Journal of Echocardiography (2019) 17:5–9
https://doi.org/10.1007/s12574-018-0396-2

REVIEW ARTICLE

Heart failure with recovered ejection fraction

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Received: 5 September 2018 / Accepted: 6 September 2018 / Published online: 14 September 2018
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Abstract

Substantial or complete myocardial recovery occurs in many patients with heart failure (HF). HF patients with myocardial recovery or recovered left ventricular (LV) ejection fraction (EF; HFrecEF) are a distinct population of HF patients with different underlying etiologies, comorbidities, response to therapies, and outcomes compared with HF patients with persistent reduced or preserved EF. Improvement in LVEF has been systematically linked to improved quality of life, and lower rehospitalization rates and mortality. However, the mortality and morbidity in HFrecEF patients remain higher than those in the normal population. Currently, data to guide the management of HFrecEF patients are lacking. This review discusses specific characteristics, pathophysiology, and clinical implications for HFrecEF.

Keywords Left ventricle · Ejection fraction · Heart failure · Echocardiography

Introduction

Measurement of left ventricular (LV) ejection fraction (EF) is a key initial step in the management of contemporary heart failure (HF). The 2013 ACCF/AHA HF guidelines divide HF cases into two cohorts, HF with reduced EF (HFrEF) involving patients with an EF of ≤ 40% and HF with preserved EF (HFpEF) [1]. A significant proportion of patients diagnosed as having HFpEF are actually patients who have recovered from an EF of > 40% [2, 3]. This heterogeneity of HFpEF is reflected in the ACCF/AHA guidelines by further dividing this EF category into (1) the “true” HFpEF population of individuals who have always had an EF of at least 50%, (2) patients with borderline function at an EF of 41-49%, and (3) patients who previously had an EF of ≤ 40% but have improved or recovered EF to > 40% [1]. The European Society of Cardiology 2016 guidelines rename the second, borderline category as HF with mid-range EF (HFmrEF) [4].

In 2011, Punnoose et al. reported that nearly 70% of patients with symptomatic HFpEF had recovered from a previously low EF [2]. These patients were clinically distinct from those with HFpEF, and further studies found that HFrecEF is associated with a better biomarker profile, quality of life, and event-free survival than continued HFrEF and HFpEF. However, these patients still have abnormalities in biomarkers and experience a significant number of HF hospitalizations, which suggest persistent HF risk [3].

Change in EF over time in HFrEF

In a community cohort study by Dunlay et al. [5], 39% of patients with HFrEF had an EF of ≥ 50% at some point after diagnosis. Improvement in LVEF in patients with profound systolic dysfunction has been reported. In trial populations with HFrEF, adding beta-blockers and renin–angiotensin–aldosterone system antagonists resulted in 4-8% improvement in EF within the first year after treatment [6, 7].

Improvement in LVEF has been increasingly observed in various clinical settings. In some etiologies of HF such as acute myocarditis, peripartum cardiomyopathy (Fig. 1) [8], some forms of cancer therapeutics-related cardiac dysfunction (Fig. 2) [9, 10], tachycardia-induced cardiomyopathy, recovery and normalization of LV structure and function can occur in up to 40–50% of patients [11–13].

HFrecEF (defined as a previous LVEF of < 40 but ≥ 40% at the time of study inclusion) was relatively prevalent in a single tertiary HF clinic setting [2]. Within a sample of 358 HF patients, 56 had HFpEF, 181 had HFrEF, and

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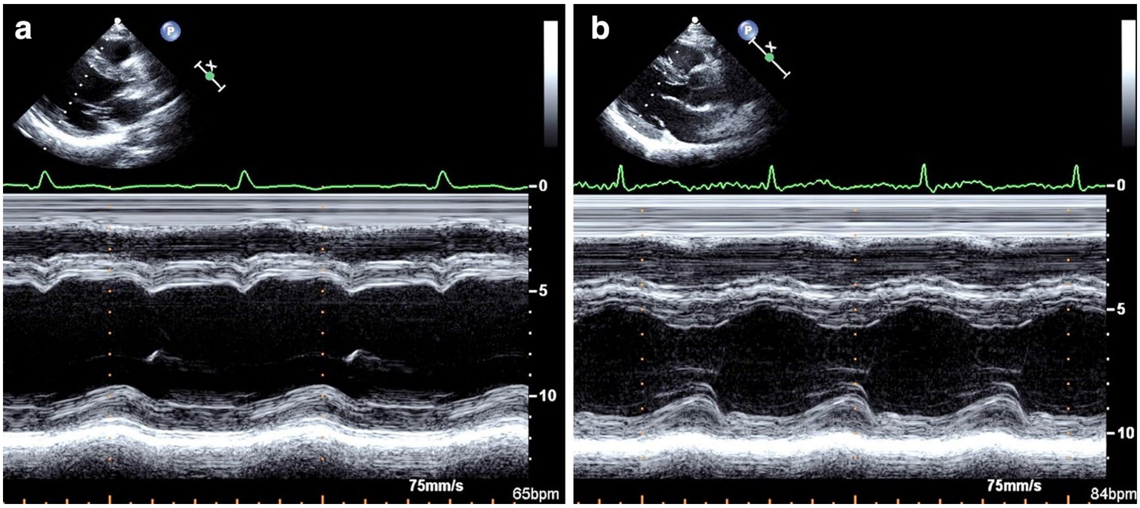

