Heart failure (HF) is a clinical syndrome characterized by breathlessness (dyspnea) at normal or at low-level exertion, fatigue, and fluid retention. As the name implies, HF centrally involves impaired heart function, and the percent of blood volume ejected with each beat, or ejection fraction (EF), has traditionally served as an indicator of pump dysfunction, being low in dilated hearts with depressed systolic performance. However, nearly half of all patients with HF symptoms have an EF that is preserved (exceeding 50%). Importantly, the prevalence of HF with preserved EF (HFpEF) is rising, with morbidity, mortality, and healthcare costs on par with HF with reduced EF, and as the list of failed treatments continues to grow, HF with preserved EF clearly represents a major unmet medical need. The field is greatly in need of a more unified approach to its definition and view of the syndrome that engages integrative and reserve pathophysiology beyond that related to the heart alone. We need to reflect on prior treatment failures and the message this is providing, and redirect our approaches likely with a paradigm shift in how the disease is viewed. Success will require interactions between clinicians, translational researchers, and basic physiologists. Here, we review recent translational and clinical research into HF with preserved EF and give perspectives on its evolving demographics and epidemiology, the role of multiorgan deficiencies, potential mechanisms that involve the heart and other organs, clinical trials, and future directions. (Circ Res. 2014;115:79-96.)

Key Words: diastole ■ heart failure ■ hypertension ■ hypertrophy ■ therapy
features were recognized, the disease was renamed HF with normal EF, though as of only 8 years ago, there was sufficient debate that diastolic HF and HF with normal EF were suggested to be used interchangeably.\(^1\) As more studies questioned whether systole is truly normal,\(^{1,9-21}\) the name changed to HFP EF;\(^{22,23}\) which is now the accepted standard.

### Making the Diagnosis of HFP EF

To an extent, the diagnostic criteria for HFP EF have evolved along with its name. By the late 1990s, criteria included signs and symptoms of HF with an objective measurement of exercise intolerance; normal left ventricular (LV) function defined as LVEF >45%; and abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness.\(^{24}\) Several embellishments were made involving morphological changes in the heart (eg, hypertrophy, atrial enlargement, diastolic dysfunction),\(^{25}\) but these have gradually been removed as many patients often lacked a particular diastolic or structural defect, yet had all the hallmarks of an HF syndrome. Recent guidelines from the 2013 American College of Cardiology/American Heart Association consensus statement reconfirm that in practice, the diagnosis of HFP EF is based on typical symptoms and signs of HF in a patient with a normal LVEF and no significant valvular abnormalities by echocardiography.\(^{26}\) Diastolic abnormalities are mentioned, but nothing specific. The European Society of Cardiology requires normal or mildly abnormal LV function and evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness.\(^{27}\) We agree that although patients with HFP EF often have diastolic dysfunction, this should not be required for the diagnosis. In cases where dyspnea of unknown cause is present and EF is >50%, then objective evidence of cardiac dysfunction at rest or more likely with exertion would be important to demonstrate to assign an HF diagnosis. It is important for experimental biologists to appreciate that many humans have abnormal diastolic function with a normal EF, and that this combination per se does not mean they have HF. Too often one sees animal models presented as HFP EF where diastolic pressures are elevated or relaxation is delayed and EF is in the normal range. This may be a model of diastolic abnormalities, but it is not a priori HFP EF.

### Epidemiology of HFP EF

Cross-sectional studies from Westernized countries have established a view of HFP EF as occurring in elderly, predominantly female patients, with small hypertrophied hearts and a high prevalence of hypertension, diabetes mellitus, and atrial fibrillation.\(^{3,4,28-30}\) Those reporting race have found a white predominance.\(^{29,30}\) However, growing evidence suggests that HFP EF patients are far more diverse (Table 1). Melenovsky et al\(^{13}\) studied HFP EF in an urban population, finding a somewhat younger, predominantly black (76%) population with high rates of hypertension, marked ventricular hypertrophy, and obesity. Similar findings were reported by the New York Heart Failure Registry, with black HFP EF patients also reporting worse renal function.\(^{31}\) These differences as recently reviewed by Shah\(^2\) likely impact therapy responses and net outcome. Increasingly, epidemiological data report a much more balanced sex distribution.\(^{33}\)
and this is seen in most clinical trials. The National Ambulatory Cohort of Veterans study examined nearly all men with HF: 30% had HFrEF. Compared to those with HFrEF, they were older, were more likely white, had higher systolic blood pressure, and had a higher prevalence of comorbidities (diabetes mellitus, hypertension, anemia, chronic obstructive pulmonary disease, cancer, and psychiatric disorders). Internationally, HFrEF can be more common than HFrEF, as in Hong Kong where it accounts for 67% of HF admissions, occurring equally in men and women with high rates of hypertension. In Germany, HF is more common in elderly women, largely because of HFrEF. These data reveal that HFrEF spans sex, race, and ethnicity and affects increasingly younger patients. The traditional concept that hypertension and hypertrophy are dominant features conflicts with clinical studies in which patients display near normal blood pressures on average and less than half have LVH. This affects our understanding of the disease and patient selection for clinical trials.

The clinical outcomes of HFrEF are similar to those with HFrEF, including in-hospital morbidity and hospital readmission rates. Although in-hospital mortality may be slightly higher in HFrEF, 30-day to 1-year mortality after discharge is similar between groups. Patients with either HF syndrome have comparable functional limitations and poor quality of life. Risk factors for mortality in HFrEF include advanced age, renal impairment, and hemodynamic instability (hypotension, tachycardia). There are differences in the

### Table 1. Comparison of Clinical Characteristics From Population-Based Studies of Heart Failure With a Preserved Ejection Fraction

