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Congestion in heart failure: a circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology

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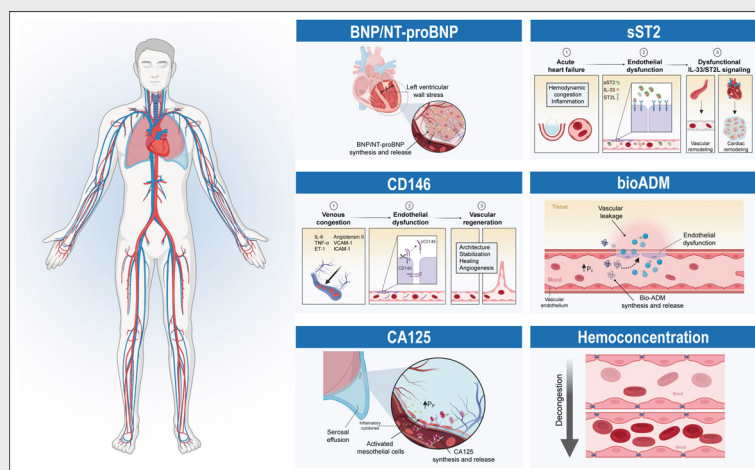
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Congestion is a cardinal sign of heart failure (HF). In the past, it was seen as a homogeneous epiphenomenon that identified patients with advanced HF. However, current evidence shows that congestion in HF varies in quantity and distribution. This updated view advocates for a congestive-driven classification of HF according to onset (acute vs. chronic), regional distribution (systemic vs. pulmonary), compartment of distribution (intravascular vs. extravascular), and clinical vs. subclinical. Thus, this review will focus on the utility of circulating biomarkers for assessing and managing the different fluid overload phenotypes. This discussion focused on the clinical utility of the natriuretic peptides, carbohydrate antigen 125 (also called mucin 16), bio-adrenomedullin and mid-regional pro-adrenomedullin, ST2 (also known as interleukin-1 receptor-like 1), cluster of differentiation 146, troponin, C-terminal pro-endothelin-1, and parameters of haemoconcentration. The utility of circulation biomarkers on top of clinical evaluation, haemodynamics, and imaging needs to be better determined by dedicated studies. Some multiparametric frameworks in which these tools contribute to management are proposed.

Graphical Abstract



Schematic summary of circulating surrogate biomarkers of congestion. bioADM, biologically active adrenomedullin; BNP, B-type natriuretic peptide; CA125, carbohydrate antigen 125; CD146, cluster of differentiation 146; ET-1, endothelin-1; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TNF- α , tumour necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

Keywords

Congestion • Acute heart failure • Biomarkers

Congestion in heart failure (HF) is defined as signs and symptoms of extracellular fluid accumulation that result from increased cardiac filling pressures.¹ It is induced and perpetuated by an imbalance between neurohormonal axes with opposite actions: sodium/water retention and vasoconstriction (mainly adrenergic, renin–angiotensin–aldosterone, and vasopressin systems) versus natriuretic and vasodilatation (mainly cardiac endocrine function).^{1–4} Congestion is also a central component in the definition of HF,⁵ and most HF hospitalizations are due to congestion either as predominantly fluid overload, compartmental fluid redistribution,

or a mix of both mechanisms.^{1,3,4} Beyond the traditional view as a surrogate for HF severity, the current perspective considers fluid accumulation/redistribution are causally involved in HF and organ damage progression. Thus, congestion contributes to the HF-associated impairment of functional and structural changes in multiple organs and systems (Figure 1).

Despite most patients with worsening HF (WHF) experience a substantial clinical improvement when treated with diuretics, there are several gaps in knowledge. First, the severity of congestion is not linearly associated with the severity of HF (left

