A Review

A review on application of biomarkers in heart failure

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Heart failure (HF) remains the leading cause of death in the elderly population. Since last decade there is an advance in the field of biomarkers in managing these patients. Hence identifying novel and potential biomarkers that help in accessing the risk, predicting the disease and monitoring the prognosis is very crucial in reducing the overall morbidity and mortality. These biomarkers are elevated mainly in response to myocardial stress, dynamic changes in extracellular matrix, myocyte necrosis, oxidative stress, and inflammation. The biomarker that has good clinical correlations may be useful in diagnosis, prognosis, and therapeutic management of HF. Understanding the role of each biomarker and their clinical implication is very crucial. In this review, we summarize the attainments and challenges of using different types of biomarkers in HF.

Keywords: Atrial natriuretic peptide, B-type natriuretic peptide, Galectin-3, Heart failure, High sensitivity troponin, Natriuretic peptides, Neutrophil gelatinase-associated lipocalin, Peptides, ST2

Heart failure (HF) is generally a chronic condition and is the major public health problem in developed countries like the USA with a prevalence of over 5.8 million, and over 23 million worldwide. India is the second most populous country in the world and cardiovascular diseases (CVDs) are the main cause of morbidity and mortality. The global burden of the disease study has revealed that the age-standardized cardiovascular disease death rate was 272/100000 population in India, which is higher than the global average of 235/100000 population. A recent study survey from rural north India adult population of 10163 patients revealed that 1.3% of them exhibit chronic breathlessness and 9% (1.2/1000) of the population had HF, among which 33% of the patients were found to have systolic dysfunction. In the same study, they also showed that the prevalence of HF in individuals below 30 years was 22.5% and above 50 years was 14.9%, indicating that most of the young population are affected with HF.

Heart failure is a pathological state in which an abnormality of myocardial function, failure of the heart to pump blood at proportionate rate to metabolizing tissues during regular activity. The various factors such as ischemic heart disease (IHD), hypertension, obesity, diabetes, age, sex, smoking, alcohol consumption, renal disease, sleep apnea, and depression are known to be the risk factors for HF. Heart failure is seen more in men than women, and its prevalence greatly increases with aging. Different models (hemodynamic model, cardio-renal model, neurohumoral model, abnormal Ca2+ cycling model, cell death model) have been proposed to explain unique mechanisms involving in HF. The hemodynamic changes that result in HF are primarily ventricular remodeling, renal failure, extracellular matrix (ECM) remodeling, myocardial fibrosis and myocardial necrosis. As a result of these pathogenic mechanisms, the various kinds of biomarkers will be released into the body fluids which are useful in diagnosis, severity and estimating the HF prognosis with appropriate therapy.

Biomarkers

Biomarkers are substances that are elevated in an early stage of disease and also during the disease progression which helps in assessing the risk associated with each stage of the disease. The biomarkers play an important role in HF which provides the information about the mechanisms involved in specific types of HF and helps in identify the patients at higher risk. The biomarkers are proteins that are released from the particular sites in...
the body in response to stress or damage and that can be objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or the response to a therapeutic intervention (Table 1). Several promising novel biomarkers have been identified for the diagnosis and prognosis of HF and tested for their clinical utility in chronic HF which includes those of myocardial stretch: brain natriuretic peptide (BNP), NT-proBNP, mid-regional pro-adrenomedullin (MR-pro ADM), markers of myocyte injury such as troponins and other biomarkers that show promising utility in HF are C-reactive protein (CRP), Galectin-3 (Gal-3), Interleukin-6 (IL-6), ST-2, neutrophil gelatinase-associated lipocalin (NGAL), growth differentiation factor-15 (GDF-15). Some of these markers have been tested and introduced for their clinical use in chronic HF (Fig. 1).