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Olmsted Co, MN⁴⁰</th>
<th>Olmsted Co, MN (2006)⁴⁶</th>
<th>Ontario, CA¹</th>
<th>Framingham¹¹</th>
<th>OPTIMIZE²⁹</th>
<th>ADHERE³⁰</th>
<th>Baltimore, MD³¹</th>
<th>NY HF Consortium³²</th>
<th>Chicago, IL³³</th>
<th>China³⁸</th>
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<tbody>
<tr>
<td>Sample size, n</td>
<td>244</td>
<td>2167</td>
<td>880</td>
<td>220</td>
<td>10,072</td>
<td>26,322</td>
<td>37</td>
<td>619</td>
<td>419</td>
<td>132</td>
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<tr>
<td>Age, y</td>
<td>76</td>
<td>74.4±14.4</td>
<td>75.4±11.5</td>
<td>80</td>
<td>75.6±13.1</td>
<td>73.9±13.2</td>
<td>65±10</td>
<td>71.7±14.1</td>
<td>65±13</td>
<td>72.3</td>
</tr>
<tr>
<td>Women, %</td>
<td>55</td>
<td>55.7</td>
<td>65.7</td>
<td>65</td>
<td>68</td>
<td>62</td>
<td>84</td>
<td>72.5</td>
<td>62</td>
<td>55.3</td>
</tr>
<tr>
<td>Black, %</td>
<td>15</td>
<td>17</td>
<td>76</td>
<td>30</td>
<td>39</td>
<td></td>
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<tr>
<td>LVEF, %</td>
<td>62±6</td>
<td>61±7</td>
<td>62.4</td>
<td>≥45</td>
<td>62±7</td>
<td>≥40</td>
<td>72±11</td>
<td>60</td>
<td>≥50*</td>
<td>≥45</td>
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<td><strong>Outcomes</strong></td>
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<tr>
<td>% 1-y survival</td>
<td>71</td>
<td>78</td>
<td>80†</td>
<td>65†</td>
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<td><strong>Comorbidities</strong></td>
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<tr>
<td>Hypertension, %</td>
<td>96</td>
<td>62.7</td>
<td>55.1</td>
<td>77</td>
<td>77</td>
<td>100</td>
<td>78.2</td>
<td>77</td>
<td>57</td>
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<tr>
<td>CAD, %</td>
<td>53</td>
<td>52.9</td>
<td>35.5</td>
<td>37</td>
<td>32</td>
<td>50</td>
<td>42</td>
<td>43.1</td>
<td>48</td>
<td>39</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>37</td>
<td>33.1</td>
<td>31.7</td>
<td>22</td>
<td>41</td>
<td>45</td>
<td>61</td>
<td>45.9</td>
<td>33</td>
<td>35</td>
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<tr>
<td>Chronic kidney disease, %</td>
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<tr>
<td>Atrial fibrillation, %</td>
<td>41.3</td>
<td>31.8</td>
<td>29</td>
<td>32</td>
<td>21</td>
<td></td>
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<tr>
<td>SBP, mm Hg</td>
<td>132±23</td>
<td>156</td>
<td>145±24</td>
<td>150±33</td>
<td>153±33</td>
<td>143±25</td>
<td>160±36</td>
<td>125±20</td>
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<tr>
<td>DBP, mm Hg</td>
<td>67±14</td>
<td>76±13</td>
<td>75±19</td>
<td>79±21</td>
<td>69±14</td>
<td>84±20</td>
<td>70±12</td>
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<tr>
<td>BMI, kg/m²</td>
<td>32±21</td>
<td>30±8</td>
<td>27±5</td>
<td>37±8</td>
<td>31±9</td>
<td>33±9</td>
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<td><strong>Laboratory values</strong></td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8±2.1</td>
<td>12.4±2.2</td>
<td></td>
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<td></td>
<td></td>
<td>11.8±2.2</td>
<td>11.9±1.9</td>
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<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.6±1.1</td>
<td>1.5±0.9</td>
<td>1.2</td>
<td>1.7±1.5</td>
<td>1.4±0.7</td>
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<td>1.6±1.5</td>
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<tr>
<td>Diuretic, %</td>
<td>57</td>
<td>65</td>
<td>87</td>
<td>63</td>
<td>74</td>
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<tr>
<td>ACE-I, %</td>
<td>34</td>
<td>36</td>
<td>68</td>
<td>40</td>
<td>55 (ACE-I or ARB)</td>
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<td>ARB, %</td>
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<td>13</td>
<td>14</td>
<td>10</td>
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<tr>
<td>β-blocker, %</td>
<td>50</td>
<td>46</td>
<td>81</td>
<td>35</td>
<td>67</td>
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<td>Digoxin, %</td>
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<td>Statin, %</td>
<td>37</td>
<td>5</td>
<td>5</td>
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</tbody>
</table>

ACE-I indicates angiotensin-converting enzyme inhibitor; ADHERE, Acute Decompensated Heart Failure National Registry; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; NY HF, New York Heart Failure; OPTIMIZE, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; and SBP, systolic blood pressure.

*Mean/median values not given; enrollment criteria LVEF values reported.
†Estimated survival based on Kaplan–Meier curves.
causes of morbidity and mortality between the groups, with morbidity in HFpEF often being driven more by non-HF cardiovascular conditions, and ≈40% of deaths being linked to noncardiac causes.

Mechanisms of Disease

Given the multifaceted constellation of comorbidities that are almost invariably present in HFpEF patients, its underlying pathophysiology remains subject to debate. Among the leading contenders are diastolic dysfunction, impaired systolic rest and/or reserve function, abnormal ventricular–arterial coupling, inflammation and endothelial dysfunction, depressed heart rate response (chronotropic incompetence), altered myocardial energetics and peripheral skeletal muscle metabolism and perfusion, pulmonary hypertension (PH), and renal insufficiency. Several of these mechanisms are noncardiac. A major challenge to the field is that truly representative experimental models of HFpEF do not exist, and human data, particularly direct myocardial analysis, remain limited. There are no data from beating muscle or cells from human hearts. Animal models usually focus on 1 or 2 features common to HFpEF such as pressure overload (aortic banding or hypertension), obesity, diabetes mellitus, renal disease, aging, or ischemic heart disease without infarction. For practical reasons, however, multiple defects are rarely combined, and in this sense, existing animal models fall short of capturing the complexity of the human disease. Finally, there has long been a debate that HFrEF and HFpEF differ only in the letters r and p; that they are part of a continuum sharing key mechanisms. As attractive as this seems, we think that mechanistic data and trial experience to date would suggest otherwise. In this section, we address current cellular/tissue and integrative mechanisms, relying principally on data obtained in humans. These mechanisms are shown in Figures 1 and 2.

Myocardial Abnormalities

Diastolic Relaxation

HFpEF often presents with diastolic abnormalities including delayed early relaxation, myocardial and myocyte stiffening, and associated changes in filling dynamics. Slow relaxation has been documented in patients by means of invasive pressure recordings or echo-Doppler imaging parameters. Chamber-level analysis has consisted of invasively measured steady-state pressure–volume relations, as well as simplified noninvasive estimates including the end-diastolic volume at a pressure of 20 mm Hg. The causes for myocardial stiffening are divided into factors influencing the extracellular space such as fibrosis and infratropic processes, and those intrinsic to the myocyte itself (Figure 1).

Myocardial and Myocyte Stiffening

Passive myocardial stiffness is often observed in HFpEF and is considered an important contributor to disease manifestations. Chamber-level analysis has consisted of invasively measured steady-state pressure–volume relations, as well as simplified noninvasive estimates including the end-diastolic volume at a pressure of 20 mm Hg. The causes for myocardial stiffening are divided into factors influencing the extracellular space such as fibrosis and infratropic processes, and those intrinsic to the myocyte itself (Figure 1).

Myocardial fibrosis is a well-established feature of HFrEF, and total collagen volume is similarly increased in HFpEF endomyocardial biopsy tissue. Both collagen type I and type III expression and tissue staining are elevated in HFpEF and are coupled to reduced collagenase, metalloproteinase-1, but increased tissue inhibitor of matrix metalloproteinase-1 expression, which may further enhance fibrosis. Potential mechanisms for the altered matrix structure include inflammation, diabetes mellitus, and neurohumoral stimuli such as the renin–angiotensin–aldosterone system (RAAS). Markers of inflammatory cells are found in HFpEF tissue and have been proposed to play an important role in the disease. The high prevalence of diabetes mellitus in HFpEF suggests a mechanism for fibrosis and AGE deposition. However, biopsy studies have found such correlations in HFrEF but not in HFpEF. RAAS activation stimulates pathological fibrosis in many animal models and has long been presumed to be a major factor in HFpEF. However, the failure of multiple anti-RAAS clinical HFpEF trials suggests either that other factors or mechanisms are more important, or that fibrosis is not as central as assumed.