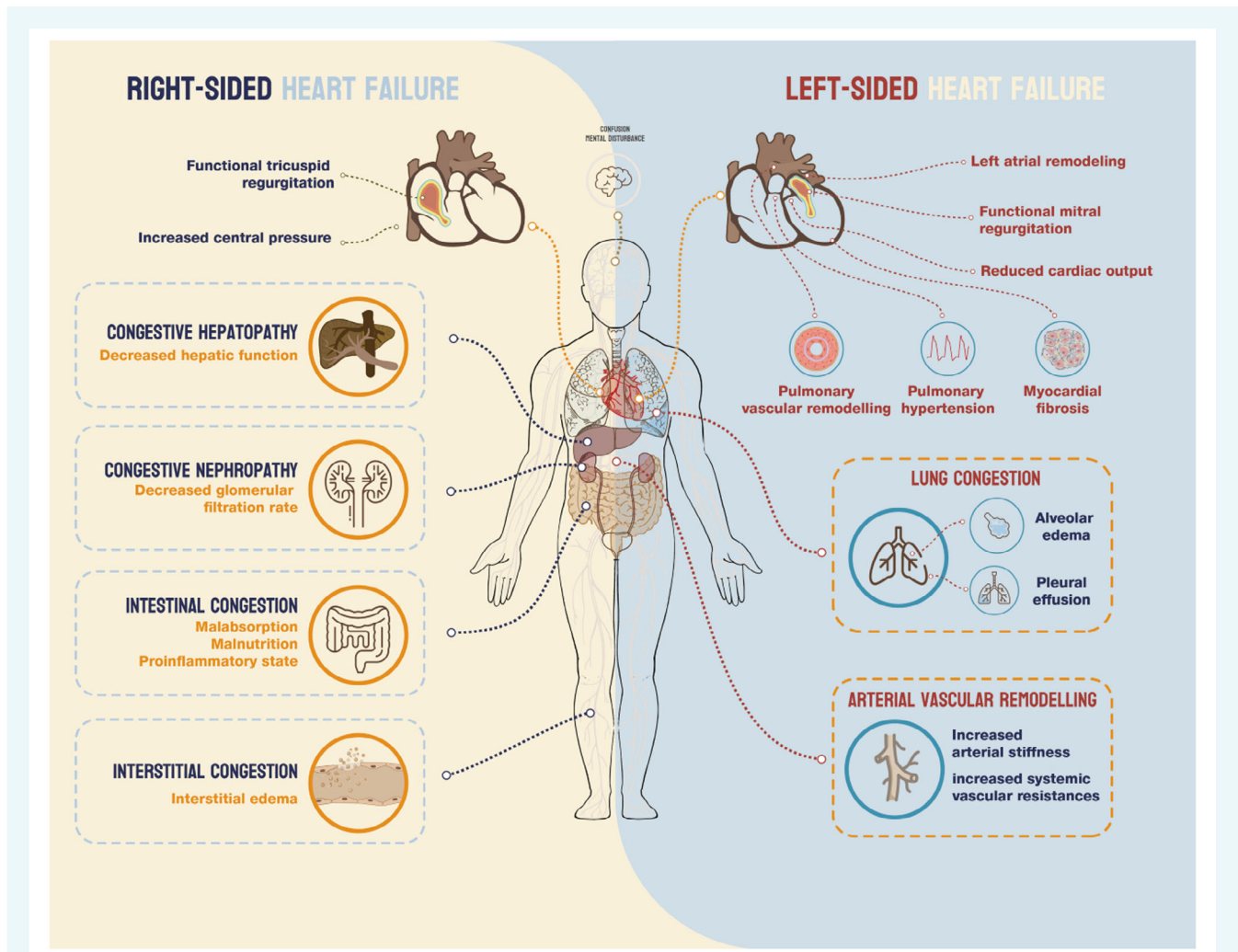


Figure 1 Clinical implications of organ congestion in heart failure. Congestion can lead to organ injury, dysfunction, and, ultimately, the failure of target organs (i.e. heart, lungs, kidneys, liver, intestine, vessels, and brain). Pulmonary congestion is the net result of increased left-sided filling pressures, which may lead to cardiopulmonary remodelling (i.e. endothelial dysfunction, fibrosis, and thickening of the extracellular matrix), pulmonary vasoconstriction, and, finally, pulmonary hypertension. Congestion of organs in the abdominal cavity is the net result of right-sided dysfunction and venous congestion. Passive congestive hepatopathy due to increased central venous pressure may initially lead to cholestasis. However, chronic hepatic congestion may result in hepatic fibrosis and cirrhosis. Congestive nephropathy due to increased central venous pressure and extrarenal compression (i.e. intra-abdominal hypertension) may lead to a pressure-induced reduction in renal blood flow, renal hypoxia, increased interstitial pressure, and finally, interstitial fibrosis. Intestinal congestion leads to increased gut permeability and translocation of endotoxins (pro-inflammatory state), gastrointestinal hypoperfusion, protein-losing enteropathy, and cardiac cachexia. Furthermore, gut involvement complicates chronic heart failure treatment by decreasing intestinal absorption. For instance, oedematous changes in the intestinal wall may alter the absorption rate of certain drugs such as furosemide. Additionally, the pro-inflammatory cytokine milieu resulting from bacterial and lipopolysaccharide translocation to the systemic circulation can also alter the expression of various drug-metabolizing enzymes and transporters.

or right ventricular dysfunction). In other words, some patients with severe left ventricular (LV) dysfunction remain euvolaemic and show no signs of congestion. In contrast, other patients have severe congestion with relatively mild objective structural or functional abnormalities.^{1,6} For instance, high-output HF does not necessarily require significant structural cardiac abnormalities and should also be considered in differential diagnoses of patients with clinical congestion. Among them, high-output HF

includes a wide variety of underlying conditions (i.e. obesity, severe anaemia, cirrhosis, arteriovenous shunts, chronic hypercapnia, among others) associated with reduced arterial vascular resistance and high output. The common factor in all these conditions seems to be a reflex increase in sympathetic activity through baroreceptors that leads to decreased renal blood flow, activation of the renin–angiotensin–aldosterone system, and sodium and water retention.^{3,4} Second, the optimal decongestion strategy

remains elusive in most HF patients regardless of LV ejection fraction,^{3,4} mostly reflecting the heterogeneous severity and organ distribution of fluid overload and the low accuracy of classic symptoms and signs in grading congestion.¹ Thus, searching for new clinical tools, especially those widely available in clinical practice, should be a research priority in the HF field.

Historically, fluid overload in HF was considered a homogeneous and uni-compartmental epiphenomenon that identified patients with more advanced disease. In contrast, current evidence shows that fluid and sodium accumulation in HF are heterogeneous in quantity and distribution. An updated view of congestion advocates for the classification of HF-related fluid overload according to onset (acute vs. chronic), regional distribution (systemic vs. pulmonary), compartment of distribution (intravascular vs. interstitial vs. third spaces), and clinical versus subclinical. A better understanding and identification of the different congestion ‘phenotypes’ could probably translate into improving HF management.

Therefore, this review will focus on the utility of circulating biomarkers in identifying and managing different congestion phenotypes.

Pressure–volume disconnection: fluid overload versus fluid redistribution

The pathophysiology of congestion in HF is highly complex and multifactorial. Although too simplistic, it can be viewed as a dynamic interplay between cardiac function, the roles of interstitial and intravascular fluid compartments, the integrity of the endothelium, and how the kidney manages the sodium/liquid homeostasis at the tubular level.⁷ This multifactorial and complex pathogenesis may be conditioning the disconnection between congestion-driven pressures and congestion-driven volume expansion, resulting in patterns that varied widely between patients on severity and organ distribution.^{6–9} For instance, some patients presenting with WHF and elevated cardiac filling pressures may have a predominant fluid redistribution (from splanchnic to pulmonary vascular territory) (Figure 2). In contrast, others may show a long-standing and gradual interstitial volume expansion (tissue congestion)⁹ (Figure 2).

Congestion phenotypes

Congestion in HF can be characterized based on the compartment and regional distribution (Figure 3).

Regional distribution: pulmonary versus systemic

As stated before, regional/organ distribution of congestion is not a homogeneous process in HF.^{6–9} In patients with predominant left-sided HF, pulmonary congestion dominates; however, with the involvement of right-sided chambers and/or pulmonary arterial hypertension, systemic congestion becomes a dominant presentation.^{3,6–9} These differences in the distribution of fluid overload are

also the basis of the re-classification of acute HF (AHF) recently proposed in the 2021 European Society of Cardiology (ESC) guidelines in (i) HF with predominant peripheral fluid accumulation, (ii) acute decompensated HF as patients with acutely decompensated HF where lung congestion – favoured by splanchnic district venoconstriction – led to acute pulmonary oedema.³

Compartment distribution: intravascular versus extravascular

Patients with decompensated HF showed marked elevation of cardiac filling pressures. In normal hearts and afterload held constant, LV torsion is a preload-dependent phenomenon in which volume loading results in a net increase in peak systolic LV twisting and subsequent early diastolic untwisting rate.¹⁰ This interdependence between systolic twisting and diastolic untwisting (viscoelastic suction) explains why healthy hearts can accommodate a larger preload volume without significantly increasing pulmonary capillary wedge pressures. In HF, however, there are diverse LV twisting alterations and reduced and delayed untwisting. Consequently, the failing heart cannot adequately accommodate preload volume increase at rest or during exercise, leading to elevated pulmonary capillary wedge pressures.¹¹ Moreover, pulmonary pressures may also be high due to enhanced ventricular interdependence in the context of right ventricular–pulmonary arterial uncoupling at rest (i.e. isolated right-sided HF) or during exercise.¹¹ Although this elevation in filling pressures is commonly related to the inability of the heart to accommodate and distribute central blood volume, changes in systemic venous function also play a crucial (and under-appreciated) role in regulating central haemodynamics.¹²

Most blood volume resides within the venous circulation, and its distribution can be divided into stressed and unstressed volumes.^{11,12} The unstressed volume (approximately 70% of venous blood volume) refers to the amount of blood necessary to fill the vascular space at a transmural pressure equal to zero. It represents a blood reservoir pooled in venous capacitance veins that can be mobilized into the central circulation when needed^{11,12} (Figure 4). In contrast, the stressed volume (approximately 30% of venous blood volume) describes the additional volume of blood that increases wall tension, determining venous return and cardiac preload¹¹ (Figure 2). Importantly, the autonomic nervous system tightly regulates the distribution of stressed and unstressed blood volume.¹³ Accordingly, increased sympathetic activation – common in patients with decompensated HF – may lead to a functional shift of blood from the unstressed volume (mainly from splanchnic veins) into the central circulation, resulting in a striking and acute increase in central venous pressures and the development of congestion-related symptoms.¹³ Therefore, a substantial proportion of patients present with a predominantly vascular type of congestion.^{3,13,14} In these patients, acute venous tone dysregulation rather than total blood volume expansion seems to be the principal underlying mechanism.

