



# The emerging role of new biomarkers of congestion in heart failure

Hesham R. Omar<sup>1</sup>, Maya Guglin<sup>2</sup>

<sup>1</sup>Internal Medicine Department, Mercy Medical Center, Clinton, Iowa, USA; <sup>2</sup>Division of Cardiovascular Medicine, Linda and Jack Gill Heart Institute, University of Kentucky, Lexington, KY, USA

Correspondence to: Hesham R. Omar. Internal Medicine Department, Mercy Medical Center, Clinton, Iowa, USA.

Email: hesham.omar@apogeephysicians.com.

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The prevalence of heart failure (HF) continues to grow rapidly and is projected to rise by 46% by 2030 (1). High morbidity and mortality in patients with this condition creates a need for reliable and affordable non-invasive monitoring tools that can guide the therapy and predict outcomes. In a recent paper by Arrigo and colleagues (2), authors investigate a novel biomarker, Soluble CD146, and compare it with a well-established natriuretic peptide: NT-proBNP. In order to better understand the value of this study, we'll briefly summarize the history, biology, and significance of natriuretic peptides and briefly review other biomarkers of congestion in HF.

## Natriuretic peptides

The advent of natriuretic peptides represented a diagnostic breakthrough in the field of HF. The initial discovery of the atrial natriuretic peptide (ANP) by de Bold and colleagues who found a natriuretic response in rats following parenteral injection of atrial myocardial extract (3), was followed in 1984 by the purification and isolation of this 28-amino-acid polypeptide from the cardiac atria (4,5). Four years later, a closely related 32-amino acid polypeptide was identified in pig brains, now known as the B-type natriuretic peptide (BNP) (6). Subsequently, BNP was found at much higher concentrations in cardiac tissues (7). Both peptides cause a diuretic, natriuretic and vasorelaxant effect and suppression of the renin angiotensin aldosterone system (8). Prior to activation, BNP is stored as a 108 amino acid polypeptide

precursor named proBNP in the ventricle and, to a lesser degree, in the atria. Following secretion in response to volume overload and myocardial stretch, proBNP is cleaved to a 76-peptide, N-terminal fragment NT-proBNP, and the biologically active BNP, and both are then secreted in the plasma. BNP is then cleared from the circulation by natriuretic peptide receptors and endopeptidases, explaining its short half-life of ~20 minutes (9) unlike NT-proBNP which has a longer half-life of ~1–2 hours due to lack of receptor-mediated clearance in the latter. Hence, levels of NT-proBNP are 3–5 times higher than BNP. Although both peptides are affected by kidney function, the impact on NT-proBNP is more pronounced (10). Since elevated ventricular filling pressure was found to be the main stimulus for their release, both peptides have been extensively studied in HF and were found to have value in diagnosis, and risk stratification of patients. The utility and value of natriuretic peptides has also been extended to other cardiovascular and pulmonary pathologies including myocardial ischemia, cor pulmonale, aortic dissection, pulmonary embolism and pulmonary hypertension.

However, there are multiple limitations hindering this diagnostic and prognostic utility of BNP in HF. Understanding these limitations requires awareness of BNP pharmacokinetics and pharmacodynamics. Important considerations when interpreting a BNP value in a patient with acute or chronic HF should take into account its half-life and time of its measurement relative to the onset of symptoms and its dependence on renal function

for clearance. Also, BNP levels vary by multiple factors including—but not limited to—patients' age, sex (11), body mass index (12) and genetic polymorphism (13). Among the reported BNP limitations in acute HF is the lack of linear relationship between BNP and patient symptoms (14). Looking at a single BNP value on admission in patients with acute HF did not predict the degree of congestion, whether assessed clinically, by echocardiography or through central hemodynamic variables of congestion measured by the pulmonary artery catheter (15). Extremes of BNP levels (e.g., very low or very high level) were not associated with the degree of congestion. For example, a normal admission BNP in patients with acute systolic HF had no diagnostic or prognostic effect (16). Also, extremely elevated BNP was not associated with more severe congestion (17-19). Clinical presentation rapidly after symptom onset may not allow sufficient time for BNP elevation since approximately 2-hours are required to reflect changes due to HF because of its half-life of ~23 minutes. Several case reports highlighted this limitation and emphasized the importance of repeat BNP measurements to confirm the diagnosis of HF (20). Also, studies that examined the value of BNP-guided therapy in HF showed conflicting results with some studies showing improved outcomes (21-23) and other showing no benefit (24-26). Moreover, several reports indicated that extreme elevation of BNP occurs in some patients with malignancies with no association with volume status or HF (27). Besides, it is known that existing commercial laboratory assays pick up multiple forms of BNP, different from biologically active BNP or NT-proBNP. Hawkrige and colleagues found that uncleaved monomers of BNP, and noncovalently linked trimers or tetramers of prohormone BNP with high molecular mass interact with commercial BNP assays and could confound the results (28).

