of other noncardiogenic mechanisms involved in the progression of acute pulmonary edema, particularly catecholamine overactivity, lymphatic drainage, inflammatory and oxidative stress, high surfactant protein. The classic, hemodynamic treatment approach in pulmonary edema with the coexistence of other contributing factors may not provide adequate clinical benefit during treatment.

Keywords: Pulmonary edema, acute heart failure, catecholamine, capillary pressure, adrenoblocking therapy, alpha and beta adrenergic mechanism, surfactant B protein

Introduction

Pulmonary edema represents severe form of acute heart failure and is associated with higher morbidity and mortality rates, prolonged intensive care unit stay, where most compromised patients may require mechanical ventilation and an extended length of treatment [1-3].

Clinical manifestation in PE depends on the excessive accumulation of extravascular lung water, which represents the final result of several pathogenic steps, such as increase in the amount of filtered fluid secondary to marked increases in pulmonary hydrostatic pressure, local proinflammatory mediators overactivity and/or an increase in pulmonary capillary permeability, with further water and protein extravasation [1].

Other mechanisms, such as dysfunction of lymphatic drainage most dominant in lung resection surgery, may also be involved in cardiogenic pulmonary edema (PE) [4, 5]. Regardless of the etiology, the final outcome is fluid accumulation in the lungs, which alters respiratory gas exchange, resulting in respiratory distress and the need for mechanical ventilation in advanced stages [4].

In this review, we discuss the studies demonstrating the role of hemodynamic, adrenergic and other associated mechanisms in the development of PE and opportunities to intervene apart from current accepted treatment strategies in cardiogenic PE. This review may guide clinicians to acknowledge other possible mechanisms in the development of cardiogenic PE,

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which will promote a better clinical approach in the treatment of PE.

Current pathophysiologic concepts and pathology

The fluid exchange balance between the microvascular and interstitial spaces has been studied by Ernest Starling in 1896, and explained the main hemodynamic mechanism of hydrostatic pressure role in reabsorption process from plasma protein oncotic pressure through capillary endothelium acting as a semipermeable membrane [6]. Fluid accumulation may be compensated by increase of lymphatic flow volume at the compensatory stages. Further increase of hydrostatic pressure leads to increase in fluid accumulation at surrounding the bronchioles and alveolar vasculature, causing the typical pattern of interstitial pulmonary edema (Kerley B lines and vessels prominence at X ray pattern) [7, 8]. Alveolar edema may develop in advanced stages following further accumulation of interstitial fluid in alveolar spaces, resulting in impairment in gas exchange [9]. Hydrostatic pressure and vascular permeability nonlinear relationship mismatch shows that only the classic Starling mechanism may not explain fluid accumulation in the lung parenchyma, and other mechanisms involved in this process have also been developed.

Data from experimental studies demonstrated that high capillary pressures can cause alveolar capillary injury with increased permeability and transfer of fluid and protein into the lung parenchyma. Moreover, fluid in alveolar spaces may alter surfactant function, which promotes to fluid flux out of capillaries into the lung parenchyma [10, 11]. It is established, that patients with acute cardiogenic pulmonary edema have increased levels of surfactant protein B in their plasma, which is associated with abnormal gas exchange in patients with chronic heart failure. Patients with exercise-induced left ventricular dysfunction have been shown to have higher levels of surfactant protein B after short periods of exercise. Pathology studies in patients with chronic heart failure have found increased connective tissue in alveolar capillary units and increased numbers of type II alveolar cells, which represent an adaptive response in these patients [12]. Another barrier toward fluid accumulation in alveoli is the endothelial glycocalyx layer, which acts as a mechanosensor transmitting shear stress from blood flow to the endothelium cytoskeleton, initiating intracellular signaling, which increases capillary permeability [13, 14]. Following a marked increase in capillary hydrostatic pressure, fluid extravasates out of the capillaries and accumulates in the interstitial space. The detailed assessment of endothelial glycocalyx physiologic role allow us to reevaluate our traditional understanding of the pathophysiology of pulmonary edema. Both damage of glycocalyx layer and marked hydrostatic capillary pressure may lead to excessive fluid accumulation into the interstitial space [15].