Another compartment phenotype is characterized by impaired sodium and water excretion due to increased neurohormonal activation and cardiorenal dysfunction.¹ As a result, there is a

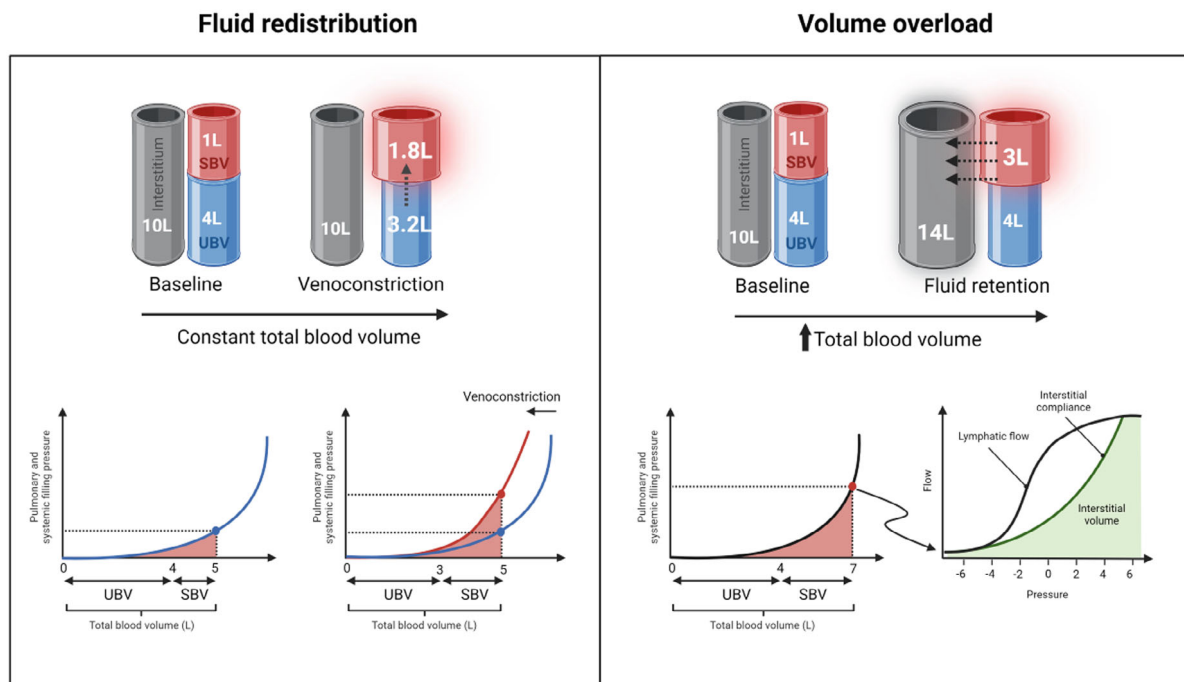


Figure 2 Fluid redistribution (A) versus volume overload (B). (A) The relationship between circulatory filling pressures (pulmonary and systemic) and total blood volume (unstressed blood volume [UBV] + stressed blood volume [SBV]) is non-linear, such that a significant amount of volume is required before any significant rise in circulatory filling pressures occurs. However, the venous tone is a crucial modifier of SBV in the setting of constant total blood volume. For instance, increased sympathetic activation – common in patients with decompensated heart failure – may lead to a functional shift of blood from the unstressed volume (systemic and pulmonary capacitance vessels), increasing circulatory filling pressures despite constant total blood volume. (B) Total blood volume progressively increases as fluid start to accumulate due to sodium and water retention since the early stages of an exacerbation. Because UBV is constant, there is a progressive rise in SBV and circulatory filling pressures. Together with other factors such as vascular permeability and Starling forces between the plasma and interstitium, part of the fluid overload is shifted towards the interstitial compartment because of net capillary filtration. Because of markedly increased lymphatic function, interstitial fluid is initially efficiently drained without fluid accumulation. Nevertheless, when lymph flow reaches a plateau, the rate of transudation from capillaries into the interstitium exceeds lymphatic capacity, and fluid starts to build up in the interstitial space.

relatively gradual development of vascular congestion reflecting an absolute increase in extracellular fluid and sodium content (tissue congestion), as is illustrated in *Figure 2*. The above will lead to a progressive and sustained increase in venous pressures that finally shift the Starling forces between the plasma and interstitium towards net capillary filtration. However, due to the limited compliance of the interstitial glycosaminoglycan (GAG) network and increased lymphatic function, interstitial fluid is initially efficiently drained, and there is no interstitial fluid accumulation.¹⁵ However, once lymph flow is maximized, the rate of transudation from capillaries into the interstitium may then exceed lymphatic capacity, and fluid accumulates in the interstitial space.¹⁵ Moreover, the long-term positive sodium balance may compromise the interstitial GAG network's integrity and buffering capacity, lowering its tensile force.¹⁵ Consequently, the interstitial matrix becomes highly compliant, and slight increases in hydrostatic capillary pressure are sufficient to drive interstitial fluid expansion.^{15,16} Other factors such as lower plasma osmolarity, inflammation and increased vascular permeability,^{3,17} may also be playing a role in the pathogenesis of tissue congestion. Additionally,

third-space fluid accumulation in serosal cavities is not uncommon.^{2,3} However, the mechanisms behind the shift to a third-space fluid accumulation are not fully understood, requiring more evaluation.

Clinical implications

An integrative assessment of symptoms and signs, imaging, and circulating biomarkers seems necessary for identifying the predominant congestion phenotype (*Figure 3*). Additionally, some clinical characteristics may help to reveal the predominant phenotype. For instance, those with an acute presentation more frequently present intravascular pulmonary congestion due to fluid redistribution. On the other extreme, patients with predominant tissue congestion will also show long-term evolution, gradual onset, and greater severity of systemic congestion (*Figure 3*). Not infrequently, these distinct phenotypes overlapped, resulting in mixed clinical patterns. Moreover, these phenotypes may change over time – patients may transition from one predominantly to another along the course of the disease.

