Are Systolic and Diastolic Heart Failure Overlapping or Distinct Phenotypes Within the Heart Failure Spectrum?

Diastolic and Systolic Heart Failure Are Distinct Phenotypes Within the Heart Failure Spectrum

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Heart failure (HF) is a major worldwide public health problem. One in 5 people aged 40 years in the United States will develop HF during his or her lifetime,[1] and HF remains the leading cause for hospitalization among the elderly.[2] Although age- and sex-specific HF incidence is not increasing,[3] overall HF survival has improved, and the number of people aged >65 years is increasing rapidly. Thus, the absolute number of patients with HF will continue to increase. Half of the patients with HF have a preserved ejection fraction (HFpEF), and the remainder display reduced ejection fraction (HFrEF).[4–6] The proportion of patients with normal ejection fraction (EF) is increasing steadily because of increased incidence and/or increasing physician recognition of the syndrome.[4] Resource utilization associated with HF is high in both the inpatient and outpatient settings, regardless of EF.

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Heart failure is a syndrome that can be defined clinically by a collection of symptoms (dyspnea, fatigue, exertional intolerance) and signs (edema, gallop, rales) that are attributable to a cardiac disorder.[2] Heart failure may also be defined hemodynamically by an inability to provide adequate cardiac output to the body at rest or with exertion, or to do so only in the setting of elevated cardiac filling pressures. The cardiovascular system responds to a wide variety of insults (eg, myocardial disease, ischemia, valvular or pericardial disease) in a finite number of ways, both hemodynamically (elevated filling pressures, depressed output) and symptomatically (dyspnea, fatigue, angina). However, these similarities in clinical expression do not indicate that the underlying mechanisms of disease are the same or that treatment will be similar. For example, a headache may be noted with a migraine or brain tumor; dyspnea may be reported with HF, emphysema, or neuromuscular disease; and diarrhea may be observed with infection, dysmotility, or sprue. In each case, common treatments (analgesics, oxygen, and rehydration) will improve symptoms, but only unique interventions targeted to the specific insults causing each disease will be effective to modify long-term outcomes.

HFpEF and HFrEF share the same clinical phenotype. Signs, symptoms, exercise intolerance, hemodynamics, and outcomes may be identical or highly similar in each form of HF,[5–11] but this does not indicate that these disorders are due to a common pathogenesis, or that they should be treated in the same way. Indeed, the principal rationale to taxonomically distinguish diseases is based on cause and treatment. In this review, we examine the wealth of evidence proving that, despite multiple similarities in clinical expression, HFpEF and HFrEF represent 2 distinct disorders in the HF spectrum and, as such, should be studied and treated separately.

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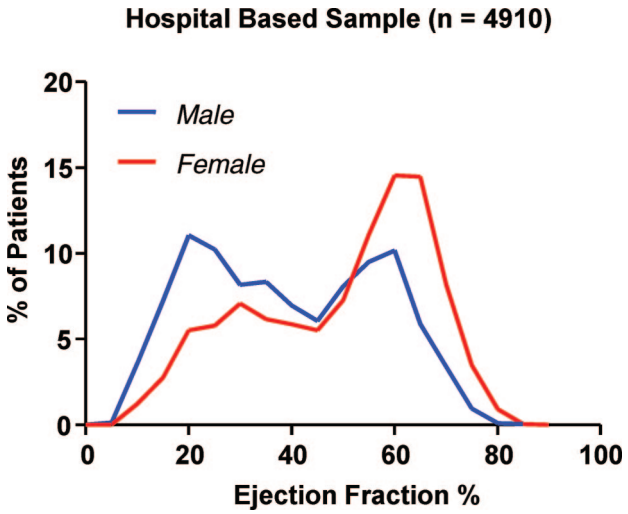

Figure 1. Bimodal distribution of ejection fraction in heart failure.

