

Biomarkers of lung congestion and injury in acute heart failure

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Abstract

Acute heart failure (AHF) classification and management are primarily based on lung congestion and/or hypoperfusion. The quantification of the vascular and tissue lung damage is not standard practice though biomarkers of lung injury may play a relevant role in this context. Haemodynamic stress promotes alveolar and vascular derangement with loss of functional units, impaired lung capillary permeability and fluid swelling. This culminates in a remodelling process with activation of inflammatory and cytokines pathways. Four families of lung surfactant proteins (i.e., SP-A, SP-B, SP-C, and SP-D), essential for the membrane biology and integrity are released by alveolar type II pneumocytes. With deregulation of fluid handling and gas exchange pathways, SPs become sensitive markers of lung injury. We report the pathobiology of lung damage; the pathophysiological and clinical implications of alveolar SPs along with the newest evidence for some classical HF biomarkers that have also shown to reflect a vascular and/or a tissue lung-related activity.

Keywords Acute heart failure; Alveolar-capillary unit; Lung biomarkers

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Introduction

Heart failure (HF) negatively impacts on the physiology of multiple organ systems.¹ Given the complexity of this disease, the advantages of using circulating biomarkers reflecting organ damage specific pathways have become established over years.² This is especially true for acute heart failure (AHF), a condition in which the multiple organ involvement represents the opportunity for a better phenotyping, implementing therapeutic strategies and risk prediction.³ HF guidelines propose four AHF classifications based on congestion and/or hypoperfusion signs including (1) acute decompensated heart failure (ADHF); (2) acute pulmonary oedema; (3) isolated right ventricular failure; and (4) cardiogenic shock.³ The most common AHF presentations are ADHF and acute pulmonary oedema,^{3,4} which share lung fluid retention.

Dyspnoea is the most typical symptom of AHF, pointing to the lung as main target of congestion.¹ The lungs and the heart are mutually involved in impairing each other's functionality, and during the last two decades, remarkable information has been gained on how hydrostatic mechanical injury impairs the lungs in AHF yielding to endothelial and alveolar cells derangement.^{1,5,6}

However, beyond the quantification of pulmonary fluid retention by the B-lines analyses,⁷ the precise assessment of underlying acute lung injury and alveolar-capillary membrane dysfunction is not standard practice.

Natriuretic peptides such as NT-proBNP, BNP, and MR-proANP are blood biomarkers routinely used in AHF for clinical decision making³ with a well known dependency on wall stress, but their link to lung injury is not documented. Thus, the study of lung specific biomarkers is relevant to better understand the sequelae of alveolar capillary membrane stress

failure (ACMSF) and fluid handling disruption in AHF. Although biomarkers are associated with imaging findings, physiological, functional tests, tissue biopsies, and genetic variants, this review will primarily focus on the intrinsic role of circulating biomarkers of lung organ damage aiming at clarifying which biomarker may be sensitive and specific to play a role in pulmonary phenotyping and clinical practice.

What an 'ideal' biomarker for lung injury in acute heart failure should be?

The term biomarker was introduced in 1989 and standardized in 2001 by National Institute of Health (NIH) Working Group.⁸ The NIH definition is 'a biological marker that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to therapeutic interventions'.⁹

Accordingly, an ideal biomarker in HF should be reflective of a main pathophysiological pathway, providing information unavailable through the physical exam and laboratory investigation; it should also provide diagnostic insights and management directions.³ The clinical use should be supported by specific criteria such as (1) methodological accuracy; (2) easy availability of the assay that should offer a reliable interpretation at a reasonable cost; and (3) quick analytic process with recognition of the methodological limitations. The multiple pathways involved in the pulmonary congestion process represent unique opportunities to find the most suitable biomarker out with a sensitivity high enough to reflect the acute and chronic maladaptation of the alveolar capillary unit to fluid retention and inflammation. Thus, the pulmonary biomarker approach should help to implement knowledge on those pathways that modulate fluid handling and reparation under pressure injury¹⁰ extending the practical implications.