Frequently, in clinical practice, we face with gap between the expression of clinical symptoms, particularly dyspnoea, lung congestion and left atrial pressure, measured through pulmonary capillary wedge pressure. Other mechanisms, such as barrier mechanical injury and increased permeability sympathetic overactivity-induced changes, may contribute to the development of PE.

Therefore, analysis of different pathophysiologic mechanisms could provide better incorporation into clinical management approaches in patients with cardiogenic PE.

Adrenergic and inflammatory mechanisms

Sympathetic overactivity with elevation of plasma catecholamine concentrations may play a definite role in the pathogenesis of cardiovascular-associated PE. Pathogenetic triggers of such activation may be postcapillary vasoconstriction in the lungs, increased alveolar-capillary permeability and neutrophil accumulation in the lung [16, 17]. The development of PE in pheochromocytoma may represent a typical example of adrenergic overactivation and expressed alpha adrenergic stimulation-induced acute heart failure.

In the study of Rassler B [18], it was shown that norepinephrine infusion in experimental studies may induce an inflammatory response with proinflammatory cytokine activation. After an 8-hour infusion of NE (1 mg/kg/hour) in rats, the IL-6 concentration in serum was increased to 6-fold compared to controls and was at peak concentration after 48 h. These changes were

associated with histologic patterns of expressed lung interstitial and alveolar edema.

High catecholamine activity also provokes significant proinflammatory cytokine overproduction [19]. One of the mechanisms of such interaction is the presence of M1 macrophages and the persistence of the intermediate ($CD14^{++}CD16^{+}$) monocyte subset during 5-month period in patients with acute myocardial infarction. This long term cytokine induced inflammatory response causes myocardial reparation abnormality compared with similar stages in other patients. It has been shown in many studies that myocardial macrophage inflammatory infiltrate changes with an increase in systemic proinflammatory cytokines are present in catecholamine-induced Takotsubo syndrome. Postmortem examination of human hearts from patients who died during the acute phase of Takotsubo catecholamine-induced syndrome determined, that these macrophages are predominantly of the M1 proinflammatory type as opposed to the reparative M2 type [20]. According to data of De Pasquale C.G. and coauthors [16], along with initial increase in plasma surfactant protein-A and -B, which provokes hydrostatic stress disorder of the alveolocapillary barrier, the prolonged elevation of tumor necrosis factor-alpha activity may deteriorate alveolocapillary membrane structure. It should be emphasized, that the inflammatory response may contribute to alveolocapillary barrier permeability following extravasation of fluid and gas exchange dysfunction.

However, several other mechanisms may be involved and trigger the development of edema, such as catecholamine-induced alpha-adrenergic stimulation and venoconstriction in the lungs. This effect may increase the pulmonary-capillary hydrostatic pressure, elevate pulmonary blood volume as well as increase of alveolar-capillary permeability. Inflammatory reactions with neutrophil accumulation in the lungs may be involved in catecholamine induced mechanisms [21-23].

Both beta adrenergic and alpha adrenergic overactivity can provoke pulmonary edema with further inflammatory reaction, although alpha adrenergic treatment-induced PE in experiments was shown to be more severe [22]. In patients with pheochromocytoma, PE development is also associated with alpha-adrenoreceptor overactivity [23].

It is well established that norepinephrine and epinephrine infusions in a rat model may provoke pulmonary edema [18, 24]. Different mechanisms may be involved in such development, including hemodynamic and direct toxicity to pulmonary vasculature and tissue [21, 25, 26].

Catecholamine infusion may cause pulmonary inflammation with cytokine release, provoking tissue injury [21, 27]. It was shown that the IL6 concentration in blood serum and pulmonary tissue was significantly increased after 6-12 hours and sustained pronounced after 72 hours [22]. The influence of proinflammatory catecholamines is mediated by alpha-1 adrenergic mechanisms, while alpha 2 adrenergic stimulation prevents neutrophil-dependent inflammatory cytokine release [17].

In a model of Sprague-Dawley rats receiving continuous intravenous infusion of norepinephrine and of separate alpha- or beta-adrenergic stimulation over 6-24 h, both alpha-adrenergic and beta adrenergic treatments increased right ventricular systolic pressure (RVSP), Meanwhile total peripheral resistance was increased during alpha adrenergic, but decreased by beta-adrenergic stimulation. Severe interstitial edema and diffuse pulmonary inflammation and pleural fluid accumulations were present in these experimental rats (Rassler B, 2003).

