Biomarkers for Congestion in Heart Failure: State-of-the-art and Future Directions

Antonio Luca Maria Parlati [1,2] Cristina Madaudo [1,3] Vincenzo Nuzzi [4] Paolo Manca [4] Piero Gentile [5] Daniela Di Lisi [3] Antonio Jordán-Ríos [6] Aamir Shamsi,[1] Mattia Manzoni [1] Matthew Sadler,[1] Cosmo Godino [7] Egle Corrado [3] Stefania Paolillo [2] Giuseppina Novo [3] Antonino Tuttolomondo [8] Alfredo Ruggero Galassi [3] Pasquale Perrone Filardi [2] Daniel Bromage [1] and Antonio Cannata [1]

1. Department of Cardiovascular Sciences, British Heart Foundation Centre of Research Excellence, School of Cardiovascular Medicine, Faculty of Life Sciences and Medicine, King's College London, London, UK; 2. Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; 3. Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Cardiology Unit, University of Palermo, University Hospital P Giaccone, Palermo, Italy; 4. Clinical Cardiology and Heart Failure Unit, Mediterranean Institute for Transplantation and Advanced Specialized Therapies IRCCS, Palermo, Italy; 5. De Gasperis Cardio Center and Transplant Center, Niguarda Hospital, Milan, Italy; 6. Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico; 7. Department of Cardiac Surgery, Heart Valve Center, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy; 8. Internal Medicine and Stroke Care Ward, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy

Abstract

Congestion in patients with heart failure (HF) predicts adverse outcomes and is a leading cause of hospitalisation. Understanding congestion mechanisms helps in HF management and underscores the importance of tailored therapies to treat vascular and tissue congestion, improving patient outcomes. In this setting, several tools are available to detect congestion. Biomarker measurement is a simple, valid and affordable method to evaluate congestion in patients with HF. Natriuretic peptides are the most widely available tool in acute and chronic HF, helping diagnosis, risk stratification and management. Novel biomarkers can potentially become reliable allies in diagnosing and monitoring patients with HF. This review aims to assess the current scientific literature on biomarkers for managing HF, evaluate their clinical utility and explore future perspectives in this field

Keywords

Heart failure, congestion, natriuretic peptides, troponin, novel biomarkers

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Correspondence: Cristina Madaudo, Department of Cardiovascular Sciences, British Heart Foundation Centre of Research Excellence, School of Cardiovascular Medicine, Faculty of Life Sciences and Medicine, King's College London, The James Black Centre, 125 Coldharbour Lane, London SE5 9NU, UK. E: cristina.madaudo@kcl.ac.uk