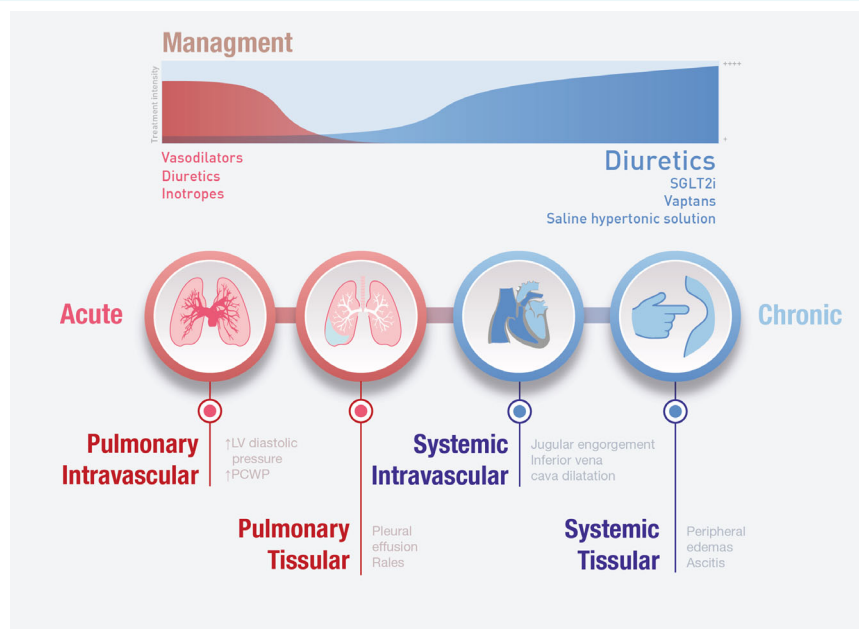


Figure 3 Congestion phenotypes. Time onset, utility of circulating biomarkers, and potential therapeutic implications. We propose four congestion phenotypes: pulmonary intravascular, pulmonary tissular, systemic intravascular, and systemic tissular. An integrative assessment using symptoms, signs, imaging, and circulating biomarkers may be useful for identifying the predominant congestion phenotype. Identification of the predominant congestion phenotype may imply crucial therapeutic implications as proposed. LV, left ventricle; PCWP, pulmonary capillary wedge pressures; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Beyond the pathophysiological considerations, this classification may also have important therapeutic implications. For instance, and contrary to those with dominant fluid overload – requiring more aggressive diuretic therapy – patients with predominant fluid redistribution may benefit from the use of vasodilators and not as much of an aggressive depletive strategy. In patients with predominant tissue congestion, strategies aiming to reduce vascular permeability and increase vascular refill, such as using hypertonic solutions with high doses of loop diuretics and sodium–glucose cotransporter 2 inhibitors (SGLT2i), or vaptans, may be more beneficial than other traditional diuretic approaches (Figure 3).¹⁷ Also, congestion phenotyping may influence the pertinence and timing of other guideline-directed medical therapy. For instance, early initiation of SGLT2i and sacubitril/valsartan has been associated with a greater decongestive effect.^{18,19} Conversely, early initiation of beta-blockers in patients with overt congestion status should be avoided.^{3,4}

Role of circulating biomarkers for assessing the severity and distribution of congestion

A growing body of evidence supports an integrated and multi-parametric evaluation of congestion by means of validated clinical scores, circulating biomarkers, and technical assessments (imaging, haemodynamics, and impedance-based tools).^{1,20}

The current article provides an overview of the novel and established circulating biomarkers for identifying different modalities of congestion (*Graphical Abstract*). The biomarkers included in this review are those identified by the Biomarkers Working Group of the Heart Failure Association as the more relevant contemporary biomarkers in HF.

Ideal characteristics of a congestion biomarker

An ideal biomarker should be expressed and produced in different organs and systems affected by fluid accumulation. Indeed, several HF biomarkers predominantly reflect stress in other affected tissues and provide information beyond the heart.²¹ An ideal biomarker in HF should include the following characteristics: (i) non-invasive, low-cost, easy, and standardized assessment, (ii) high sensitivity, allowing early detection and no overlap in values between wet and dry patients, (iii) provide specific information about the congestion phenotype, (iv) be unaffected, or minimally affected by comorbid conditions, and (v) their levels should be modified in response to treatment.

Natriuretic peptides

Several studies have correlated B-type natriuretic peptide (BNP) and its co-secreted amino-terminal propeptide congener (NT-proBNP) with increased left intracardiac filling pressures and


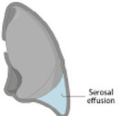
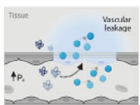
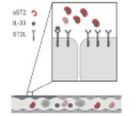
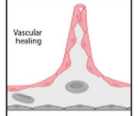
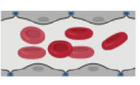
Circulating biomarker	Mechanisms of production	Regional distribution	Compartmental distribution	Pros	Cons	Reference values
 <p>BNP/NT-proBNP</p>	Released in response to myocardial wall tension due to increased transmural pressure	Pulmonary	Intravascular	<ul style="list-style-type: none"> - Widely available - Useful for diagnosis, triage, and prognostication 	<ul style="list-style-type: none"> - Less accurate in obese individuals, elderly patients, and severe kidney dysfunction - Conflicting results for guiding HF therapy 	<ul style="list-style-type: none"> - Diagnosis: >300 pg/mL in acute HF - Monitoring decongestion: >30% drop at the end of hospitalization
 <p>CA125</p>	Released by mesothelial cells in response to mechanical stress and inflammation	Pulmonary and systemic	Extravascular / tissue	<ul style="list-style-type: none"> - Useful for assessing congestion severity, guiding diuretic therapy, and risk stratification - Standardized commercially available assays, low cost 	<ul style="list-style-type: none"> - Long half-life - Lagged effect - Non-HF-specific 	The optimal cut-off for defining normal vs. abnormal values in different HF scenarios should be established, as the cut-off of 35 U/mL was derived primarily from cancer studies
 <p>bioADM</p>	Released to maintain vascular integrity and endothelial barrier function (reduce vascular leakage)	Systemic	Extravascular / tissue	May be useful for identifying patients at risk of residual congestion at discharge	<ul style="list-style-type: none"> - No information for guiding therapy - Is not widely available for routine use 	The best cut-off value of bio-ADM to assess congestion (defined as a congestion score > 1) is 34 pg/mL
 <p>sST2</p>	Released in response to hemodynamic congestion and inflammation by vascular endothelium and lungs	Pulmonary and systemic	Intravascular	Useful for risk-stratification	Limited information about its utility for guiding therapy/monitoring decongestion	Available data have indicated an increase in risk when registering an sST2 concentration ≥ 35 ng/mL with the Presage ST2 assay
 <p>CD146</p>	Released in response to vascular stress. Mediates pleiotropic functions involved in vessel homeostasis and healing	Systemic	Intravascular	Preliminary data suggest that could be a specific biomarker of venous congestion	<ul style="list-style-type: none"> - No information about its utility for risk stratification, guiding therapy or monitoring decongestion - Is not widely available for routine use 	Not available
 <p>Hemoconcentration</p>	Reflect a relative increase in haemoglobin levels as a result of a reduction in plasma volume	Systemic	Intravascular	<ul style="list-style-type: none"> - Widely available - Low cost - May help to interpret kidney function changes during decongestion 	<ul style="list-style-type: none"> - May not be useful in patients with anemia or active bleeding - Long-term kinetics are not useful for monitoring decongestion 	Not available

Figure 4 Biomarkers in a clinical context. bioADM, biologically active adrenomedullin; BNP, B-type natriuretic peptide; CA125, antigen carbohydrate 125; CD146, cluster of differentiation 146; HF, heart failure; NT-proBNP, aminoterminal pro-B-type natriuretic peptide; sST2, soluble ST2.