In our previous study by Sisakian S. and coauthors [24], it was shown that high doses of adrenaline infusion induced edema and hemorrhagic changes in pulmonary tissue and hemomicrocirculatory alterations of the myocardium that rapidly became lethal. Preliminary lung mechanical ventilation treatment prevented adrenaline-induced cardiac fibrillation and subsequent death, with nonsignificant hemomicrocirculatory changes. These data provide further evidence that increased permeability of pulmonary capillaries due to damage of capillary walls through alpha adrenergic and, to a lesser degree, beta-adrenergic stimulation are determinants of the pathogenic mechanism of PE. These experimental data also show that mechanical ventilation may prevent ventricular fibrillation and severe catecholamine-induced

lung injury mainly through an increase in blood oxygenation.

Cardiovascular mechanisms involved in the development of PE include increased oxygen consumption, dysbalance of energy supply and needs resulting in areas of myocellular hypoxia, hypoxic injury from toxic effects of catecholamines and increased heart rate cardiac contractility [28]. It is well established that myocardial hypoxia can be deteriorated through metabolic mechanisms with excessive deposition of lipids in cardiomyocytes [25, 26]. These biochemical abnormalities may result in an uncoupling of oxidative phosphorylation in mitochondria, with further failure of ATP synthesis [29, 30].

Catecholamines are considered potential triggers of calcium overload influx into cardiomyocytes with free radicals overactivation, resulting in additional dissociation of mitochondrial oxidation and phosphorylation and further l contractile dysfunction [31, 32]. Such catecholamine-induced myocardial toxicity with injury contributes to left ventricular (LV) dysfunction similar to Takotsubo syndrome and pheochromocytoma [33].

In a study by Ferrari W. and coauthors [34], dose-dependent injection of phentolamine (246-3933 nmol/kg, i.v.) prevented epinephrine-induced pulmonary edema in anesthetized and bivagotomized rats. This study provides definite evidence that the alpha 1 adrenergic mechanism has pathogenetic role in the development of PE.

Numerous *in vitro* and animal studies have shown that alpha 1-adrenergic receptor stimulation may induce PE through inflammatory and hemodynamic effects. In particular, such deleterious effects may be conditioned by increased pulmonary capillary pressure, microvascular disorders, inflammatory cell migration and pro-inflammatory cytokine effects on the lung [35].

Consequently, cardiovascular protective effects by blocking alpha adrenoreceptors may have a protective effect, suppressing the underlying mechanisms. Combined beta and alpha anti-adrenergic influence can prevent pulmonary edema development through prevention of pro-inflammatory cytokine generation by blocking alpha and moderately beta receptors, neutrophilic and eosinophilic mediated inflammation and enhanced pulmonary capillary permeability [29, 36, 37].

Clinical aspects of cardiogenic PE

Cardiogenic pulmonary edema (PE) is associated with left ventricular (LV) systolic and/or diastolic dysfunction. The development of PE depends mainly on elevated filling pressures and left atrial hypertension degree, which is directly results backward elevation of hydrostatic pressure in pulmonary veins and capillaries [7, 38, 39]. Reduction of left atrial hypertension through monitoring of pulmonary capillary wedge pressure is considered as the main treatment strategy in patients with chronic heart failure and severe arterial hypertension and reduces the symptoms of congestion in pulmonary circulation, primary and repeated hospitalizations as a result of PE prevention. This treatment approach is important both in HF with reduced EF and in HF with preserved EF.

Several acute cardiovascular conditions, such as acute severe mitral regurgitation, myocardial ischemia, atrial fibrillation (AF) paroxysm with a high rate ventricular response and hypertensive crisis, may lead to pulmonary edema without fluid retention [40, 41]. In these pathologies, the interplay of different mechanisms promoting acute PE is evident. Meanwhile, patients with long term chronic heart failure on guideline based treatment may be less likely to develop acute PE at a given left atrial pressure because of hypertrophy and constriction of precapillary arterioles, increased lymphatic drainage or reduced alveolar-capillary membrane permeability [42].