**Natriuretic peptides**

Natriuretic peptides (NPs) are considered the gold standard and they were recognized as important predictors in patients with HF. The heart secretes natriuretic peptides in response to the homeostatic signal to maintain the cardio-renal homeostasis. In humans, the peptides are classified based on the origin which consists of peptides with a 17-amino acid disulfide ring structure those are cardiac origin- ANP, BNP, renal origin-urodilatin, and endothelial origin-circulating natriuretic peptides (CNPs). These three peptides are involved in the maintenance of cardio-

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### Table 1—Heart failure diagnostic performance of various biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Optimal cut-point</th>
<th>Rule out</th>
<th>Grey zone</th>
<th>Rule in</th>
<th>Sensitivity</th>
<th>specificity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>100 pg/mL</td>
<td>&lt;100 pg/mL</td>
<td>100-400 pg/mL</td>
<td>&gt;400 pg/mL</td>
<td>100%</td>
<td>97.1%</td>
<td>36</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>300 pg/mL</td>
<td>&lt;300 pg/mL</td>
<td>300-450 pg/mL</td>
<td>&gt;450 pg/mL</td>
<td>-</td>
<td>-</td>
<td>36</td>
</tr>
<tr>
<td>NT-proBNP &lt;50 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&gt;450 pg/mL</td>
<td>97%</td>
<td>93%</td>
<td>36</td>
</tr>
<tr>
<td>NT-proBNP 50-75 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>900 pg/mL</td>
<td>90%</td>
<td>82%</td>
<td>36</td>
</tr>
<tr>
<td>NT-proBNP &gt;75 years</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1800 pg/mL</td>
<td>85%</td>
<td>73%</td>
<td>36</td>
</tr>
<tr>
<td>ST2</td>
<td>140.0 pg/mL</td>
<td>-</td>
<td>-</td>
<td>263.3 pg/mL</td>
<td>-</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>1.4-94.8 ng/mL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>GDF-15</td>
<td>1200-1800 ng/mL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>NGAL</td>
<td>60-123 ng/mL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>hsTnT</td>
<td>14 ng/mL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>94</td>
</tr>
</tbody>
</table>

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Fig. 1—Various biomarkers and pathways involved in the development of heart failure
renal homeostasis and all have cardio-renal protective properties. NPs elicit their physiological action through natriuretic peptide receptors (NPR) A, B, and C binding, which activates the guanylate cyclase to produce cGMP, a classic intracellular second messenger. The protein kinases G (PKGs) are like serine and threonine kinases that are activated by cGMP binding to exert their mechanism of action on targeted tissues.

**Atrial natriuretic peptides (ANP)**

Atrial natriuretic peptide (ANP) is a 28-amino acid peptide that is secreted from the atria in response to atrial wall stretch caused by increased intravascular volume or cardiac transmural pressure. The biosynthesis of ANP takes place in the ventricles and its expression increased in HF. In order to maintain the normal cardio-renal homeostasis, the secreted ANP perfuse into the coronary sinus and distributed into various target organs to exert endocrine functions. ANP exerts a wide range of protective effects on various organs, including the heart, blood vessels, kidneys, and lung and possesses natriuretic, vasoactive, and renin-inhibiting actions. In humans, it causes diuresis and natriuresis and reduces the blood pressure. The plasma levels of ANP in normal individuals are found to be 20 pg/mL and are elevated 10-100 fold in patients with CHF. Both ANP and NT-proANP have been used as markers for the diagnosis of asymptomatic LV dysfunction and plasma ANP levels have been shown to correlate with the severity of symptomatic HF. Ham et al. have reported that elevated plasma ANP levels in patients with low ejection fraction, reflects the severity of CHF and cardiac dysfunction. It has been reported that in patients with severe chronic HF, ANP infusions in pharmacologic doses have to shown to possess the beneficial effects on cardiac function by reducing the preload and afterload. In a study, Bold et al. have reported that ANP is elevated in the presence of HF in proportion to the severity of the disease, suggesting that ANP might be important in the pathophysiology of cardiac failure.

In another study Okamoto et al. have investigated the molecular mechanism of ANP/GC-A signaling in endothelial cells, and observed that ANP acts on vascular endothelial cells and exerts protective effects like anti-fibrotic and inflammatory effects in BLM-induced pulmonary fibrosis by attenuating the phosphorylation of Smad2 in TGF-β signaling. The determination of plasma ANP levels is a sensitive indicator of the degree of severity of CHF and it might be useful in the assessment of the efficacy of the treatment for HF. However, in the last few years, due to higher stability, BNP determinations were preferred to ANP for diagnostic and prognostic use in HF.