pulmonary capillary wedge pressures in patients with HF.^{22–25} A summary of the evidence endorsing the association between natriuretic peptides (NPs) and haemodynamic parameters is presented in online supplementary *Appendix S1*. The reason why these peptides correlate with left cardiac pressures lies in their origin. The

biomechanical wall stress induced by plasma volume expansion and/or pressure overload triggers the release of pre-synthesized proBNP and transcription of the NP precursor B (*NPPB*) gene, leading to the production of the 134-amino acid proBNP hormone precursor (pre-proBNP).^{26,27} Following its production,

pre-proBNP is rapidly processed to yield proBNP_{1–108}, which is further cleaved into the bioactive BNP and its biologically inactive equivalent NT-proBNP by the action of proteases such as corin or furin.^{28,29} After this initial processing, within minutes of their synthesis, both BNP and NT-proBNP are liberated into the plasma, providing a valuable reflection of the overall cardiac load.^{2,3,22–25} The biologic actions of elevated BNP hormone (natriuretic and vasodilator effects) are counteracted by the peripheral resistance, which is established at receptorial and post-receptorial level,³⁰ making HF a condition characterized by second messenger cyclic guanosine monophosphate (cGMP) insufficiency, hence a target for several treatments.³¹

Despite the proven value of BNP and NT-proBNP for diagnosis and prognosis across the spectrum of HF syndromes,^{3,4,32} several properties may limit their usefulness for assessing and grading congestion. First, NPs are mainly expressed by the heart, while fluid overload is systemically extended.^{1,32,33} Thus, NPs are indirect congestion measures making them not the ideal markers for congestion. Second, a broad range of structural and functional cardiac and non-cardiac abnormalities are associated with increased ventricular wall tension leading to substantive elevation of levels of plasma NPs without being necessarily linked to fluid retention, such as ischaemia and atrial fibrillation.^{32,33} Third, LV wall stress is the most potent trigger for NP synthesis and release.²⁷ Accordingly, NPs may fail to capture the contribution of right-sided HF and its consequences (systemic and extravascular congestion).^{9,34} For instance, in-hospital single-measurements of NPs in AHF did not predict the severity of clinical congestion,³⁵ and it lacked prognostic effect in those with predominant right-sided HF, such as in patients with severe tricuspid regurgitation.³⁶ Fourth, in addition to primary generation via increased intracardiac pressures, plasma concentrations of both NT-proBNP and BNP levels are also influenced by common conditions in HF such as older age, atrial fibrillation, and renal dysfunction. Conversely, NPs are inversely related to body mass index.³³ Fifth, NPs are not perfect surrogates for filling pressures and are less accurate in ruling out HF with preserved ejection fraction (HFpEF), especially in the outpatient setting.³⁷ Furthermore, some specific conditions are associated with NP deficiency, such as polymorphisms in the *NPPB* gene, African ancestry, increased androgenicity in women, insulin resistance, hypercortisolism, and certain medications (e.g. spironolactone).³⁸ Thus, it is important to account for these factors when interpreting NP levels in the clinical setting.³³

The role of repeated measurement for monitoring changes in fluid status is also a property that needs to be commented. In general, patients with a greater relative reduction in NPs after treatment exhibit a lower risk of adverse events.^{33,39–41} For instance, in chronic HF with reduced ejection fraction (HFrEF), short-term changes in NP levels predicted the risk of hospitalization for WHF.³⁹ Likewise, recent observational data showed, in at least two consecutive outpatient visits in an ambulatory setting, that a decrease in NT-proBNP was associated with improved mortality and morbidity also in patients with HF and mildly reduced and preserved ejection fraction during routine care.⁴⁰ Following an episode of AHF, long-term repeated measurements of high NPs have also been shown to be independently associated with the risk

of death.⁴¹ A descending kinetic pattern identified those at lower risk of death, although the ability of serial measurements to predict survival was blunted at longer follow-up.⁴¹ However, despite a clear relationship to cardiac filling pressures and prognosis, changes in NPs may show either absent or weak to moderate relationship with indicators of decongestion in AHF.¹⁷

The evidence endorsing the utility of NPs for guiding therapy is mixed. The largest trial and the more recent meta-analysis showed no prognostic benefit compared to usual care.^{42,43} The GUIDE-IT included 894 patients with stable LV ejection fraction $\leq 40\%$ and elevated NT-proBNP in the previous month.⁴³ The authors recommended therapy intensification in this study to achieve a target NT-proBNP of <1000 pg/ml.⁴³ The NT-proBNP guided therapy included, among others, up-titration of diuretic therapy if NT-proBNP >5000 pg/ml.⁴⁴ No differences were found in the mean loop diuretic dose over time between both treatment arms.⁴³ Thus, a single value of NPs may not provide relevant additional information about the overall congestion status.

From a practical point of view, changes in NPs should be interpreted together with cardiac structural and functional characteristics and clinical evaluation. Evaluating the relative modifications (%) based on each patient's plasma levels when stable ('dry levels') may be more informative about the severity of intracardiac pressure/volume overload than using a single measurement. In this context, a practical approach would consider changes $>30\%$ as clinically relevant.^{32,45} For example, in stable ambulatory patients, a change of 50% seems to indicate a shift in filling pressures.^{32,33} Despite the current evidence not supporting NPs as guiding therapy in HF, its short-term changes are useful for monitoring and guiding initial decongestive therapy in WHF with high levels at presentation (those with predominant pulmonary congestion).

Pitfalls in interpreting serial changes of natriuretic peptides in heart failure

First, NPs show a high intraindividual biological variation, hampering the clinical interpretation of serial measurements.⁴⁶ Second, the utility of kinetic of NPs in patients with intrinsically higher levels, such as the elderly, atrial fibrillation, and those with severe kidney dysfunction, needs to be more carefully evaluated.^{33–36} Third, their utility in monitoring decongestion is even less clear in patients with overt systemic intravascular and tissue congestion, such as those with predominant right-sided HF.^{33,36}

The clinical utility of mid-regional sequence of pro-A-type natriuretic peptide as a biomarker of congestion is less well documented despite its promising utility for long-term risk stratification.^{33,47}

Carbohydrate antigen 125

Carbohydrate antigen 125 (CA125, also called mucin 16 [MUC16]) is a high molecular weight (220 kDa) glycoprotein encoded by the *MUC16* gene in humans.^{48,49} It is expressed on the surface of cells derived from the coelomic epithelium (i.e. pleura, peritoneum, and pericardium) as a membrane-bound protein, or released in a soluble form via proteolytic cleavage, making it available as a circulating biomarker.^{50,51} Although primarily used in monitoring

ovarian cancers,⁴⁸ CA125 has also been shown to be elevated in a wide range of other conditions related to volume expansion, including cirrhosis, renal failure, and AHF.⁵¹ It has been postulated that elevated hydrostatic pressure, mechanical stress, and inflammatory stimuli in the setting of congestion may activate mesothelial cells in serosal surfaces, leading to CA125 overproduction and release.^{50,51} Indeed, cumulative evidence supports the positive association between plasma levels of CA125 with tissue congestion/serosal effusions, increased cardiac filling pressures, and other proxies of right-sided HF.^{34,51} CA125 levels have been shown to be substantially higher in patients with large serosal effusions and peripheral oedema than in those without these particular clinical surrogates of volume overload.⁵¹ In a recent study including 2949 patients hospitalized for AHF, the severity of tricuspid regurgitation, presence of pleural effusion, and peripheral oedema were factors closely associated with the magnitude of circulating CA125.³⁴ Likewise, in a substudy of BIOSTAT-CHF, CA125 was positive and significantly associated with a clinical congestion score in patients with WHF.⁵² More recently, CA125 has also been associated with intrarenal venous congestion and high intra-abdominal pressure in patients with AHF,^{53,54} adding to the growing body of evidence supporting the role of this biomarker in identifying a phenotype of predominant systemic and extravascular congestion.⁵¹ Evidence summarizing the association between CA125 and haemodynamic parameters is presented in online supplementary Appendix S1.