An alternative mechanism perhaps is myocardial infiltration by amyloid proteins such as transthyretin. This liver-synthesized protein is a common form of amyloid whose genetic variations cause hereditary amyloidosis. Recent autopsy data of HF hearts with an EF>40% at the time of diagnosis found moderate to severe wild type transthyretin deposition in 5%, with evidence of amyloid deposition in 19%. Whether
transthyretin polymorphisms associated with disease play a role in HFpEF remains unknown.

Extracellular matrix abnormalities are generally similar between HFrEF and HFpEF, whereas myocyte stiffness differs, being higher in cells from HFpEF. Borbély et al first reported higher passive stiffness in isolated HFpEF myocytes versus controls. This stiffening was normalized by incubation of cells with protein kinase A, PKG, and calcium–calmodulin activated kinase II, which subsequently renders sarcoplasmic reticular (SR) calcium release by the ryanodine receptor (RyR2) more promiscuous. ROS and CamKII also impact titin to influence stiffening. Last, the upper right depicts the role of matrix modulation by cytokines/inflammation and the bidirectional interaction of these factors with the myocyte. IL indicates interleukin; SERCA, sarcoplasmic reticular ATPase; sST2, soluble ST2; and TNF, tumor necrosis factor. Illustration credit: Ben Smith.

Figure 1. Schematic of myocardial abnormalities revealed in human heart failure with a preserved ejection fraction (HFpEF). The left side shows components of the β-adrenergic (β-AR) pathway from the receptor to adenyl cyclase (AC) and generation of cAMP to activation of protein kinase A (PKA). The latter is involved in the modification of L-type calcium channels (LTCC), phospholamban (PLN), titin, and other regulatory thin-filament proteins (eg, troponin I, TnI), which influence myofilament stiffness and contractile activation. Evidence suggests a deficiency in this signaling pathway in HFpEF, with increased titin stiffness and depressed β-AR responsiveness. The middle section shows transforming growth factor β (TGFβ)– and Gq-protein–coupled receptor (GqPR) signaling involving transcription factors (Smad), phospholipase C (PLC), and mitogen-activated kinases (MAPK), which are involved in the activation of profibrotic and hypertrophic cascades. At the right is the nitric oxide synthase (NOS) pathway resulting in nitric oxide (NO) activation of soluble guanylate cyclase (sGC), generation of cyclic guanosine monophosphate (cGMP), and activation of protein kinase G (PKG). In the middle is reactive oxygen species (ROS) activated by TGFβ–, β-AR–, and GqPR–coupled signaling, which inhibits the NOS-cGMP generation and thereby PKG activity, stimulates calcium–calmodulin activated kinase II (CamKII), which subsequently renders sarcoplasmic reticular (SR) calcium release by the ryanodine receptor (RyR2) more promiscuous. ROS and CamKII also impact titin to influence stiffening. Last, the upper right depicts the role of matrix modulation by cytokines/inflammation and the bidirectional interaction of these factors with the myocyte. IL indicates interleukin; SERCA, sarcoplasmic reticular ATPase; sST2, soluble ST2; and TNF, tumor necrosis factor. Illustration credit: Ben Smith.
on cyclase generation of cGMP, so this imbalance has clinical implications for treatments.

Resting Systolic Function: Is It Normal?
EF largely informs us about chamber dilation as until end-stage HF, stroke volume (the numerator) is usually maintained and end-diastolic volume (the denominator) rises. Preserved EF does not imply that systole is normal, and indeed a key set of observations that favored the name change to HFP EF suggested the opposite.19,20,83,84 This has been recently observed using tissue Doppler speckle tracking; HFP EF patients had reduced longitudinal and circumferential strain compared with age- and sex-matched hypertensive patients with diastolic dysfunction but no clinical HF.55 However, studies using catheterization with imaging or conductance catheter measurements to derive pressure–volume relations have found that resting load–discrections) induce marked swings in blood pressure and thus filling as altered by diuresis or sodium loading (eg, dietary indiscretions) induce marked swings in blood pressure and thus cardiac energetic demands, and fluid-pressure shift sensitivity. Illustration credit: Ben Smith.

Figure 2. Schematic of the integrative physiology of heart failure with a preserved ejection fraction (HFP EF) showing various extracardiac mechanisms and how they are involved. From top left, counterclockwise: lung involvement including primary lung disease leading to pulmonary arterial hypertension, secondary pulmonary venous hypertension (PVH), impaired lung muscle mechanics, and eventual increased pulsatile right ventricular (RV) load; abdominal compartment mechanisms including splanchic circulation (preload), bowel congestion leading to endotoxin translocation and systemic inflammation; skeletal muscle mechanisms including impaired metabolism and peripheral vasoconstriction; renal mechanisms including passive congestion leading to renal impairment, changes in neurohormonal axis activation, hypertension, abnormal fluid homeostasis, eventual oliguria/renal insufficiency; ventricular–vascular mechanisms including ventricular stiffening leading to systolic and diastolic impairment, diminished systolic reserve, increased cardiac energetic demands, and fluid-pressure shift sensitivity. Illustration credit: Ben Smith.

Ventricular–Arterial Coupling
Systolic ejection involves the interaction of time-varying properties of the ventricular pump and the vascular impedance to which it is connected. Vascular stiffening has long been associated with aging and is exacerbated by comorbidities such as hypertension, obesity, diabetes mellitus, and chronic kidney disease. To preserve adequate coupling of the heart to arterial system, ventricular systolic stiffening also increases, and this combined ventricular–vascular (VV) stiffening is a feature of HFP EF.15,40,87 This limits systolic reserve that would normally accompany further rises in Ees, contributes to increased cardiac energy demands required to enhance cardiac output,15 and plays a central role in arterial pressure lability accompanying small changes in chamber preload volume. VV coupling is often represented by the ratio of effective arterial elastance (the ratio of end-systolic pressure to stroke volume) that lumps systemic resistance, pulsatile loading, and heart rate effects, into a single afterload parameter. VV coupling is then indexed by effective arterial elastance/Ees ratio that normally ranges from 0.5 to 1.2 to optimize cardiac work and efficiency.88 In HFP EF, effective arterial elastance and Ees both increase, although similar increases are observed in patients with hypertension (±LVH) but without HF.15,58 When both Ees and effective arterial elastance are increased, modest changes in LV filling as altered by diuresis or sodium loading (eg, dietary indiscretions) induce marked swings in blood pressure and thus cardiac work with little change in stroke volume.15

Limitations of Cardiovascular Reserve
The vast majority of HFP EF hemodynamic and myocardial data pertain to resting conditions, but arguably, this syndrome is first and foremost one of limited reserve and exertional intolerance. Multiple mechanisms likely play a role, including depressed systolic augmentation, limited heart rate augmentation (chronotropic incompetence), diastolic filling abnormalities, and reduced peripheral vascular dilation.

