Congestive Biomarkers in HFrEF

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In heart failure with reduced ejection fraction, edema and congestion are related to reduced cardiac function. Edema and congestion are further aggravated by chronic kidney failure and pulmonary abnormalities. Furthermore, together with edema/congestion, sodium/water retention is an important sign of the progression of heart failure. Edema/congestion often anticipates clinical symptoms, such as dyspnea and hospitalization; it is associated with a reduced quality of life and a major risk of mortality. It is very important for clinicians to predict the signs of congestion with biomarkers and, mainly, to understand the pathophysiological findings that underlie edema. Not all congestions are secondary to heart failure, as in nephrotic syndrome.

biomarkers congestion HFrEF heart failure

1. Introduction (Congestion in HFrEF)

Heart failure (HF) is a complex syndrome consisting of symptoms (e.g., breathlessness and fatigue) usually accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise [1].

Researchers can distinguish specific phenotypes based on the assessment of left ventricular ejection fraction (LVEF). Reduced LVEF (i.e., significant reduction in LV systolic function) is defined as ≤40%; those with HF symptoms and signs in the presence of reduced LVEF are designated as HF with reduced ejection fraction patients (HFrEF).

Despite recent advances in HFrEF management (either pharmacological or non-pharmacological), HFrEF remains a highly prevalent disorder with a high mortality rate and is burdened by several hospitalizations for acute decompensated heart failure (ADHF) [1].

ADHF hospitalizations are generally associated with signs and symptoms of congestion [2]. ADHF recurrence is often the consequence of fluid retention, which leads to both systemic and pulmonary congestion [3][4][5]. In HFrEF patients, congestion may be an important target for therapy. Moreover, the lack of congestion resolution during HF hospitalization or the occurrence of residual edema after discharge may be associated with poor outcomes [6]. Increased severity of congestion evaluated by a simple orthodema assessment is related to augmented morbidity and mortality [7].

Systemic congestion is not exclusively related to cardiac congestion, and the simple absence of clinical signs of fluid overload cannot exclude increased left ventricular filling pressures (LVEDP) [8].

Researchers can distinguish two different forms of congestion: the intravascular one if congestion is predominantly present in the vascular system, and the tissue one if it is interstitial. Although most HF patients have a combination of both forms, one phenotype can prevail. Each of these kinds of congestion has a specific pathophysiology and requires a different diagnostic approach.

Peripheral congestion occurs in the form of peripheral edema, with a palpable swelling in the body tissues caused by an expanded interstitial fluid volume. This occurs if the capillary filtration exceeds the amount of fluid conducted out by lymphatic drainage. It is observed in different clinical conditions like HF, renal failure, liver failure, or pathologies affecting the lymphatic system. Edema usually becomes clinically apparent when the interstitial volume exceeds 2.5–3 L.

Assessment of congestion by a simple clinical evaluation remains unsatisfactory. The most commonly used and traditional strategy is clinical evaluation, associated with chest radiography and natriuretic peptide (NP) measurement [9][10].

It is very important for clinicians to predict the presence of congestion with biomarkers and to understand the pathophysiological mechanisms that underlie edema.

There is increased attention not only on the role of congestion biomarkers in recognizing patients at risk of developing HF who are potential candidates for targeted treatments for its prevention, but also on their role in formulating an initial diagnosis and a prognostic stratification.

2. Definition of Biomarkers

A biomarker is a biological molecule found in blood, other body fluids, or tissue and may relate to data obtained from vital parameters (e.g., blood pressure), or from imaging/instrumental tests [11].

Biomarkers can help in identifying disease peculiarities (risk factor or risk marker), disease state (preclinical or clinical), or disease outcome (rate of progression) [12]. Biomarkers can be classified as antecedent biomarkers (assessing the risk of developing a disease), screening biomarkers, diagnostic biomarkers, staging biomarkers (categorizing the disease severity), or prognostic biomarkers (if helpful in predicting the evolution) [13]. They play different roles in diagnosis, prognostic prediction, and assessment of therapy response, like natriuretic peptides in HF or sputum nanoparticles in inflammatory lung disease do [14].

Ideal biomarkers should be precise, standardized, patient-acceptable, easily interpretable by clinicians, sensitive, and highly outcome-specific.

3. Congestive Biomarkers

Many researchers have sought out cardiac biomarkers to improve the prediction, diagnosis, and prognosis of HF. Several biomarkers related to different findings in HF pathophysiology have been studied (**Table 1**) [15][16].

Table 1. Established and emerging biomarkers in HF.

Main Group	Subgroup	Biomarker
Myocardial insult	Myocyte stretch	ANP, BNP, NT-proBNP, MR-proANP, GDF-15, neuregulin
	Myocardial injury	Troponin T, TRoponin I, hsTN, heart type fatty acid protein, myosin light-chain kinase1, creatinine kinase MB fraction
	Oxidative stress	Myeloperoxidase, MR-proADM, oxidized low-density lipoprotein, urinary biopyrrins, plasma malondialdehyde
Neurohormonal activation	Renin-Angiotensin System	Renin, Angiotensin II, Aldosterone
	Sympathetic Nervous System	Norepinephrine, Chromogranin A
	Arginine Vasopressin system	Arginine vasopressin, copeptine
	Endothelin	Endothelin-1, big proET-1
		Chromogranin A and B
Myocardial Remodeling	Inflammation	C-reactive protein, TNF-α, Fas (APO-1), interleukins 1, 6, and 18, cytokines, procalcitonin, adipokines, adiponectin
	Hypertrophy/Fibrosis	SolubleST2, Galectin-3, matrix metalloproteinases, collagenpeptide

ANP—atrial natriuretic peptide; BNP—B-type natriuretic peptide; GDF-15—growth differentiation factor 15; NT-proBNP—N-terminal pro B-type natriuretic peptide; MR-proANP—mid-regional pro atrial natriuretic peptide; MR-proADM—mid-regional pro-adrenomedullin; TNF-α—tumor necrosis factor 1.