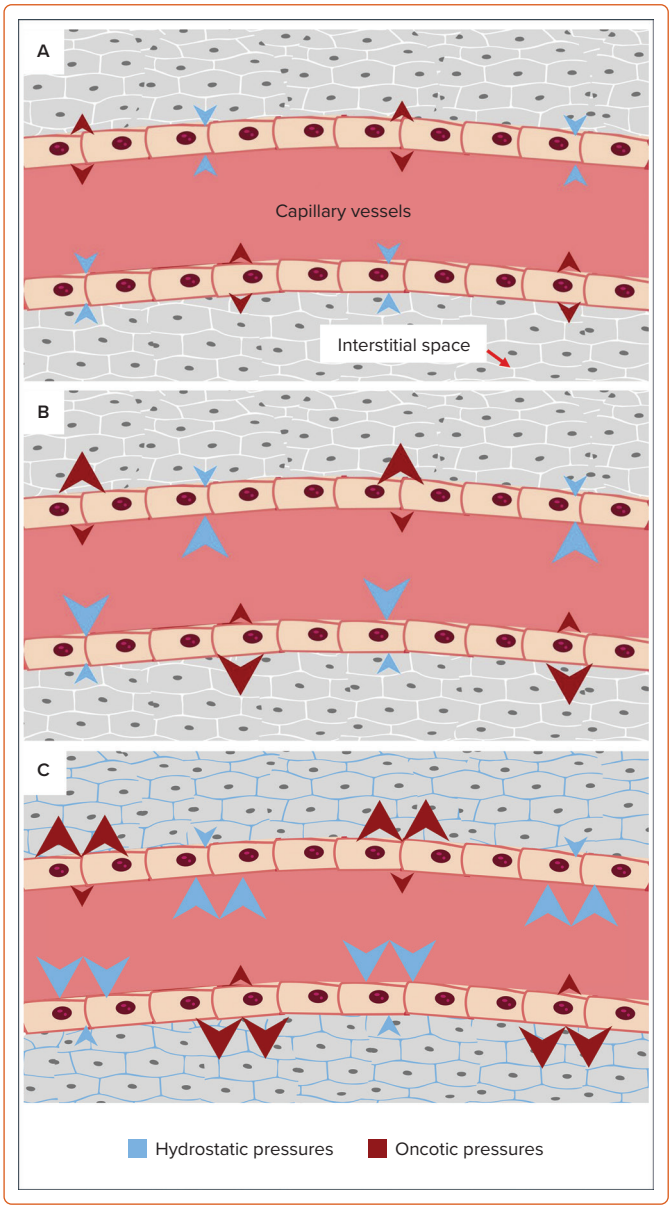
Congestion

Congestion is abnormal fluid accumulation in the intravascular and interstitial spaces.[1] This condition arises due to elevated cardiac filling pressures, primarily attributed to the kidney's maladaptive retention of water and sodium.[1] It is a strong predictor of adverse outcomes in patients with heart failure (HF) and the leading cause of HF hospitalisation.[2,3] Appropriate management of congestion is associated with a more favourable prognosis and prevention of worsening episodes of HF.[4,5]

Oedema results from the imbalance between hydrostatic and oncotic pressures within the interstitium, formed by glycosaminoglycans (GAGs), collagen fibres and elastin. *Figure 1* shows the basic mechanisms and pathophysiology of congestion. In a healthy interstitium, a small increase in interstitial pressure triggers a significant increase in hydrostatic pressure within the capillaries, promoting fluid movement into the surrounding tissues to maintain fluid balance and prevent excessive accumulation in the interstitium. Furthermore, the lymphatic system exhibits high sensitivity to changes in pressure, facilitating the removal of fluids at rates up to 10–50 times faster in response to increased hydrostatic pressure and effectively draining excess proteins, thus reducing colloid osmotic pressure inside the interstice.[6] During compensated HF, hydrostatic pressure in the capillary vessel rises and oncotic pressure in the capillary vessel decreases. Compensatory mechanisms responsible for maintaining the equilibrium are impaired during decompensated HF. The interstitium can no longer manage fluid properly once the hydrostatic and oncotic pressure balance is disrupted. As a result, capillaries begin to leak more fluid, accumulating in the interstitium, leading to oedema formation. Additionally, although the lymphatic system is sensitive to pressure changes, it cannot effectively drain the excess fluid, worsening congestion and contributing to the accumulation of proteins.

Some comorbidities, such as diabetes, inflammation, sepsis or ischaemia, can increase vascular permeability due to vascular tissue damage.[7] Patients with tissue congestion present with a gradual increase in cardiac

Figure 1: Pathophysiology of Tissue Congestion



A: Healthy conditions. B: Compensated heart failure. C: Decompensated heart failure.

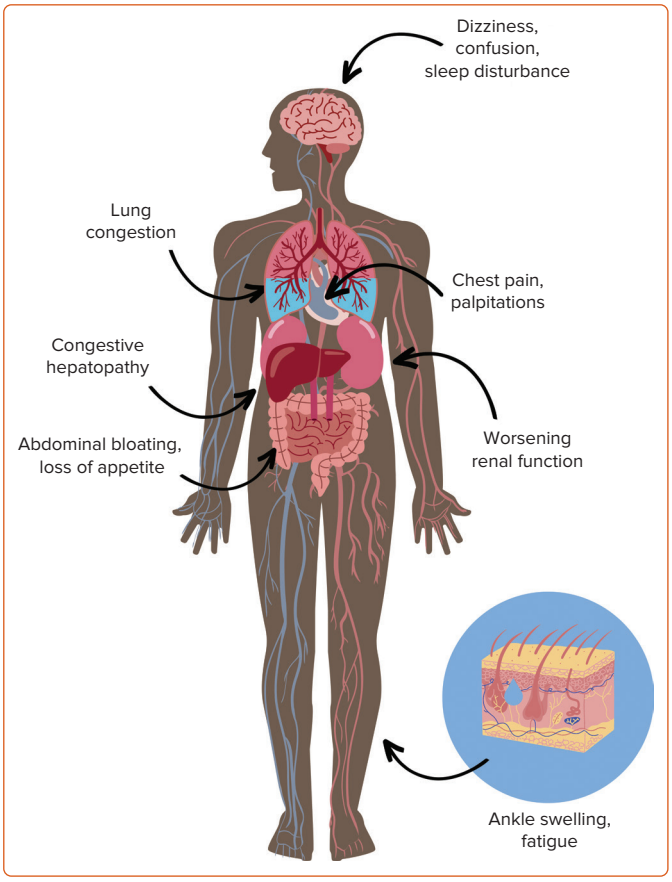
filling pressures and a slow progression of pulmonary, abdominal, and peripheral oedema.[8] This may be related to several adaptive pathophysiological changes, such as increases in alveolar-capillary membrane thickness, increased lymphatic drainage, and/or pulmonary hypertension.