Despite the fact that LV pathology is central in the pathogenesis of PE, several other mechanisms are triggers in the progression of PE. Apart of the hemodynamic induced increased fluid transfer out of capillaries into the interstitium and alveolar spaces, other mechanisms may coexist or even more dominant such as capillary pressures induced alveolocapillary barrier disruption, increased permeability. Fluid in alveoli may alter surfactant function and increase surface tension [12], which can lead to expressed edema formation and atelectasis with impaired gas exchange. Patients with barrier disruption have increased levels of surfac-

tant protein B in the circulation for a long time period after clinical improvement.

In the study by Magri D. and coauthors [43] in 71 patients with chronic heart failure and 19 healthy controls, surfactant B protein levels were found to be increased in outpatient heart failure patients. High levels of this protein were associated with decreased membrane diffusion capacity on pulmonary function testing and decreased peak O_2 consumption at exercise testing. The study results also provide further support that higher circulating surfactant protein B levels were associated with membrane injury with alveolar gas diffusion failure.

Clinical assessment by auscultation may not reveal patients with increased extravascular fluid in the lungs. Meanwhile, lung ultrasound can easily detect high risk patients, who may develop PE. Comprehensive cardiovascular ultrasound with assessment of B-lines of lungs and LV filling pressure noninvasively with frequent outpatient monitoring identifies vulnerable, patients for acute heart failure development [44-46].

The conventional management of cardiogenic pulmonary edema includes loop diuretics and pre- and post-vasodilators, aiming preload and afterload reduction and, in severe cases, inotropic medication support, noninvasive and invasive mechanical ventilation [47]. Meanwhile, the prevention of recurrent acute PE episodes and worsening of heart failure (HF), lung congestion in ambulatory patients depends on appropriate guideline-based treatment and the strategy of frequent outpatient fluid monitoring. Beta-adrenoblocking treatment is considered a necessary first-line component in guideline-oriented treatment of systolic HF. The initiation of such therapy in the acute phase of HF patients was previously the point of debate because of its acute negative inotropic effect and frequent need for positive inotropic agent therapy. Recently, several studies have proven the safety and efficacy of alpha- and beta-adrenoblocker therapy during acute decompensation of HF.

In Kyoto Congestive Heart Failure registry significant lower in-hospital mortality was observed in 3817 patients with congestive HF receiving beta-blockers at admission relative to those not receiving beta-blockers at admission regardless of ischemic etiology and left ventricular ejection fraction (LVEF) [48]. Moreover, the risk of noncardiovascular death was lower in patients on beta-blocker treatment as well.

The lower risk of noncardiovascular death in patients taking beta-blockers was determined from death by infection. Other studies also demonstrated the association between premorbid beta-blocker exposure and lower mortality in sepsis [49].

Data from the Italian Survey on Acute Heart Failure showed beneficial effect of beta-blockers in patients admitted for worsening HF on in-hospital mortality (2.8%) in 362 patients receiving beta-blockers at admission and continuing during hospitalization compared to 10.1% in 811 patients not starting beta-blockers at admission and during hospitalization [50]. However, the beneficial effect of other than beta-blocking HF medications, including renin angiotensin-aldosterone inhibitors, diuretics and nitrates, in the treatment of these patients on hospital admission cannot be denied. The analyses of the COMET clinical trial, aiming to compare effects of two different beta blockers-nonselective cardvedilol with beta 1 selective metoprolol suggest that the difference in the mortality effects of metoprolol and carvedilol is not related to a difference in the magnitude or duration of their beta 1 blocking effects, but is conditioned by additional alpha adrenoblocking effect of carvedilol [51].

The presented data may suggest that initiation and continuation of alpha adrenoblocking agents and beta-blockers for myocardial protection in PE reduces adverse events in short-term rehospitalizations and long-term mortality. The data from the IMPACT-HF [52] study show that the rate of beta-blocker use at 60 days after discharge was 91% when initiated before discharge, in contrast to 73% when initiated postdischarge, highlighting the inertia that can follow decisions made in the patient management.