Kitzman et al89 reported among the first studies of exercise capacity in HFP EF patients and highlighted failure of these patients to increase end-diastolic volume and thus engage the Frank–Starling mechanism. However, this study was limited with 3 of the 7 patients having classic hypertrophic or restrictive cardiomyopathy, diseases known to impair preload
reserve. Borlaug et al\(^9\) studied 17 HFP EF patients versus a similar number of non-HF controls matched for comorbidities (in particular both LVH and hypertension) and found reduced exercise capacity and peak oxygen consumption (\(V_{\text{O}_2}\)) in the HFP EF group related to reduced cardiac output reserve. However, rather than being from impaired diastolic filling, low cardiac output augmentation was related to a failure to enhance heart rate and peripherally vasodilate.\(^9\) Chronotropic incompetence has since been reported by multiple investigators\(^9,92\) and been found in large trials.\(^3\) This has implications for the use of \(\beta\)-blockers and sinus node suppressors (I\(_f\) blockers) in the syndrome. The normally rapid heart rate decline after cessation of exercise is delayed in HFP EF, and this behavior is thought to be due to autonomic dysfunction and an independent risk factor for cardiac death.\(^9,92,93\) Impaired peripheral vasodilation has been documented in exercised HFP EF patients using MRI.\(^94\) Borlaug et al\(^95\) examined cardiac systolic reserve in exercising HFP EF subjects and found that in addition to peripheral dilation and heart rate limitations, contractility increases were also depressed, resulting in VV mismatching.

Even if heart rate were to increase in HFP EF, studies found that the ventricular response would likely be abnormal. The normal positive force frequency was depressed in patients with LVH, many having presented with HF symptoms.\(^9\) However, in 2 subsequent HFP EF studies, LV function with incremental pacing increased contractility compared with controls or showed no difference,\(^43,96\) although reserve was limited because of impaired diastolic filling. The normal controls in both studies surprisingly showed no decline in either end-diastolic filling or stroke volume at faster heart rates, as has previously been shown.\(^9\) Thus, the HFP EF response was more consistent with normal physiology. Preload reserve limitations were not observed in several HFP EF exercise hemodynamic studies\(^16,90\), whether diastolic filling is truly restricted in HFP EF during tachycardia remains uncertain.

### Myocardial Energetics and Skeletal Muscle Metabolism

Among potential mechanisms for limited cardiac systolic reserve with HFP EF are abnormalities of myocardial energetics, including adenosine triphosphate (ATP) generation and shutting between phosphocreatine and ATP by the creatine kinase reaction. Smith et al\(^97\) used NMR spectroscopy to assess patients with non-HFP EF (few technically had HFP EF) and found that myocardial [ATP] was not significantly reduced in LVH or in LVH+HF compared with controls. However, cardiac [phosphocreatine] was 30% less in LVH with or without HF, reducing the phosphocreatine/ATP ratio in both groups. In addition, creatine kinase flux was 65% lower in LVH+HF than in controls, more than double the decline in LVH alone.

Another study examining HFP EF found a significant decline in phosphocreatine/ATP compared with controls.\(^98\) In a recent study to evaluate whether skeletal muscle abnormalities contribute to decreased peak exercise \(V_{\text{O}_2}\) (peak \(V_{\text{O}_2}\)) in HFP EF, Kitzman et al\(^99\) performed cardiopulmonary exercise testing and needle biopsies of the vastus lateralis muscle to assess muscle fiber type distribution, capillary density, and peak \(V_{\text{O}_2}\). HFP EF patients had reduced type I oxidative muscle fibers, type I/II fiber ratio, and capillary-to-fiber ratio compared with healthy controls; the percent of type II fibers was greater in HFP EF. The type I fibers and capillary-to-fiber ratio was significantly associated with peak \(V_{\text{O}_2}\). Exercise intolerance may also be impaired by endothelial dysfunction and abnormal skeletal muscle metabolism, including reduced mitochondrial volume and enzymes, and muscle atrophy. Although the specific defects remain to be identified in HFP EF, several studies have found that limited cardiac reserve fails to explain exertional intolerance and have highlighted abnormal skeletal muscle performance as likely contributors.\(^100,101\)

### Role of Inflammation

Results from LV endomyocardial biopsy\(^70\) and analyses of inflammatory cell markers\(^63\) suggest that increased oxidative stress and depressed NO signaling resulting in inflammation play a key role in HFP EF.\(^66,67\) The multitude of HFP EF co-morbidities may contribute to a proinflammatory state;\(^102\) circulating inflammatory cytokines such as interleukin 6, tumor necrosis factor \(\alpha\), soluble ST2, and pentraxin 3 are elevated in HFP EF.\(^103,104\) Systemic inflammation could lead to endothelial dysfunction supported by higher expression of vascular cell adhesion molecules such as VCAM-1, E-selectin, and ROS.\(^63\) Increased ROS lowers bioavailable NO and thus reduces cGMP/PKG activation, which can worsen myocyte stiffness as already noted, and also contribute to hypertrophic disease and fibrosis. TGF\(\beta\) signaling may also be increased in HFP EF myocardium,\(^64\) although data remain limited. The complex and cell-specific signaling linked to this cytokine suggests that therapeutic targeting could prove difficult.\(^107,108\)

### Biomarkers in HFP EF: A Clue to Mechanisms?

Plasma biomarkers consisting of proteins, peptides, and micro-RNAs can reflect chronic and acute changes in structure and function of the myocardium, as well as changes in volume status, loading conditions, and vascular tone. Several of these biomarkers are of interest in HFP EF to aid in diagnosis and prognosis and to help better understand mechanisms of disease. The natriuretic peptides are perhaps the best characterized biomarkers in HFP EF. B-type natriuretic peptide (BNP) is typically higher in HFP EF than in non-HF patients, but lower than in HFr EF.\(^109,110\) BNP linearly correlates with LV diastolic pressure and with LV diastolic wall stress in HFP EF; the smaller LV cavity size and thicker walls with resultant lower end-diastolic wall stress may account for lower BNP levels.\(^111\) Biomarkers of extracellular matrix turnover and fibrosis in HFP EF have recently been reviewed, including soluble ST2, galectin-3; collagen propeptide (PICP [type 1 procollagen C-terminal propeptide], PINP [amino-terminal propeptide of type I collagen], PIINP [amino-terminal propeptide of type II collagen]); collagen telopeptides; matrix metalloproteinases (MMP-1, MMP-2, MMP-8, and MMP-9); tissue inhibitor of MMPs (TIMP-1, TIMP-4); and osteopontin, all of which can be elevated.\(^111\) Additional biomarkers including renal biomarkers (cystatin C, urinary albumin), cardiac troponins, and inflammatory markers (discussed previously) have also been noted to be elevated in HFP EF.\(^112\) Although nearly all of these biomarkers support the diagnosis of HFP EF to some extent, a smaller subset may help predict outcomes, and even fewer may be used to guide therapies (primarily the natriuretic...
peptides). Micro-RNAs as biomarkers for outcome and treatment selection have been described in HFrEF, but to date, no results have been reported in human HfPpEF.