Congestion is a pivotal clinical prognostic marker. Residual congestion at the time of hospital discharge is one of the main contributors to readmission risk.[3,9] In a *post hoc* analysis of the LUS-HF study, the presence of subclinical pulmonary congestion at discharge was a risk factor for the occurrence of the combined endpoint of rehospitalisation, unexpected visit for HF worsening or death at 6-month follow-up (HR 2.63; 95% CI [1.08–6.41]; p=0.033).[10] Therefore, effective pulmonary decongestion and careful clinical monitoring during the first weeks after discharge are primary goals to improve the prognosis of patients with HF.[11]

Signs and Symptoms of Congestion

Figure 2 summarises a list of typical signs and symptoms of congestive HF. Dyspnoea, orthopnoea, peripheral oedema, bendopnoea, increased

Figure 2: Signs and Symptoms of Congestive Heart Failure



jugular venous pressure (JVP) and third heart sound are typical findings associated with congestion. Dyspnoea is the resulting symptom in patients with congestive status due to the predominant redistribution of fluids (from the splanchnic vascular territory to the lungs) in cases of raised cardiac filling and pressures.[12] Dyspnoea is usually measured using the New York Heart Association (NYHA) score in patients with chronic HF (CHF).[13] Bendopnoea, orthopnoea and paroxysmal nocturnal dyspnoea are typical symptoms of HF due to congestion.[14,15]

Peripheral oedema and pulmonary oedema are the main signs of congestion in HF.[16] Rapid weight fluctuations usually indicate sodium and water retention, specifically in the third space, rather than changes in intravascular volume.[17]

The presence of congestion is often detected through the physical examination, with third heart sound as the most sensitive and rales the most specific sign of congestion.[18] However, physical examination is not accurate in intercepting initial signs of congestion, and the use of other techniques such as chest X-ray, cardiac ultrasound and lung ultrasound is common in clinical practice. Lung ultrasound is capable of assessing preclinical congestion (vertical echogenic lines arising from the pleura, i.e. B-lines), which already constitutes a prognostic determinant.[19]

In patients with advanced HF, the ultrasound-assessed jugular vein distensibility can help identify patients with normal right atrial pressure: patients with a higher jugular vein distensibility (threshold >1.6 of Valsalva/rest diameter ratio) have significantly lower pulmonary capillary wedge and pulmonary artery pressures and better outcomes than those with lower jugular vein distensibility.[20]

Table 1: Main Characteristics of Current Biomarkers Used to Assess Congestion in Heart Failure Patients

Biomarkers	Proposed Cut-off	References	Advantages	Disadvantages	Cost
BNP	100 pg/ml	McDonagh et al. 2021.[27]	• Widely available • Useful for diagnosis, stratification and prognosis	Low specificity in older people, high BMI and CKD	Low
NT-proBNP	300 pg/ml	McDonagh et al. 2021.[27]			
Troponin Hs	Not specified for CHF	N/A	• Widely available • Useful for predict occurrence of HF	Low specificity in multiple settings	Low
Troponin T	Not specified for CHF	N/A			
Troponin I	Not specified for CHF	N/A			
CA125	35 U/ml	D'Aloia et al. 2003.[59]	• Useful for stratification and guiding diuretic therapy	Low specificity in cancer patients, long half-life	Low
Soluble ST2	35 ng/ml	Aimo et al. 2017.[69]	• Useful for stratification	Not widely available	High
ADM	34 pg/ml	ter Maaten et al. 2019.[77]	• Useful for detecting patients with higher risk of residual congestion following discharge	Not widely available	High
Soluble CD146	Not specified for CHF	N/A	• Specific biomarker of venous congestion	Not widely available	High
Haemoconcentration	Not specified for CHF	N/A	• Widely available • Useful in CKD patients	Low specificity in patients with anaemia or bleeding, dehydration, haemorrhage and shock	Low

ADM = adrenomedullin; BNP = brain natriuretic peptide; CA125 = carbohydrate antigen 125; CD146 = melanoma cell adhesion molecule; CA = cardiac amyloidosis; CHF = chronic heart failure; CKD = chronic kidney disease; HF = heart failure; Hs = high sensitivity; NT-proBNP = N-terminal pro b-type BNP; ST2 = suppression of tumorigenicity 2.

The use of pulmonary artery catheterisation to detect congestion is reserved for cases in which non-invasive methods are not diriment.

Biomarkers are an important non-invasive method for measuring congestion in patients with HF. The present review aims to examine the existing scientific literature, compare different biomarkers and assess their use in clinical practice to detect and manage congestion in patients with HF.

Biomarkers

Biomarkers are quantifiable biological indicators in samples such as blood, urine or tissues.[21] Biomarkers represent a versatile tool for screening, detecting, monitoring and managing patients with HF, as well as for risk stratification. Several biomarkers are available to detect congestion (*Table 1*).