Conclusive Evidence That Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction Are Distinct Diseases

Among Patients With Clinical Diagnosis of Heart Failure, the Distribution of Ejection Fraction Is Bimodal

If HFpEF and HFrEF are part of the same disease process, one would expect to observe a unimodal distribution of EF within HF populations. In an analysis of data from patients enrolled in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program, Solomon and colleagues[12] observed such a unimodal distribution of EF. This has been interpreted to support the notion that HFpEF and HFrEF are part of the same disease spectrum.[13] However, as pointed out by Gaasch et al,[14] the CHARM program enrolled more patients with HFrEF than HFpEF, which may skew the distribution, and analysis of 2 other HF trials that did not prespecify EF enrollment criteria revealed bimodal distributions of EF. These data are limited by selection bias, because the populations examined were referred or selected for a clinical trial, but community-based data show similar findings. Data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients (OPTIMIZE) registry of >30 000 patients admitted for acutely decompensated HF have also shown a bimodal distribution of EF among HF patients.[9] We analyzed all consecutive patients admitted with HF to our own institution over a 16-year period (from previously published data)[4] (Figure 1). This plot clearly shows a bimodal EF distribution. Inspection of the EF histogram stratified by sex further shows a greater female preponderance in HFpEF, as has been shown in numerous studies. These data provide strong a priori evidence that HFpEF and HFrEF represent 2 distinct disease processes.

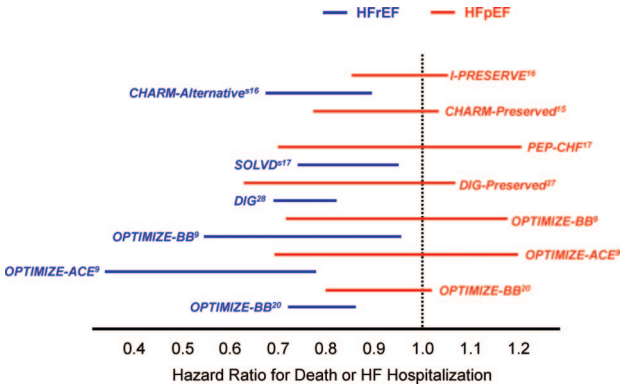

Figure 2. Differential response to treatment in heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). Summary of hazard ratios observed in trials or registries studying patients with HFpEF and HFrEF is shown. I-PRESERVE indicates Irbesartan in Heart Failure With Preserved Ejection Fraction Study; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; PEP-CHF, Perindopril for Elderly People With Chronic Heart Failure; SOLVD, Studies of Left Ventricular Dysfunction; DIG, Digitalis Investigation Group; OPTIMIZE, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients; BB, β-blocker; ACE, angiotensin-converting enzyme; and HF, heart failure.

Therapies With Proven Benefit in Heart Failure With Reduced Ejection Fraction Have Failed to Improve Outcome in Heart Failure With Preserved Ejection Fraction

If HFpEF and HFrEF were part of the same HF disease spectrum, they would be expected to respond similarly to treatment. However, medications that have been shown to produce unequivocal improvements in HFrEF have not produced similar beneficial effects in HFpEF (Figure 2). Whereas survival for patients with HFrEF has improved over the past 2 decades, there has been no improvement in HFpEF survival.[4] The CHARM-Preserved study (n=3023) compared the angiotensin receptor blocker candesartan versus placebo in patients with HF and EF >40%, and did not show a significant reduction in the composite outcome of death and cardiovascular hospitalization.[15] There was a trend toward benefit overall, but this study included a large proportion of patients with mild systolic dysfunction (EF 40% to 49%) and more patients with coronary disease and male sex than are typically noted in community-based HFpEF populations. The larger Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE) (n=4128) similarly showed no reduction in death or hospitalization with the angiotensin receptor blocker irbesartan over 4 years of follow-up.[16] Angiotensin-converting enzyme inhibitors have also failed to show benefit in HFpEF. The Perindopril for Elderly People With Chronic Heart Failure (PEP-CHF) trial (n=850) randomized HFpEF patients aged ≥70 years to perindopril or placebo and found over the 3-year study period that there was no reduction in mortality or HF hospitalizations.[17] A recent trial of enalapril in elderly patients with HFpEF reported no

improvement in exercise capacity, aortic distensibility, or neurohormonal profile compared with placebo.[18]

