Understanding Heart Failure

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KEYWORDS

• Heart failure • HFrEF • Ejection fraction • β-Blockers • ACE inhibitors • Neurohormonal blockade • Treatment

KEY POINTS

- Heart failure (HF) is a progressive, clinical syndrome hallmarked by the inability of the heart to efficiently fill or provide systemic blood flow, resulting in symptoms of fatigue, dyspnea, and ultimately, significant morbidity and mortality.
- Current guidelines support the use of HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction to replace systolic HF and diastolic HF, respectively.
- Although neurohormonal and sympathetic inhibition form the foundation of HFrEF medical therapy, the future role of these and other therapies, such as combined angiotensin-receptor blocker-neprilysin inhibition, implantable cardioverter-defibrillators, and cardiac resynchronization therapy, may be better optimized with more precise subgroup phenotyping within the HFrEF population.

INTRODUCTION

Heart failure (HF) is a significant public health concern, affecting nearly 20 million people worldwide, with a projected 25% increase in prevalence by 2030.[1] Concomitantly, HF-associated health care expenditures are expected to more than double by 2030.[1] For example, current US costs for HF are estimated at $30 billion. More importantly, HF significantly impacts the lives of those suffering from this condition, resulting in significant morbidity and mortality.[2]

HF is a complex clinical syndrome that can result from abnormalities in myocardial function (systolic and diastolic function), valvular or pericardial disease, any of which lead to impaired forward flow of blood with resultant fluid retention, often manifesting as pulmonary congestion, peripheral edema, dyspnea, and fatigue (**Box 1**).[3] This cycle is fueled by neurohormonal upregulation that initially serves as a compensatory mechanism to maintain Frank-Starling mechanics, but ultimately proves to exacerbate fluid overload and cardiac dysfunction.[2,4]

The HF guidelines on both sides of the Atlantic recommend differentiating between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[2,3] Although HFrEF and HFpEF each comprise roughly half of the HF population, they encompass different demographics and are associated with different proportions of comorbidities and responses to medical interventions (**Table 1**).[2,5–8] In fact, although the exact cutoff for preserved ejection fraction (EF) remains debatable (EF range from >40% to ≥55%), the presence of HFrEF suggests a different trajectory in response to current medical HF therapy as compared with HFpEF, regardless of the exact EF cut-point for HFpEF used. Moreover, the overwhelming majority of treatment approaches for HF, including both medical and device therapy, has targeted or shown benefit specifically in the HFrEF population as opposed to the HFpEF population.

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Box 1
Diagnosis of heart failure

The diagnosis of HFrEF requires 3 conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Reduced LVEF

The diagnosis of HFpEF requires 4 conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Normal or only mildly reduced LVEF and LV not dilated
4. Relevant structural heart disease (LV hypertrophy/left atrial enlargement) and/or diastolic dysfunction

Adapted from McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14(8):809; with permission.

This review, in the context of cardiac resynchronization therapy (CRT), primarily focuses on patients with chronic HFrEF.

PATHOPHYSIOLOGY

The syndrome of HF develops from an index event that results in ventricular dysfunction and ultimately HF symptoms. The index event, depending on cause, can be abrupt in onset (ie, myocardial infarction [MI], viral myocarditis) or may be gradual and develop over time (ie, left ventricular [LV] hypertrophy, genetic).[4] This index event results in compensatory mechanisms that at first serve to maintain adequate cardiac output in the face of LV dysfunction. Over time, however, salt and water retention become the predominant feature of HF symptoms. Specifically, the sympathetic nervous system and neurohormonal cascade (including the renin-angiotensin-aldosterone system [RAAS], as well as neprilysin, endothelin, and various inflammatory cytokines), are upregulated after the index event, helping to preserve cardiac output by increasing heart rate and stroke volume.[4,9,10] Eventually, this neurohormonal activation results in deleterious effects, including LV hypertrophy and remodeling, pulmonary edema, and excessive vasoconstriction, all of which serve to promote disease progression.[4,9] Levels of endogenous vasodilatory peptides, including natriuretic peptides, prostaglandins, and nitric oxide, are increased in this setting to counteract the vasoconstrictive effects of neurohormonal activation, but are often insufficient (**Figs. 1** and **2**).[4,9] Further perturbations include abnormalities in cellular signaling, with increased myocyte apoptosis,[11] fibrosis,[12] necrosis,[13] and inflammation,[14] which contribute to ventricular remodeling. Ventricular interaction and valvular function (ie, mitral or tricuspid regurgitation) are compromised, and a predisposition to the development of supraventricular and ventricular arrhythmias ensues.[9,15]

Thus, the HF syndrome is the following:

- The interaction between hemodynamic dysregulation via alterations in myocardial preload, afterload, and contractility (hemodynamic model), and
- Neurohormonal disarray (neurohormonal model) that results in symptom development and disease progression.[4,15]

Current treatment approaches, as described later, target elements within and across these models to slow disease progression as well as to improve symptoms and outcomes.

CAUSE OF HEART FAILURE

HF often develops from intrinsic myocardial structural or functional abnormalities. This dysfunction, first termed cardiomyopathy in 1957, can result from a myriad of causes; many remain unknown.[16] Clinically, the initial distinction in categorizing a cardiomyopathy, specifically in the setting of HFrEF, is to identify whether the myocardial dysfunction is associated with coronary artery disease (CAD). CAD can be assessed by either invasive or noninvasive means.[2,3,17,18] Treatment of ischemic cardiomyopathy (ICM) with revascularization may improve or resolve the myocardial dysfunction. Next, the identification of an underlying systemic condition or genetic disorder may allow for disease-specific treatment and may also highlight other associated sequelae for which the patient (or relatives) may be at risk. The classification and subclassification of cardiomyopathies will grow in importance as therapies may ultimately be cause-specific, or genetically precise.[19,20]

Proposed by Maron and colleagues[16] and depicted in **Fig. 3**, nonischemic cardiomyopathies (NICM) are classified into genetic, mixed (in which some forms may be genetic in origin), and acquired causes. Within the mixed category, there is a significant proportion (20%–35%) of those diagnosed with dilated cardiomyopathy (DCM) who may have familial cardiomyopathy,