**Circulating natriuretic peptides**

Circulating natriuretic peptides (CNPs) belongs to a family of natriuretic peptides, mainly produced by endothelial cells plays an important role in cardiovascular homeostasis, regulation of local blood flow, systemic blood pressure, and vascular tone. A study reported that exogenous and endogenous CNPs may protect the heart from ischemia-reperfusion injury. CNPs infusion in post-myocardial infarction reduces cardiac fibrosis and LV hypertrophy. Another study found that CNPs levels were higher in patients with low EF, which clearly indicates that CNPs acts as an antihypertrophic and antifibrotic factor in the heart.

In other study observed that the plasma levels of cGMP and CNPs were significantly elevated in HF compared with the levels observed before the HF induction. CNPs infusion caused similar (about 2.5 fold) increases in plasma cGMP concentrations from baseline and were significantly higher in HF, suggesting an enhanced response in HF. The intravenous infusion of CNPs decreases blood pressure, cardiac output, urinary volume, and sodium excretion. Furthermore, the hypotensive effects of CNPs are less than those of ANP and BNP, but strongly stimulate cGMP production and inhibit VSMC proliferation. While all 3 NP isoforms inhibit the renin–angiotensin–aldosterone system (RAAS), CNPs unlike ANP and BNP failed to induce significant hemodynamic changes in sheep, such as depression of cardiac output, reduction in blood pressure, and plasma volume contraction, supporting the widely accepted concept that ANP and BNP are the major circulating NPs, whereas CNPs is largely considered a local regulator of vascular structure/tone.

**B-type natriuretic peptide (BNP)**

Brain natriuretic peptide (BNP) is a member of a family of four human natriuretic peptides that share a common 17-peptide ring structure. Brain natriuretic peptide (BNP), also referred to as B-type natriuretic peptide and emerged as an important biomarker in the diagnosis of CHF, myocardial infarction, right-sided heart failure and in acute pulmonary embolism (PE). The function of BNP is to counteract volume overload...
by inducing vasodilation, natriuresis, and diuresis\(^{31}\). BNP is released in response to myocardial stretch due to pressure or volume overload conditions in patients with CHF and promotes diuresis and vasodilation and they correlated with New York Heart Association functional classifications\(^{31}\). Generally, BNP is produced as a 108 amino acid polypeptide precursor, known as pro BNP and subsequently cleaved to the 76-peptide, which is biologically inert N-terminal fragment and the 32-peptide, biologically active BNP hormone. Both the fragments are released into the plasma in equimolar ratio, and have clinical importance in evaluation and management of CHF\(^{32,33}\).

Daily monitoring of concentrations of BNP levels and body weight for 60 days on 163 patients with HF signs and symptoms of acute clinical heart failure decompensation (ADHF) has indicated that the utility of home finger-stick BNP measurements and improves the clinical outcome and prevents hospital readmissions\(^{34}\). BNP has a lesser half-life of 20 min, which exactly reflects ventricular status, whereas NT-proBNP has a half-life of 1-2 h\(^{35}\). While the use of cut-off value has been criticized for clinical usefulness, the specific cut-off values may provide criterion in correlating with relevant statistical thresholds. Defined cut off values has been given to both BNP and NT-proBNP. Normal healthy individuals without HF may have BNP levels <100 pg/mL. If the levels exceeding >400 pg/mL the person may likely to have HF. Whereas, NT-proBNP levels >450 pg/mL at age <50 years, between at age 50-75 years, >900 pg/mL and at age >75 years, >1800 pg/mL likely to have HF\(^{36}\). The elevated levels of the plasma BNP are shown to be more particularly related to left ventricular hypertrophy (LVH) and serve as a vital plasma biomarker for ventricular hypertrophy in dialysis patients with end-stage renal disease (ESRD). BNP levels were much higher in patients with CHF than in those without CHF (990±550 vs 80±67 pg/mL, \(P<0.0001\)) and also patients with systolic dysfunction had higher BNP levels than those with preserved systolic function (1180±641 vs 753±437 pg/mL, \(P=0.03\)). A cutoff BNP blood concentration of 200 pg/mL had a sensitivity of 100%, a specificity of 97.1%, the positive predictive value of 97.3%, and negative predictive value of 100%. Hence the measurement of BNP levels is a very useful biomarker in the diagnosis of CHF in patients presenting to the emergency department with dyspnea\(^{37,38}\). But as the age and gender influence the plasma BNP levels, interpretation should be made for the independent effects of age and sex\(^{39}\). In recent study, it was observed that elevated hs-CRP levels and NT-proBNP \(\geq 25\) ng/mL in men aged 50 years were found to be predictive biomarkers for HF over a 21 years follow up\(^{40}\).