Observational data from the OPTIMIZE registry have failed to demonstrate a reduced hazard of mortality and hospitalization in association with discharge angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use in HFpEF, in striking contrast to reductions in events observed in HFrEF.[9] The unique disease-specific responses to antiangiotensin therapies is further highlighted by a recent ancillary analysis of the very large Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (n=42 418), in which chlorthalidone reduced incidence of both HFpEF and HFrEF compared with amlodipine and doxazosin; however, lisinopril was only effective in reducing incident HFrEF, with no benefit in HFpEF incidence compared with the other agents.[19]

The efficacy of β-blockers (BB) in HFpEF remains unresolved, although BB remain one of the most prescribed medications in this population.[9] Observational studies from OPTIMIZE observed no reduction in morbidity and mortality in short-term[9] or long-term[20] follow-up in HFpEF, in contrast to HFrEF, in which significant reductions in maladaptive remodeling, HF hospitalizations, and mortality were observed with BB in both registry[9,20] and trial data.[2] Ancillary analysis from the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) suggested that the benefits of the BB nebivolol were also observed in patients with preserved EF,[21] although few patients in the trial had EF >50% to 55%. A recent observational study noted that women with HFpEF (EF >50%) discharged on BB had higher 6-month rehospitalization rates compared with those not prescribed BB,[22] and it is speculated that this could be related to deleterious effects of heart rate reduction in normal to small ventricles in HFpEF, in which chronotropic incompetence is common.[23–25] The effects of BB on cardiomyocytes appear to differ in HFpEF and HFrEF, with higher resting tension observed in HFpEF patients treated with BB but no apparent BB effect on myocyte stiffness in HFrEF.[26]

In an ancillary analysis of 988 patients with HFpEF (EF >45%) enrolled in the Digitalis Investigation Group (DIG) trial, Ahmed et al[27] found that, although digoxin lowered HF hospitalization, this benefit was overcome by an equivalent increase in coronary syndrome hospitalizations.[28] Other therapies with proven benefit in HFrEF, such as aldosterone antagonists or devices, are less investigated in HFpEF. Myocardial ischemia and infarction cause systolic and diastolic dysfunction, and revascularization for triple-vessel disease among patients with reduced EF is associated with improved survival.[29] The role of revascularization is less well studied in HFpEF, although a case series from Little and colleagues[30] found that episodes of pulmonary edema tend to recur despite revascularization in this setting.

Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction Display Unique Patterns of Ventricular and Cellular Remodeling

Although increased left ventricular mass is characteristic of most forms of HF, the patterns of ventricular remodeling in HFpEF and HFrEF are highly distinct.[10] Left ventricular chamber dilation is a defining characteristic of HFrEF. Indeed, in chronic, compensated HFrEF, the EF is reduced because the chamber size (denominator of EF equation) is larger, whereas the stroke volume (numerator) is typically similar to that of normal controls.[7,10] Chamber dilation in HFrEF is coupled with pathological electric remodeling because left bundle-branch block is much more common in HFrEF than in HFpEF.[31,32] In contrast, most[6,7,25,33–40] although not all[41,42] studies have reported that ventricular chamber size is normal or near normal in HFpEF, with increased wall thickness, greater ratio of wall thickness to chamber dimension, and increased ratio of ventricular mass to chamber volume compared with HFrEF patients and healthy controls. These changes are similar to those observed with chronic pressure overload due to arterial hypertension,[43] and indeed, abundant data suggest that HFpEF develops as a progression from asymptomatic hypertensive heart disease.[25,33,34,44] In contrast, although hypertension is a potent risk factor for all forms of HF,[45] it is an uncommon solitary cause of HFrEF.[46]

These disparate ventricular structural changes in HFpEF and HFrEF are associated with diametrically opposed effects on ventricular-arterial interaction, particularly involving the end-systolic pressure-volume relationship or end-systolic elastance.[47] End-systolic elastance is markedly reduced in HFrEF, and, as a result, HFrEF patients respond very favorably to arterial vasodilators, with minimal drop in blood pressure and substantial improvement in stroke volume.[47,48] In contrast, end-systolic elastance is elevated in HFpEF patients.[33,44,49] This leads to more exaggerated drops in blood pressure with vasodilator therapy in HFpEF while similarly promoting more marked increases in blood pressures during stress.[48] These fundamental differences in clinical response to alterations in ventricular loading may partially explain the failure of vasodilators to improve outcomes in clinical trials for HFpEF.[15–18] Remodeling in both forms of HF may be associated with mechanical dyssynchrony,[2,50] although the type of dyssynchrony that is amenable to device therapy[51] (bundle-branch block) is much more common in HFrEF, in which eccentric remodeling predominates.[31,32]

