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Management of Patients With Recovered Systolic Function

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ABSTRACT

Advancements in the treatment of heart failure (HF) with systolic dysfunction have given rise to a new population of patients with improved ejection fraction (EF). The management of this distinct population is not well described due to a lack of consensus on the definition of myocardial recovery, a scarcity of data on the natural history of these patients, and the absence of focused clinical trials. Moreover, an improvement in EF may have different prognostic and management implications depending on the underlying etiology of cardiomyopathy. This can be challenging for the clinician who is approached by a patient inquiring about a reduction of medical therapy after apparent EF recovery. This review explores management strategies for HF patients with recovered EF in a disease-specific format.

Advancements in the treatment of heart failure (HF) with systolic dysfunction have given rise to a new population of HF patients who have improved their left ventricular (LV) ejection fraction (LVEF). These advancements include pharmacologic therapy, revascularization, valve repair and replacement, cardiac resynchronization therapy (CRT), and mechanical circulatory support. This growing population has only recently been recognized as a distinct clinical subpopulation.

The management of patients with recovered LVEF, however, is not well described in the literature, and this is conveyed in the most recent 2013 AHA/ACC HF guidelines.[1] This is in part due to a lack of consensus on the definition of myocardial recovery, scarcity of long-term data on the natural history of patients with improved LVEF, and the absence of clinical trials focusing on this patient population.

We now know that cardiac remodeling occurs in response to injury and manifests by an alteration of cardiac size, shape and function.[2] Over the past two decades, there has been a paradigm shift in HF management to specifically target pathways of cardiac remodeling in an effort to improve HF survival. Neurohormonal antagonism and wall stress reduction pharmaceutically or mechanically have resulted in improvement in LV size and function in a process known as LV reverse remodeling (LVRR). There is a subset of these patients who do not just show improvement, but have complete resolution of signs or symptoms of disease. In other words, they exhibit true myocardial recovery. Unfortunately, distinguishing these patient populations is challenging and has not previously been done[3]; Fig 1 summarizes this concept. The following paper reviews these concepts and explores management strategies for HF patients with recovered LVEF.

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Abbreviations and Acronyms

ACEI = angiotensin converting enzyme inhibitors

ACM = alcohol-induced cardiomyopathy

AF = atrial fibrillation

BB = beta blockers/beta blockade

CABG = coronary artery bypass grafting

CCT = chemotherapy-induced cardiomyopathy

CRT = cardiac resynchronization therapy

CV = cardiovascular

HF = heart failure

ICD = implantable cardioverter defibrillator

ICM = ischemic cardiomyopathy

IDCM = idiopathic dilated cardiomyopathy

LV = left ventricle or left ventricular

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

LVRR = left ventricular reverse remodeling

MRI = magnetic resonance imaging

OMT = optimal medical therapy

PPCM = peripartum cardiomyopathy

RAAS = renin–angiotensin–aldosterone system

ROCM = recent-onset cardiomyopathy

SCD = sudden cardiac death

TIC = tachycardia-induced cardiomyopathy

TTC = taku-tsubo cardiomyopathy

Defining recovery

The definition of myocardial recovery has not been consistent in the literature. Typically it has involved a measure of LVEF and sometimes LV size/shape. Some studies will utilize absolute numbers, whereas others will look at relative improvement. An LVEF cutoff point is sometimes arbitrarily drawn between 40% and 50%, which is an epidemiologic grey zone in HF, despite the current AHA guidelines utilizing LVEF ≥50% for cutoff for preserved LVEF.[1] As of this publication, only a few studies have characterized patients with LVRR and/or myocardial recovery either longitudinally or in cross-section (Table 1).[4–8] These studies exhibit variability in their definition of LVRR/Recovery.

General findings

It appears that, in general, patients who respond well to HF therapies and exhibit evidence for LVRR and/or recovery have a better prognosis than patients who do not.[4] Kramer et al performed a novel meta-analysis evaluating the mortality effect of LVRR, utilizing a number of drug therapy trials in HF.[9] They showed that short-term improvements in LV size and function are associated with long-term survival benefit. This trend appears to hold true in a community-based longitudinal study as well.[10] Certain factors may predict response to medical therapy resulting in LVRR, such as age, duration of HF symptoms, presence of left bundle branch block (LBBB), and baseline blood pressure.[4] Female sex, non-ischemic etiology, shorter duration of symptoms, presence of LBBB, milder mitral regurgitation, smaller LV end diastolic diameter, and smaller left atrial size are predictors of CRT-mediated LVRR, also known as "super-responders".[11–13]

Despite an improvement in outcomes, however, patients who improve LV size and function may not be normal. For example, there is biomarker evidence for ongoing myocardial tissue injury, inflammation, and neurohormonal activation in patients with HF and recovered LVEF. Furthermore, although this group has improved survival compared to HF and reduced LVEF, they have a similar risk for cardiac hospitalization to a preserved LVEF cohort, suggesting persistent pathology.[6] de Groote et al similarly reported a favorable overall prognosis in a recovered LVEF cohort after beta-blocker (BB) therapy, but noted ¼ of this cohort had a subsequent degradation in LVEF.[7] Other studies have shown abnormal exercise capacity and poor contractile reserve in patients with apparently normal LVEF.[14,15] CRT "super-responders", patients who have apparently normalized LVEF after CRT, have a favorable overall long-term prognosis. Despite low cardiovascular (CV) mortality (1.5%) in the cohort over a >5 year follow-up period, 11% had an appropriate implantable cardioverter defibrillator (ICD) shock, suggesting continued risk.[16] The term heart failure with better EF was recently suggested to reflect this concept that a normalization of LV size and function does not imply disease cure.[17]

Continuation of HF medications as part of the management of recovered patients is often recommended for these reasons. However, it may be reasonable to consider wean or cessation of therapy in a select group of patients if accompanied by close follow-up (which may include the serial assessment of biomarkers) and serial imaging of LV size and function. Diuretics in particular should be weaned as tolerated but specific neurohormonal antagonists, e.g. BB, angiotensin converting enzyme inhibitors (ACEI), and aldosterone antagonists, should be carefully considered before cessation is entertained. The rest of this review focuses on disease-specific management of patients with recovered LVEF. Table 2 shows a summary of disease types, natural history, and suggested management strategies.

Ischemic cardiomyopathy

Myocardial recovery appears to occur less frequently in ischemic cardiomyopathy (ICM) patients compared to non-ischemic patients, particularly with respect to pharmacologic therapy. Wilcox et al found that ischemic etiology was independently and inversely related to LVEF improvement in a nearly 4000 patient cohort.[18] Ischemic etiology makes up as little as 8% but no more than 32% of recovered or improved LVEF cohorts.[5,6,8,19] Myocardial recovery data in the LV assist device (LVAD) population confirm these findings. Nearly all published reports of durable LVAD explantation in a bridge to recovery population have been done in non-ischemic patients.[20–26]

There is early evidence that revascularization of patients with ICM can result in improved LV function and clinical outcomes.[27,28] These benefits may be magnified with improved patient selection using myocardial viability studies.[29] In acute coronary syndromes, revascularization has resulted in LVRRR