The close correlation between plasma changes in this biomarker with disease severity and clinical outcomes was described more than 20 years ago. Nägele *et al.*⁵⁵ found, in 71 candidate patients for heart transplantation, a significant decrease in this biomarker after heart transplantation (401 ± 259 U/ml vs. 33 ± 22 U/ml), and this trajectory was significantly associated with prognosis. Similarly, D'Aloia *et al.*⁵⁶ showed in 286 patients with predominant systolic dysfunction that mid-term fluctuations of plasma CA125 were correlated with clinical evolution and prognosis. More recent studies have confirmed the incremental predictive utility of CA125 changes, especially during the first months after a decompensated HF event, for predicting mortality and readmission.^{41,51} For instance, a longitudinal study of 946 consecutive patients discharged for AHF showed that the long-term trajectory delineated by repeated measures of CA125 (3402 observations) predicted the risk of long-term mortality.⁴¹ Most of the substantial decrease occurred within the first month after discharge, and this trajectory identified the subgroup of lower risk. In contrast, there was a higher risk in patients in whom CA125 levels remained high or increased along the course of follow-up.⁴¹

Regarding therapeutical implications, two small randomized clinical trials endorse the role of CA125 in guiding diuretic therapy.^{57,58} In CHANCE-HF, 380 patients with a recent AHF decompensation and CA125 ≥ 35 U/ml were randomized to standard of care versus CA125-guided therapy. In the active arm, up/down-titration of diuretics was more frequent, and it translated to a significant reduction of the composite outcome of 1-year death/HF admissions, mainly by reducing HF hospitalizations.⁵⁷ The IMPROVE-HF trial tested the utility of CA125 for guiding diuretic therapy at presentation in patients with WHF and renal dysfunction.⁵⁸ In this last

study, the CA125-guided diuretic therapy translated into a better short-term renal function performance.⁵⁸

To correctly interpret CA125 as a surrogate marker of congestion and its evolution, it is important to highlight some fundamental aspects of its biology. First, there is a time gap between congestion onset and CA125 upregulation and release (lagged effect intrinsically related to long half-life that ranges from 5 to 12 days).^{51,59} Accordingly, the subset of patients with progressive and long-standing fluid retention (days to weeks) are more likely to have elevated CA125 plasma levels than those presenting with a more acute-onset (minute to hours) presentation.⁵¹ Therefore, besides being valuable for assessing and grading the severity of tissue/third space fluid accumulation, CA125 could also help estimate the chronicity of the congestion process.⁵¹ Likewise, serial changes in CA125 following therapeutic intensification may not capture information about short-term decongestion (hours-days).^{51,60} Conversely, weeks after depletive intensification, most patients reached CA125 < 35 U/ml regardless of the wet peak value, and this trajectory was closely related to prognosis.⁵¹ Along this same line, in a recent study in patients with AHF, variations in CA125 > 10 days from admission, but not before, were associated with the risk of 1-year mortality.⁶⁰ Second, and in contrast to NPs, circulating CA125 levels are not meaningfully modified by age, LV status, and kidney function.⁵¹ These properties may be advantageous for its assessment in the elderly, HFpEF, and those with cardiorenal syndrome. The clinical utility of this biomarking for tailoring decongestive therapy, despite initial encouraging results, requires larger confirmatory trials. Lastly, the low cost and wide availability of this biomarker make it easy to implant into daily clinical practice.⁵¹

Bio-adrenomedullin and mid-regional pro-adrenomedullin

Adrenomedullin (ADM) is a 52-amino acid peptide encoded by the ADM gene located on chromosome 11.⁶¹ Upon its translation, the ADM precursor (a pre-prohormone composed of 185 amino acids) is cleaved to yield first proADM and then glycine-extended, inactive ADM.⁶² The latter is subsequently converted to biologically active ADM (bio-ADM) by enzymatic amidation.^{63,64} Although ADM is involved in a wide range of biological processes,⁶⁵ its dominant role is thought to be maintaining vascular integrity and permeability barrier function and regulating vascular tone.⁶⁶ ADM diffuses freely across the vascular barrier and exerts a differential effect on vascular endothelial cells (predominantly barrier stabilization) and vascular smooth muscle cells (vasodilatation).⁶⁷ Thus, in situations like HF and sepsis characterized by endothelial dysfunction, increased plasma bio-ADM levels may be interpreted as a compensatory attempt to limit vascular leakage by stabilizing the endothelial barrier function.^{66,67} A growing body of literature suggests the utility of this peptide as a surrogate marker of congestion in HF.^{66,68–72} In patients hospitalized for AHF, bio-ADM was associated with the severity of clinical congestion score at admission in a stepwise fashion, and its baseline values were significant predictors of the presence of residual congestion assessed by clinical congestion score by day 7.⁷⁰ In recent large cohorts, bio-ADM was associated with the presence of oedema, orthopnoea, hepatomegaly,

and elevated jugular venous pressure.^{71,72} Interestingly, and even though CA125 and bio-ADM correlated positively in patients with WHF (either in-hospital or in the outpatient setting), the magnitude of the association was moderate ($r = 0.35$).⁵² In a recent cohort of patients with stable advanced HF_{rEF} undergoing right heart catheterization, bio-ADM correlates positively with both pulmonary capillary wedge pressure ($r = 0.37$, $p = 0.003$), mean right atrial pressure ($r = 0.46$, $p < 0.001$), and NT-proBNP ($r = 0.43$, $p < 0.001$).⁷³ Thus, bio-ADM may reflect the integrated assessment of both vascular and tissue types of congestion.

The activity of the ADM system may even help to personalize post-discharge diuretic treatment. Among 1886 patients with AHF, patients with above-median bio-ADM concentrations derived disproportional long-term benefits if treated with diuretics.⁷⁴ In the same study, mid-regional pro-ADM (MR-proADM), a stable precursor of ADM, had even higher accuracy for predicting 1-year all-cause mortality versus bio-ADM.⁷⁴ This last biomarker has shown to be strongly correlated with mean pulmonary artery pressure and pulmonary capillary wedge pressure and inversely correlated with pulmonary artery compliance in subjects with HF_{rEF}.⁷⁵ A recent study suggests that the association between levels of bio-ADM and pulmonary capillary pressures decreased in patients with body mass index ≥ 35 kg/m². Interestingly, in this work, MR-proADM showed a robust correlation with pulmonary capillary pressures ($r = 0.62$, $p < 0.001$), with no differential relationship based on the presence of obesity.⁷⁶

The information regarding the clinical value of changes over time of these biomarkers for monitoring is more limited. In patients with clinical signs of residual congestion 7 days after hospital admission, bio-ADM levels were high at baseline and remained high throughout the first week of hospitalization.⁷⁰ Serial short- and long-term increases in bio-ADM and MR-proADM concentrations have been reported in patients with HF following sacubitril/valsartan initiation due to inhibition of neprilysin.⁷⁷ However, no studies are available exploring the long-term kinetics of bio-ADM or MR-proADM across congestion status and clinical outcomes. Therefore, the role of bio-ADM and MR-proADM in monitoring congestion and guiding therapy remains to be defined. Additionally, further research is required to clarify whether its plasma levels are influenced by age, body mass index, LV systolic function, HF aetiology, and liver and renal function.