Pathophysiology of lung injury and alveolar function in acute heart failure

In AHF, left atrial pressure elevation challenges the integrity and biological properties of the pulmonary microcirculation and generates an imbalance in the capillary Starling forces. This generates fluid transudation and different degrees of congestion within the lungs, that is, interstitial and/or alveolar. Hydrostatic forces, such as cyclic stretch, which acts on all cells in the vascular wall and shear stress, which acts on the cells that line the lumen, expose the alveolar-capillary membrane unit to a circumferential tension,¹¹ well described in animal and human conditions¹¹ under the wide term of ACMSF.^{5,11}

ACMSF is characterized by small vessels and lung architecture derangement and deregulation of cellular pathways

involved in fluid permeability, reabsorption control, and gas exchange.¹²

The ultrastructural characteristics of the blood-gas barrier are typical with the alveolar epithelium layer less permeable than the capillary endothelium, which is formed by two types of pneumocytes: type I and type II cells. Type I cells form the main alveolar structure in the 90% of the total surface, while type II cell's primary functions are nourishment and surfactant production. In the presence of abnormal biomechanical forces, pulmonary capillaries and alveolar epithelium compensate for increased fluid transudation through enhancement of ion transport and removal H₂O.

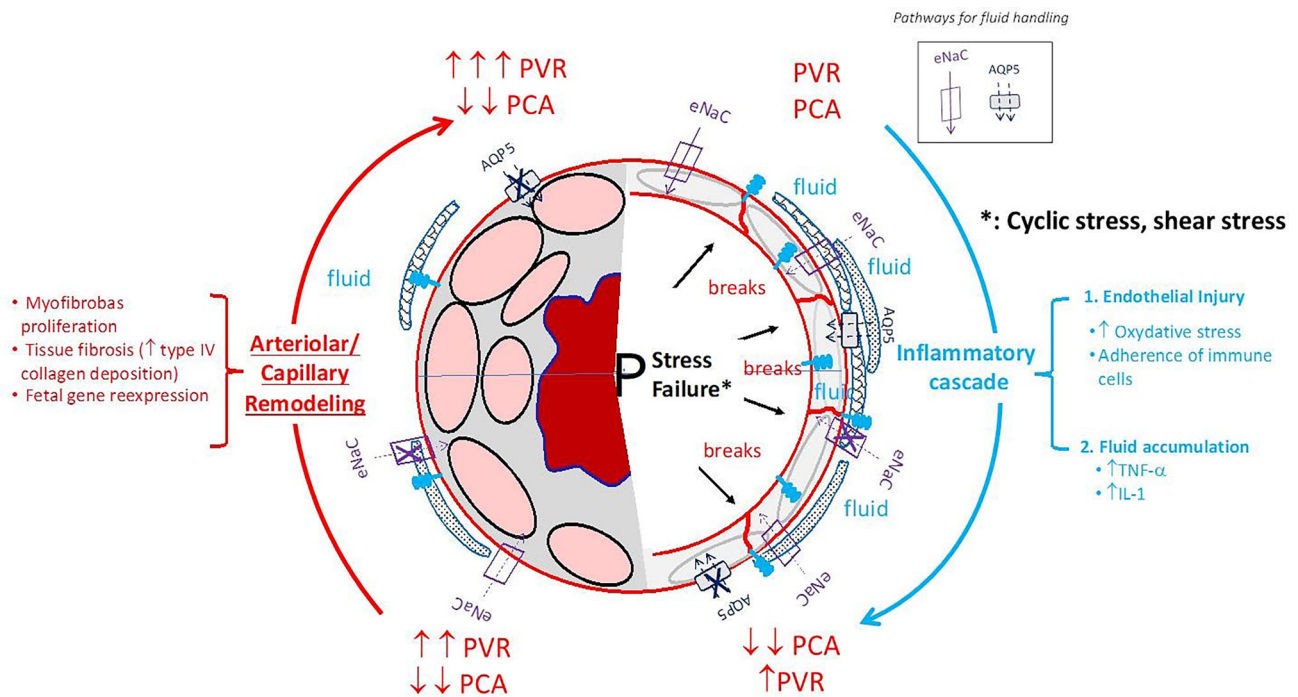
The alveolar clearance occurs through two types of channels: (1) the differentiated ENaC channel and (2) the non-selective cation channel, both on the apical surface of type II cells. H₂O reabsorption passively follows the osmotic gradient of active Na⁺ transport across the alveolar epithelium. Aquaporins (AQPs), such as AQP5, may be found on the apical surface of alveolar type I cells and contribute to some H₂O removal from the alveoli.^{10,12} The complex interaction between dynamic stress forces, that is, cyclic and shear stress, fluid handling, and reparation processes remains largely unexplored, but once the net final result yields to oedema development, it sets off a cascade of proinflammatory response.⁵

