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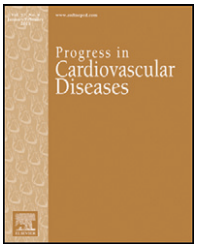

Heart Failure with Myocardial Recovery - The Patient Whose Heart Failure Has Improved: What Next?

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ABSTRACT

In an important number of heart failure (HF) patients substantial or complete myocardial recovery occurs. In the strictest sense, *myocardial recovery* is a return to both normal structure and function of the heart. HF patients with myocardial recovery or recovered ejection fraction (EF; HFrecEF) are a distinct population of HF patients with different underlying etiologies, demographics, comorbidities, response to therapies and outcomes compared to HF patients with persistent reduced (HFrEF) or preserved ejection fraction (HFpEF). Improvement of left ventricular EF has been systematically linked to improved quality of life, lower rehospitalization rates and mortality. However, mortality and morbidity in HFrecEF patients remain higher than in the normal population. Also, persistent abnormalities in biomarker and gene expression profiles in these patients lends weight to the hypothesis that pathological processes are ongoing. Currently, there remains a lack of data to guide the management of HFrecEF patients. This review will discuss specific characteristics, pathophysiology, clinical implications and future needs for HFrecEF.

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Abbreviations and Acronyms

AAs = aldosterone receptor antagonists

ACEI = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

BB = beta blocker

CRT = cardiac resynchronization therapy

EF = ejection fraction

HF = heart failure

HFmrEF = heart failure with mid range ejection fraction

HFrEF = heart failure with reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrecEF = heart failure with recovered ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

ICD = intracardiac cardioverter defibrillator

NTproBNP = N-terminal of the prohormone of Brain Natriuretic Peptide

NYHA = New York Heart Association

Four to five decades ago, heart failure (HF) was a deadly disease with few options to stabilize the disease process, let alone improve or cure HF. However, due to the success of neurohumoral blockers and implantable devices, HF has become treatable.[1] Only a minority of patients will rapidly decline despite therapy to end-stage HF warranting heart transplantation or mechanical circulatory support. In contrast, in a large part of HF patients, stabilization and often improvement of symptoms and cardiac dysfunction is possible. Moreover, in an important number of HF patients substantial or complete myocardial recovery occurs, and it is expected that this number of HF patients will further increase in the future. These patients differ from HF patients with persistent reduced ejection fraction (EF; HFrEF) as well as preserved EF (HFpEF) in underlying mechanisms of cardiac dysfunction, comorbidities and prognosis. In this review we will discuss specific characteristics, pathophysiological and clinical implications and future needs for HF patients with myocardial recovery.

Myocardial recovery and definitions

The main terminology used to describe HF is historical and based on clinical signs and symptoms as well as measurements of left ventricular (LV) EF (LVEF) (Table 1). Three distinct categories are defined: those with normal LVEF (considered as ≥50%; HF with preserved EF (HFpEF)), those with HFrEF (<40%) and recently, patients with an EF of 40–49% defined as HF with mid range ejection fraction (HFmrEF) or in the 2013 American guidelines defined as "HFpEF, improved" (41–49%).[2,3] However, this group is probably a heterogeneous population consisting of patients with mild systolic HF and patients with improved HFrEF.[3] It is well recognized that EF is dynamic over time with 39% of HFpEF patients progressing to an LVEF < 50% and 39% of HFrEF patients progressing to an LVEF ≥ 50% at some point after diagnosis over a mean 5-year follow up (Fig 1).[4]

Reverse remodeling, the opposite of (negative or maladaptive) remodeling, is the process associated with a decrease in LV volume and mass leading to a (more) normal elliptical shape of the LV which can occur spontaneously or due to medical or device therapy.[5] In the strictest sense, *myocardial recovery* is a return to both normal structure and normal function of the heart.[6] Due to the absence of a strict definition of patients with improved or recovered EF (HFrecEF) there remains to be heterogeneity regarding the cut-off value for LVEF (≥40% to ≥50%) in the literature. However, a correct differentiation between HFrEF, HFpEF, HFmrEF and HFrecEF is important. All these patient categories often have different underlying etiologies, demographics, comorbidities, response to therapies and outcomes; which is crucial information for the patient as well as the treating physician. Moreover, correct definitions are necessary to stimulate research which can lead to the development of successful individualized management strategies in HF.

Myocardial processes associated with reverse remodeling

The progression of HF is associated with LV remodeling, which manifests as gradual increases in LV end-diastolic and end-systolic volumes, wall thinning, and a change in chamber geometry to a more spherical, less elongated shape. This process is usually associated with a progressive decline in LVEF. Different triggers can lead to a decline in LVEF and the process of remodeling (Fig 2). The process is influenced by hemodynamic load, neurohumoral activation and other factors. Due to continuous maladaptive remodeling, myocardial dysfunction is usually a progressive condition. In contrast, the biology of myocardial recovery is not well understood. It is likely a spectrum of improvement with (partial) reversal of biological processes which occur in the failing heart. These may be categorized into those that occur in cardiac myocyte versus changes within the extracellular matrix of the myocardium (Fig 2).[5] During the process of reverse remodeling several studies showed that changes