Online supplementary *Appendix S1* summarizes the evidence endorsing the association between both biomarkers and haemodynamic congestion.

Soluble ST2

ST2 (also known as interleukin-1 receptor-like 1 [IL1RL1]) is a member of the Toll-like/interleukin-1 receptor superfamily and is encoded by the gene *IL1RL1* located on chromosome 2.⁷⁸ Alternative splicing generates multiple ST2 isoforms, including a transmembrane form (ST2 ligand or ST2L) and a soluble circulating form (sST2),^{79,80} which is a valuable prognostic biomarker in acute or chronic HF.^{81,82} The biological action of the ST2 protein is mediated by the extracellular engagement of ST2L with its ligand, interleukin-33 (IL-33).⁸⁰ IL-33/ST2L signalling has anti-hypertrophic

and anti-fibrotic effects via its activation of diverse intracellular pathways.⁸³ However, sST2 also avidly binds to IL-33 and is viewed as a decoy receptor, diminishing net transduction of the favourable effects of IL-33 through ST2L.⁸⁰

Although sST2 levels are usually low in patients with stable HF, striking increases in plasma levels are common in AHF and provide valuable prognostic information.^{84,85} The mechanisms behind sST2 upregulation in AHF seem to be related to the peripheral release of pro-inflammatory cytokines by activated vascular endothelial cells and lung tissue in response to haemodynamic congestion and inflammation.^{86–88} Indeed, sST2 positively correlates with echocardiographic indicators of right-sided HF,⁸⁹ and invasively measured central venous pressure in AHF.⁹⁰ It has been recently identified as a surrogate marker of diuretic resistance in patients with AHF and renal dysfunction at presentation.⁹¹ Accordingly, sST2 may be a surrogate marker of pulmonary and vascular congestion in HF.⁹² Furthermore, the interaction between congestion/inflammation and sST2 upregulation results in dysfunctional IL-33/ST2L signalling that blocks its cardioprotective and vascular benefits.⁸³ Thus, this pathophysiological link could be one of the mechanisms by which congestion drives further progression of HF.

A single determination of ST2 is associated with additive prognostic information to those provided by clinical variables and cardiac biomarkers in chronic and acute HF.^{85,93,94}

Interestingly, the prognostic value of sST2 appears not to be influenced by renal function.⁹⁵ However, longitudinal studies are scarce. In a population of 150 patients with decompensated HF undergoing daily blood sampling for sST2, percent change in ST2 was strongly predictive of 90-day mortality: patients whose ST2 values decreased by 15.5% or more during the study period had a 7% chance of death, whereas patients whose ST2 levels failed to decrease by 15.5% in this time interval had a 33% chance of death.⁹⁶ In this study, the prognostic value of sST2 changes was independent of variations in NT-proBNP.⁹⁶ In a recent subanalysis of the PIONEER-HF trial (comparison of the effect of sacubitril/valsartan vs. enalapril on NT-proBNP in patients stabilized from an AHF episode), baseline sST2 concentrations yielded prognostic significance for the composite outcome of cardiovascular death or HF rehospitalization.⁹⁷ Notably, patients in the sacubitril/valsartan arm displayed a greater reduction in circulating sST2 than those receiving enalapril by as early as 1 week, as well as a potentially better outcome.⁹⁷

The exact mechanisms explaining the kinetic of sST2 and the relationship between changes in this biomarker with clinical outcomes warrants a more profound evaluation. Additionally, further studies evaluating potential interactions with common confounders in HF and the ability of this biomarker for monitoring congestion status or guiding depletive therapy are warranted. A summary of the data linking the association between sST2 and vascular congestion is presented in online supplementary *Appendix S1*.

CD146

Cluster of differentiation 146 (CD146) is a 113 kDa glycoprotein encoded by the *CD146* gene located on chromosome 11.⁹⁸ It

contains a signal sequence of 28 amino acids, an extracellular portion composed of five immunoglobulin-like domains, a hydrophobic transmembrane region of 24 amino acids, and a short intracytoplasmic domain.⁹⁹ Three isoforms of CD146 have been described: two membrane-bound isoforms (lgCD146 and shCD146), and a soluble form (sCD146), which results from the shedding of the extracellular portion of CD146 through cleavage by matrix metalloproteinases.⁹⁹ CD146 is expressed on endothelial cells (mainly at the endothelial junction), smooth muscle cells, and pericytes within the whole vascular tree regardless of vessel size and location.^{100,101} This glycoprotein interacts with various ligands and mediates pleiotropic functions in vessel homeostases, such as permeability, angiogenesis, vessel architecture, stabilization, and healing.⁹⁹ Not surprisingly, sCD146 is overexpressed in conditions associated with inflammation, vascular injury, and endothelial dysfunction (all usually present in AHF syndromes).^{102–105}

Current data points to sCD146 as an emerging surrogate of congestion in HF.^{106,107} Higher sCD146 levels have been reported in patients with peripheral oedema and/or dilated vena cava than in those without signs of congestion.¹⁰⁷ Moreover, sCD146 accurately identified overhydrated haemodialysis patients irrespective of their BNP values.¹⁰⁸ Similarly, a peripheral venous stress study performed by inflating a pressure cuff over forearm veins induced a rapid and pronounced increase in circulating sCD146 but not of NT-proBNP in the congested arm.¹⁰⁹ Taken together, these preliminary data further indicate that sCD146 is a specific biomarker of venous congestion and, accordingly, could be of value in differentiating between central and peripheral congestion. However, to date, the evidence endorsing the association of this biomarker with haemodynamics and its clinical utility over symptoms/signs and other proxies of congestion is weak or even missing. Additionally, how this biomarker is influenced by common comorbidities and different clinical scenarios in HF requires further clarification.

Troponin

There is a paucity of data linking high levels of troponin with clinical congestion. In patients with advanced HF, after optimization of medical therapy, patients with detectable cardiac troponin I showed higher pulmonary artery and pulmonary capillary wedge pressures.¹¹⁰ In another study including 133 subjects hospitalized for decompensated HF, the authors showed that peripheral oedema and pulmonary rales on admission were associated with troponin levels on discharge.¹¹¹ More recently, an elevated troponin was associated with clinical congestion score in multivariable models after controlling for ventricular filling pressures and NP levels, suggesting that subclinical myocardial injury may be an important contributor to the pathophysiology of congestion.¹¹² However, the greatest elevation of this biomarker occurs in situations outside acute and chronic HF.⁴ This fact and the lack of studies correlating the changes over time of this biomarker and clinical congestion limits the clinical applicability of using troponin as a surrogate of congestion. Online supplementary *Appendix S1* summarizes the evidence endorsing troponin and haemodynamic congestion.

