Editorial

Pulmonary Congestion in Acute Heart Failure: From Hemodynamics to Lung Injury and Barrier Dysfunction

Congestión pulmonar en la insuficiencia cardiaca aguda: de la hemodinámica a la lesión pulmonar y la disfunción de la barrera alveolocapilar

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Acute heart failure (AHF) has been defined as new-onset or worsening heart failure (HF) signs and symptoms requiring urgent therapy.[1] AHF is a leading cause of morbidity and mortality.[2] Despite the considerable variation of clinical profiles and the substantial heterogeneity of underlying causes, the vast majority of patients with AHF present with symptoms and signs of pulmonary and systemic congestion rather than low cardiac output. Accordingly, dyspnea is the cardinal presenting symptom among patients hospitalized for AHF.[3]

Although many patients respond to initial therapy,[1] a significant percentage do not experience early dyspnea relief.[1] Additionally, there is dissociation between pulmonary capillary wedge pressure (PCWP) and dyspnea severity, such that patients with a high PCWP may be minimally dyspneic, while patients with a relatively lower PCWP may experience severe dyspnea.[4] Moreover, the short-term mortality and readmission rate is up to 50%.[5] These observations highlight the incomplete understanding of pulmonary congestion pathogenesis in AHF.

PATHOPHYSIOLOGY OF PULMONARY CONGESTION

Pulmonary congestion is defined as accumulation of fluid in the lungs, resulting in impaired gas exchange and arterial hypoxemia. It occurs sequentially, first developing in the hilar region of the lungs, followed by filling of the interstitial space and finally, in its most severe form, by alveolar flooding. High left ventricular (LV) filling pressure leading to pulmonary venous hypertension (increased PCWP) is the main underlying mechanism of pulmonary congestion. Elevation of LV diastolic pressure (LVDP) results from fluid overload caused either by fluid retention or by fluid redistribution.[6] On the other hand, a rapid increase in blood pressure (afterload), particularly in patients with diastolic dysfunction, may precipitate severe pulmonary congestion.[7] Often, elevation of LVDP (hemodynamic congestion) precedes clinical congestion by days or even weeks.[8]

OLD AND NEW CONCEPTS IN THE PATHOGENESIS OF PULMONARY EDEMA

Pulmonary edema is the result of an imbalance between the forces that drive fluid into the alveoli and the mechanisms for its removal. Filtration of fluid across the pulmonary capillary wall is described by the Starling equation:[9]

$$Jv = LpS[(Pc - Pi)] - \sigma(\pi c - \pi i)]$$

where Jv is the net transcapillary filtration rate, Lp is the hydraulic conductivity of the barrier, S is the surface area of the barrier, Pc is the pulmonary capillary hydrostatic pressure, Pi is the interstitial hydrostatic pressure, πc is the capillary plasma colloid oncotic pressure, πi is the interstitial fluid oncotic pressure, and σ is the average osmotic reflection coefficient of the barrier. LpS has been defined as the capillary filtration coefficient (Kfc).

According to the Starling equation, the equilibrium between the hydrostatic pressures ($Pc - Pi$) and the oncotic pressures ($\pi c - \pi i$) constitutes the driving force for fluid filtration. Based on this simplistic model, pulmonary edema has been traditionally classified into cardiogenic and noncardiogenic categories. Cardiogenic or hydrostatic pulmonary edema results from high pulmonary capillary hydrostatic pressures which disturb Starling's equilibrium while the alveolar-capillary barrier remains intact. On the contrary, noncardiogenic or high permeability edema is characterized by injury to the alveolar-capillary barrier with leakage of protein-rich fluid into the interstitium and air spaces.[10] However, this pathophysiologic model of passive fluid movement, which depends on the oncotic and hydrostatic gradients across the blood-gas barrier, seems to be an oversimplification. Studies based on the ratio of edema fluid protein to serum protein in patients with cardiogenic and noncardiogenic pulmonary edema have shown that frequently there is a combination of high hydrostatic pulmonary capillary pressure and high permeability of the alveolar-capillary barrier, leading to a significant overlap between the two groups. If increased hydrostatic pulmonary capillary pressure per se were responsible for pulmonary edema formation, protein concentration of the alveolar lining fluid would be expected to decrease due to the influx of plasma ultrafiltrate. Paradoxically, it nearly doubles.[11,12] Therefore, hydrostatic and high permeability pulmonary edema may represent the extremes