Natriuretic Peptides

Natriuretic peptides (NPs) are biomarkers routinely used in clinical practice.[22] Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are neurohormones synthesised and secreted into the circulation by atria and ventricles, respectively. NPs undergo a sequential synthesis process, beginning as preprohormones, followed by cleavage into prohormones. These prohormones are further processed to yield active hormones, ANP and BNP, alongside their inactive counterparts, mid-regional proANP (MR-proANP) and N-terminal pro-b-type natriuretic peptide (NT-proBNP). Their release is induced by increased end diastolic wall stress resulting from pressure or volume overload.[23] BNP and ANP function as adaptive counter-regulatory agents, engaging natriuretic peptide receptor-A (NPR-A) expressed at various levels, such as kidney, heart and vascular smooth muscle tissue, to induce vasodilation, natriuresis and diuresis.[24] In addition, NPs have several pleiotropic effects, including anti-inflammatory, anti-ischemic and antiproliferative.[25] ANP and BNP have a short circulating half-life of around 5 and 20 minutes, respectively, making them less practical for routine measurement.[26] Conversely, circulating NT-proBNP has a longer half-life of around 90–120 minutes, making it a stable and reliable biomarker for assessment.

According to the European Society of Cardiology (ESC) guidelines, the assessment of NPs plasma levels is recommended (class I) as the first step in all patients with suspected CHF based on risk factors, ECG, symptoms and signs. A plasma concentration of BNP <35 pg/ml, NT-proBNP <125 pg/ml, and MR-proANP <40 pmol/l rule out the diagnosis. On the contrary, values above the threshold increase the suspicion of CHF, prompting the performance of an imaging test to rule out HF or confirm the diagnosis, simultaneously determining the phenotype.[27] In addition, NPs plasma levels are helpful for prognostication.[28] In the suspect of acute HF (AHF), values of BNP <100 pg/ml, NT-proBNP <300 pg/ml and MR-proANP <120 pg/ml rule out the diagnosis, whereas values above the threshold confirm the diagnosis alongside clinical and imaging findings.[27] Similar to the ESC guidelines, the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines recommend in class I the measurement of plasma NPs values, with the same thresholds, to either exclude or support the diagnosis of CHF and to establish the prognosis.[29] In addition, ACC/AHA/HFSA recommends the measurement of NPs for HF risk stratification.[30]

The role of NPs is also crucial in the subgroup of patients with HF and cardiac amyloidosis (CA); these biomarkers provide a non-invasive, easily accessible, relatively inexpensive method for evaluating cardiac disease and its progression and have the potential to take on a more expansive role in the diagnosis and ongoing assessment of patients with CA.[31]

Although the use of NPs is fundamental in diagnosing HF and detecting congestion, their role in managing HF is debatable. In patients with AHF, lower levels of NPs are associated with a lower risk of 180-day mortality compared to patients with higher levels.[32] However, randomised evidence from the PRIMA II trial did not show differences in all-cause mortality and rehospitalisation for HF at 6 months for patients undergoing NPs guided management of HF.[33]

In CHF, NPs have a significant role in both HF with reduced (HFrEF) and preserved (HFpEF) ejection fraction.[34,35] Multiple studies have assessed the role of NPs in guiding therapy. The randomised controlled trial (RCT)

STARS-BNP enrolled 220 patients with left ventricle ejection fraction (LVEF) <45% on optimal medical therapy. Patients were randomised to BNP-guided treatment to reach BNP levels <100 pg/ml or standard of care (SOC). After a median follow-up of 15 months, the BNP-guided group showed significantly lower rates of combined endpoint of death related to HF or hospital stay for HF compared to the unguided group, with no differences in all-cause death and all-cause hospitalisations.[36] The RCT PROTECT study was conducted on 151 patients with LVEF ≤40% at least once in the 6 months prior to enrolment, hospital admission, emergency department visit and outpatient therapy for destabilised HF. Patients were randomised to SOC plus NT-proBNP or SOC alone. At 1-year follow-up, cardiovascular (CV) events were significantly reduced, with a greater improvement in quality of life in the NT-proBNP group compared to the unguided group.[37] The larger GUIDE-IT trial showed that in 894 patients with LVEF ≤40% and a history of prior HF event, guiding treatment based on NT-proBNP levels was not superior compared to SOC strategy in improving the composite outcome of CV death or time-to-first HF hospitalisation.[38] These findings may be attributed to the influence of elevated NPs on the treatment decisions made by the physician. In an attempt to lower NP levels, physicians often increase the diuretic dose, a strategy that may have an unfavourable prognostic impact.[39] For patients with HFrEF on sacubitril/valsartan, the routine use of BNP as the substrate of neprilysin inhibition is not recommended. In these patients it is recommended to use NT-proBNP instead.[40] Elevated serum levels of NPs are associated with a higher risk of adverse events. Therefore, the assessment of NPs is also important as enrichment criteria for patients in clinical trials. A recent review has underlined how in 3,446 HF trials about 10% used NPs as eligibility criteria, with a different cut-off according to the goal and population of the study.[41]