Future of PE clinical implications: the opportunities for anti-inflammatory and antiadrenergic treatment

Hemodynamic mechanisms in acute PE with only hydrostatic derived fluid flux may not explain the complex spectrum of pathophysiolog-

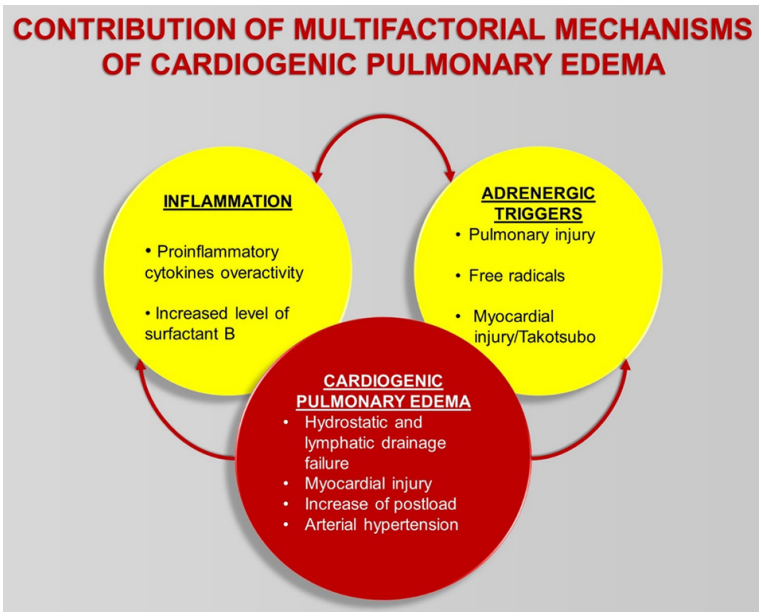

Figure 1. Illustrates the spectrum of effects of different mechanisms on development of pulmonary edema in patients with acute heart failure.

ic changes of PE in patients with acute heart failure. It is evident that clinical mismatch is present between clinical development and hemodynamic deterioration of pulmonary circulation mechanisms. Other noncardiogenic mechanisms, particularly catecholamine overactivity, lymphatic drainage, inflammatory and oxidative stress and high surfactant B protein, are involved in the progression of cardiogenic PE.

Catecholamine-induced pulmonary injury is one of the key mechanisms in acute cardiogenic PE triggering proinflammatory cytokine overactivation, oxidative stress, and myocardial injury.

Stress-induced hypersecretion of catecholamines apart from myocardial injury, similar to Takotsubo syndrome, may provoke bronchoalveolar injury, lung edema and hemorrhagic alterations followed by respiration disorders.

The prolonged mentioned pathophysiologic disorders at the level of alveolocapillary barrier after acute cardiogenic pulmonary edema may contribute to the vulnerability of these patients to recurrent pulmonary fluid accumulation (**Figure 1**). Although local and systemic inflammatory responses may alter alveolocapillary complexity, clinical trials on an anti-inflammatory therapy have proven mostly unsuccessful [53-56].

Before anti-inflammatory - focused treatment may be implemented successfully in PE, more clinical studies are needed with systematic approach, including acute inflammatory markers and surfactant B protein activity based management, more focused alpha and beta blocker therapy. For this, correct interpretation of acute phase markers in PE is important and physiologic interactions in comorbid states in acute HF may outline personalized treatment in these patients. Our ability to predict acute PE manifestations in HF patients has to be improved based on our understanding of HF pathophysiology. We assume that surfactant B protein along with C reactive protein potentially may serve as predictor markers of alveolar structural and systemic inflammatory abnormalities of PE development. Further studies are needed to increase the clinical and prognostic validity of surfactant B in everyday practice. Adequate target and up-titrated antiadrenergic treatment in HF chronic phase may prevent significantly both acute pulmonary and cardiovascular complications. To provide new research and investigations we will need coordinated collaboration between basic, translational and clinical researchers.

Taken together, these data suggest that discontinuation of adrenoblocking agents during hospitalization results in reduced pharmacotherapy at follow-up, which is likely to contribute to poorer long-term outcomes. Additional clinical studies are needed to determine alpha and beta-adrenoblocking therapy initiation, dose adjustment immediately after PE and further optimal treatment strategies.

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Disclosure of conflict of interest

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Address correspondence to: Hamayak S Sisakian, Department of Cardiology and Clinic of General and Invasive Cardiology, University Hospital #1, Yerevan State Medical University, Koryun Street 2, Yerevan 375025, Armenia. Tel: +374-10582028, +374-10541310; Fax: +374-10541350; E-mail: hamayak.sisakian@doctor.com

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