Heart Failure With Better Ejection Fraction
A Modern Diagnosis

Lynne Warner Stevenson, MD

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.

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 midlevel 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

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

© 2014 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.114.010194
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. 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 detection of ongoing troponin release in almost half of patients suggests that myocardial injury may still be smoldering. Although lower than in the other 2 EF groups, B-type natriuretic peptide and ST2 were still elevated in a substantial proportion of patients, consistent with ongoing myocardial stretch or stress. Almost half of patients have elevated uric acid levels, which may reflect oxidative stress and continued diuretic use. It is not clear from the current analysis how many patients had multiple abnormalities and whether there were patients whose profiles were entirely normalized. It will be informative to compare these profiles with those from patients after varying durations of left ventricular assist device support. As we gain more experience correlating outcomes with biomarker profiles, and eventually with metabolomics and possibly analyses of gene expression and microRNAs, we will better learn which patients can perhaps be reassured with a life expectancy no longer shadowed by the diagnosis of cardiomyopathy.

With the demonstration that the biochemical profile and risk of hospitalization do not return to normal, true recovery is not present here, although the EF has moved into the normal distribution. Initially applied optimistically to the patients with EF increasing only to >0.40, the term recovered EF still seems misleading even when defined by EF ≥ 0.50. The distinction between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) has been a useful one both for pathophysiology and therapies. For terminology that reflects both the advances and limits of our current information, it may be most appropriate to label the third population of the contemporary HF clinic as HF better EF (pronounced Heff better E-eff).

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.25 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.21 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 up to 26% of patients during a median follow-up of 9 years, associated with 4-fold higher mortality than those who maintained a better EF.26

Modern Diagnosis as Vital Catalyst
HF is an ancient disease. In Egypt 3 millenia BC, dyspnea was attributed to a blockage of blood flow, later in Greece described as a seething heard in the chest and recognized to be worse in the recumbent position. Dropsy continued to be explained as an excess of evil humors and, during the past 4 centuries, has been treated with digitalis glycosides and vivid methods to drain fluid. As described by Braunwald, the pace of progress was agonizingly slow in the past but is now accelerating rapidly.27 HF better EF is a new state that was only created during the past 10 to 20 years of advancing therapies, was not recognized as a diagnosis until 3 years ago, and is now profiled biochemically in this Penn Heart Failure project study.1

The spirit of inquiry during the course of clinical service is more relevant than ever before as new diagnoses turn up in the wake of modern therapies. In-stent restenosis, recurrent sudden death, and vasodilator-responsive pulmonary hypertension could never have been described by Galen. Cancer could not recur unless the original tumors responded to therapies, which can create novel forms of cardiotoxicity not yet recognized. In infectious disease, the major organisms under perpetual evolution are identified by the new antibiotics that could not recur unless the original tumors responded to therapies, which can create novel forms of cardiotoxicity not yet recognized. Infectious disease, the major organisms under perpetual evolution are identified by the new antibiotics that could not recur unless the original tumors responded to therapies, which can create novel forms of cardiotoxicity not yet recognized. Infections disease, the major organisms under perpetual evolution are identified by the new antibiotics that could not recur unless the original tumors responded to therapies, which can create novel forms of cardiotoxicity not yet recognized. Infections disease, the major organisms under perpetual evolution are identified by the new antibiotics.29 As recently emphasized by Nohria regarding new signatures of congestion,24 clinical observation will never be obsolete. Vigilance for new clinical presentations and connections was never more likely to catalyze discovery than in the current era.

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
Heart Failure With Better Ejection Fraction: A Modern Diagnosis
Lynne Warner Stevenson

Circulation. 2014;129:2364-2367; originally published online May 5, 2014;
doi: 10.1161/CIRCULATIONAHA.114.010194
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/129/23/2364

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/