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, its morbidity and mortality are 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

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 (HFrEF) is rising, with morbidity, mortality, and healthcare costs on par with HF with reduced EF (HFrEF). This syndrome has proven particularly challenging on virtually every front: (1) consensus-based diagnostic criteria result in a heterogeneous population that has proven challenging for clinical studies and trials; (2) multiple mechanisms have been proposed but many remain hypothetical because of limited access to live human heart tissue; (3) good experimental models do not really exist, as many capture components of the human disease but do not reflect its integrative complexity; and (4) HFpEF patients are afflicted with multiple common comorbidities, such as hypertension, diabetes mellitus, vasculopathy, renal disease, atrial fibrillation, metabolic syndrome, that have a major impact on the syndrome and mortality. Given this, it is perhaps not surprising that we have yet to find an evidence-based HFpEF therapy beyond...
### Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
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<tr>
<td>cGMP</td>
<td>cyclic guanosine monophosphate</td>
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<tr>
<td>C_{pa}</td>
<td>pulmonary arterial compliance</td>
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<tr>
<td>E_{es}</td>
<td>end-systolic elastance</td>
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<tr>
<td>EF</td>
<td>ejection fraction</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<tr>
<td>HFpEF</td>
<td>heart failure with a preserved ejection fraction</td>
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<tr>
<td>HFrEF</td>
<td>heart failure with a reduced ejection fraction</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
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<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>PAH</td>
<td>pulmonary arterial hypertension</td>
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<tr>
<td>PCWP</td>
<td>pulmonary capillary wedge pressure</td>
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<tr>
<td>PDE5A</td>
<td>phosphodiesterase type 5A</td>
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<tr>
<td>PH</td>
<td>pulmonary hypertension</td>
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<tr>
<td>PKG</td>
<td>protein kinase G</td>
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<tr>
<td>PVH</td>
<td>pulmonary venous hypertension</td>
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<tr>
<td>RAAS</td>
<td>rennin–angiotensin–aldosterone system</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>R_{pa}</td>
<td>pulmonary arterial resistance</td>
</tr>
<tr>
<td>RV</td>
<td>right ventricular</td>
</tr>
<tr>
<td>VO_{2}</td>
<td>oxygen consumption</td>
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<tr>
<td>VV</td>
<td>ventricular–vascular</td>
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Diuretics for fluid overload, and conventional treatments for comorbidities.

In this article, we provide an overview of HFpEF for both the clinician and basic research scientist, which includes a brief examination of its diagnostic criteria and evolving epidemiology, a summary of proposed mechanisms involving the heart and other organs, a discussion of our valiant but unsuccessful prior efforts to develop an effective therapy, and a review of newer potential approaches. The literature refers to HFpEF by several names including diastolic HF and HF with normal EF. HFpEF is currently the accepted form, and we stick to that here. The companion review in this issue by Loffredo et al focuses on the basic science underlying age-related cardiac disease, most notably diastolic dysfunction. Many of these changes are thought to be relevant to HFpEF, though direct evidence remains limited for most of them. In this presentation, we focus on the major human data findings.

**HFpEF: What’s in a Name?**

Until fairly recently, patients with clinical HF yet with a normal-range EF and evidence of slow chamber relaxation were given a diagnosis of diastolic HF.7–9 However, subsequent studies of such patients showed minimal diastolic dysfunction in many.10–12 Similar abnormalities in elderly patients with hypertensive heart disease but no HF,13,14 and key non-diastolic features such as limited systolic reserve, abnormal volume regulation, and maladaptive ventricular–arterial interaction,15,16 In other words, a normal-range EF did not imply normal systolic function. As these and other noncardiac 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.18 As more studies questioned whether systole is truly normal,19–21 the name changed to HFpEF,22,23 which is now the accepted standard.

**Making the Diagnosis of HFpEF**

To an extent, the diagnostic criteria for HFpEF 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 HFpEF 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 HFpEF 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 normal 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 HFpEF 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 HFpEF.