Therefore, utilizing natriuretic peptides in managing HF patients is heralded by multiple limitations. Healthcare providers treating these patients should be familiar with these limitations and to avoid using natriuretic peptides as the sole determinant of volume status and degree of diuresis in patients with suspected HF. Since the concentrations of circulating natriuretic peptides released by the failing heart reflect only indirectly the severity of systemic congestion (29) and are affected by multiple other confounding variables, other biomarkers were investigated for the same purpose.

Biomarkers of myocardial stretch investigated in HF include ANP, the analysis of which has been infeasible

because of its short plasma half-life and the instability of NT-proANP (30), hence, analysis of mid-regional pro-atrial natriuretic peptide (MR-proANP) has been attempted. In a meta-analysis of five previous trials investigating the diagnostic value of MR-proANP, Hu and colleagues found a 90% sensitivity and a 68% specificity for diagnosing HF in patients with shortness of breath (31). Other considerations include confounding effect of atrial arrhythmias due to the atrial origin of ANP (32). It is also not well studied in chronic HF. The role of MR-proANP is therefore mainly restricted for patients with equivocal BNP values. The limitations in utilization of natriuretic peptides resulted in search of different biomarkers.

### Other biomarkers

Other HF biomarkers include galectin-3 which can identify HF as a cause of dyspnea with a reasonable AUC of 0.72, but inferior to NT-proBNP (33) and these findings were reproduced by subsequent researchers and have been listed in the ACC/AHA guidelines for HF management (34). Mid-regional proadrenomedullin (MR-proADM) is another biomarker of myocardial strain with ability to diagnose acute HF in dyspneic individuals, but was inferior to NT-proBNP in the PRIDE study with an AUC of 0.8 compared with 0.94 for NT-proBNP (32). The addition of MR-proADM to NT-proBNP improved the diagnostic accuracy via an increase in AUC from 0.81 to 0.84 (35). ST2 is another inflammatory marker that was found in higher levels in those with acute HF (36). Growth differentiation factor-15 (GDF-15) is another biomarker of HF that was elevated in patients with stages A–C HF compared with healthy controls, and its level increased with worsening heart disease (37). It may also identify subjects with HF and preserved ejection fraction (38) and distinguish between patients with asymptomatic left ventricular diastolic dysfunction and those with normal diastolic function (39).

### Soluble CD146

Arrigo and colleagues recently investigated soluble CD 146—which is released by veins in response to stretch—as a marker of systemic congestion (2). They found that induction of venous stress was associated with a rise in soluble CD146 in the congested arm (+60 µg/L) compared to control arm (+16 µg/L,  $P=0.025$ ), while no difference in NT-proBNP concentrations was seen. This

finding is not surprising because, unlike NT-proBNP, soluble CD146 is an endothelial marker released by peripheral vasculature. Similarly, the lower soluble CD146 concentrations in coronary sinus than in peripheral veins add nothing to clinical significance of this biomarker but confirm its extracardiac origin. The only clinically relevant finding is that increased peripheral vein concentrations of soluble CD146 were associated with higher risk of major adverse cardiac events at two years. At this point, it would be important to do a side-by-side comparison of NT-proBNP and CD146. The advantage of adding CD146 as yet another biomarker would be indicated if it has clear advantages over established biomarkers. For not entirely explained reasons, the author chose to instead calculate the risk of the events predicted by soluble CD146 and adjust it to the concentrations of NT-proBNP.

In conclusion, this study certainly adds to the knowledge of the biomarkers in HF, including those secreted in the endothelium of peripheral vessels. However, the clinical importance of this marker still remains unproven. Larger prospective studies are needed to show whether soluble CD146 is able to detect subclinical congestion, its diagnostic and prognostic utility and its potential to guide decongestive therapy.

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