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Circulating Biomarkers in the Diagnosis of Silent Heart Failure

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ABSTRACT

There is increasing prevalence of heart failure due to rising trend in the occurrence of coronary artery disease, hypertension, diabetes mellitus, obesity, pulmonary conditions, atrial fibrillation. This is further aggravated by life style changes like smoking, alcoholism, sedentary life style and poor food habits. More than 5 million patients suffer from heart failure in United States, which is expected to increase to 8.5 million by 2030. Economic costs amount to 40 billion dollars per year, which is expected to double by 2030. During the last 25 years, clinical trials have shown great improvements in the treatment of patients with HFrEF. HFpEF is common in individuals who have comorbid conditions. HFpEF is characterized by diastolic dysfunction with impairment in ventricular filling, slow relaxation of myocytes, increased thickness of ventricular wall, concentric remodelling of left ventricle and excessive proliferation of extracellular matrix. The extent of these changes varies among individuals. Natriuretic Peptides are being used in diagnosis and prognosis of patients with HFrEF. In most of the patients with HFpEF, NPs tend to be normal, leading to under-diagnosis and thus delayed or inappropriate treatment. The pathophysiology and management of HFpEF is challenging. MicroRNAs play a significant role in the early diagnosis of heart failure, especially in the presence of asymptomatic highly prevalent essential hypertension. miRNA signature in heart failure augments the discriminative power of NT-proBNP (>125pg/mL) in nonacute setting. MicroRNA can be applied in community practice and in outpatient settings for early detection of incipient HF /partly treated HF, triggering timely diagnosis and clinical intervention. Manipulation of levels of miRNAs using techniques can show promising results as therapeutic strategies in heart failure.

Keywords: Heart failure, Biomarkers, MicroRNAs, Cardiac injury, Cardiac remodelling, Cardiac hypertrophy

Abbreviations

HF: Heart Failure; HFrEF: Hear Failure with reduced Ejection Fraction; HFpEF: Hear Failure with preserved Ejection Fraction; EF: Ejection Fraction; THFR: The Trivandrum Heart Failure Registry; INTER-CHF: International Congestive Heart Failure; ADHERE: Acute Decompensated Heart Failure Registry; NPs: Natriuretic Peptides; BNP: Brain Natriuretic Peptide; NT-prp-BNP: N-Terminal-pro-BNP; MiRs: MicroRNAs

INTRODUCTION

Heart failure (HF) is a diverse clinical disorder due to defect in the structure and function of the heart. In the clinical setting, heart failure can present as Heart Failure with reduced Ejection Fraction (HFrEF) with Ejection Fraction (EF) of ≤40%; the precipitating factors being cardiac ischemia or cardiomyocyte loss. It can also present as Heart Failure with preserved Ejection Fraction (HFpEF) where the EF is ≥50%; this occurs in 40-70% of all HF cases and is prevalent among females. HFpEF is usually asymptomatic and is the consequence of uncontrolled lifestyle disorders [1]. The symptoms of HF are due to impaired left ventricular

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filling or ejection of blood from left ventricle. In the Framingham classification, the diagnosis of heart failure is based on the concurrent presence of either two major criteria or one major and two minor criteria [2].

EPIDEMIOLOGY OF HF

HF has been emerging as a major global health burden, with an estimated worldwide prevalence of more than 37.7 million [3]. Around 5,00,000 new cases are detected annually in the USA. It affects 1-3% of adults and 6-10% of the affected individuals are of 65 years of age [4]. Studies have shown that the mortality rate is 50% at 5 years from the initial diagnosis of HF [5]. The risk of frequent hospitalizations is almost 50% in one year thus compromising the quality of life [6]. The incidence of HF in India varies widely from 1.3 to 23 million. The Trivandrum Heart Failure Registry (THFR) reported that HFpEF accounted for 25% of the total HF burden. The mean age in the THFR, Medanta Registry and the International Congestive Heart Failure (INTER-CHF) Indian subset, study was 61.2, 58.9 and 56 years, respectively, as compared to 72.4 years in the Acute Decompensated Heart Failure Registry (ADHERE) of the USA. The in-hospital mortality observed in the THFR (8.4%) was almost double compared to that reported in the ADHERE registry (4%) of the USA [7]. Economic burden in India is high since majority of the Indian patients are from low socio-economic strata, who cannot afford for adequate and appropriate treatment.