**Epidemiology of HFpEF**

Cross-sectional studies from Westernized countries have established a view of HFpEF 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 HFpEF patients are far more diverse (Table 1). Melenovsky et al13 studied HFpEF 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 HFpEF patients also reporting worse renal function.31 These differences as recently reviewed by Shah22 likely impact therapy responses and net outcome. Increasingly, epidemiological data report a much more balanced sex distribution.
and this is seen in most clinical trials.\textsuperscript{34–36} The National Ambulatory Cohort of Veterans study examined nearly all men with HF: 30\% had HFpEF.\textsuperscript{37} 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, HFpEF can be more common than HFrEF, as in Hong Kong where it accounts for 67\% of HF admissions,\textsuperscript{38} occurring equally in men and women with high rates of hypertension. In Germany, HF is more common in elderly women, largely because of HFpEF.\textsuperscript{39} These data reveal that HFpEF 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.\textsuperscript{33–35} This affects our understanding of the disease and patient selection for clinical trials.

The clinical outcomes of HFpEF are similar to those with HFrEF, including in-hospital morbidity and hospital readmission rates.\textsuperscript{4,29,30} Although in-hospital mortality may be slightly higher in HFrEF, 30-day to 1-year mortality after discharge is similar between groups.\textsuperscript{4,29,30} Patients with either HF syndrome have comparable functional limitations and poor quality of life.\textsuperscript{32,43} Risk factors for mortality in HFpEF include advanced age, renal impairment, and hemodynamic instability (hypotension, tachycardia).\textsuperscript{30} 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, MN\textsuperscript{40}</th>
<th>Olmsted Co, MN (2006)\textsuperscript{46}</th>
<th>Ontario, CA\textsuperscript{4}</th>
<th>Framingham\textsuperscript{11}</th>
<th>OPTIMIZE\textsuperscript{23}</th>
<th>ADHERE\textsuperscript{30}</th>
<th>Baltimore, MD\textsuperscript{13}</th>
<th>NY HF Consortium\textsuperscript{29}</th>
<th>Chicago, IL\textsuperscript{33}</th>
<th>China\textsuperscript{38}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>244</td>
<td>2167</td>
<td>880</td>
<td>220</td>
<td>10,072</td>
<td>26,522</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>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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<tr>
<td>Outcomes</td>
<td>% 1-y survival</td>
<td>71</td>
<td>78</td>
<td>80†</td>
<td>65†</td>
<td>86</td>
<td>1.5 y</td>
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<td>Comorbidities</td>
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<tr>
<td>Hypertension, %</td>
<td>96</td>
<td>62.7</td>
<td>55.1</td>
<td>37</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>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>
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<tr>
<td>Chronic kidney disease, %</td>
<td></td>
<td>26</td>
<td>9.5</td>
<td>33</td>
<td>9 (end-stage renal 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>23.4</td>
<td>26</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>
<td></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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<tr>
<td>Laboratory values</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>
<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>
<td>1.6±1.5</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Diuretic, %</td>
<td></td>
<td>57</td>
<td>65</td>
<td>87</td>
<td>63</td>
<td>74</td>
<td></td>
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<tr>
<td>ACE-I, %</td>
<td></td>
<td>34</td>
<td>36</td>
<td>68</td>
<td>40</td>
<td>55 (ACE-I or ARB)</td>
<td></td>
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<tr>
<td>ARB, %</td>
<td></td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>10</td>
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<tr>
<td>β-blocker, %</td>
<td></td>
<td>50</td>
<td>46</td>
<td>81</td>
<td>35</td>
<td>67</td>
<td></td>
<td></td>
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<tr>
<td>Digoxin, %</td>
<td></td>
<td>15</td>
<td>19</td>
<td>20</td>
<td>14</td>
<td>10</td>
<td></td>
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<tr>
<td>Aldosterone antagonist, %</td>
<td></td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<td></td>
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<tr>
<td>Statin, %</td>
<td>37</td>
<td>23</td>
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</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.66,67

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.11,13,15,40,48–50 The magnitude of delay is such that its impact on resting diastolic stiffness is generated similar delay.13