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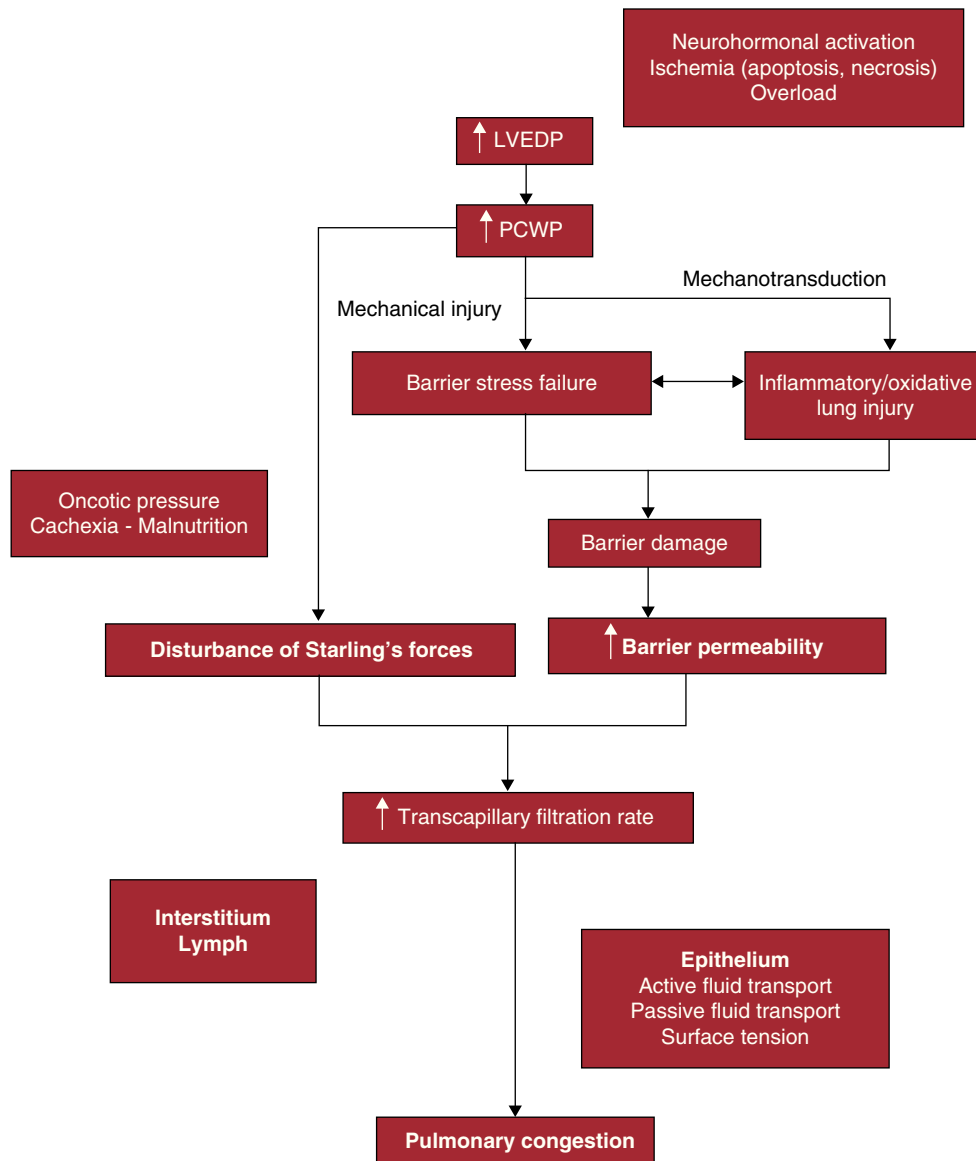*E-mail address:* geros@otenet.gr (G. Filippatos).

Figure 1. Diagram showing the involvement of mechanical injury as well as inflammatory and oxidative lung injury in alveolar-capillary barrier dysfunction and pulmonary congestion in patients with acute heart failure. LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure.

in the spectrum of pulmonary edema.[11,12] Two fundamental processes may lead to alveolar-capillary barrier dysfunction in AHF: *a)* mechanical injury of the barrier due to increased hydrostatic pulmonary capillary pressures, and *b)* inflammatory and oxidative lung injury (Fig. 1).

