Heart Failure With Better Ejection Fraction
A Modern Diagnosis

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The emerging population of heart failure with improved ejection fraction, characterized in this issue of Circulation by Basuray et al for 3 heart failure centers, testifies to the cumulative benefit of therapeutic advances during the past 30 years. The initial triage for referral to heart failure centers, many of which were launched with the approval of cyclosporine in 1984, was an assumed “less than six months to live,” derived from the classic Stanford experience in which most waiting transplant candidates who did not receive transplantation were dead within 6 months. Although the prognosis was not uniformly grim, most patients referred to transplant centers were dead within 1 to 2 years on the limited medical therapy of that time.

The direct vasodilators hydralazine and nitrates were the first proven in a randomized trial to improve outcomes in any heart failure population. Angiotensin-converting enzyme inhibitors then were shown to improve outcomes in patients with myocardial infarction, asymptomatic and symptomatic chronic heart failure, and acute decompensated heart failure in hospital. In comparison with the hydralazine/nitrate regimen, the angiotensin-converting enzyme inhibitors offered superior survival benefit for New York Heart Association class I to II ambulatory patients, but outcomes were equivalent for class III. Benefit was subsequently shown in hospitalized class IV patients for captopril over hydralazine, when both were titrated to the same hemodynamic goals achieved on intravenous nitroprusside and diuretics, usually requiring the addition of oral nitrates to both. Increasing survival for the heart failure center referral population could soon be attributed to both the increasing use of angiotensin-converting enzyme inhibitors (ACEIs) and the diminished use of type I antiarrhythmic therapy, which was being replaced by amiodarone.

During this time, experience was growing with β-blocker therapy, first used in Sweden to treat tachycardia in 7 patients with decompensated heart failure. Trials with carvedilol, metoprolol succinate, and bisoprolol added to ACEI in ambulatory populations all showed substantial additional decrease in mortality and hospitalizations, over shorter follow-up than required to see the impact of renin-angiotensin system inhibition alone.

The translation of the ACEI/β-blocker combination from trials into standard of care confirmed efficacy. Patients referred into the Valsartan Heart Failure Trial (ValHeFT) on a baseline of both β-blocker and ACEI had a 2-year mortality of 12% in comparison with 19% on β-blocker alone, 23% on ACEI alone, and 32% on neither. The increasing penetration of β-blocker therapy into community practice was associated with substantial decrease in heart failure mortality. The United Kingdom Heart Study demonstrated a decrease in 1-year mortality from 12.5% in the mid-1990s to 7.8% after 2000, as β-blocker use increased from 8.5% to 80% and ACEI therapy remained >80%. At the same time, the proportion of sudden death declined from 34% to 8% without implantable defibrillators. Similar trends were seen after 2000 in referrals to the advanced heart disease program at Brigham and Women’s Hospital, with β-blocker use more than doubling since before 2000, similar ejection fraction 0.19 but a median 2 years later from diagnosis, and 1-year mortality after referral declining from 34% to 18%.

After 2000, cardiac resynchronization therapy offered the next major improvement in left ventricular function, winning the Triple Crown first with increased function and quality, subsequently decreased hospitalizations and increased survival. As with β-blocker therapy, increases of ejection fraction were common with resynchronization therapy, frequently with changes large enough to elevate patients to the better ejection fraction range described in the accompanying study. Benefits of mineralocorticoid antagonists and the hydralazine-nitrate combination in blacks have also clearly been shown in trials but may be harder to detect in communities because of more restricted indications.

Heart failure management has undergone steady refinement since the recognition of the value of continuity care with mid-level professionals to improve outcomes in clinical research trials and transplant programs. In addition to patient education, a major focus of ongoing care has become the maintenance of cardiac filling pressures well below the symptom threshold. Successful programs to apply guidelines have accomplished high levels of adherence to ACEI and β-blocker recommendations. Although adjustments of neurohormonal antagonists are facilitated by heart failure management, the majority of interventions are changes in diuretic doses. Availability of torsemide for more consistent absorption and metolazone as an intermittent booster of diuresis have likely contributed to the maintenance of fluid balance without hospitalization. It is not yet known how the evolving financial incentives to focus on care transitions and outpatient access to decrease readmissions will impact the more fundamental
patient outcomes of quality of life and survival with heart failure.