Differences between HFrEF and HFpEF extend to the level of the interstitium and cardiomyocyte. The balance of matrix metalloproteinases and their inhibitors differs in HFrEF and HFpEF, and this difference is hypothesized to contribute to the distinct patterns of chamber remodeling observed in these diseases.[52] Histopathological studies from Paulus and colleagues have shown that the cardiomyocyte is narrow and elongated in HFrEF, with reduced myofibrillar density, whereas myocyte diameter and resting tension are both

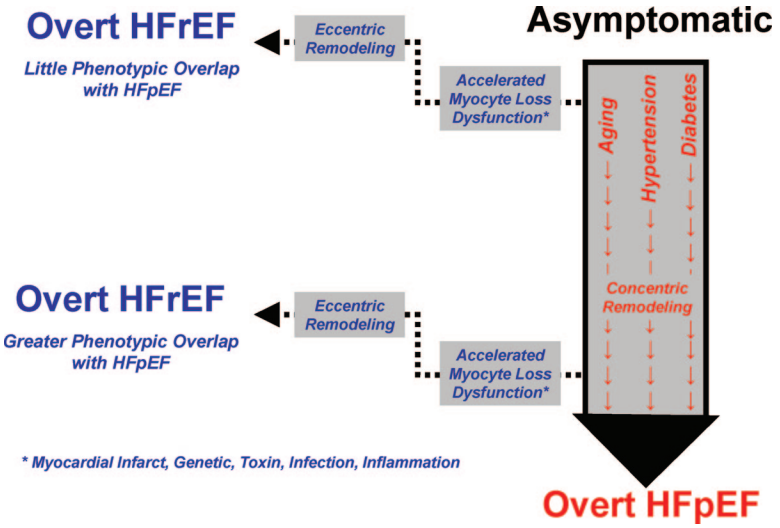

Figure 3. Distinct pathophysiology of heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).

increased in HFpEF,[40,53] particularly among diabetics.[54] Furthermore, the mechanisms responsible for increased myocyte stiffness appear to differ in diabetic HFrEF, in which enhanced deposition and cross-linking of advanced glycation end-products predominate, in contrast to HFpEF, in which higher cardiomyocyte resting tension has been observed, presumably related to sarcomeric protein phosphorylation status.[54] There is an increased ratio of the stiffer isoform of the macromolecule titin in HFpEF compared with HFrEF, which may contribute to higher resting tension and the larger drop in tension in response to phosphorylation.[40]

Suggestive Evidence That Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction Are Distinct Diseases

Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction Tend to Arise Among Different Patient Populations

Community-based studies have demonstrated that HFpEF patients differ from HFrEF in a number of characteristic ways, although there is considerable overlap when large community-based studies are examined[4–6,8,9,31,32,36] (see Table and References in the online-only Data Supplement). Most studies have found that HFpEF patients are older (weighted average, 74 versus 70 years), more often hypertensive (weighted average, 74% versus 65%), and less likely to have coronary disease (weighted average, 46% versus 58%). The most robust difference is female sex (weighted average, 63% versus 38%), which is possibly related to less coronary disease, enhanced concentric remodeling, and age-related vascular stiffening in women.[55,56] These differences in age, sex, hypertensive history, and coronary disease become more prominent when HFpEF is defined more stringently by EF ≥50% to 55%,[9,57] providing further evidence that these represent 2 distinct disease processes.