This, in turn, promotes metalloproteinase activation and degradation of matrix proteoglycans, both of which have the potential to contribute to the progression of pulmonary tissue damage, microvascular deregulation, enhancing the likelihood of pulmonary oedema.¹ While a single burst of pressure elevation creates breaks in the alveolar-capillary unit that are reversible,¹³ repetitive episodes trigger a remodelling process characterized by endothelial dysfunction, myofibroblasts proliferation, fibrosis, thickening of the extracellular matrix and re-expression of fetal genes, overall impairing alveolar gas exchange diffusing properties and pulmonary haemodynamics.^{5,12} Remodelling does not appear to be reversible, as documented by the persistence of impaired alveolar gas diffusion for years after heart transplantation.¹⁴ Implications are that a tight monitoring of the alveolar-vascular injury/remodelling processes should be maintained high even after a first acute episode of congestion, with the lung to be considered a noteworthy early therapeutic target (*Figure 1*).^{1,15,16}

Pulmonary circulating biomarkers

The role of circulating biomarkers of lung oedema and injury in HF have been only partially investigated, but information are consistent and appear promising for clinical decision-making. The pulmonary surfactant proteins (SPs), in their four different forms (i.e., A, B, C, and D),¹⁷ represent solid biological references for investigating the ACMSF (*Figure 2*).

Figure 1 Schematic representation of the alveolar-capillary membrane stress failure cascade showing mechanisms alveolar fluid clearance through the differentiated ENaC channels and AQP5. Occurrence of mechanical injury (breaks) and fluid swelling in the interstitial space due to dynamic forces (shear and cyclic stresses) triggers the inflammatory cascade by endothelial dysfunction and fluid accumulation. Overall, the complex interaction of these molecular processes yields myfibroblasts proliferation, fibrosis, and re-expressions of fetal genes altering the anatomical architecture and functional correlates of lung microvessels.



Recent isolated reports point to evidence that type II alveolar cells are also important source of the soluble form of suppression of tumorigenicity-2 (sST2), a biomarker of inflammation and fibrosis.¹⁸ On the endothelial side, adrenomedullin (ADM), especially its biologically active form, is a marker of congestion useful to evaluate the amount of pulmonary oedema and the consequent lung injury.¹⁹ Furthermore, other circulating biomarkers such as galectin-3 (GAL-3), growth differentiation factor-15 (GDF-15), and urocortin-2 (Ucn-2) seem to be potential additional biological mediators of lung congestion, although additional studies are needed.

Surfactant proteins

SPs are a superfamily of four high molecular-weight hydrophilic molecules (SPA-A, SP-B, SP-C, and SP-D) with immunological functions such as lungs protection from infections induced by inhaled particles and micro-organisms. The primary alveolar surfactant activity, that is, prevention of small alveoli collapse and overexpansion of larger ones, translates at the whole-organ level in (1) beneficial modulation of pulmonary compliance; (2) prevention of atelectasis; and (3) recruitment of collapsed airways.

SP-B and SP-C are low-molecular weight hydrophobic proteins with biophysical functions essential to the alveolar epithelial membrane integrity.²⁰

The SP-B gene is located on chromosome 2 and encodes for a 2 kb long RNA that in turn gives rise to an immature form, pre-pro-SP-B (40kDa), which in the endoplasmic reticulum undergoes N-glycosylation and signal peptide cleavage processes resulting to another precursor, pro-SP-B (42 kDa). Post-transcriptional processes between the Golgi apparatus and multivesicular bodies lead to mature SP-B form (8 kDa), normally present in homodimeric form and stored in lamellar bodies until it is secreted.²¹

AHF is characterized by loss of lung capillary permeability, with profound compromise of surfactant activity. In this condition, circulating levels correlate with lung injury.²²

SP-B appears the most promising in this context with the largest evidence gained for chronic HF (CHF). High circulating levels of SP-B in stable CHF are strong predictors of adverse outcome.²³ Table 1 reports the studies addressing the role of SPs in HF.^{22–26}

In a study by Pascual-Figal et al.,²⁶ circulating SP-B correlated with exercise ventilatory inefficiency as demonstrated by a steep minute ventilation to carbon dioxide production (VE/VCO₂) slope. Similar findings on exercise VE have been found in association with impaired gas diffusion for carbon monoxide (DLco) enhancing the association between impaired gas exchange in HF and circulating SP-B levels.²² In another landmark study by the same group performed in a

Figure 2 Biomarkers of lung injury with the main source of their production (left hand) and representative scheme of alveolar-capillary functional unit biomarkers and anatomical consequences of increased hydrostatic pressure (right hand).