Fig. 1 M-mode echocardiograms in a patient with peripartum cardiomyopathy. A 38-year-old woman who delivered a baby by cesarean section complained of dyspnea immediately after delivery. Her left ventricle (LV) was dilated, and dyssynchrony was observed (**a**). After medical treatment with a beta-blocker and an angiotensin converting enzyme inhibitor for 2 years, the LV size and systolic function recovered to normal (**b**) [8]

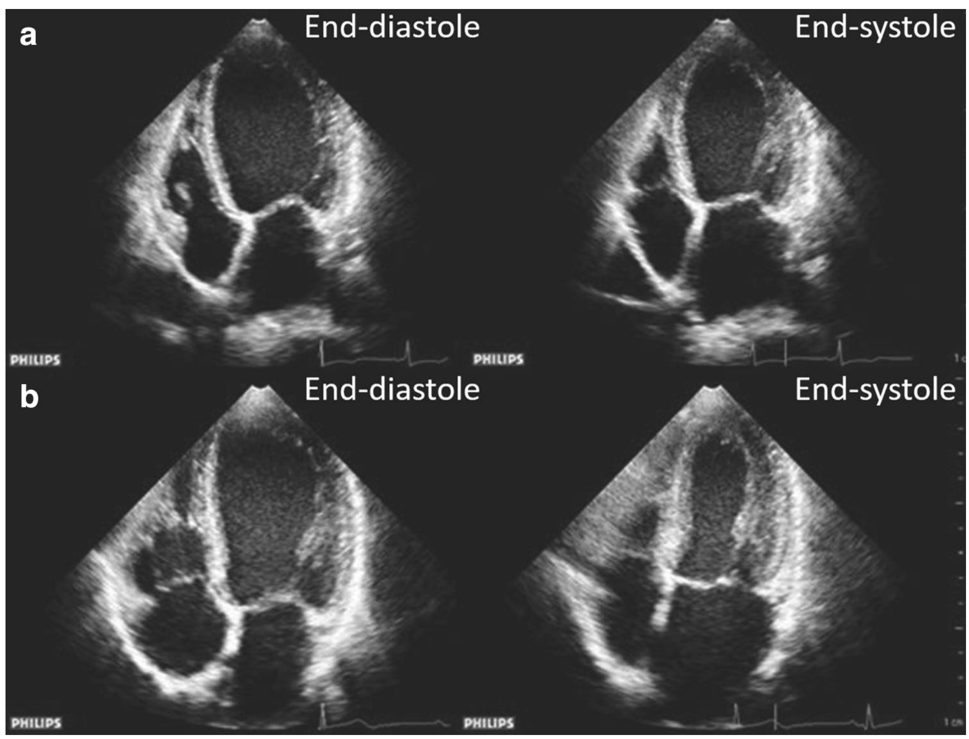

Fig. 2 Two-dimensional echocardiograms in a patient with cancer therapy related cardiomyopathy. A 79-year-old woman had a surgery for breast cancer. She received chemotherapy, including trastuzumab, and her LV ejection fraction (EF) decreased to 33% (**a**). After discontinuation of the trastuzumab therapy and initiation of medical treatment with a beta-blocker and an angiotensin converting enzyme inhibitor, LVEF recovered to 65% (**b**) [9]

121 (34%) had HFrecEF. Another report identified 10% of chronic HF patients as having HFrecEF, but defined HFrecEF as an LVEF of $\geq 50\%$ that was previously $< 50\%$ [3]. Patients with HFrecEF are typically younger than patients with HFpEF and HFrEF, and have a lower prevalence of comorbidities such as hypertension, diabetes and atrial fibrillation [2]. The non-ischemic origin of HF and absence of prior myocardial infarction were associated with improvement in LVEF in the large IMPROVE-HF cohort [14].