Arterial loading conditions differ in HFpEF and HFrEF: Vasoconstriction is common to both forms of HF, but pulse pressure is higher in HFpEF, and this vascular stiffening produces greater blood pressure lability with changes in preload, afterload, and stress in HFpEF.[48,49,57]

Pathogenesis and Disease Progression in Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction Appear Distinct

Hypertension is the single largest risk factor for development of HF, regardless of EF,[45] and although prevalence of hypertension is greater in HFpEF, it is common to both forms of HF. Changes in cardiovascular structure and function in arterial hypertension are similar to those seen with normal maturation, leading some to refer to hypertension as "accelerated aging."[43] The dominant risk factors for HFpEF are age and hypertension, and many of the pathophysiological derangements in HFpEF present as a continuum with asymptomatic hypertensive heart disease,[25,33,34,44] suggesting that HFpEF may be a form of accelerated hypertension. Age-, hypertension-, and, in some cases, diabetes mellitus–related ventricular remodeling thus create the slowly progressive substrate on which HFpEF is formed (Figure 3), and recent evidence suggests that progression of a number of abnormalities in cardiovascular function may promote the transition to overt HFpEF, including loss of contractile reserve, diastolic reserve, chronotropy, vasodilation, and endothelial function.[23–25,58] In contrast, HFrEF most commonly develops in response to distinct pathophysiological perturbations, leading to accelerated and larger-scale myocyte loss/dysfunction, with the most common pathogeneses including acute myocardial infarction, genetic abnormalities, myocarditis, or toxin effects (eg, alcohol or chemotherapy).[2] These more distinct processes may occur in younger patients, in whom they predom-

inate, or later in life on a background of age/hypertension/diabetic remodeling (eg, anterior myocardial infarction in an elderly woman with hypertension), leading to the appearance of greater overlap between the clinical phenotypes. However, the common appearance of some characteristics such as this in both forms of HF should not be taken as evidence that they represent the same underlying disease process.

It has been suggested that HFpEF may progress to HFrEF, consistent with the notion that the 2 diagnoses exist in a continuum. However, in the absence of coronary disease/myocardial infarction (the leading cause of HFrEF), there is little evidence that this transition occurs.[59] Increased left ventricular mass is indeed a risk factor for the development of depressed EF, but this relationship is observed principally in the setting of eccentric hypertrophy and not in concentric remodeling, as is typical of HFpEF.[60] These longitudinal data provide further evidence that HFpEF and HFrEF develop in 2 distinct mechanistic pathways: eccentric remodeling in the latter, and concentric in the former.

Features That Are Shared by Heart Failure With Preserved Ejection Fraction and Heart Failure With Reduced Ejection Fraction Yet Do Not Prove a Common Disease Process

Ventricular and Vascular Dysfunction Are Common to All Heart Failure

Diastolic dysfunction is characteristic of both forms of HF, and is evidenced clinically by the presence of elevated filling pressures, abnormal relaxation, and increased chamber stiffness.[10,35] Systolic dysfunction had traditionally been considered to be unique to HFrEF,[38] but a number of recent studies have shown that regional and chamber-level systolic dysfunction are also common in HFpEF,[10,25,44] although not as severe as in HFrEF. Systolic dysfunction becomes more apparent and limiting during the stress of exercise in HFpEF,[23,25] in which it is potently associated with depressed functional capacity,[25] possibly because mild systolic dysfunction has more severe consequences in the absence of chamber dilation. Chronotropic incompetence is also common in both HFpEF and HFrEF, likely related to autonomic dysfunction and/or β-receptor desensitization,[23–25,61] processes that are common to all HF. Abnormal vasorelaxation and endothelium-dependent vasodilation are observed in both HFpEF and HFrEF in both the systemic circulation[23,25,62] and the pulmonary vasculature.[63,64] Each of these abnormalities may exacerbate ventricular dysfunction in either form of HF. However, the presence of many common abnormalities in ventricular-vascular functional response to HF does not indicate that HFpEF and HFrEF share the same initial or predominant pathogenic mechanism.

Neurohormonal Activation and Renal Dysfunction Are Common to All Heart Failure

Pathological activation of the renin-angiotensin-aldosterone axis, natriuretic peptides, and the sympathetic nervous system are characteristic of both HFrEF and HFpEF, but have been studied much more extensively in HFrEF. Norepinephrine levels are similarly elevated in HFpEF and HFrEF.[7] Natriuretic peptide levels are elevated in both forms of HF, although they are elevated to a greater extent in HFrEF.[7,65,66] This is not surprising, because the stimulus for myocardial brain natriuretic peptide release is wall stress, which varies directly with filling pressures (elevated in both HFpEF and HFrEF) and chamber size (elevated in HFrEF but normal in HFpEF).[65] Aldosterone levels are similar in HFrEF and HFpEF,[66] but other neurohormones, such as plasma renin activity, angiotensin II, and vasopressin have not been compared in these groups.