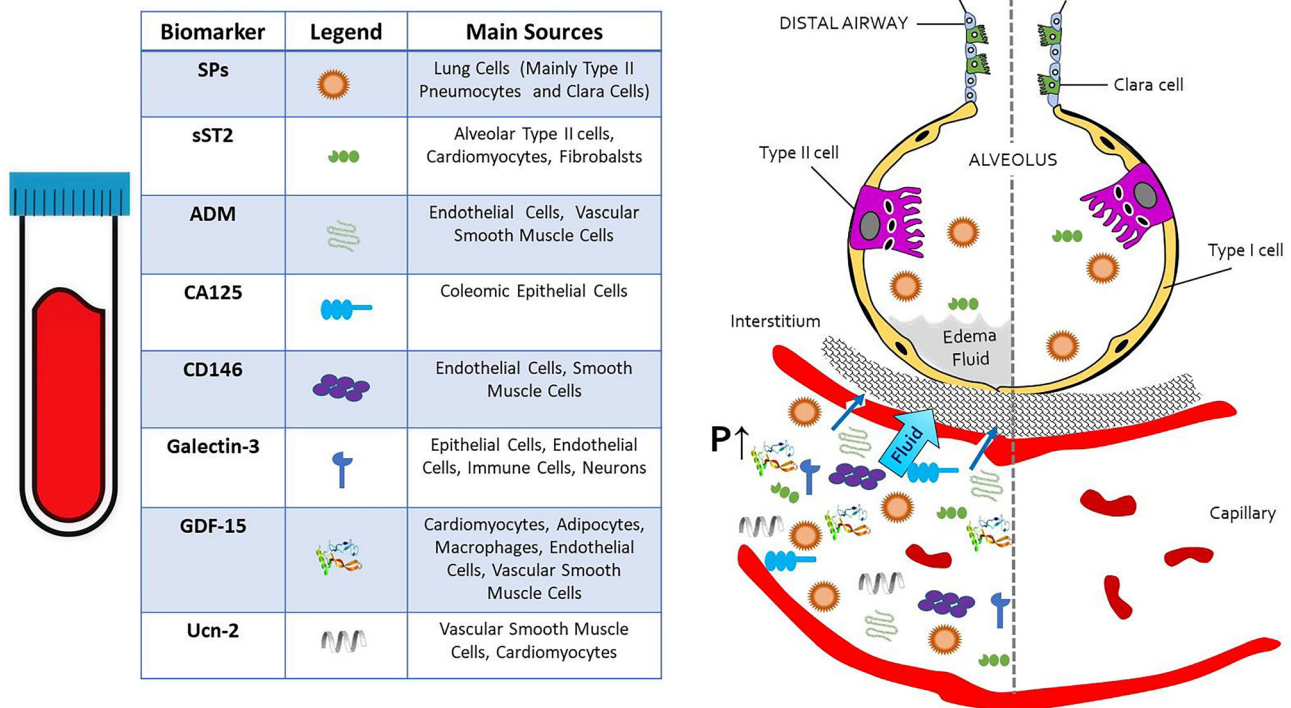
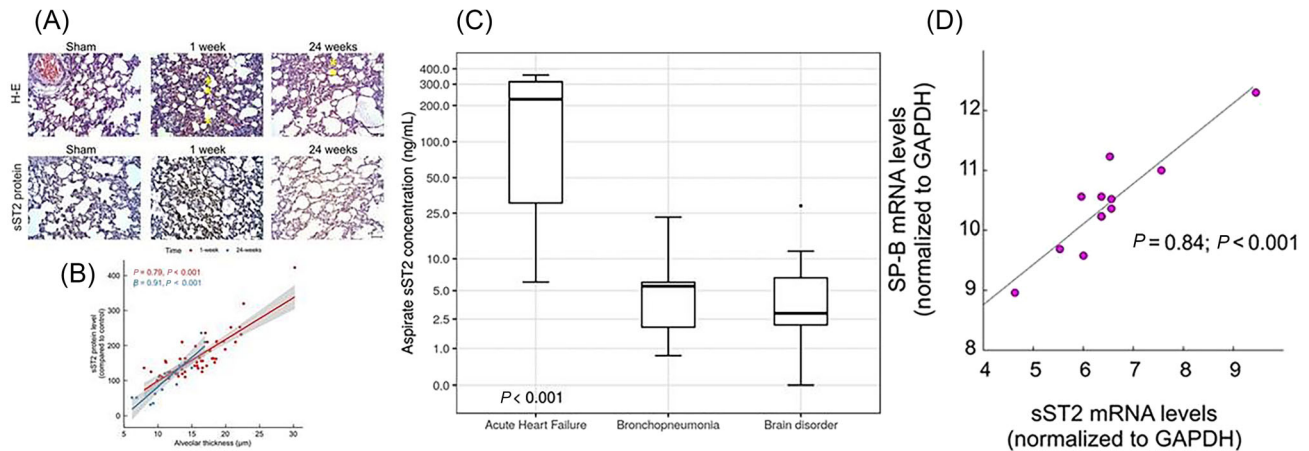