ST2 cardiac biomarker

ST2 is a protein biomarker which is encoded by the gene called IL1RL1. ST2 is an interleukin (IL)-1 receptor family member and has two isoforms namely as soluble ST2 (sST2) and a membrane-bound receptor form (ST2L). ST2 protein is elevated when cardiac myocytes encounter mechanical stress. ST2L exhibits function like antihypertrophic, antiﬁbrotic and antiapoptotic effects by binding to the functional ligand, interleukin-33 (IL-33)\(^{41}\). Soluble ST2 form competes for IL-33 and makes it unavailable to the ST2 receptor, which results in the blockage of the IL-33/ST2 pathway (cardio protective), hence elevated sST2 levels may cause increased cardiac stress.

Patients with pulmonary arterial hypertension showed increased serum sST2 levels and associated with right ventricular dilatation and systolic dysfunction signifying sST2 as a candidate biomarker in the setting of pulmonary arterial hypertension\(^{42}\). The sST2 levels were measured in 100 patients with AMI resulting in LV systolic dysfunction and gradual decrease of median sST2 levels from 263.3pg/mL at baseline to 140.0 pg/mL at 24 weeks (\(P>0.001\)).This study confirms that the serum sST2 levels may be useful in understanding the pathophysiological changes in ventricular and infarct re-modelling after AMI\(^{43}\). A nested case-control study on 36 cases of sudden cardiac deaths (SCD) and 63 control patients observed with elevated sST2 concentrations are predictive of SCD in patients with chronic HF\(^{44}\). A study on 151 patients with chronic HF due to left ventricular systolic dysfunction was followed up over 10 months and measured NT-proBNP, sST2, GDF-15, and hsTnT on every follow-up. Among all the studied biomarkers, only sST2 serial measurement have found to be independently associated with the cardiovascular (CV) risk and predicted the reverse myocardial remodeling\(^{45}\). A study on 1401 patients (age of 67 years among which 61% of them were men) with myocardial infarction were followed up to 5 years and their sST2 measurements revealed 51% of the patients exhibited increased levels of sST2, 388 persons died and 360 developed HF indicating that
sST2 levels are associated with the HF and high risk of death46.

Galectin-3

Galectin-3 (Gal-3) is a β-galactosidase binding lectin, is majorly produced from activated macrophages and binds to extracellular matrix proteins, such as fibronectin or laminin and cell surface receptors. Gal-3 is primarily involved in the inflammation and cardiac fibrosis which is an important contributor to the pathophysiology of LV systolic and diastolic dysfunction47. Gal-3 has also had a role in tumour development, progression of atherosclerosis, diabetes and pulmonary hypertension48-50.

In normal human hearts, the expression of galectin-3 is minimal and is detectable in the plasma of all the age categories with the clinical reference range of 1.4-94.8 ng/mL. However, as the disease progresses, Gal-3 becomes rapidly and significantly up regulated at peak of fibrosis. Analysis of 1092 healthy individuals aged ≥55 years showed that the 95% of them have normal reference interval of 3.8-21.0 ng/mL. Gal-3 concentrations were found to be higher in women along with men and the concentrations were also shown to be influenced by age, diabetes, hypertension, hypercholesterolaemia, body mass index and renal function52.