Renal dysfunction is similarly problematic in HFpEF and HFrEF,[4–6,8] but recent evidence suggests that patients with HFpEF may be more vulnerable to the development of renal dysfunction during the course of treatment for HF decompensation,[57] and renal-associated mortality was higher in HFpEF in a post hoc analysis from the DIG trial.[67] Regardless of the similarities in neurohormonal activation and renal dysfunction in both forms of HF, these maladaptations are fundamentally a common response to hemodynamic derangements (elevated filling pressures and low output) that are shared by both HFpEF and HFrEF, but that do not indicate that the disease processes are the same.

Natural History of Heart Failure With Preserved Ejection Fraction: Implications for Diagnosis and Mode of Death

Exertional dyspnea and fatigue are common symptoms in patients with HF, particularly among the elderly. When echocardiography demonstrates a depressed EF, these symptoms are usually ascribed to HFrEF. However, when symptoms of exertional intolerance are noted in a patient with preserved EF, diagnosis is more challenging, and symptoms may be related to deconditioning, obesity, pulmonary disease, pulmonary vascular disease, or HFpEF. In relation to a lack of awareness and/or a lack of established treatment options, the diagnosis of HFpEF is often not entertained, even among cardiovascular specialists. Many patients with earlier-stage HFpEF may be younger, more active, or have fewer comorbidities and present with predominantly exertional (New York Heart Association functional class II) symptoms at a time when the severity of the underlying cardiovascular remodeling and dysfunction is less severe and potentially still amenable to treatment (Figure 4). Indeed, recent studies have shown that, despite normal examination, echocardiography, and resting hemodynamics, patients with early-stage HFpEF may display hemodynamic abnormalities (elevated filling pressures) exclusively during the stress of exercise.[58]

Earlier recognition of HFpEF may enable investigation of treatment and preventive strategies in which the potential for benefit is increased. In contrast, elderly patients who are inactive and have many comorbidities may present with more severe symptoms (New York Heart Association functional class III to IV) during an episode of hemodynamic stress (often due to a

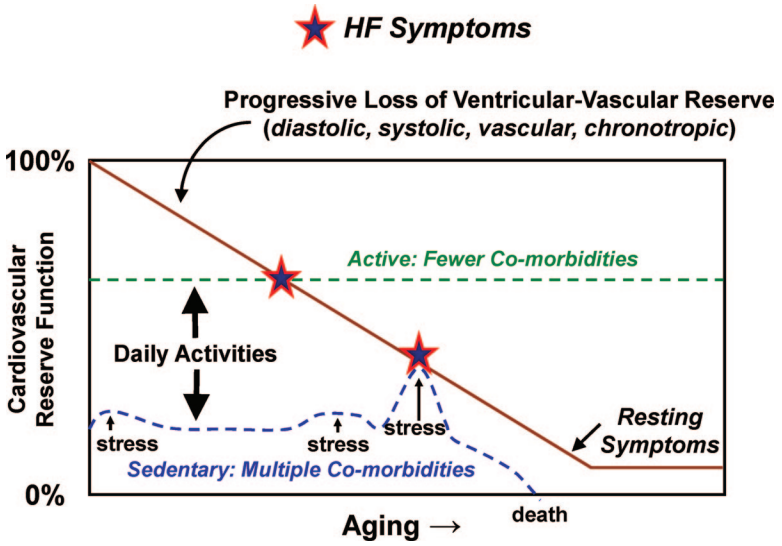

Figure 4. Variable natural history in heart failure (HF) with preserved ejection fraction.