PHYSIOLOGICAL PROPERTIES OF THE ALVEOLAR CAPILLARY BARRIER

In its thinnest parts, the blood-gas barrier consists of the capillary endothelial layer, the alveolar epithelial layer, and the extracellular matrix, which is made up of the fused basement membranes of the two cell layers.[13,14] The blood-gas barrier of the human lung has to play 2 conflicting roles. On the one hand, it has to be extremely thin in order to promote efficient exchange of oxygen and carbon dioxide through passive diffusion. On the other hand, it needs to be strong enough to overcome the stress imposed by high capillary hydrostatic pressure. Loss of its structural

integrity can result in alveolar edema or hemorrhage. The strength of the blood-gas barrier can be attributed to the type of collagen in the basement membranes.[15]

ACUTE AND CHRONIC BLOOD-GAS BARRIER DYSFUNCTION IN HEART FAILURE

The term "stress failure" has been introduced to describe mechanical injury to the alveolar-capillary barrier resulting from an abrupt rise in the pulmonary capillary hydrostatic pressure.[16] Several experimental models have shown that pressure-induced trauma leads to ultrastructural changes of the blood-gas barrier involving disruption of the pulmonary capillary endothelial layer as well as the alveolar epithelial layer.[16] The result is a progressive transition from a low permeability form to a high permeability form of pulmonary edema.[17] There is experimental evidence to suggest the reversibility of ultrastructural changes of the blood-gas barrier observed during acute mechanical injury.[18] On the other

hand, sustained elevation of pulmonary capillary pressure leads to thickening of the alveolar-capillary barrier due mainly to excessive deposition of collagen type IV.[15] This remodeling process may be protective against further high pressure damage and may increase resistance of the lung to the development of pulmonary edema in chronic HF patients.[11] However, it causes a significant decrease in alveolar diffusion capacity and impairs gas transfer and exercise capacity. Lung epithelium–specific proteins can leak across the alveolar-capillary barrier into the circulation and may serve as markers of barrier damage in several pathological conditions.[19] Surfactant protein-B (SP-B) is the smallest of the surfactant-specific proteins detectable in the circulation. SP-B plays a pivotal role in the formation and stabilization of pulmonary surfactant and is synthesized exclusively by type II alveolar epithelial cells from which it is secreted through their apical surface into the alveoli, such that, under normal conditions, an epithelial lining fluid: plasma gradient of >1500:1 is maintained.[20] However, in case of barrier damage, increased amounts leak into the bloodstream. Thus, circulating SP-B levels increase acutely in response to exercise-induced LV dysfunction, probably due to barrier dysfunction resulting from an acute increase in pulmonary capillary hydrostatic pressures.[21] Moreover, a prolonged circulating SP-B increase has been reported after acute cardiogenic pulmonary edema, suggesting ongoing barrier damage in these patients.[22] Finally, circulating plasma SP-B levels are related to alveolar gas diffusion, overall exercise performance, and efficiency of ventilation, which demonstrates a link between anatomic and functional alveolar-capillary barrier damage in HF patients.[23]

The Role of Inflammatory and Oxidative Lung Injury in the Setting of Acute Heart Failure

Severe inflammatory insult to the pulmonary capillary endothelium and the alveolar epithelium, leading to barrier dysfunction and high permeability pulmonary edema formation, plays a pivotal role in the pathophysiology of acute lung injury and its most severe manifestation, acute respiratory distress syndrome (ARDS). However, there is increasing evidence to suggest that hydrostatic lung injury in the setting of AHF is related to lung inflammation.[24] Pulmonary edema fluid in AHF has increased concentrations of neutrophils,[25] proinflammatory cytokines,[26] and biomarkers of oxidative stress. Furthermore, prolonged blood-gas barrier dysfunction after acute cardiogenic pulmonary edema may be related to pulmonary parenchymal inflammation.[22]

Lung inflammation may be part of the repair mechanism after pulmonary hydrostatic injury. As already noted, "stress failure" of the blood-gas barrier may lead to a progressive transition from a low permeability form to a high permeability form of pulmonary edema. Macrophage-driven alveolar clearing of precipitated protein during pulmonary edema resolution may incite inflammatory activity, including tumor necrosis factor α release.[27,28]

On the other hand, lung inflammation in the setting of AHF may be a direct response to mechanical stress of the pulmonary microcirculation. Pulmonary endothelium can transduce the mechanical signal into a biological response by inducing several intracellular signaling pathways, which may result in increased inflammatory cytokine production, macrophage activation, acute inflammation, and barrier dysfunction.[29] Among various signaling pathways induced by mechanical stress of the pulmonary microcirculation, a role of reactive oxygen species receives increasing attention. Oxidative stress plays an important role in blood-gas barrier compromise, either by direct oxidative damage to basic cellular components of the barrier or through the activation of redox-sensitive signaling pathways leading to apoptosis and inflammation.[29]

Inflammatory and oxidative lung injury may play a significant pathophysiological role in HF decompensation by further damaging the alveolar-capillary barrier and increasing its permeability. As a consequence, the pulmonary capillary hydrostatic pressure threshold for pulmonary fluid accumulation decreases. This parameter could account for the vulnerability of AHF patients to recurrences.