C-terminal pro-endothelin-1

Endothelin-1 (ET-1) is a strong vasoconstrictor, which is involved in inflammation and neurohormonal activation.¹¹³ C-terminal pro-endothelin-1 (CT-proET-1) is the stable circulating precursor protein of ET-1.¹¹³ Circulating levels of CT-proET-1 are higher in patients with HFpEF compared to controls at rest and during exercise.⁷⁵ In this same study, CT-proET-1 was strongly correlated with mean pulmonary artery pressure ($r = 0.73$) and pulmonary capillary wedge pressure ($r = 0.67$).⁷⁵ In a more recent study of subjects with unexplained dyspnoea, CT-proET-1 was highly correlated with pulmonary capillary wedge pressures and mean pulmonary artery pressures and did not display any differential relationship with body mass index.⁷⁶ Future studies are warranted to confirm prior findings and expand the evidence about the utility of this parameter as a surrogate of congestion.

Haemoconcentration

Haemoconcentration, as indicated by increases in haemoglobin or haematocrit following intensive depletive treatment, has also been proposed as a parameter of decongestion.¹⁷ Large studies have shown that haemoconcentration is associated with greater weight and fluid loss, greater reductions in filling pressures, and greater decongestion.^{114–116} Interestingly, decongestion with stable haematocrit during treatment has been suggested as a marker of adequate intravascular plasma refill rate.¹¹⁷

Likewise, widely accessible indices for estimating changes in plasma volume, which incorporates haemoglobin and/or haematocrit and/or weight, have been shown to correlate with plasma volume assessed by isotopic techniques in healthy volunteers patients with HF.^{118,119} Although other studies have questioned their reliability for volume estimation,¹²⁰ estimated plasma volume status (ePVS) has been related to adverse outcomes in different HF studies.^{118,119,121}

Based on the latest published data with the Duarte's Strauss-derived instantaneous assessment of ePVS (Strauss–Duarte) in acutely decompensated or chronic HF, an actionable threshold of >5.5 ml/g was proposed to define an excessive congestive status associated with poor outcomes, which may allow a prospective evaluation to be used as a trigger for therapeutic action.¹²²

Changes in kidney function parameters (serum creatinine and estimated glomerular filtration rate) have also been proposed to play a role as markers of haemoconcentration in HF. In patients with successful decongestion, an increase in creatinine may reflect haemoconcentration rather than worsening renal function.^{123–127} In contrast, a decrease in renal function together with clinical data showing persistent congestion is more likely to indicate true 'worsening renal function'.^{122–127} Along this line, a recent analysis of two large cohorts of patients with AHF (PROTECT, $n = 1698$ and RELAX-AHF-2, $n = 5586$) showed that worsening renal function, defined as a creatinine increase ≥ 0.3 mg/dl, in the first 4 days was not associated with worse outcomes when patients had an adequate diuretic response.¹²⁸ However, it is fair to recognize that haemoconcentration parameters lacked specificity, and their utility in a single patient required a careful and comprehensive evaluation.

Putting the circulatory biomarkers in the clinical context and future roadmap

A summary of the congestion-related clinical information provided by circulating biomarkers is presented in *Figure 4*, together with tips and caveats for their use and interpretation.

Evaluating congestion in HF is a difficult task as it is crucial to tailor diuretic treatment to the patient's needs,¹²⁹ and strongly recommended as class I by the ESC guidelines.⁴ The various available tools need to be applied coherently and effectively within each stage of the patient management cycle (i.e. pre-hospital, at the emergency room, during hospitalization, and post-discharge). Whether all patients or a subset could benefit from a multiparametric approach – including clinical evaluation, biological biomarkers, haemodynamics, and imaging (either sequentially or combined) – to detect signs of congestion, help optimize treatment, and improve outcomes has yet to be determined in dedicated studies. Some frameworks in which these tools could (co)-operate have already been proposed in the current document.¹²⁰ The optimal set of tools required to identify the predominant congestion phenotype in each patient is still to be determined. Therefore, we postulate that further evaluation of different multiparametric approaches requires the inclusion of NPs and additional circulating biomarkers, especially those related to tissue congestion. A proposal for an integrative assessment is provided in *Figure 3*.

Other less specific circulating biomarkers related to congestion status, such as blood urea nitrogen to creatinine ratio, cholestatic parameters, and serum sodium, may also have a useful clinical role in a proper clinical context.^{4,20,130}

Another issue that deserves to be evaluated is the interactions between circulating biomarkers and common associated conditions in patients with HF, such as renal dysfunction.¹³¹ As already emphasized, the interplay between the heart and the kidney is crucial in HF while also contributing to cardiorenal syndromes.^{123–128,131} Importantly, such mutual engagement may jeopardize the interpretation of variations in the estimated glomerular filtration rate. Indeed, 'true' worsening renal function may be associated with worse clinical outcomes, while 'pseudo' worsening renal function – when initiating depletive therapies – would not.¹²⁷ The magnitude of changes in traditional renal function markers for defining true worsening renal function remains to be better defined. Prior studies suggest traditional cutpoints for determining worsening renal function (a drop $\geq 20\%$) in patients with AHF treated with intensive intravenous diuretics are not associated with increased markers of kidney tubular injury.¹²³ The value of acute kidney injury biomarkers in helping to discriminate between true versus pseudo worsening renal function is yet uncertain.^{123,127,132,133} For instance, serum neutrophil gelatinase-associated lipocalin (sNGAL), a biomarker that predicts acute kidney injury in multiple conditions, has shown inconsistent findings in AHF.¹³³ The AKINESIS study showed that sNGAL proved not to be superior to creatinine for predicting worsening renal function or in-hospital adverse events in a large cohort of patients with AHF.¹³³ However, more recent substudies suggest

an interaction with parameters of decongestion.¹³⁴ The value of serum and urinary novel tubular markers in HF requires more evaluation.

Moreover, the interpretation of congestion biomarkers might also be challenging in the setting of acute or chronic variations in kidney function. Indeed, there is no consensus on cut-off values used to define HF in patients with acute kidney injury. In patients with chronic kidney disease, independent of HF status, elevated plasma levels of NPs are often found as a result of reduced renal clearance.^{32,33}

Similar uncertainties about the clinical interpretation of circulating biomarkers in the setting of elderly patients with HF and those with concomitant atrial fibrillation, liver dysfunction, and obesity deserve to be clarified.

Additionally, we must be extremely rigorous in analysing and implementing novel biomarkers to adopt only those that provide an extra added value to the physician in terms of understanding and handling the disease. Antoniou *et al.*¹³⁵ have recently undertaken a comprehensive review of biomarker-guided adaptive trial designs. Their in-depth overview provided clarity in definition, methodology, and terminology for biomarker-guided adaptive trial designs.¹³⁵ Eventually, this should help in designing future trials in a more homogeneous and reproducible way. Finally, a cost-effectiveness evaluation of implementing these biomarkers into clinical practice requires profound consideration.

Conclusions

Together with NPs, some circulating biomarkers may help clinicians identify the predominant congestion phenotype of each patient with HF. Ideally, some circulating biomarkers may also be useful for monitoring and guiding decongestive therapies. However, further studies are required to determine which subset of circulating biomarkers should be included in a multiparametric approach for assessing congestion.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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