Table 1 Summary of studies addressing the role of SP-B in both CHF and AHF

Author	Year	Sample size (n)	Control group (n)	Study design and main findings
Gargiulo et al. ²²	2014	89	17	<ul style="list-style-type: none"> 89 CHF patients investigated to identify the most reliable marker of alveolar capillary function, assessed by DLco. Immature circulating SP-B form related to DLco, peak VO_2, VE/VCO_2 slope, and BNP.
Magri et al. ²³	2015	151	37	<ul style="list-style-type: none"> 151 CHF patients evaluated to establish the prognostic role of circulating SP-B. Immature SP-B predictive of HF hospitalization. Immature SP-B independently associated to DLco, peak VO_2, and VE/VCO_2 slope.
De Pasquale et al. ²⁴	2003	28	13	<ul style="list-style-type: none"> SP-B levels and other biomarkers tested in 28 patients with acute cardiogenic pulmonary oedema and 13 age-matched normal volunteers. SP-B levels abnormally elevated at day 0 compared with healthy subjects ($P = 0.01$), maximum peak on day 3 ($P < 0.008$) and drop below the day 0 at day 14 ($P = 0.001$).
De Pasquale et al. ²⁵	2004	53	19	<ul style="list-style-type: none"> 53 CHF patients prospectively assessed over an 18-month period. Plasma SP-B was found to be higher in CHF patients ($P < 0.001$), with NYHA class and NT-pro-BNP range correlations ($P < 0.001$). High levels of circulating SP-B associated with CHF hospitalization ($P < 0.001$). Increasing diuretic dose led to a 12% decrease in SP-B levels at follow-up ($P < 0.001$).
Pascual-Figal et al. ²⁶	2009	43	26	<ul style="list-style-type: none"> SP-B assessed at rest and during the first minute of exercise in 43 CHF patients performing a cardiopulmonary exercise test. High SP-B linked to a lower LVEF ($P = 0.01$). VE/VCO_2 slope emerged as best multivariate correlate ($\beta = 1.45$; $P = 0.02$). Peak-exercise SP-B level highly correlated with the resting level ($r = 0.980$; $P < 0.001$), but there are no observed significant increase with exercise ($P = 0.164$).

Figure 3 Histology showing changes after 1 week and 24 weeks of post AHF (A) and positive correlation reported between alveolar wall thickness and sST2 protein levels in a murine model of AHF (B). In human findings of exaggerated sST2 concentration in the bronchial aspirate of AHF patients compared with pneumonia and brain disorder (C) and positive correlation between SP-B and sST2 mRNA levels during ACSF condition (D).¹⁸



combined experimental (rat model) and human setting a clear correlation was observed between ST2 pattern level and alveolar wall thickness (Figure 3A,B). In humans, the elevated sST2 concentration was much higher in AHF than representative cases of pneumonia and brain disorders (Figure 3C). Interestingly, the sST2 mRNA levels tightly correlated with SP-B mRNA levels (Figure 3D).¹⁸