ASSESSING LUNG INJURY IN ACUTE HEART FAILURE

Investigation of the epithelial lining fluid may give useful information about the alveolar-capillary barrier damage in patients with HF, particularly with regard to important pathophysiologic processes such as inflammation and redox disturbance. So far, access to this fluid has been based on bronchoalveolar lavage, which is an invasive technique requiring bronchoscopy and may influence the levels of airway inflammation. Consequently, there is limited information from a small number of patients with cardiogenic pulmonary edema requiring mechanical ventilation.[26,30] Recently, there has been increasing interest in lower respiratory tract sampling by noninvasive means including sputum induction, measurement of exhaled nitric oxide and collection and analysis of exhaled breath condensate (EBC).

EBC has emerged as a potential tool in the study of the alveolar epithelial lining fluid. It consists primarily of water with trapped aerosolized droplets from the airway lining fluid, as well as water-soluble volatile and nonvolatile compounds.[31] Its principal component is condensed water vapor, which represents nearly all of the volume (>99%) of fluid collected in EBC.[32] Collection of EBC is simple, completely noninvasive, safe, and reproducible. It is accomplished by exhaling tidally into a cooled condensing apparatus. A wide range of biomarkers have been investigated in EBC, including pH, cytokines, isoprostanes, leukotrienes, nitrogen oxides, peptides, adenosine, arachidonic acid metabolites, ammonia, hydrogen peroxide, and DNA.[33] Consequently, EBC has been increasingly used as a research and clinical tool in the study of airway inflammation, oxidative stress, and acid-base balance in many lung diseases, including asthma, chronic obstructive pulmonary disease, ARDS, cystic fibrosis, bronchiectasis, and lung cancer.[34] With the aim of providing new insights into the role of lung injury and blood-gas barrier dysfunction in AFH we have demonstrated that during episodes of HF decompensation EBC shows an increase in EBC markers of inflammatory activity and oxidative stress (unpublished data).

In conclusion, pulmonary congestion in AHF is a complex pathophysiologic process, beyond fluid overload and hemodynamics. Inflammatory and oxidative lung injury leading to blood-gas barrier dysfunction seems to play a pivotal role in the pathogenesis of pulmonary edema and may be a novel therapeutic target. Further research is needed to clarify whether preventing barrier injury instead of merely controlling hydrostatic pulmonary capillary pressures will improve the treatment and prognosis of AHF.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, et al. Acute heart failure syndromes: current state and framework for future research. Circulation. 2005;112:3958–68.

2. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, et al. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2010;12:1076–84.

3. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J. 2010;31:832–41.

4. Gheorghiade M, Filippatos G, De Luca L, Burnett J. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. Am J Med. 2006;119:S3–10.

5. Alla F, Zannad F, Filippatos G. Epidemiology of acute heart failure syndromes. Heart Fail Rev. 2007;12:91–5.

6. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure —re-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail. 2008;10:165–9.

7. Nieminen MS, Böhm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al; Grupo de Trabajo sobre la Insuficiencia Cardíaca Aguda de la Sociedad Europea de Cardiología; la Sociedad Europea de Medicina Intensiva (ESICM). Guías de Práctica Clínica sobre el diagnóstico y tratamiento de la insuficiencia cardíaca aguda. Versión resumida. Rev Esp Cardiol. 2005;58:389–429.

8. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al; European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12:423–33.

9. Starling EH. On the absorption of fluids from the connective tissue spaces. J Physiol. 1896;19:312–26.

10. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149:818–24.

11. Sprung CL, Rackow EC, Fein IA, Jacob AI, Isikoff SK. The spectrum of pulmonary edema: differentiation of cardiogenic, intermediate, and noncardiogenic forms of pulmonary edema. Am Rev Respir Dis. 1981;124:718–22.

12. Fein A, Grossman RF, Jones JG, Overland E, Pitts L, Murray JF, et al. The value of edema fluid protein measurement in patients with pulmonary edema. Am J Med. 1979;67:32–8.

13. Low FN. Electron microscopy of the rat lung. Anat Rec. 1952;113:437–49.

14. Filippatos G, Hughes WF, Qiao R, Sznajder JI, Uhal BD. Mechanisms of liquid flux across pulmonary alveolar epithelial cell monolayers. In Vitro Cell Dev Biol Anim. 1997;33:195–200.