Myocardial tissue biopsies collected from the murine models showed that increased expression of Gal-3 along with activated myocardial macrophages specifically in the rats that later rapidly developed into HF. Further, the infusion with Gal-3 in the pericardial sac of normal, healthy rats led to the development of cardiac re-modelling with left ventricular dysfunction and 3fold elevated expression of collagen I over collagen III indicating its critical role in the HF and disease progression53. Gal-3 concentrations were measured in 3353 participants in the Framingham Offspring Cohort and they were follow-up for a period of 11.2 years among which 166 participants developed HF and 468 died during the follow-up time and Gal-3 was associated with risk for incident HF and mortality (HR 1.28, CI 1.14 to 1.43, P =0.001)54. In a controlled rosvastatin multinational study in heart failure (CORONA) on 1462 participants, aged >60 years with systolic ischemic heart failure (HF) revealed that Gal-3 was significantly associated with the primary endpoint (HR 1.53 CI 1.10-2.12, P =0.011) as well as all-cause (HR:1.61, 95% CI 1.20-2.29, P =0.002) and cardiovascular mortality (HR: 95%1.70 CI 1.19-2.42, P =0.003), sudden death [HR: 1.83, 95% CI: 1.14-2.94], P =0.012], and the coronary end point (HR: 1.48, 95%CI 1.03-2.12, P =0.035). However, adjustment for NT-proBNP had no longer significance indicating the limited use of Gal-3 in the prognosis of elderly patients with systolic HF in clinical practice55. The data from 2 large cohorts [CORONA and Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure (COACH)] of patients revealed that repeated measurements of Gal-3 levels may provide an important prognostic value in identifying patients with HF at elevated risk for subsequent HF morbidity and mortality56. A study on 592 patients with HF revealed that Galectin-3 levels were correlated with higher IL-6 and CRP levels (P =0.002) and also LVEF has an interaction with the predictive value of plasma galectin-3 in patients with preserved LVEF (n =114) compared to patients with reduced LVEF (P=0.001)57. A follow-up study on 232 patients with mean age of 71 ± 10 years, 72% were male with chronic HF (96% were in New York Heart Association functional class III) revealed that 98 patients died and Gal-3 was a significant predictor of mortality risk after adjustment for age and sex57. Galectin-3 was also associated with renal dysfunction (r =−0.619, P = 0.001) and increased in patients with higher NT-proBNP levels (r =0.265, P =0.001). Both galectin-3 levels (20.1 ± 8.1 vs. 17.5 ± 7.4 ng/mL, P =0.01) and NT-proBNP levels (577 ± 751 vs. 363 ± 477 pmol/L, P =0.01) were significantly elevated in patients who died, than in survivors58. Serial echocardiography was performed at baseline and at 3 months on 240 HF patients and showed decreased left ventricular end-diastolic volume (LVEDV) was associated with lower levels of Gal-3 compared to patients in whom the LVEDV was stable or increased indicating Gal-3 is an independent marker for ventricular re-modelling and mortality in patients with chronic HF59. Galectin-3 is found to be superior to sST2 in distinguishing heart failure with preserved ejection fraction (HFpEF) from controls and HFrEF60. The inhibition of galectin-3 using N-acetyl lactosamine inhibitor attenuates the cardiac fibrosis, LV dysfunction, and development of HF. Hence, the drugs against Gal-3 may be useful in preventing HF with extensive fibrosis59.

Growth differentiation factor-15 (GDF-15)

GDF-15 is a member of the TGF-β cytokine superfamily, which is expressed in response to tissue hypoxia,
inflammation, acute injury and oxidative stress. GDF-15 was first cloned from a human placental cDNA library and the deduced sequence revealed that identical to macrophage inhibitory cytokine-1 (MIC-1)\(^6\). GDF-15 is generally expressed on the surfaces of various tissues including the heart, lung, brain, prostate and colon\(^6\). GDF-15 is involved in the various biological process including growth arrest, differentiation, cell protection, and immune response\(^5\). It is a stress-responsive cytokine widely expressed in cardiomyocytes, macrophages, adipocytes, vascular smooth muscle cells, and endothelial cells in a pathological condition, its expression is induced and increased by several stimuli such as inflammatory cytokines, ischemia/reperfusion, and neurohormones\(^6\).