HF is the consequence of the disorders involving the pericardium, myocardium, endocardium, heart valves and great vessels. The cardiac diseases include myocardial infarction, valvular heart diseases, cardiomyopathies, restrictive and infiltrative heart diseases and myocarditis. It also may be a consequence of lung disorders, advancing age, sedentary lifestyle, improper food habits, stressful life, associated hypertension, diabetes mellitus, obesity, anaemia, smoking and alcoholism. The recent incidence in HF is due to exponential increase in the incidence of hypertension and diabetes mellitus [8]. The treatment depends upon managing heart failure in addition to treating the underlying precipitating factor for heart failure.

PATHOGENESIS

The pathogenesis of HF occurs in stages due to inflammation, oxidative stress, endothelial dysfunction, alterations in myocardial signaling and matrix remodeling and capillary rarefaction. The pathogenic mechanisms cause cardiac myocyte changes in the form of ischemia/injury, fibrosis, apoptosis, hypertrophy etc.; the sequence of events varies between individuals with heart failure. Biomarkers reflecting these processes could aid in the diagnosis and pathophysiological stratification of HF patients [9] are given in **Figure 1**.

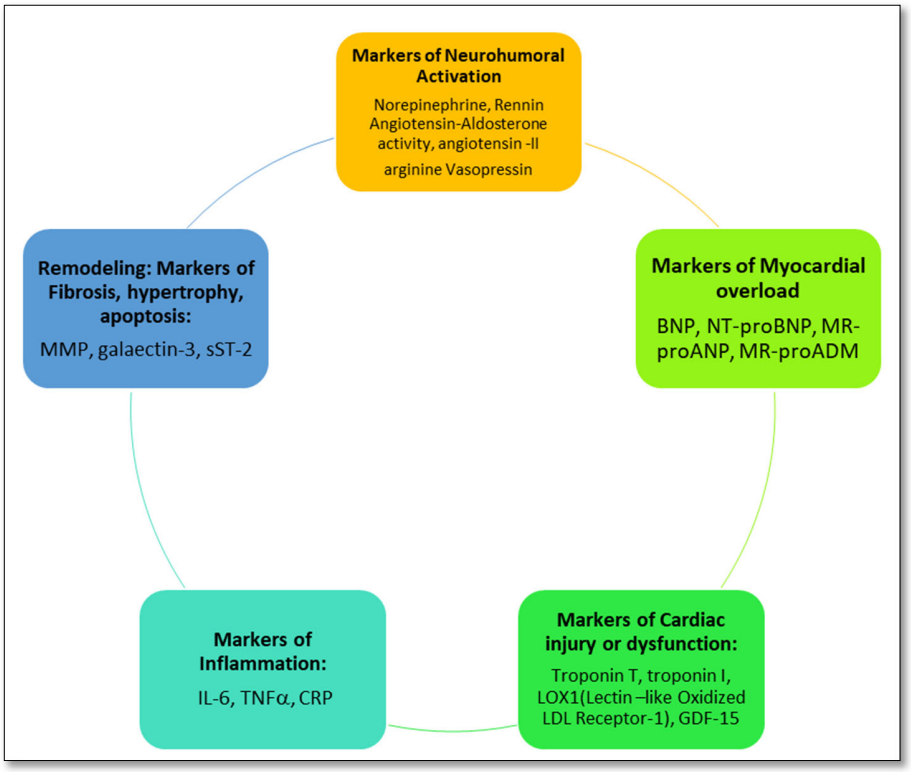

Figure 1. The biomarkers reflecting the progression of HF includes [8].

DIAGNOSIS

Early diagnosis of HF is important to initiate appropriate treatment to reduce mortality, hospitalizations and healthcare costs. Lot of research has been done with conflicting results regarding the pathogenesis and clinical presentation of HF patients to the hospital. There are multiple challenges in the management of HF especially HFpEF such as consensus-based diagnostic criteria is followed which has resulted in heterogenous population with great difficulty in diagnosis; single approach applicable to all patients is not applicable to HFpEF, the mechanisms proposed in the pathogenesis of HF remain hypothetical, good experimental models do not exist, multiple comorbidities exist with HFpEF which might have direct and indirect impact on this disorder [10].