PH and the Right Ventricle

PH defined by a mean pulmonary artery pressure >25 mm Hg is commonly associated with HFrEF and harbinger of a worse outcome. Data on PH in HfPpEF are more limited, but studies are reporting a fairly high prevalence that importantly predicts increased morbidity and mortality. Pulmonary artery systolic pressure rises along with pulmonary capillary wedge pressure (PCWP) in patients with both hypertension and HfPpEF; however, after adjusting for PCWP, pulmonary systolic pressure is still higher in HfPpEF. This indicates that PH is due to more than pulmonary venous hypertension (PVH). Distinguishing these factors can be challenging. By definition, pulmonary arterial hypertension (PAH) is differentiated from PVH in that the latter has an elevated PCWP >15 mm Hg. Estimation of PCWP by noninvasive methods is not always possible, and PCWP obtained at the time of right heart catheterization is influenced by the patient’s volume status when the procedure is done. Robbins et al.115 performed a fluid challenge at the time of catheterization to differentiate PAH from PVH, and of 207 patients meeting criteria for PAH, 22% developed elevated PCWP after a fluid bolus and were thus reclassified as overt PVH. Borlaug et al.8 has demonstrated that many HfPpEF patients who have normal PCWP at rest display marked increases with supine exercise associated with PAH. The implications of such data are that many patients with PH may have an under-recognized component of PVH linked to left-sided HF (including HfPpEF), which is manifested more under conditions of exertion or volume loading.116

An additional role of PCWP from LV disease to PAH was revealed by Tedford et al.117 who studied the inverse relation between total pulmonary arterial compliance (Cpa) and resistance (Rpa) in patients with varying levels of PAH and PCWP elevation. The Cpa–Rpa relation is hyperbolic with a tight interdependence between the two properties, which is unique to the pulmonary vasculature. This results from having vascular compliance reside with the smaller peripheral vessels where resistance is also regulated, unlike the systemic arteries where the aorta provides most of the compliance but no resistance. The Cpa–Rpa relation was remarkably invariant, but it did change with a rise in PCWP, with Cpa declining at the same Rpa. This indicates that PCWP affects pulmonary arterial pulsatile load and thus right ventricular (RV) systolic load and likely has implications for HfPpEF and PH. As with PH, RV dysfunction is a well-established predictor of poor outcomes in increased mortality in HfPpEF, and this may apply to HfPpEF in that RV wall thickening was predictive of worse outcomes.33

Renal Dysfunction

Chronic kidney disease occurs in 26% to 53% of HfPpEF and is associated with poor prognosis. Beyond baseline impairment, worsening renal function during HfPpEF hospital admission predicts higher mortality at 6 months, with a 7-year survival of only 9%. Albuminuria is an established independent risk factor of mortality in the general population, reflecting glomerular injury, activation of the RAAS system, and systemic inflammation, and has been reported in a third of HfPpEF patients. During a 2.5-year follow-up period, those with albuminuria at all strata of estimated glomerular filtration rate had higher rates of cardiovascular and noncardiovascular death. Finally, albuminuria can limit the efficacy of furosemide by binding the compound in tubular fluid, preventing its interaction with ion transporters.

In HfPpEF, the mechanism of renal dysfunction is classically related to low cardiac output and decreased renal perfusion. Given that impaired volume homeostasis is a prominent presenting feature of HfPpEF, it is quite likely that renal insufficiency is partly to blame; the question is by what mechanism. Does intrinsic renal dysfunction (as a complication of other comorbidities) lead to myocardial inflammation, fibrosis, and resultant HfPpEF? Does HfPpEF cause renal dysfunction by triggering RAAS pathway activation, by promoting venous congestion, or from side effects of HF medications? There are intriguing pathways that may link renal and cardiac disease such as transsient receptor potential channel 6, a Gq-receptor-and ROS-activated nonelective cation channel that plays an important role in proteinuria, glomerular dysfunction, cardiac hypertrophy, and fibrosis. Impaired renal regulation combined with enhanced cardiovascular sensitivity to fluid retention because of VV stiffening and diminished diuretic efficacy can coconspire to worsen symptoms in HfPpEF patients.

Abdominal Contributions

In many HfPpEF patients, fluid retention is less apparent in the periphery but not infrequently occurs in the abdominal cavity. This may play a significant role in cardiorenal disease in HF beyond vascular congestion, as recently reviewed by Verbrugge et al. Although this pathophysiology is not unique to HfPpEF, it does likely play a role in fluid homeostasis, and is an area deserving attention. The splanchnic vasculature normally contains ~25% of total blood volume in capacitance veins. This capacitance function is impaired in HF, with increased neurohormonal activation resulting in venaconstriction in the setting of long-standing congestion. Splanchnic microcirculation and lymphatic flow are essential to preserve fluid homeostasis, and with HF, increased capillary hydrostatic pressure drives filtration of fluid through to the lymphatic system. Once lymph efflux is maximal, however, interstitial fluid with associated proteins cannot be adequately drained, leading to protein-rich edema and expansion of the interstitial space. With the splanchnic vasculature and microcirculation no longer able to cope with progressive volume overload, intra-abdominal pressure increases. Normal intra-abdominal pressure is 5 to 7 mm Hg; intra-abdominal hypertension with intra-abdominal pressure >12 mm Hg can lead to organ dysfunction. Consequences include abnormal hepatic regulation of renal function; splanchic bed congestion, which creates a false state of hypovolemia; and nonocclusive bowel ischemia, which may eventually result in circulating endotoxin.

Treatment of HfPpEF

A Brief History of Neutral Trials

Targeting the RAAS and β-adrenergic stimulation pathways has long been considered reasonable for HfPpEF, the former based on its link to hypertension, fibrosis, and fluid imbalance,
and the latter to improve time for diastolic filling. Yet, despite their clear success in HFrEF, no clinical trial of these standard therapies has revealed similar mortality benefits, and only a few trials have shown symptomatic improvement in HfPfEF. The major recent neutral trials are summarized in Table 2. These include studies of β-blockade (Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure [SENIORS],126 Japanese Diastolic Heart Failure [J-DHF],127 and Effects of Nebivolol on Clinical Symptoms, Exercise Capacity, and Left Ventricular Function in Diastolic Dysfunction [ELANDD]128), angiotensin-converting enzyme inhibitors (Perindopril in Elderly People with Chronic Heart Failure [PEP-CHF]),129 angiotensin receptor blockers (Irbesartan in Heart Failure with Preserved Ejection Fraction [I-PRESERVE]),130 aldosterone antagonists (Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients with Heart Failure with Preserved Ejection Fraction [ALDO-DHF]),131 Randomized Aldosterone Antagonist in Heart Failure with Preserved Ejection Fraction [RAAMPEF],131 and Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist [TOPCAT]35, digoxin (Digitalis Intervention Group-Preserved Ejection Fraction [DIG-PeF]),156 and sildenafil (RELAX).35 Despite broad acceptance of diastolic impairment as a contributor to HfPfEF, few of these studies actually report diastolic analysis or cardiac structural data, making it difficult to assess the impact of therapy on these characteristics.

A few studies have showed positive signals for potential benefits in HfPfEF. The PEP-CHF study evaluated angiotensin-converting enzyme inhibitors in HF patients without demonstrable LV dysfunction and was underpowered for its primary composite end point of all-cause mortality and unplanned HF-related hospitalization, but did see some improvements in symptoms, exercise capacity, and fewer HF hospitalizations in the first observation year.129 The Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (CHARM-Preserved) trial demonstrated that compared with placebo, HfPfEF patients who received the angiotensin receptor blocker candesartan had fewer hospital admissions for HF, although there was no mortality benefit from the medication compared with placebo.132 Many HfPfEF patients are treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for hypertension, and our clinical outcome data reflect this background therapy.