Ultimately, NPs are good markers to detect congestion since plasma volume expansion and/or pressure overload, two key factors in a congestion state, induce biomechanical stress that, in turn, triggers the release of NPs precursors. Despite this close connection, several limitations exist in extensively using NPs to assess congestion appropriately. Primarily, demographical characteristics like older age and female sex, as well as several cardiac conditions, such as ischaemia, AF and hypertension, and non-cardiac conditions, such as hyperthyroidism and cancer, can lead to elevated NPs concentrations without necessarily indicating fluid retention.[42] On the contrary, obesity is associated with a suppression of NPs, resulting in a lower level of NPs. This creates the need for a lower cut-off for this group of patients.[43] Secondarily, left ventricular wall stress is the strongest trigger for NPs synthesis and release, as a result, NPs may not fully reflect the impact of right-sided HF and its associated systemic and extravascular congestion.[44] Third, NPs are not ideal substitutes for measuring filling pressures, making them less reliable in excluding HFpEF, especially in outpatient settings.[45] Fourth, due to uncertain evidence, there is no unanimous consensus on the use of NPs to guide management for patients with both AHF and CHF. Therefore, while NPs are a valid tool for detecting congestion and predicting the outcomes, given these limitations, the interpretation of NPs levels should always be associated by carefully assessing clinical and imaging findings.

Troponin

Troponin (Tn) is a contractile protein that regulates the process of cardiac muscle contraction. During situations of stress or cardiac damage, such as in acute coronary syndrome, its levels increase. Therefore, measuring serum Tn levels is a useful diagnostic tool for acute coronary syndromes. It is not widely used in clinical practice to diagnose, evaluate and manage congestion. Tn is increased in many situations other than HF; therefore, due to its poor specificity, it is little used as a biomarker in managing congestion in a patient with AHF.[27]

Patients with detectable cardiac Tn I were demonstrated to have higher pulmonary artery and capillary wedge pressures.[46] Additionally, congestion symptoms such as peripheral oedema and rales on admission were associated with Tn levels at discharge.[47] More recently, elevated Tn has been associated with clinical congestion scores, suggesting that subclinical myocardial damage may contribute to congestion.[48] Patients with a positive Tn level on admission or during hospitalisation had higher mortality and readmission rates than patients with negative Tn during hospitalisation.[49] High-sensitivity cardiac Tn (Hs-cTn) tests have also been shown to be useful for prognostic stratification in patients with AHF. Very low levels of Hs-cTn predict a good prognosis, while higher baseline values were associated with a higher risk of CV mortality and hospitalisation for HF.[50]

Carbohydrate Antigen 125

Mesothelial cells synthesise carbohydrate antigen (CA125) in response to increased hydrostatic pressures, mechanical stress and cytokine activation.[51] CA125 is used as a circulating biomarker for ovarian cancer monitoring. However, elevated CA125 levels can also be detected in other forms of cancer, even in benign conditions. Although the myocardium does not produce it, CA125 has emerged as a promising biomarker of congestion and inflammation.[51] CA125 is widely used and has a lower cost than NP. The half-life of CA125 is 5–12 days.[51] Most studies of CA125 in cancer patients have shown that in patients with stable HF, the CA125 value is mostly <35 U/ml.[51,52]

In patients with AHF, CA125 was strongly associated with signs of intravascular congestion (inferior vena cava diameter) and clinical congestion (peripheral oedema and pleural effusion).[53]

A study examining the prognostic abilities of NT-proBNP and CA125 according to tricuspid regurgitation (TR) status performed in 2,961 patients with AHF showed that CA125 surpassed NT-proBNP in predicting long-term mortality. NT-proBNP was significantly linearly associated with mortality in non-severe TR (p<0.001), but not in severe TR (p=0.308). In contrast, CA125 was associated with an increased risk of mortality both in patients with severe TR (HR 1.28; 98% CI [1.11–1.48]; p=0.001) and in the entire population (HR 1.09; 95% CI [1.03–1.14]; p=0.001).[54]

A meta-analysis of 16 studies in patients with AHF reported that elevated CA125 levels were associated with an increased risk of all-cause mortality (HR 1.44; 95% CI [1.21–1.72]; p<0.001) and HF-related hospitalisations (HR 1.51; 95% CI [1.11–2.04]; p<0.01).[55] CA125 emerged as an independent predictor of 6-month mortality, providing additional prognostic value over standard prognostic risk factors, including NP. In a subgroup of the BIOSTAT-CHF study, which included 2,516 patients with worsening HF, CA125 was strongly associated with the risk of 1-year mortality and the composite of death/hospitalisation for HF.[51]

In a prospective study of a group of 1,538 patients diagnosed with AHF, normalisation of CA125 (<35 U/ml) was associated with a lower risk of all-cause mortality or CV death at a median follow-up of 21 months.[51,52,56]

The IMPROVE-HF study evaluated CA125-guided therapy in 160 patients with AHF and renal dysfunction at presentation. It showed a trend towards a lower risk of clinical adverse events at 30 days in the CA125-guided group.[57]

CA125 also has a potential role in personalising diuretic therapy after hospitalisation for AHF. The CHANCE-HF trial enrolled 380 patients with AHF discharged with elevated CA125 levels (>35 U/ml).[58] In the study, the CA125-guided strategy was superior to the standard of care in reducing the composite endpoint of death or hospitalisation for AHF within 1 year.