**Who Are the Patients?**

Spontaneous improvement in left ventricular ejection fraction has long been recognized, even in the absence of disease-modifying therapies. This occurs most commonly in previously healthy young patients with a recent onset of symptoms, usually within 3 to 6 months of diagnosis. Although recovery is more common in those patients without severe hemodynamic compromise at presentation, the special case of fulminant myocarditis is characterized by rapid circulatory collapse that may require urgent temporary mechanical support, followed within days to weeks by return to normal ejection fraction in more than half of the patients. Cardiomyopathy that is truly caused rather than just unmasked by pregnancy has the best prognosis, with improvement in up to 70% of patients. Tachycardia can cause cardiomyopathy that is reversible, but it often remains ambiguous whether the cardiomyopathy arose solely from the tachycardia, or whether both reflect underlying myocardial disease.

The current study by the collaborative group from the University of Pennsylvania, Case Western Reserve, and the University of Wisconsin provides valuable characterization of the population in whom left ventricular ejection fraction (EF) has improved to >0.50. The proportion of patients meeting this definition was 10% in this study, which appears consistent with the 30% in the initial description of this population. Although recovery is more common in those patients without severe hemodynamic compromise at presentation, the special case of fulminant myocarditis is characterized by rapid circulatory collapse that may require urgent temporary mechanical support, followed within days to weeks by return to normal ejection fraction in more than half of the patients. Cardiomyopathy that is truly caused rather than just unmasked by pregnancy has the best prognosis, with improvement in up to 70% of patients. Tachycardia can cause cardiomyopathy that is reversible, but it often remains ambiguous whether the cardiomyopathy arose solely from the tachycardia, or whether both reflect underlying myocardial disease.

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**Implications for Therapy of HF Better EF**

This population of HF with a low EF that improves has been recognized as a distinct population in the latest American College of Cardiology Foundation/American Heart Association guidelines, where it has been recommended that further investigation be devoted to optimizing therapies for this new diagnosis.

**Neurohormonal Antagonists**

There is strong consensus that ACEI/angiotensin receptor blockers and β-blockers should be continued once begun as recommended therapy for left ventricular EF < 0.40. As neurohormonal activation declines, dose reduction may be necessary in some patients to address symptomatic hypotension or chronotropic incompetence. Other patients may require escalation of doses to control hypertension. The occasional patient with alopecia or other side effects that limit quality of life may seek discontinuation of β-blockers, for which risk/benefit considerations are unknown.

**Digitalis**

What should be done with digitalis therapy in these patients? Digoxin was prescribed for 23% of HF better EF patients in the current study and 18% of patients in the initial report. Unlike the neurohormonal antagonists, digoxin has been the subject of specific withdrawal trials, which have shown clinical deterioration in some patients. However, risk/benefit considerations suggest a higher relative toxicity in class I and II patients, for whom the counterbalancing risk of HF hospitalization is lower.

**Diuretics**

When should diuretic doses be titrated down in HF better EF? The average daily dose of loop diuretics in HF better EF from the Punnoose study was 110 mg. The persistence of mild elevation of natriuretic peptides and ST2 suggest that ventricular wall stress is not normalized in the HF better EF population. The challenge of fluid balance in HFpEF emphasizes that severe volume retention can occur despite normal EF. Higher daily doses of loop diuretics have been associated with higher risk that likely reflects the severity of fluid retention and renal dysfunction rather than diuretic toxicity. For patients who may no longer need high doses of diuretics, it is suspected but...
not known that they may confer toxicity. There is currently no standardized approach to weaning diuretic therapy after improvement.

**Exercise and Activity**

We do not know what to expect for exercise capacity after a low left ventricular EF has increased to 0.50. Only 28% of the patients in the current study were described as New York Heart Association class I, 56% in the initial study. From previous exercise research, patients with recovered EF after myocarditis reached only 53% of predicted peak oxygen consumption, with slower peak filling rates and more increase in left ventricular volume with exercise than healthy subjects. It will be important to avoid setting exercise prescriptions and expectations too high.

Vigilance is clearly warranted for the HF better EF population. As for stage B HF, general measures continue to include meticulous control of blood pressure and other risk factors for coronary artery disease, moderate restriction of sodium, and avoidance of excessive alcohol consumption or illicit drugs. The appropriate frequency of follow-up measurement of EF is unknown, but regression to lower EF after improvement to >0.45 on β-blocker therapy has been noted by De Groote in β >0.45 on is unknown, but regression to lower EF after improvement to >0.45 on β-blocker therapy has been noted by De Groote.

The delineation of HF better EF is 1 example of an important new diagnosis arising and defined from our recent therapies. Collaborative clinical and molecular scrutiny of this modern population will catalyze new insight into fundamental questions of how HF recompenses and what can truly recover, and ultimately help us to support and sustain recovery for patients with HF.

**Disclosures**

None.

**References**


**KEY WORDS:** Editorials • cardiomyopathies • heart failure • stroke volume
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Circulation. 2014;129:2364-2367; originally published online May 5, 2014; doi: 10.1161/CIRCULATIONAHA.114.010194

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