In 2013, the ALDO-DHF study tested the impact of an aldosterone antagonist in HfPfEF with the primary end points being improved diastolic function and exercise capacity.36 Some measures of diastolic function improved, though maximal exercise capacity, clinical symptoms, and quality of life were not changed. One critique of the study was that patients had early-stage HfPfEF without overt signs of volume overload. The larger 2014 TOPCAT study also did not meet its primary composite end point (cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of HF).34 There was a small, borderline significant decline in hospitalizations. Interestingly, a major interacting factor was where patients were recruited and the criteria used for their entry; Eastern European patients were entered based on HF hospitalization criteria, but follow-up course in the placebo arm of this group was surprisingly benign. By contrast, patients in the United States met natriuretic peptide level entry criteria and had a higher event rate. Spironolactone improved the latter group.

The Effect of Phosphodiesterase 5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX) trial tested a new concept that by blocking PDE5A, cGMP/PKG signaling in HfPfEF might be enhanced, with associated benefits.35 PDE5A hydrolyzes cGMP primarily generated by NO–sGC by blocking the enzyme, drugs such as sildenafil can augment cGMP and thus PKG activity in multiple organs relevant to HF. Experimental studies in mice with pressure overload,133 cytotoxicity from doxorubicin,134 and myocardial infarction135–137 have shown benefits from chronic PDE5A inhibition. PDE5A inhibition also enhanced natriuretic peptide-stimulated pulmonary vasodilation in a canine HF model.138 Prior single-center studies had reported benefits of PDE5A inhibition in patients with HFrEF, particularly those with PH, and in PH patients with preserved EF.139–141 However, RELAX was neutral, reporting no benefit of sildenafil compared with placebo in the primary end point (change in peak VO2 after 24 weeks of therapy) or in any of a myriad of secondary functional and structural end points including markers of clinical status. Some argued that choosing exercise capacity as the end point was problematic because of the high number of comorbidities and noncardiac factors that influence this outcome in HfPfEF.142 In addition, the patient population may have played a major role in the neutral findings, as they had relatively mild diastolic dysfunction, the majority lacked LVH (only 53% met criteria and median LV mass index was essentially normal), and many had no overt PH or RV dysfunction, with minimal systolic hypertension. This means that there likely was little for PKG to affect in the heart as experimental studies have shown that sildenafil has negligible effect in mild LVH but far more efficacy if applied to severe disease, as only the latter triggers maladaptive signaling that PKG can offset.143 As noted, HfPfEF patients have low myocardial cGMP,70 so there would be insufficient cGMP for PDE5a inhibition to modify, natriuretic peptide levels were mildly increased in some patients in RELAX and were minimally elevated in many of the patients, so an alternative cGMP source was not active.

Lessons Learned From Trials to Date

There are several potential reasons why these established HFrEF therapies have failed to benefit in HfPfEF. First, our fixation on RAAS signaling may indeed be misplaced. It seems unlikely that neurohormonal stimulation is not involved in HfPfEF, but it may not be as sustained, with less impact gleaned by its blockade. Perhaps HfPfEF is less a neurohormonal-driven disease as compared with HFrEF but rather is an integrative physiology disorder where hemodynamics and the control of blood volume and its distribution are more important.

In the case of sildenafil, the question remains whether one needs to stimulate cGMP generation first and then perhaps add in a PDE5A inhibitor. While combining nitrates and PDE5A inhibitors remains relatively contraindicated, low doses of a
synthetic stimulator such as a direct sGC activator or natriuretic peptides might still prove effective, particularly if then combined with a blocker of cGMP hydrolysis.

Another important contributing factor is the patient population enrolled in clinical trials. In comparing population-based cohort descriptions to patients enrolled in clinical trials of HFpEF, it seems that the adverse outcome rates in the placebo groups in trials are markedly less than what is observed at the population-study level (compare Table 1 and Table 2). How do we explain this discrepancy? In comparing the cohorts, patients enrolled in HFpEF therapy trials (irrespective of which treatment arm) have a lower prevalence of hypertension (lower systolic blood pressure), less LVH (when reported), and somewhat less coronary artery disease. Each of these individual morbidities portends increased risk of adverse outcome; together their lower rates reflect a healthier cohort in the trials. This may reflect the multicenter and often international recruitment in trials versus more local and homogeneous sources in population studies, as well as involvement in a trial itself versus uncontrolled longitudinal observations. It argues for improving our capture of the truly at-risk HFpEF group, something we are not presently doing. It also suggests that more intensive clinical engagement, as accompanies being a participant even in the placebo arm, is rather effective.

Finally, HFpEF is a simple enough label to apply to a patient, but the result is often profoundly heterogeneous, and differences among nations and medical practices can make it nearly impossible to create meaningful clinical trials. The different constellations of comorbidities also raises the bar very high for a therapeutic home run, as these may play a greater role in symptoms and treatment responses than generally assumed. An approach to this was recently suggested by Shah,144 who described the concept of matching HFpEF patients to clinical trials. Subgroups involving major features such as hypertension/LVH or PH may respond differentially to a given therapy, and better population selection for clinical trials could yield more promising results.

**New Therapeutic Avenues for HFpEF**

**HMG-Co-A Reductase Inhibitors**

The use of HMG-Co-A reductase inhibitors, or statins, has yet to be tested in a large-scale trial. Observational reports of statin therapy in HFpEF have shown mixed findings for effects on diastolic parameters, although meta-analyses of 11 studies, mostly retrospective, suggest a significant benefit on survival.145,146 This is speculated to involve pleomorphic anti-inflammatory effects. Definitive trials have yet to be performed and may prove difficult given existing widespread use of statins in many HFpEF patients.

**Ivabradine**

The neutral results of β-blocker trials in HFpEF led investigators to pursue therapies targeting the sinus node, including the inward funny (I,) channel blocker, ivabradine, which slows sinus rate but has no impact on contractility or the peripheral vasculature, unlike β-blockade.147,148 Experimental data in mice with obesity and diabetes mellitus148 found reduced aortic stiffness and fibrosis and improvement in LV function from 4 weeks of ivabradine therapy.147,148 Kosmala et al149 recently published findings from a 7-day randomized clinical trial of ivabradine versus placebo in 61 HFpEF patients. Patients had improved peak VO2, exercise capacity, and decreased exercise-induced E/E’ ratio (index of diastolic pressure). There were no adverse events. Using a fairly homogenous cohort of patients with early-stage HFpEF may have helped this particular study. However, heart rate lowering seems unlikely to benefit all HFpEF patients, particularly those with resting bradycardia or chronotropic incompetence, where further blunting heart rate increase could worsen cardiac output reserve and thus exercise capacity. Also, patients with advanced diastolic disease with restrictive physiology are unlikely to benefit as filling occurs early and rapidly in these patients anyway, and heart rate becomes a primary determinant of cardiac output. Larger-scale, multicenter studies will be needed to test the utility of this approach.