In patients with CHF, elevated CA125 levels were also associated with signs of congestion and inflammation.[59] CA125 levels >35 U/ml are associated with a higher risk of death and hospitalisation for worsening HF and are consistently high in patients on the waiting list for cardiac transplantation.[59,60] Recently, a *post hoc* analysis of 1,111 participants from the EMPEROR-Reduced and EMPEROR-Preserved trials showed that levels of CA125 were not associated with signs or symptoms of congestion and that higher levels of CA125 were associated with a higher incidence of hospitalisation for HF or CV death in HFrEF but not in HFpEF.[61] Furthermore, changes in levels of CA125 reflect the clinical status. Increased values or lack of normalisation in the first few weeks after discharge may indicate persistent congestion and represent a higher risk of adverse events.

In stage D patients with HF, elevated CA125 levels were highly predictive of all-cause death, CV mortality, all-cause death/HF readmission and major adverse cardiovascular events (MACE), independently of NT-proBNP and other clinical risk factors, indicating an independent role of CA125 in predicting prognosis in this HF stage.[62] Similarly, these results were replicated in another cohort of stage D patients with HF, including mostly HFpEF subjects.[63]

Suppression of Tumorigenicity 2

Suppression of tumorigenicity 2 (ST2) is a receptor belonging to the interleukin (IL)-1 receptor family.[64] ST2 exists in four isoforms, but only two are biologically active: the membrane-bound receptor form (ST2L) and the soluble form (sST2). Both isoforms bind to IL-33. The interaction between ST2L and IL-33 triggers prevents apoptosis, hypertrophy and myocardial fibrosis. On the other hand, ST2s act as a decoy receptor on IL-33, neutralising the effects of the cardioprotective pathway, and promoting myocardial fibrosis, ventricular remodelling and congestion.[65] Recently, several studies have highlighted the prognostic role of ST2s in patients with HF. In the acute setting, elevated levels of ST2 at admission are associated with the degree of clinical severity and a significant increase in 1-year mortality.[66] Manzano-Fernández et al., in a cohort of 72 patients with decompensated AHF, showed how ST2 concentrations tend to have a prognostic value both at presentation and during hospitalisation.[67] In the PRIDE study, this substantial prognostic value resulted independently from NT-proBNP levels.[68] In CHF, ST2 strongly predicts both overall and CV death, as well as worsening renal function.[69,70] As already observed in the acute setting, the prognostic value of ST2s is independent of NT-proBNP and high-sensitivity troponin T levels.[71] Interestingly, Piper et al. observed in a cohort of 50 patients with CHF that the biological variability of ST2s is significantly lower compared to NPs, both at baseline and at up to 6-month follow-up.[72] This finding, combined with considering the independent prognostic role of ST2s in CHF, provides further evidence that ST2s may represent a useful biomarker for patient monitoring and clinical decision-making.[70]

Bio-adrenomedullin and Mid-regional Pro-adrenomedullin

Adrenomedullin (ADM) is a 52-amino acid peptide encoded by the ADM gene located on chromosome 11.[73] ADM derives from a preprohormone composed of 185 amino acids, which, once translated, is activated by enzymatic amidation.[74] The main role of ADM is to stabilise vascular endothelial cells and the vascular barrier, regulating vascular tone via vasodilation. It is released as a counteracting response to volume overload. In HF, endothelial dysfunction leads to increased plasma levels of bio-ADM to limit vascular leakage by stabilising endothelial barrier function.[75] For this reason, it has a potential role as a marker of vascular and tissue congestion in HF.[76]

The proposed cut-off value of bio-ADM to assess congestion (defined as a congestion score calculated as the sum of peripheral oedema, JVP and orthopnoea >1) was defined as 34 pg/ml.[77]

Bio-ADM was associated with the presence of symptoms of congestion, such as oedema, orthopnoea and elevated JVP.[77] Furthermore, bio-ADM is correlated with haemodynamic parameters such as pulmonary capillary wedge pressure (PCWP) and right atrial mean pressure, and is also associated with NT-proBNP.[78] The midregional pro-adrenomedullin (MRproADM), a non-functional fragment of bio-ADM, larger and more stable than the active ADM, is also strongly correlated with pulmonary artery mean pressure and PCWP and inversely correlated with compliance of the pulmonary artery in subjects with HFpEF.[79] Bio-ADM levels are often elevated at admission in patients with AHF and remain elevated throughout the first week of hospitalisation.[76] Similar to CA125, bio-ADM could help personalise post-discharge diuretic treatment. MRproADM had even greater accuracy in predicting 1-year all-cause mortality than bio-ADM, with no difference based on obesity as for bio-ADM.[79]

Furthermore, bio-ADM could become a therapeutic target in HF. Adrecizumab, a humanised monoclonal antibody that binds but does not inhibit bio-ADM, significantly increases plasma bio-ADM, displacing bio-ADM from the interstitium into the vascular system. Decreasing interstitial ADM might improve vascular integrity and vasodilation.[80] Two randomised phase IIa clinical trials are currently investigating the safety, tolerability and efficacy of adrecizumab compared to placebo in 301 patients with sepsis and in 30 patients hospitalised for AHF (NCT04252937). The results could greatly assist in addressing the clinical needs of patients with severe interstitial congestion and normal intravascular volume.