In AHF patients, De Pasquale et al.²⁴ monitored the changes in SP-A and SP-B for 17 days after acute pulmonary oedema. SP-A and SP-B were elevated on day 0 compared with controls (367 ± 17 ng/mL vs. 303 ± 17 and 3821 ± 266 ng/mL vs. 2747 ± 157 for AHF vs Controls, $P < 0.05$), and although clinical, haemodynamic, and radiographic variables of lung congestion improved rapidly ($P < 0.001$), SP-A and SP-B rose further until day 3 supporting the hypothesis that lung injury consequences need attention well over the short term. SP-A and SP-B elevations were paralleled by elevated TNF- α plasma levels, reflecting pulmonary inflammation. These data fit well with previous findings obtained in acute setting of acute pulmonary oedema compared with ARDS syndrome.²⁷ Overall, it should be acknowledged also that SPs sensitivity is high for infective and inflammatory conditions of primary pulmonary origin such as pneumonia, ARDS, and COPD.²⁸

The kinetics of plasma SPs during decongestion and other steps of the HF clinical course remain unknown. Figure 4 illustrates a few representative cases of SP-B changes, sampled at hospital admission for AHF and discharge compared with controls.

sST-2

Suppression of Tumorigenicity-2 sST-2 is a member of the interleukin 1 (IL-1) receptor family that is present in two main

isoforms: transmembrane (ST2L) and soluble (sST2). ST2L is a plasma membrane receptor for which IL-33 is the functional ligand. IL33 through binding to ST2L exerts cardioprotective effects by acting on myocardial hypertrophy and fibrosis and cardiomyocyte apoptosis. Binding between sST2 and IL33, on the other hand, subtracts IL33 molecules from binding to ST2L and inhibits the positive effects by playing a negative role in cardiac remodelling.²⁶

ST2L is constitutively expressed primarily in haematopoietic cells (Th2 and mast cells) and cardiomyocytes, whereas sST2 is mainly released in response to vascular congestion, inflammatory, and profibrotic stimuli.²⁹

Interestingly, sST2 also plays an important role in pulmonary diseases involving fibrosis and inflammation.²⁹ A recent landmark study has identified type II alveolar cells as a major source of sST2 expression and synthesis in HF.¹⁸

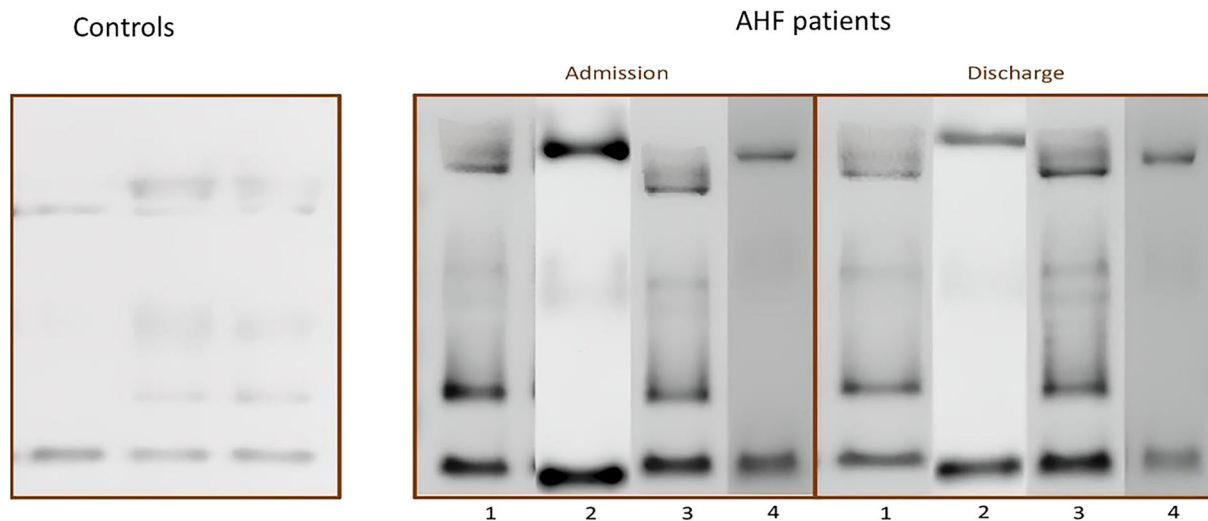
In the PRIDE study, sST2 concentrations strongly predicted mortality at 1 year in dyspnoeic patients with or without AHF.³⁰ These findings point on a thorough biomarker assessment for risk stratification irrespective of NT-proBNP.³⁰