GDF-15 is emerging as a prognostic biomarker in patients with HF. GDF-15 gene is shown to be up-regulated in cultured cardiomyocytes due to nitrosative stress and also GDF-15 level was also induced in cardiomyocytes subjected to simulated ischemia/reperfusion (I/R) and protects from I/R injury\(^5\). GDF-15 levels were higher in CAD patients with CHF than those in coronary atherosclerosis patients without CHF and healthy controls\(^6\). Plasma GDF-15 is an independent predictor of ischemic stroke in patients with hypertension\(^6\). GDF-15 levels are associated with LVH in hypertensive patients\(^6\) and can differentiate HF with a normal diastolic function from asymptomatic LVDD\(^6\). GDF-15 have a role in the metabolism of type I and type III collagen turnover specifically collagen degradation that may affect the cardiac function\(^6\). Doubling in concentrations of GDF-15 was associated with a 2.5 fold increased rate of cardiovascular events in patients with stable ischemic heart disease\(^7\).

A study measured GDF-15, together with C-reactive protein, cardiac troponin I, CKMB and NT-proBNP levels in plasma at time points of 12 h and 36 h after surgery. The GDF-15 level was found to be increased significantly at 12 h after surgery, attaining nearly 2.5 times the baseline levels \((P <0.001)\) correlated positively with cTnl \((P =0.003)\). The release of the cardiac-enriched GDF-15 reflected the extent of myocardial injury as measured by cTnl release into circulation\(^7\). Postoperative plasma GDF-15 was found to be the best biomarker to predict the pre-operative cardiac injury, compared with cTnl, CK-MB, and Euro SCORE II\(^7\). Kempf et al. determined the mortality rate to the risk of death during one-year follow-up in ST-segment elevated myocardial infarction with increased levels of GDF-15 and found to be associated with the higher risk of death during the one-year follow-up. The mortality rates at 1 year were 2.1, 5.0, and 14.0\% in patients with GDF-15 levels 1200, 1200-1800, and >1800 ng/L, respectively \((P =0.001)\). Similarly, Anand et al. measured the circulating concentration of GDF-15 and observed abnormally high (>1200 ng/L) in 85\% of patients with HF. The higher levels of plasma GDF-15 was found to be associated with features of worse HF and biomarkers of neurohormonal activation, inflammation, myocyte injury, and renal dysfunction\(^7\). Dinh et al. observed significantly elevated levels of GDF-15 in patients with LVDD grade I \((P <0.001)\) compared to controls \((P =0.003)\). Several studies have also reported the higher plasma GDF-15 levels in patients with cardiovascular pathologies such as CAD or CHF that provides prognostic information well beyond the established clinical and biochemical markers\(^7\).
clinical severity of CHF. Hence the prognostic value of NGAL may be beneficial for elderly patients in the assessment of survival. The elevated levels of urinary NGAL levels were observed in CHF patients compared to controls (175 μg/g Cr vs 37 μg/g Cr) and significantly associated serum creatinine (r = 0.26, P = 0.006) and eGFR (r = 0.29, P = 0.002). In a study out of 71 children underwent cardiopulmonary bypass, 20 children (28%) developed an acute renal injury. A significant increase in NGAL levels of urine (1.6 ug/L vs 147 ug/L) and serum (3.2 ug/L vs 61 ug/L) in this 28% of the cases was observed. Early detection of NGAL in urine will allow the clinician to provide the prompt and effective treatment of human acute renal failure.

High-sensitivity troponin

The troponins comprise 3 proteins (troponin T, I, and C) that regulate actin and myosin interactions during muscle contraction. Troponins T and I have distinct isoforms that exist in skeletal and cardiac muscle. The majority of cardiac troponin (cTn) is bound to myofilaments, and the remaining is free in the cytosol which accounts for 3-8% of the total amount. In peripheral blood, cTnT levels were increased within three to four hours after the onset of myocardial injury and remain increased for 10-14 days. The release of these proteins into the bloodstream from cardiomyocyte necrosis shows their utility as biomarkers of acute coronary syndromes. There is an increasing interest in the role of circulating cardiac troponin (cTn) in detecting myocardial injury in those with HF. Subsequently, a high-sensitivity (hs) cTnT assay was introduced into routine clinical practice. This assay can measure cTn concentrations in the single digit range of nanograms per litre (ng/L) and some research assays even allow detection of concentrations <1 ng/L. Missov et al. used a highly sensitive research assay to demonstrate elevated concentrations of troponin I in 35 patients with advanced HF. Latini et al. found that hsTnT was the most significant predictor of all-cause mortality in HF. Reichlin et al. developed an algorithm for the 2h rule-out strategy in patients with acute myocardial injury (AMI), they ruled-out initial hsTnT< 14ng/L and 2h hsTnT< 4ng/L in AMI patients with 98.7% sensitivity and 99.8% specificity. Hs-TnT were elevated in a well-characterized heart failure with preserved ejection fraction (HFrEF) population, which was associated with larger left ventricular and atrial size, as well as associated with the higher NT-proBNP (r = 0.43; P < 0.001). These findings suggest that chronic troponin release is either due to myocyte stretch or injury, may contribute to the pathophysiology of HF.