15. West JB, Mathieu-Costello O. Strength of the pulmonary blood-gas barrier. Respir Physiol. 1992;88:141–8.

16. West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. J Appl Physiol. 1991;70:1731–42.

17. Tsukimoto K, Yoshimura N, Ichioka M, Tojo N, Miyazato I, Marumo F, et al. Protein, cell, and LTB4 concentrations of lung edema fluid produced by high capillary pressures in rabbit. J Appl Physiol. 1994;76:321–7.

18. Elliott AR, Fu Z, Tsukimoto K, Prediletto R, Mathieu-Costello O, West JB. Short-term reversibility of ultrastructural changes in pulmonary capillaries caused by stress failure. J Appl Physiol. 1992;73:1150–8.

19. Hermans C, Bernard A. Lung epithelium-specific proteins: characteristics and potential applications as markers. Am J Respir Crit Care Med. 1999;159:646–78.

20. Doyle IR, Nicholas TE, Bersten AD. Partitioning lung and plasma proteins: circulating surfactant proteins as biomarkers of alveolocapillary permeability. Clin Exp Pharmacol Physiol. 1999;26:185–97.

21. De Pasquale CG, Arnolda LF, Doyle IR, Aylward PE, Russell AE, Bersten AD. Circulating surfactant protein-B levels increase acutely in response to exercise-induced left ventricular dysfunction. Clin Exp Pharmacol Physiol. 2005;32:622–7.

22. De Pasquale CG, Arnolda LF, Doyle IR, Grant RL, Aylward PE, Bersten AD. Prolonged alveolocapillary barrier damage after acute cardiogenic pulmonary edema. Crit Care Med. 2003;31:1060–7.

23. Magrì D, Brioschi M, Banfi C, Schmid JP, Palermo P, Contini M, et al. Circulating plasma surfactant protein type B as biological marker of alveolar-capillary barrier damage in chronic heart failure. Circ Heart Fail. 2009;2:175–80.

24. Haupt MT. Cardiogenic pulmonary edema: an inflammatory disorder? Crit Care Med. 2003;31:1282–3.

25. Nakos G, Pneumatikos J, Tsangaris I, Tellis C, Lekka M. Proteins and phospholipids in BAL from patients with hydrostatic pulmonary edema. Am J Respir Crit Care Med. 1997;155:945–51.

26. Cohen AB, Stevens MD, Miller EJ, Atkinson MA, Mullenbach G, Maunder RJ, et al. Neutrophil-activating peptide-2 in patients with pulmonary edema from congestive heart failure or ARDS. Am J Physiol. 1993;264:490–5.

27. Parissis JT, Venetsanou KF, Mentzikof DG, Ziras NG, Kefalas CG, Karas SM. Tumor necrosis factor-alpha serum activity during treatment of acute decompensation of cachectic and non-cachectic patients with advanced congestive heart failure. Scand Cardiovasc J. 1999;33:344–50.

28. Filippatos G, Leche C, Sunga R, Tsoukas A, Anthopoulos P, Joshi I, et al. Expression of FAS adjacent to fibrotic foci in the failing human heart is not associated with increased apoptosis. Am J Physiol. 1999;277(2 Pt 2):H445–51.

29. Birukov KG. Cyclic stretch, reactive oxygen species, and vascular remodeling. Antioxid Redox Signal. 2009;11:1651–67.

30. Schütte H, Lohmeyer J, Rosseau S, Ziegler S, Siebert C, Kielisch H, et al. Bronchoalveolar and systemic cytokine profiles in patients with ARDS, severe pneumonia and cardiogenic pulmonary oedema. Eur Respir J. 1996;9:1858–67.

31. Hunt J. Exhaled breath condensate: an evolving tool for noninvasive evaluation of lung disease. J Allergy Clin Immunol. 2002;110:28–34.

32. Effros RM, Hoagland KW, Bosbous M, Castillo D, Foss B, Dunning M, et al. Dilution of respiratory solutes in exhaled condensates. Am J Respir Crit Care Med. 2002;165:663–9.

33. Horváth I, Hunt J, Barnes PJ, Alving K, Antczak A, Baraldi E, et al; ATS/ERS Task Force on Exhaled Breath Condensate. Exhaled breath condensate: methodological recommendations and unresolved questions. Eur Respir J. 2005;26:523–48.

34. Mutlu GM, Garey KW, Robbins RA, Danziger LH, Rubinstein I. Collection and analysis of exhaled breath condensate in humans. Am J Respir Crit Care Med. 2001;164:731–7.