comorbidity) and at a time when pathological abnormalities may be less reversible (Figure 4). In many such patients, their subsequent clinical course may be driven more by the comorbidity than their HF. Indeed, patients with HFpEF are more likely to die of noncardiovascular causes than patients with HFrEF.[15,68,69] Importantly, a recent community-based study directly comparing mode of death in HFpEF and HFrEF found that the greater rate of noncardiovascular death in HFpEF was primarily attributable to fewer coronary disease deaths in HFpEF, with similar rates of HF death and otherwise comparable comorbidity scores in the 2 groups.[70]

The Problem of the Intermediate Group (Ejection Fraction 40% to 50%)

The definition of preserved EF has varied considerably between studies, ranging from ≥35% to ≥55%. Lumping together patients with mildly depressed EF with truly normal EF may lead to the appearance of a continuous spectrum while also producing confusing results when attempting to properly interpret the trial data. As discussed above, recent studies have suggested that this intermediate group has many features more typical of HFrEF—greater male predominance, more coronary disease, less hypertension, more chamber dilation, and greater risk of dying from cardiovascular causes—compared with more stringently defined HFpEF (>50% to 55%). It is most likely that this intermediate EF group is populated by patients with either mild or well-treated HFrEF rather than patients whose EF is gradually diminishing; in either case, these patients would be more appropriately treated according to established HFrEF guidelines. We would propose that definite HFpEF be defined by EF >50%, and that this intermediate group be included in HFrEF. At this time, there is insufficient rationale to alter the established EF-based nosology to distinguish the 2 forms of HF. Although EF is not synonymous with contractility,[44] it is easy to conceptualize, easy to measure, and universally available, making it a useful marker to distinguish the 2 forms of HF.

Conclusions

Great strides have been made to better understand the pathophysiology of HFpEF and HFrEF, but important questions remain unanswered. The 2 forms of HF differ fundamentally in the acuity and extent of myocardial loss/dysfunction, the pattern of remodeling at the chamber and ultrastructural levels, and the response to therapeutic interventions. Progression to HFpEF is gradual and tends to develops in concert with typical age-acquired comorbidities, particularly hypertension with concentric remodeling. In contrast, HFrEF may develop acutely or indolently, but typically in response to a larger-scale myocardial insult. Drug and device therapies that target maladaptive eccentric ventricular remodeling improve outcome in HFrEF, because these are the processes that drive the pathogenesis. In contrast, the pathophysiological derangements in HFpEF include concentric remodeling, ventricular-vascular stiffening, and loss of ventricular-vascular reserve function, and therefore it is not surprising that therapies targeting HFrEF pathophysiology have not improved outcome in HFpEF. Future basic and clinical research should separate these 2 distinct forms of HF so as to better understand its unique mechanisms of disease and define optimal treatment strategies.

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Disclosures

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Response to Borlaug and Redfield

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This debate on heart failure (HF) perfectly captures the controversy in the field. Whereas Borlaug and Redfield describe a typical clinician's view, we have presented the opposing physiologist's view. We appreciate that Borlaug and Redfield acknowledge the important overlapping pathophysiological features between HF with preserved ejection fraction and HF with reduced ejection fraction, such as systolic and diastolic abnormalities, endothelial dysfunction, autonomic dysfunction, and neurohormonal imbalances. We also appreciate that they mention the intermediate group of patients, which, in their opinion, is part of the HF with reduced ejection fraction subgroup, but in our opinion closes the gap in a continuous disease spectrum of overlapping phenotypes. The arguments of Borlaug and Redfield to dichotomize HF are based on the clinical diversity of HF caused by the available bedside parameter left ventricular ejection fraction, which is a measure of the ventricle as a hemodynamic compression pump, and on the variable clinical responses to currently available drugs and devices. This information is accurate and clinically relevant. Nevertheless, we approach the heart as a dissipative structure that obtains emerging properties at each level of its complexity. From this perspective, the heart is more than a hemodynamic compression pump. Hence, it is inappropriate to dichotomize the HF syndrome by selecting a single arbitrary parameter, like left ventricular ejection fraction, out of many other possible parameters or biomarkers. To gain further pathophysiological understanding of this complex syndrome (eg, during the integrative approaches of systems biology), separated (ie, biased) analyses of HF with preserved ejection fraction and HF with reduced ejection fraction should be avoided. Only with the combined efforts of clinicians and physiologists can the complexity of HF be unraveled.