Soluble Melanoma Cell Adhesion Molecule

Soluble melanoma cell adhesion molecule (CD146s) is a junctional adhesion glycoprotein that plays a role in regulating vessel integrity, and it is secreted into the blood in case of venous stretching due to congestion.[81] CD146s has a potential role as a novel biomarker of systemic congestion. Van Aelst et al. illustrated the strong correlation between congestion and CD146 levels in patients with AHF.[82] Gayat et al. found that plasma levels of CD146s have a similar discriminative power compared to NT-proBNP for diagnosing AHF in patients admitted to emergency department with acute dyspnoea, with respectively an overall area under the curve (AUC) of 0.870 (95% CI [0.819–0.915]) and 0.917 (95% CI [0.874–0.952]). Adding the assessment of CD146s to NT-proBNP measurement improved diagnostic ability in patients with borderline NT-proBNP levels, making it particularly useful for ruling out AHF. Furthermore, CD146 levels are strongly associated with both chronic diuretic therapy and the presence of peripheral oedema upon admission, as well as with a reduction in vena cava diameter from admission to discharge.[83]

Haemoconcentration and Worsening Renal Function

Although not strictly a biomarker, haemoconcentration is also a surrogate for plasma volume reduction. Haemoconcentration is an

increased concentration of the cellular components of blood (red blood cells, white blood cells and platelets) in the blood plasma. Haemoconcentration can occur in conditions such as dehydration, shock, excessive use of cigarettes or intense physical exercise. Haemoconcentration is associated with greater weight and fluid loss, more significant reductions in filling pressures and greater decongestion, and improved survival.[84]

Among the various available methods, serial measurements of estimated plasma volume (ePVS) using routine blood count and/or body weight may be helpful in HF management.[85]

Both the degree of diuretic response and haemoconcentration can be considered markers of effective decongestion. They have individually been found to predict 60-day rehospitalisation after admission for AHF. The PROTECT study is a randomised controlled trial evaluating the effect of the selective adenosine A1 receptor antagonist rolofylline versus placebo in patients with AHF and volume overload to assess the impact of treatment on renal congestion and function.[86] In this study, effective decongestion, defined as an acceptable diuretic response and the presence of haemoconcentration, was associated with a lower risk of rehospitalisation for HF (multivariate HR 0.41; 95% CI [0.24–0.70]; p<0.001).[86] Similar results were also produced by the EVEREST trial, an event-driven, randomised, double-blind, placebo-controlled study that evaluated the efficacy of vasopressin antagonism (tolvaptan) in HF outcomes. In this study, a strong association between haemoconcentration and a reduced risk of adverse events was demonstrated (multivariate HR 0.52; 95% CI [0.33–0.82]; p=0.004).[87,88]

Additionally, a retrospective study that included approximately 4,181 patients admitted to hospital with a diagnosis of decompensated AHF assessed whether haemoconcentration and worsening creatinine could better identify patients who had been treated aggressively and had better post-discharge outcomes. Those who experienced both haemoconcentration and worsening creatinine at any time had a profile consistent with aggressive hospital treatment and a longer length of stay (7.1 versus 6.2 days, p=0.001), higher doses of loop diuretics (196 versus 142 mg, p<0.001), greater weight (2.9 ± 0.21 versus 2.0 ± 0.1 kg, p=0.001), and net fluid loss (3,399 ± 176 versus 2,215 ± 64 ml, p<0.001) compared with the rest of the cohort. Notably, neither worsening creatinine (HR 0.91; 95% CI [0.81–1.02]; p=0.11) nor haemoconcentration (HR 0.94; 95% CI [0.83–1.07]; p=0.36) at any time were associated with improved survival.[89]

Worsening renal function (WRF) alone is not an independent determinant of outcome in patients with AHF and WRF has been linked to higher risks of death and CV events. It has an added prognostic value when it occurs in patients with persistent signs of congestion. Patients with WRF and no congestion had similar outcomes compared to those without WRF and no congestion. The risk of death or readmission for AHF was increased in patients with persistent congestion alone with or without WRF.[90] Furthermore, the risk of death or CV events was reduced in WRF patients with evidence of decongestion, such as improved BNP, haematocrit, and albumin.[91]