**Neprilysin Inhibitor (LCZ696)**

Neprilysin is a zinc-dependent metalloprotease that degrades biologically active NPs, including atrial natriuretic peptide, BNP, and C-type natriuretic peptide. It does not affect the biologically inactive N-terminal proBNP.150 Natriuretic peptides can promote myocardial relaxation, reduce hypertrophy, and are integral to diuresis, natriuresis, and modest vasodilatation.151 Clinical data for all of these effects are less well documented, but benefits have been observed. A recent randomized clinical trial compared LCZ696,152 which combines a neprilysin inhibitor produg AHU377 and the AT1 receptor blocker (valsartan), to valsartan alone in 266 HFpEF patients.151 LCZ696 led to a greater decline in N-terminal proBNP; however, cardiac structure and function and symptom composite metrics were similar between groups. Patients receiving LCZ696 had a greater reduction in blood pressure (=6 mm Hg) by 12 weeks and fall in N-terminal proBNP remained significant after adjusting for this blood pressure change. Adverse effects were similar between the groups; overall, LCZ696 was well tolerated. The findings of this phase 2 study are promising and a large, multicenter study is underway comparing LCZ696 to enalapril (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction [PARADIGM-HF]).

**Exercise Therapy**

Exercise intolerance is a major complaint of all HF patients. It is an independent predictor of morbidity and mortality and is increasingly a leading outcome in pharmacological trials of HFpEF. Exercise training has been used to improve outcomes in HFrEF, particularly in patients with ischemic disease, and is being viewed as a potential therapy for HFpEF.153 Exercise training provides cardioprotection against ischemia-reperfusion injury (see excellent recent review by Powers et al),154 in part by suppressing ROS-mediated cellular damage, decreasing cytosolic free calcium, and reducing inflammatory changes from leukocyte infiltration and mitochondrial damage. Cardioprotection from exercise training is biphasic. The first phase is rapid in onset and short in duration (onset at 30 minutes, lasting 3 hours) and involves activation of the endogenous antioxidant enzyme superoxide dismutase in mitochondria of ventricular myocytes. The second phase is longer...
### Table 2. Clinical Characteristics of Heart Failure With a Preserved Ejection Fraction in Negative Clinical Trials to Date

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Sample size</th>
<th>Inclusion criteria</th>
<th>Primary end point</th>
<th>Outcome</th>
<th>1-y survival, %</th>
<th>Patient characteristics, means or %</th>
<th>Comorbidities</th>
<th>Vital signs</th>
<th>Admission data</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>245</td>
<td>LVEF &gt;40%; diastolic dysfunction by Doppler echo; NYHA class II–III</td>
<td>Composite cardiovascular death and unplanned hospitalization for HF</td>
<td>Negative</td>
<td>Placebo 90*; treatment 90*</td>
<td>Age, y 73</td>
<td>Hypertension, % 80</td>
<td>SBP, mmHg 134</td>
<td>BNP, pg/mL 219</td>
<td></td>
</tr>
<tr>
<td>Nebivolol</td>
<td>116</td>
<td>LVEF &gt;45%; NYHA II–IV; hospitalization for HF within past 6 mo</td>
<td>Change in 6MWT</td>
<td>Negative</td>
<td>Placebo 90*; treatment 90*</td>
<td>Women, % 43</td>
<td>CAD, % 28</td>
<td>134</td>
<td>NT-proBNP, pg/mL 255</td>
<td></td>
</tr>
<tr>
<td>Irbesartan</td>
<td>4128</td>
<td>LVEF &gt;45%; clinical signs/symptoms of HF; normal sinus rhythm</td>
<td>Change in 6MWT</td>
<td>Negative</td>
<td>Placebo 77; treatment 77</td>
<td>White, % 94</td>
<td>Diabetes mellitus, % 28</td>
<td>DBP, mm Hg 75</td>
<td>Serum creatinine, mg/dL 1.0</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>988</td>
<td>LVEF &gt;50%; NYHA II–III, evidence of diastolic dysfunction</td>
<td>Change in 6MWT</td>
<td>Negative</td>
<td>Placebo 100; treatment &gt;99</td>
<td>Black, % 2</td>
<td>CKD, % 28</td>
<td>Body mass index, kg/m² 24</td>
<td>LV mass, g/m² 126</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>422</td>
<td>LVEF &gt;50%; NYHA II–III; elevated BNP</td>
<td>Change in combined HF mortality</td>
<td>Improved diastolic function; did not improve exercise capacity</td>
<td>6-mo survival: placebo 100; treatment 97</td>
<td>NYHA class, % I (18), II (69), III (11), IV (2)</td>
<td>Left ventricular hypertrophy, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone</td>
<td>44</td>
<td>LVEF &gt;50%; controlled hypertension (SBP &lt;140 or &lt;160 mm Hg if on 3+ medication; serum potassium &lt;5.0 mmol; history of hospitalization for HF in past 12 mo or elevated BNP/NT-proBNP)</td>
<td>Change in combined HF mortality</td>
<td>Negative</td>
<td>Placebo &gt;90; treatment &gt;90</td>
<td>Consistently</td>
<td>Hypertension, % 80</td>
<td>SBP, mmHg 134</td>
<td>BNP, pg/mL 219</td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>216</td>
<td>LVEF &gt;50%; NYHA II–III, evidence of diastolic dysfunction</td>
<td>Change in 6MWT</td>
<td>Negative</td>
<td>Placebo 100; treatment 97</td>
<td>CAD, % 28</td>
<td>Diabetes mellitus, % 28</td>
<td>DBP, mm Hg 75</td>
<td>Serum creatinine, mg/dL 1.0</td>
<td></td>
</tr>
<tr>
<td>Spirolactone</td>
<td>3445</td>
<td>LVEF &gt;45%; controlled hypertension (SBP &lt;140 or &lt;160 mm Hg if on 3+ medication; serum potassium &lt;5.0 mmol; history of hospitalization for HF in past 12 mo or elevated BNP/NT-proBNP)</td>
<td>Change in combined HF mortality</td>
<td>Negative</td>
<td>Placebo &gt;90; treatment &gt;90</td>
<td>CKD, % 28</td>
<td>Left ventricular hypertrophy, %</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
undoubtedly pose challenges, however. Treatment algorithm, along with pharmacological agents, for patients, and alternatives to traditional pharmacological therapies are being sought. Renal sympathetic denervation is an example, and early results in small, nonplacebo controlled trials,162 which are emerging as promising therapies with pleo-

tropic effects. Among the proposed mechanisms of vagal nerve stimulation are anti-inflammatory effects, increased NO signaling, anticytokine effects, improved baroreflex sensitivity, and RAAS inhibition.163 The Increase Of Vagal Tone in CHF (INOV ATE-HF) study will test vagal nerve stimulation (CardioFit system, BioControl, Israel) in HFrEF patients,163 but interest is there for HFpEF as well. While still largely in experimental stages, spinal cord stimulators is another approach that has shown some utility in HF patients.164 A HFrEF study (Defeat-HF, NCT01112579) has completed enrollment with results due in 2015. Lastly, endovascular cardiac plexus stimulation may offer an alternative way to increase contractility without increasing heart rate.165

**Pumps, Devices, and Monitors**

Device therapy has made enormous inroads into HFrEF with pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy. The role of each in HFpEF is undefined; some patients with symptomatic chronotropic incompetence receive pacemakers, and those with a history of sudden death receive a defibrillator. Dyssynchrony in HFpEF can occur although it seems more rare than with HFrEF, and the efficacy of cardiac resynchronization therapy has not yet been demonstrated in HFpEF. If anything, inducing dyssynchrony on purpose by single-site ventricular pacing was found to benefit a group of HFpEF patients with severe concentric LVH and end-systolic cavity obliteration.166,167 The rationale was that such patients have excessive contraction, at 6 months.159 This was strikingly different from the prior SYMPLICITY HTN-2 trial, which found significant blood pressure decline along with reduced LV mass and improved diastolic function in the active treatment arm, but also lacked a true placebo control.160 The reasons for the discrepancies between the trials are being debated, but certainly the unbridled enthusiasm that had first met this therapy has been tempered.