Till date diagnosis of HF relies on the clinical history, thorough physical examination, basic blood investigations, 12-lead electrocardiography, chest X-ray, 2D echocardiography and biomarkers (brain natriuretic peptide [BNP] or N-terminal pro-BNP [NT-pro-BNP]). Echocardiography is useful in assessing ventricular EF, diastolic dysfunction, chamber pressures, differentiating HFrEF from HFpEF as well as understanding the aetiologyof HF in certain cases. But it is costly and time consuming; hence its utility in routine use in the management of HF patients remains challenging [6].

ROLE OF BIOMARKERS IN THE DIAGNOSIS AND RISK-STRATIFICATION OF HF

Natriuretic Peptides (NPs)

Brain Natriuretic Peptide (BNP) and NT-pro-BNP (N-terminal pro-BNP) are extensively used biomarkers clinically [11]. In healthy adults, BNP secretion is very low. In response to abnormal myocardial stretch as in HF, the ventricular myocyte secretes a large amount of prohormone BNP, which gets cleaved to a biologically active (but less stable) BNP 1-32 and an inert (but more stable) NT-pro-BNP 1-76 [12]. NPs have high degree of clinical sensitivity and negative predictive value; the measurement of NPs has been recommended by national and international guidelines, in arriving at the diagnosis of HF in patients with dyspnoea since 2005. BNP and NT-pro BNP gets altered by many factors not related to HF such as analysis related factors-method-specific reference intervals, age- and gender-based reference interval, BNP cannot differentiate systolic or diastolic dysfunction, in situations where ECHO findings are not in parallel with that of NPs levels, falsely low values as found in obesity, falsely high values as found in hypertrophic and infiltrative cardiomyopathies, myocarditis, coronary artery disease, valvular heart diseases, arrhythmias, use of cardiotoxic drugs, renal dysfunction, iron deficiency anemia, critical illnesses, stroke and pulmonary heart disease [13,14].

MicroRNA

The discovery of microRNAs (miRs) have opened up new avenues in the study of gene expression. MiRs are highly conserved small noncoding RNAs which are widely involved in gene regulation from the normal development of heart through to the pathogenesis of cardiovascular diseases [7,8]. So far, about 150-200 miRNAs are found to be expressed in cardiovascular diseases. Many of these miRNAs are dynamically regulated in response to acute cardiac stress or in long-term compensatory response of the heart to a chronic injury or hemodynamic overload. Some miRNAs such as miR-208, miR-128, miR-302, miR-367 and miR-499 are potentially heart-specific and play an important role in the maintenance of heart development and function. These miRsare detectable in the peripheral blood also and its expression of miRs gets altered in various disease conditions; few miRs get upregulated and few may get down-regulated. Thus, its level of expression may be linked to the diagnosis and prognosis of diseases. There is no consensus on the miRNA's profiles identified by various studies till date in the diagnosis of HF. It could be due to change in phenotype of HF, acuity or severity of HF, appropriateness of controls used in studies and size of the sample used for study. miRs could be used either alone or in combination with current diagnostic tests, including NPs, to improve diagnostic accuracy. Disease-specific miRNA signatures may provide an insight into underlying disease mechanisms thus posing as therapeutic targets [15]. Manipulation of levels of miRNAs using techniques such as mimicking the miRNAs (miRmimics) and antagonistic miRNAs (antagomiRs) is making increasingly evident the enormous potential of miRNAs as promising therapeutic strategies in heart failure.

CONCLUSION

HF imposes significant economic and public health burden upon modern society. Since worldwide hypertension, diabetes mellitus and obesity are on the raise in the recent times, HFpEF is common. HFpEF do not present with the same clinical features as that of HFrEF. So, they are being ignored during regular follow up visits to the hospital. Usually the precipitating cause in HFrEF is myocardial infarction, hence these patients are treated on time with adequate and appropriate treatment. Since the precipitating causes of HFpEF are usually silent, identifying them at an early stage is highly challenging. Pathologically also they are different from that of HFrEF, hence treatment regimens are highly confusing, thus addressed according to the clinical presentation of the patient. There is no uniformity in treatment as well as there are no standardized treatment guidelines for HFpEF. Currently, BNP and echocardiography are considered as the gold standard markers to diagnose HF. But in few cases where BNP levels are normal, diagnosis is usually done by exclusion of other diseases. MicroRNAs in HF will give an insight into the

progression of the disorder, thus paving the way for appropriate therapies.

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