Novel Biomarkers to Detect Congestion

Galectin-3

Galectin-3 (GAL-3) is a multifunctional protein belonging to the lectin family, playing a role in several cellular processes, such as growth, adhesion and apoptosis, as well as in inflammation pathways. A *post hoc* analysis of the PRIDE study compared the plasma levels of NT-proBNP, apelin and GAL-3 in 209 patients admitted to hospital with a diagnosis of AHF. Although for AHF diagnosis NT-proBNP showed the greater AUC compared to GAL-3 and apelin, respectively 0.94 (p<0.0001), 0.72 (p<0.0001), 0.52 (p=0.23), the receiver-operator characteristic (ROC) analysis for 60-day prognosis showed that GAL-3 has a significantly greater AUC compared to NT-proBNP and apelin, respectively 0.74 (p=0.0001), 0.67 (p=0.009), 0.54 (p=0.33). Furthermore, in adjusted multivariate analysis, a higher concentration of GAL-3 was the best independent predictor of 60-day mortality (OR 10.3; p<0.01).[92] In a cross-sectional study that enrolled 100 patients with a new diagnosis of HF, plasma levels of GAL-3 were significantly higher among those with more severe and advanced HF according to the NYHA classification, underlining the possible use of these markers in the staging of HF.[93] Piper et al. measured the plasma concentrations of GAL-3 and NT-proBNP, at baseline and at 1, 3 and 6 months in 50 patients with stable CHF on OPT, demonstrating that both GAL3 levels change over time and at 6 months, GAL-3 outperformed NT-proBNP in predicting CV admissions (AUC 0.803; p=0.012 versus AUC 0.571; p=0.571; p=0.553).[94]

Fibroblast Growth Factor 23

Fibroblast growth factor 23 (FGF-23) is a hormone primarily released by osteocytes and osteoblasts, playing a crucial role in phosphate and vitamin D metabolism and kidney sodium reabsorption. A *post hoc* analysis of the BIOSTAT-CHF study showed how, in 2,399 patients with new onset or worsening HF, elevated plasma concentrations of FGF23 were independently associated with fluid overload and increased risk of all-cause mortality and hospitalisation for heart failure.[95] In a prospective registry that enrolled 344 patients with stable HFrEF, FGF-23 was strongly associated with both right ventricular (RV) dysfunction grade and systemic congestion in multivariate regression analysis.[96]

Endothelin-1

Endothelin-1 (ET-1) is a strong vasoconstrictor peptide produced mainly by endothelial cells, smooth muscle and epithelial cells. It is crucial in regulating vascular tone, blood pressure, inflammation and fluid balance. In a case-control study of 56 patients with congestive HF and 71 healthy control subjects, the mean plasma concentration of ET-1 was significantly higher in the HF group than in the healthy control group (12.6 ± 0.6 pg/ml versus 7.1 ± 0.1 pg/ml, p=0.001). Additionally, patients with NYHA I or II had higher concentrations of ET-1 compared to the healthy control group (11.1 ± 0.7 pg/ml versus 7.1 ± 0.1 pg/ml, p<0.001). Similarly, patients with HF and NYHA III–IV had higher values of ET-1 compared to those with NYHA I–II (13.8 ± 0.9 pg/ml, p=0.029), suggesting a positive correlation between ET-1 levels and severity of disease.[97] Recently, an observational study of 113 patients with AHF showed that higher values of ET-1 were significantly related to clinical signs of peripheral congestion and low urine sodium excretion, an essential driver of persistent congestion.[98]

Future Directions

The research for new biomarkers specific to congestion, as well as those that can predict the risk of congestive events in patients with HF, is the pivotal focus toward which research is moving. Identifying and measuring these biomarkers would allow both a faster treatment of congestive conditions and the adoption of preventive measures aimed at improving patient quality of life and prognosis while reducing healthcare associated with hospital or outpatient admissions. Furthermore, future research could investigate combining several biomarkers into a single score to make diagnosing and predicting HF

more accurate. Using advanced tools like artificial intelligence (AI) and machine learning with these biomarkers could further improve predictive models and help analyse complex biomarker data in real time. In the future, it will also be of great interest to assess how new drugs impact congestion biomarkers, such as sacubitril/valsartan, which increases circulating BNP plasma levels due to its intrinsic mechanism of action. It can also be hypothesised that future biomarkers may be useful in the phenotyping of HF patients and, based on their values, contribute to a more accurate prognostic stratification. Finally, the new biomarkers could be helpful in defining the criteria for clinical trials, helping to enrol only patients who would potentially benefit from the drugs under investigation.

Conclusion

Biomarkers are a versatile strategy for diagnosing and managing congestion in patients with HF. NPs represent the most widely available tool, helping in the diagnosis, risk stratification and management of patients with HF.

Several novel biomarkers are under investigation, showing promising results in assessing congestion. When combined with NPs, these emerging biomarkers exhibit a complementary role in diagnosing and predicting outcomes. However, further research is warranted to investigate their independent and predictive role before being recommended in clinical practice. ❑

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