**Targeting Neural Reflex Arcs: Renal Denervation and Nerve Stimulation**

Long-standing, resistant hypertension is common in HFpEF patients, and alternatives to traditional pharmacological therapies are being sought. Renal sympathetic denervation is an example, and early results in small, nonplacebo controlled studies raised substantial optimism that this would be effective.157,158 However, the 2014 Renal Denervation in Patients with Uncontrolled Hypertension [SYMPLICITY HTN 3] Trial which studied 553 patients in a 2:1 randomization between active denervation or sham procedure, found no significant difference in the primary end point of reduced systolic pressure...
and generating dyssynchrony increases end-systolic volume at rest, building back in some reserve capacity during exercise.

Another type of technology relates to monitor systems that provide physiological information, and these too may prove valuable for helping stabilize HFpEF patients and reduce their hospitalization rates. Some of the monitor data comes from existing device therapies, such as cardiac resynchronization therapy systems that also provide intrathoracic impedance measures via the RV lead, or monitor heart rate variability and patient activity level. These are limited however, to patients receiving CRT. Alternatively, devices that purely work as monitors have been developed and typically assess some pressure measure correlated with central vascular volume, with the goal of identifying critical fluid overload and symptoms before aggressive intervention is needed. These include right ventricular pressure monitors, pulmonary artery pressure monitors (CardioMEMS Heart Sensor), and left atrial pressure monitors (sensor system implanted transvenously into the atrial septum, oriented toward the left atrium). Drug delivery systems such as furosemide pumps might be linked to hemodynamic sensors as an innovative way to treat HF patients in real time, particularly targeting those patients who have a narrow range of filling pressure and fluid status tolerance, a common situation in HFpEF.

Miscellaneous Clinical Trials

Several other studies are currently underway examining the role of activation of the NO–sGC pathway. These are stimulated by appreciation for the hemodynamic sensitivity of HFpEF patients to vaso/venodilators, and the potential to stimulate a PKG signaling pathway, which is otherwise deficient. These trials are generally small and many are single center or involve small consortiums. They are examining the potential value of inorganic nitrite (NCT01932606), isosorbide dinitrate combined with hydralazine (NCT01516346), an oral sGC stimulator BAY1021189 (dose-ranging study called Effects, Safety and Tolerability, and Pharmacokinetics of Four Dose Regimens of the Oral sGC Stimulator BAY1021189 (SOCRATES PRESERVED), sponsored by Bayer, NCT01951638), and a trial of udenafil, a PDE5A inhibitor (NCT01599117). There are also several ongoing trials of renal denervation (Renal Denervation in Heart Failure With Preserved Ejection Fraction [RDT-PEF], NCT01840059, and Renal Denervation for Heart Failure With Preserved Ejection Fraction [RESPECT-HF], NCT02041130), as well as a trial of acute HF management in HFpEF, evaluating diuretic strategy with and without low-dose dopamine (Diuretics and Dopamine in Heart Failure With Preserved Ejection Fraction [ROPA-DOP], NCT01901809).

Concluding Thoughts

HFpEF remains among the more challenging of clinical presentations to diagnose and manage. Lack of a clear and consistent mechanism among the many patients that fall into a HFpEF definition, variations in the comorbidities that modify its presentation and course, and the long list of failed therapies make it a poster child for Unmet Medical Needs. Addressing this need is all the more important given the devastating morbidity and mortality and stress on the global healthcare system that the syndrome exacts. We are making progress, but it has been extraordinarily slow, and some reassessment of our concepts and perhaps some paradigm changes are in order.

1. First, we need to recognize that the face of HFpEF varies. There are marked differences in HFpEF among different populations around the world based on medical practices, urban versus rural living, racial subgroups, etc. It is increasingly a disease of younger individuals, affecting men and women equally. In many locations, obesity is a common feature, and we need to understand much more how this affects the syndrome.

2. Second, we need to better subclassify HFpEF patients. Clinical trials and our overall approach would likely be improved by identifying patients based on dominant mechanisms of disease and symptom severity; the grab-bag diagnosis of HFpEF does not tell us much. For example, patients with substantial diastolic dysfunction with or without structural heart disease may behave differently from those with marked systolic hypertension and ventricular–vascular miscoupling, or from those with substantial inflammatory conditions, or chronotropic incompetence. Some sense of the severity of the defect would be helpful.

3. Third, we need more myocardial tissue. Not only biopsy pieces but muscle that can also be used to study live beating cells so we can better identify what has happened and why. We recognize this is nontrivial because these hearts are rarely ever replaced with a transplant—although, if the heart is central enough to the disease, perhaps this will change. The recent spread of integrative pathophysiology studies in humans is welcome, and more are needed.

4. Fourth, we need to improve experimental models, if possible. Animal models are typically designed to be monothematic on purpose, and while useful, efforts to combine common comorbidities such as obesity, hypertension, and diabetes mellitus or some other proinflammatory state would be welcome. Appreciation that aortic banding or rodents fed high-fat diet is not HFpEF despite having some diastolic dysfunction and a preserved EF is important. Still, there is great value in chopping up the puzzle, and experimental efforts are revealing novel signaling cascades and therapies worth trying even from models that capture 1 or 2 dimensions of the disease. However, caveat emptor.

5. Fifth, we need to consider therapies outside of the traditional HFrEF box. The failure of many clinical anti-RASS trials and β-blocker trials sends a message about what types of pathways and mechanisms are involved, and we should listen to them. HFpEF is truly a systems physiology disease, and treatments that integrate multiple targets, such as neuromodulators or pleomorphic drugs, may prove most effective. We may soon have full feedback control systems that sense drug requirements and deliver them automatically; this could be a game changer. We call the disease HFpEF, but more and more data show skeletal muscle abnormalities are critical, and we need to start focusing on why and what this can mean for effective therapy.
Sources of Funding

This study was supported by National Institutes of Health T32-HL07227 (K. Sharma), HL114910, HL077180, and HL119012, and Fondation Leducq (D.A. Kass).

Disclosures

None.

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Heart Failure With Preserved Ejection Fraction: Mechanisms, Clinical Features, and Therapies
Kavita Sharma and David A. Kass

Circ Res. 2014;115:79-96
doi: 10.1161/CIRCRESAHA.115.302922

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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