Overall, the available evidence shows how sST2 may have a key role in assessing the patient's clinical trajectory, with evidence for a role in the acute pulmonary oedema events and outcome.³¹

Adrenomedullin

ADM is a peptide hormone synthesized by endothelial and vascular smooth muscle cells. Thanks to its small size (6 kDa), ADM diffuses freely between blood and interstitium. The receptors and binding sites for ADM are ubiquitous, but the cardiac and lung tissues exhibit a higher concentration.³² The two most important biological functions of ADM are

Figure 4 Representative western blot analysis of SP-B distribution in healthy control and four cases of AHF with analysis at ED admission and discharge (personal data).



vasodilation and the preservation of endothelial barrier function in order to maintain vascular integrity and decrease vascular leakage.³² Interestingly, a disorder of the ADM system results in vascular leakage and systemic and pulmonary oedema.^{32,33} Indeed, ADM excretion can be induced by a variety of mechanical and humoral stimuli reflecting the amount of tissue congestion and pulmonary oedema.³³

In the last decade, a sandwich immunoassay that measures plasma biologically active (bio-) ADM has been developed³⁴ and its measurements with implications on prognostic refinements in AHF. Indeed, bio-ADM has been identified as a reliable marker of AHF severity and congestion in several studies.¹⁹ Pandhi *et al.*³⁵ showed how elevated levels of bio-ADM at discharge reflected residual congestion which perpetuates the mechanical injury towards the blood-gas barrier. However, further studies are required to explore the correlation between this hormone and DLco.

In order to exploit ADM biological activity, a humanized, monoclonal, non-neutralizing antibody against adrenomedullin named Adrecizumab has been developed with an ongoing trial named ADESTE (Trial Gov. NCT04252937), involving AHF patients, will provide insights on the drug's effectiveness on oedema resolution.

Endothelial soluble cluster of differentiation 146 (CD146)

In recent years, CD146 is emerging as a biomarker of endothelial damage and systemic congestion. CD146 is expressed in the junctions of endothelial cells and is also involved in some signalling pathways of angiogenesis and in the tissue architecture preservation.³⁶

There is documentation that plasma CD146 levels can reflect the extent of pulmonary edema.³⁷ CD146 seems to have a favourable discriminatory power on the origin of

dyspnea (cardiac or not), especially if added to the panel when the NT-proBNP is close to the pathological cut-off value.³⁸ In animal models of cardiac pressure overload, the increase in lung weight is proportional to the expression of CD146.³⁸

Mucin-16 (MUC16)

The antigen carbohydrate 125 (CA125), also called MUC16, is a complex high molecular weight glycoprotein synthesized by coelomic epithelial cells at various sites, including the pericardium, pleura, or peritoneum.³⁹ Although used to monitor ovarian cancer, emerging data of the last 15 years point to its clinical utility in AHF syndromes.^{40,41}

The mechanisms leading to CA125 upregulation in AHF is a combination of increased venous pressure and inflammatory stimuli, which are interrelated phenomena, promoting and enhancing the synthesis of CA125 by pleural mesothelial cells.⁴⁰ High levels of CA125 (>35 U/mL) are observed in almost two-thirds of AHF patients,^{40,41} and its levels are positively associated with surrogates of tissue congestion.³⁹

In patients with advanced HF and AHF, some authors have reported a positive association between CA125 and invasive and non-invasive measures of PCWP.³⁹ In a study of 2949 patients admitted with AHF, the presence of pleural effusion was the main determinant accounting for the 36.8% variability of circulating CA125.⁴¹

It seems important to point it out that the interpretation of CA125 requires a comprehensive evaluation in a proper clinical context.⁴⁰ In AHF syndromes, CA125 works as a surrogate of tissue/third space fluid overload, including pulmonary and systemic congestion.

Other markers of potential interest

Other biomarkers may be of additional value in addressing the ACMSF due to their involvement in their inflammatory cascade. We summarize some of the potentiality of these biomarkers.