Table 1 Summary of disease types and suggested management in the presence of LVEF recovery

Ischemic heart disease
Acute myocarditis
Peripartum cardiomyopathy
Cancer therapeutics-related cardiac dysfunction
Tachycardia-induced cardiomyopathy
LV reverse remodeling
Beta-blockers
Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)
Aldosterone receptor antagonists
Cardiac resynchronization therapy (CRT) and ventricular assist devices (VADs)

Prognosis of HFrecEF

Improvement in LVEF has been systematically linked to improved quality of life and lower rehospitalization rates and mortality, regardless of how it is achieved [15]. HFrecEF patients have often milder symptoms, with patients mainly functioning in New York Heart Association class I or II [2]. All-cause mortality and the need for cardiac transplantation or mechanical circulatory supports are lower in patients with HFrecEF (LVEF ≥ 50%) than in those with HFrEF and HFpEF [HR for HFrEF compared with HFrecEF 4.1 (2.4–6.8); HR for HFpEF compared with HFrecEF 2.3 (1.2–4.5)]. Existing data suggest that post-treatment brain natriuretic peptide (BNP) and late gadolinium enhancement on cardiac magnetic resonance imaging (MRI) may be predictors of recovering LV function [16]. These treatment responders may improve their LVEF and reduce LV size. They may improve from HFrEF to HFmrEF and even normalize their LVEF to ≥ 50%. In our unpublished data, 12 (29%) of 41 patients with HFrEF were shifted to HFpEF (i.e., HFrecEF) 1 year after optimal treatment. The LVEF cutoff that will change HFrEF (LVEF < 50%) to HFpEF (LVEF ≥ 50%) was ≥ 36%.

Revascularization

Extensive clinical trial-based evidence supports the potential for reverse remodeling in patients with chronic HF who have received surgical interventions [17]. Significant improvement in systolic function in the days and weeks after myocardial infarction, as well as the potential for recovery after revascularization for patients with myocardial stunning or hibernation, was observed [18, 19]. Both medical and catheter-based revascularization techniques have been associated with significant rates of reverse remodeling after acute myocardial ischemia in patients with chronic ischemic heart disease [20]. More viable myocardial segments indicate a greater likelihood of improved LVEF after revascularization [21].

Medical treatment and devices

Renin–angiotensin–aldosterone inhibitors, beta-blockers, cardiac resynchronization therapy (CRT) and ventricular assist devices (VADs) have the potential to achieve reverse remodeling. To date, all therapies with mortality benefits for patients with HFrEF can induce reverse remodeling [12, 22]. Moreover, reverse remodeling strategies, whether medical or device-based therapies, seem to exhibit a dose–response relationship [17]. Indeed, the higher the intake of neurohumoral blockers or effective CRT, the higher the chance of recovery. However, not all patients exposed to these therapies achieve myocardial recovery and reverse remodeling. Optimal medical therapy appears to be a key component of achieving myocardial recovery. In the IMPROVE-HF study, a large observational cohort of outpatients enrolled in a performance measure intervention, almost one-third of patients experienced meaningful recovery of myocardial function with nearly doubling of LVEF (from 25 to 46%) [14]. Beta-blockers are the medical therapy most strongly linked to reverse remodeling. In the MRI substudy of the MERIT-HF trial, treatment with metoprolol for 6 months significantly increased LVEF by an average of 28% [23]. Several trials demonstrated early and sustained effects on LVEF and LV dimensions after initiation of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) [24, 25]. In addition, even when aldosterone receptor antagonists are added to ARB/ACEI and beta-blockers, significant beneficial effects on LV volume and function occur [26].

Among patients with HFrecEF, a challenging group is that with improved LVEF after CRT. Indeed, patients eligible for CRT had persistent LVEF of < 35% despite maximally tolerated neurohumoral blockers. However, systolic function often improves after implantation of a CRT. Substantial regression of myocardial dilatation and improvement in LVEF are likely the effects of resynchronization, which initiates a cascade of positive effects such as improved contractility and filling of the ventricles, reduction of mitral regurgitation, decreased sympathetic nerve activity, and reduction of LV wall stress [27, 28]. Table 1 summarizes the disease types and suggested management in the presence of LVEF recovery.

Management of HFrecEF

Continuation of HF medications as part of the management of recovered patients is often recommended [29]. However, weaning from or cessation of therapy in a select group of patients may be reasonable to consider if accompanied by close follow-up (which may include serial assessment of biomarkers) and serial imaging of LV size and function using echocardiography. Patients should be weaned from diuretics as tolerated, but specific neurohormonal antagonists such as beta-blockers, ACEIs/ARBs, and aldosterone antagonists should be carefully considered before cessation.

Re-worsening LVEF has been reported in patients with dilated cardiomyopathy and initial improvements in LVEF despite continued medical therapy [30]. Older patients and higher BNP levels after improvement in LVEF were associated with re-worsening of LVEF. Careful follow-up may be needed in patients with HFrecEF.

Conclusions

Many patients with HFrEF have some degree of myocardial recovery or improvement in LVEF. In our daily clinical practice, we will encounter more patients with HFrecEF. Although the prognosis of these patients is better than that of patients with HFrEF and HFpEF, outcome is not normal and periodic follow-up with echocardiographic assessment of LV function remains necessary. Until prospective data are available, pharmacotherapy and device therapy as for HFrEF should be continued.

Compliance with ethical standards

Conflict of interest Kazuaki Tanabe and Takahiro Sakamoto declare that they have no conflicts of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions.

Informed consent Informed consent was obtained from all patients for being included in this review.

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