Natriuretic peptides (NPs) are the most known and widely used biomarkers. Brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are neurohormones produced and stored in the heart, both in the atria and ventricles, and released from the heart due to increased end-diastolic wall stress in response to pressure changes and volume overload.

NPs are synthesized as prohormones and subsequently cleaved into the active hormones BNP and ANP, and into the inactive NT-proBNP and mid-regional proANP (MR-proANP). Circulating BNP and ANP half-lives are relatively short (about 20 min). Plasma endopeptidases and NP receptors remove them from the circulation. NT-proBNP and MR-proANP have longer circulating half-lives (around 90 min), and their clearance is mainly renal [17][18].

Cardiac troponins (cTn) are usually evaluated in patients with acute HF (AHF) to rule out myocardial infarction. However, congestion at the admission was significantly associated with cTn levels at the time of discharge,

implying that the high intracardiac filling pressure and the increased wall stress associated with HF decompensation can induce subclinical myocardial injury [19]. The primary function of troponin levels in HF is to stratify risk of cardiovascular events [20][21]. Higher troponin I or T levels at the hospital admission of patients with AHF were associated with lower EF and a higher rate of in-hospital mortality [20][21].

Recently accumulating data suggest cancer antigen-125 (CA-125) as a marker of congestion in HF. The increase in circulating CA-125 concentrations is due to at least two pathophysiological mechanisms that partially overlap [22]. On the one hand, there is the mechanical stress produced by excessive fluid accumulation. This increased stress activates c-Jun N-terminal kinase (JNK) pathways and raises the synthesis of CA-125 [23]. Moreover, there is the activation of the O-glycosylated extracellular domain of CA-125. The result is the release of CA-125 from the actin cytoskeleton of mesothelial cells and its increased concentration in the periphery [24]. On the other hand, there is an inflammatory mechanism. A linkage between CA125 and proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-10, has been described [25]. Venous congestion has been shown to alter the expression of certain models in the endothelium and congested perivascular tissue to the activated state, resulting in an upward regulation of pro-oxidant, proinflammatory, and vasoconstricting factors [26]. Furthermore, inflammatory stimuli worsen fluid overload by affecting the neurohumoral and endocrine systems [27]. Overall, volume overload and inflammation in HF mutually interact, increasing each other's activity in a bidirectional manner, thus creating a positive feedback loop that leads to elevated CA125 concentrations [28]. CA125 has been demonstrated to be a tool for risk stratification in patients with chronic HF and in patients admitted with ADHF [30]. CA125 <23 U/mL identifies a subgroup of patients at low risk of short-term adverse events [29].

CA125 and no NT-proBNP seem to identify patients with AHF, and congestive intrarenal venous flow (IRVF) patterns. The IRVF measured by Doppler ultrasound may be a potential surrogate marker of renal congestion and adverse outcomes in heart failure [30].

Soluble suppressor of tumorigenesis-2 (sST2, also known as interleukin-1 receptor-like 1), the circulating form of the interleukin-33 membrane receptor, is secreted by myocardial cells in response to cardiac overload. Vascular congestion, mechanical stretch, and inflammation stimulate the expression of sST2 [31]. Lungs have been documented as a relevant source of sST2 in HF. sST2 is a powerful predictor of mortality and hospitalization in AHF or chronic HF (CHF) independently from NT-proBNP, hs-troponin T, and LVEF, almost unaffected by age, sex, body mass index, renal function, or ischemic aetiology [32].

The protein galectin-3 is currently gaining interest as an eligible biomarker in cardiac disease. Galectin-3 is a biomarker of fibrosis, inflammation, and oxidative stress. Normally, Gal-3 expression in the heart is low. In the failing heart, Gal-3 is released by activated cardiac macrophages and cardiac fibroblasts [33], taking part in ventricular remodeling [34]. Elevated galectin-3 levels in patients with HFrEF are associated with concomitant RV dysfunction and exercise intolerance [35].

Cholestatic liver injury can be measured by bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase levels [36], which have been suggested as possible congestion biomarkers [37]. Moreover, the decreased cardiac

output and subsequent low liver perfusion may induce acute hepatocellular necrosis [38]. Increased levels of aspartate aminotransferase, alanine aminotransferase, and bilirubin are found in patients with low cardiac output [39].

Laboratory anomalies of liver function may predict the prognosis of patients with advanced HF, and the assessment of both cardiac and liver function is very important in the management of these patients [40].

Hemoconcentration could be another sign of congestion. Plasma volume may be indirectly estimated by several formulas using hemoglobin and/or hematocrit levels, which seem useful for monitoring congestion and decongestion both in acute and chronic settings [41].

Several other biological parameters that are routinely evaluated in patients with HF, such as serum protein, albumin, hemoglobin, and hematocrit, have been correlated with prognosis and proposed as alternative markers for monitoring congestion. However, their utility as decongestion biomarkers is limited by the fact that small changes may be caused by other conditions, and that they do not reflect the absolute change in plasma volume [42].

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