Galectin-3

Galectin-3 is a carbohydrate-binding protein, whose expression depends on the tissue type. Sustained Galectin-3 expression levels could result in organ fibrosis and inflammation.⁴² In the context of AHF and pulmonary congestion, increased Galectin-3 levels correlated with elevated pulmonary artery pressures, severe systolic dysfunction and impaired ventricular-arterial coupling.⁴³ The prognostic value of Galectin-3 in AHF and lung damage probably rely on its combination with other biomarkers such as sST2. Indeed, a study by Wang et al.⁴⁴ analysing both biomarkers documented a synergy of the biomarkers to identify patients evolving to worsening HF.

Growth differentiation factor-15 (GDF-15)

GDF-15 is a stress-sensitive cytokine and an increment in its levels can reflect a variety of disorders.⁴⁵ GDF-15 levels are elevated and associated with a greater likelihood of 60-day HF/renal failure rehospitalizations/CV death and CV death at 180 days.⁴⁶ As proof of GDF-15 potential involvement in lung damage and fibrosis, Nickel et al.⁴⁷ demonstrated a key role and showed that in PAH patients, the prognostic information on cardiac death and heart transplantation were additive to haemodynamic and NT-proBNP data.

Urocortin-2

Ucn-2 is a vasoactive peptide capable of binding the type 2 CHR receptor and producing effects on vascular and cardiac functionality (i.e., vasorelaxant and inotropic effects).⁴⁸ A recent study including 80 AHF patients firstly demonstrated an association of serum Ucn-2 levels with clinical and echocardiographic markers of volume overload and pulmonary hypertension.⁴⁹ These findings suggest the need to identify relevant novel urocortin-related pathological pathway.

Omics

Omics technologies can help to detect new pathways of disease in HF, to improve HF phenotyping, discovering biomarkers for HF diagnosis and outcome and new therapeutic targets. Especially, transcriptomic studies have identified specific patterns of RNA transcription that are associated with different HF phenotypes.⁵⁰ Non-coding RNA (ncRNA), such as microRNA (miRNA), may help to understand those disease pathways that lead to blood-gas barrier injury, but as of today, we lack sensitive information on lung congestion. Promising perspectives come from a study by Bowler,⁵¹ the

proteomic signature of plasma and bronchoalveolar lavage fluid (BALF) of healthy subjects were compared with the proteomic signature of plasma and pulmonary oedema in patients with acute lung injury (ALI). Apart from the changes in protein synthesis and protein degradation among healthy and unhealthy subjects, one of the most important confirmations of this study is the evidence of many plasma proteins in the BALF, documenting that ALI causes an increase of permeability of the alveolar-capillary barrier with consequent loss of selectivity. Moreover, the evidence of the impairment of alveolar type II cells function is suggested by the decrease in the oedema fluid of SP-A.

Considering the enormous potential of the Omics science, discovering new molecules correlated to pulmonary damage and congestion is virtually limitless and, as such, should be an attractive focus for moving forward knowledge in the field.

Conclusions and perspectives

Given the high rate of hospitalization for AHF and worsening HF over time, the study of pathways involved in pulmonary congestion and functional lung changes seems a highly attractive area of research in need of expansion. The study of lung biomarkers of AHF, embracing ACMSF and pulmonary congestion as central determinants of evolving course of lung remodelling and its clinical implications is growing rapidly. SPs, especially SP-B in its immature form, are sensitive marker of ACMSF injury, a leading unfavourable event in AHF. Although some pivotal information come from preclinical studies and human evidence is based on small number studies, these biomarkers exhibit the potential to become standard reference in clinical practice by reflecting the mechanical and inflammatory pathways that precipitate congestion and organ injury.

Along with these organ-specific sensitive biomarker the analysis of a plethora of additional biomarkers, primarily sST2, Ucn-2, and pleural CA-125 may lead to advancement in the field adding precision to the study of lung organ damage. Remarkably, costs and feasibility of routine use of SP-B overlap to those of measuring gold standard BNP levels.

Whether a lung-oriented approach would contribute to a better pathophysiological understanding and disease phenotyping on top of established clinical and predictive information provided by NT-pro-BNP levels remains a challenging perspective.

Conflict of interest

None declared.

Data availability statement

No new data were generated or analysed in support of this research.

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