Heart-type Fatty Acid Binding protein (H-FABP)

Heart-type Fatty Acid Binding Protein is a 15 kDa small hydrophilic protein consisting of 132 amino acids. It is found in large quantities within cardiomyocytes and in much lower quantities in the kidneys, skeletal muscle, and brain tissue. H-FABP is associated with the inflammatory conditions such as HF, CHD, sepsis, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and insulin resistance. Injury to myocardial cells allows this small protein to quickly leak into the bloodstream in proportion to the extent of damage and as a result, has been suggested as an alternative to other biomarkers, in a multi-marker approach for diagnosing AHF. Evidence suggests that H-FABP may be a viable biomarker for a variety of high-risk cardiac populations and may be useful in the emergency department setting.

In healthy humans, the normal range of H-FABP in serum or plasma has been reported to vary between 0.0 and 5.5 ng/mL. In view of the importance of H-FABP in myocardial function, its measurement in the plasma formed a reliable test for myocardial ischemia. A sandwich enzyme-linked immunosorbent assay (ELISA) has been developed for H-FABP that showed that the assay range of 0-250 ng/mL, with the minimum detection limit of the assay of 1.25 ng/mL. By using this assay, the plasma and urine H-FABP values were 3.65 ± 1.81 ng/mL and 3.20 ± 2.70 ng/mL, respectively in normal healthy subjects.

Specifically, in a study evaluating H-FABP alone and in combination with hs-cTnT for the diagnosis of AHF in emergency department patients presenting with symptoms of acute coronary syndrome (ACS) found that the addition of H-FABP to hs-cTnT has increased the area under the curve (AUC) of hs-cTnT alone from 0.893 (95%, CI: 0.812-0.974) to 0.908 (95%, CI: 0.839-0.977), although this difference was not statistically significant (P = 0.07). The addition of H-FABP at 5.8 ng/mL to hs-cTnT (14 ng/l) has increased both sensitivity and negative predictive value (NPV) for NSTEAM diagnosis. The authors observed that the H-FABP is not an alternative to CK-MB or cTn, but rather should be considered an additive marker for the rule-out of HF. Conversely, patients enrolled in the APACE (the Advantageous Predictors of Acute Coronary syndrome Evaluation) study were evaluated to determine the incremental diagnostic value of H-FABP to hs-cTnT in early
presenting within 1 hr emergency department patients with symptoms of ACS, found that the addition of H-FABP increased the AUC of hs-cTnT from 0.88 (95%, CI: 0.81-0.94) to 0.90 (95%, CI: 0.83-0.98), yielding the similar results to the above study. However, in repeating the analysis of patients presenting within 2 h from onset of symptoms was found that H-FABP no longer increased the AUC of hs-cTnT alone\textsuperscript{103}. Further exploration of H-FABP as an early marker of ischemia is necessary to determine its clinical utility.

Conclusion
Heart failure is a very complex clinical syndrome and various pathways involved in its progression. The determination of cardiac biomarkers has become the foremost diagnostic tools for HF and has greatly helped the clinicians in the early diagnosis and prompt treatment planning, thereby reducing the mortality rate. In addition, biomarkers not only serve as early predictors of prognosis but also help to identify high-risk patients who require closer monitoring and more aggressive therapy. Recent advances in understanding the pathophysiology of HF, one could able to identify high-risk patients, in these situations, biomarkers will definitely improve the effectiveness of HF therapy and lead to better patient outcomes. Furthermore, the multi-marker strategy would be highly beneficial for the patients with HF for better management.

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