The mechanisms for slowed chamber relaxation in HFrEF include reduction in the expression and regulation of proteins involved with calcium cycling into and out of the sarcoplasmic reticulum,14 depression of β-adrenergic signaling, oxidative stress targeting calcium-handling proteins,15 and reduced recoil of elastic elements compressed during systole.53 Many of the same abnormalities are suspected in HFpEF, though direct proof remains limited given the lack of live tissue for human myocardial analysis. Clinical studies have found β-adrenergic responsiveness to be depressed.54 In an interesting study of biopsy samples from HFpEF and HFrEF patients, Hamdani et al55 found that the expression of calcium-handling proteins and phosphorylation of myofilament proteins were similar between the groups (there were no normal controls). β1-adrenergic receptor expression was somewhat reduced in HFpEF; however, G-protein receptor kinase 2 and 5 expression, which can suppress stimulatory adrenergic signaling, was far more elevated in HFrEF. Relaxation is also controlled by passive recoil of elastic elements, notably titin, compressed during systole.53 With the termination of active force generation, these molecular springs uncoil quickly, and recoiling contributes to the kinetics of force decline. Dilated hearts have depressed recoil,56 as the heart does not contract sufficiently to compress the elastic elements. However, as HFpEF volumes are generally normal, recoil may be less affected.

Myocardial and Myocyte Stiffening
Passive my 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,48,57 as well as simplified noninvasive estimates58 including the end-diastolic volume at a pressure of 20 mm Hg.33 The causes for myocardial stiffening are divided into factors influencing the extracellular space such as fibrosis and infiltrative 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.59–61 Both collagen type 1 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.62,63 In addition to altering matrix turnover, cross-linking of collagen including the formation of advanced glycation end products contributes to fibrosis and stiffening.64,65 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 tissue64 and have been proposed to play an important role in the disease.65,66 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.64 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 type transthyretin deposition in 5%, with evidence of amyloid deposition in 19%.68 Whether
transthyretin polymorphisms associated with disease\(^6\) 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\(^5\) first reported higher passive stiffness in isolated HFpEF myocytes versus controls. This stiffening was normalized by incubation of cells with protein kinase A, a change also more prominent in myocytes from HFpEF than from HFrEF hearts.\(^6\) Analogous studies have extended this to protein kinase G (PKG) stimulation as well.\(^7\) The protein principally responsible for protein kinase A and PKG responsive cellular stiffening seems to be titin, a macromolecular spring whose elasticity varies with its isoform and post-translational modifications including phosphorylation and oxidation (reviewed by Linke et al\(^7\)). Titin is synthesized as either the more compliant (fetal) N2BA or stiffer (adult) N2B form.\(^7\) Signaling by thyroid hormone, insulin, and Gq-protein–coupled receptors to the phosphoinositide 3-kinase–protein kinase B (Akt) pathway from the receptor to adenyl cyclase (AC) and generation of cAMP to activation of protein kinase A (PKA) 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.

**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.

Protein kinase G (PKG) activity may depend on reduced nitric oxide (NO)-dependent cGMP synthesis because of oxidative stress. Reactive oxygen species (ROS) can interfere with NO-related signaling at multiple nodes, oxidation of soluble guanylate cyclase (sGC) impairs its responsiveness to NO to generate cGMP,\(^9\) NO synthase can become uncoupled by oxidation resulting in its synthesis of superoxide,\(^8\) and NO–ROS interactions thwart downstream signaling. Importantly, the capacity of PDE5A inhibition to augment PKG activity depends
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. 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. However, studies using catherization with imaging or conductance catheter measurements to derive pressure–volume relations have found that resting load–independent indexes of systolic function were essentially normal in HFP EF. Isolated skinned myocyte data from HFP EF showed similar maximal calcium-activated force, but that is about all we know from human HFP EF tissue. Some measures of systole such as end-systolic elastance (Ees), a measure of systolic stiffening, were higher in several HFP EF studies, and this seems particularly true in urban populations with a high percent of blacks. Rather than implying increased resting contractility, the higher Ees may reflect myocardial hypertrophy, fibrosis, infiltrative disease, or titin modifications.

**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. This limits systolic reserve that would normally accompany further rises in Ees, contributes to increased cardiac energy demands required to enhance cardiac output, 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. In HFP EF, effective arterial elastance and Ees both increase, although similar increases are observed in patients with hypertension (±LVH) but without HF. 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.

**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 al 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\textsuperscript{90} studied 17 HFpEF 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 (VO\textsubscript{2}) in the HFpEF 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.\textsuperscript{90} Chronotropic incompetence has since been reported by multiple investigators\textsuperscript{91,92} and been found in large trials.\textsuperscript{35} This has implications for the use of β-blockers and sinus node suppressors (I\textsubscript{f} blockers) in the syndrome. The normally rapid heart rate decline after cessation of exercise is delayed in HFpEF, and this behavior is thought to be due to autonomic dysfunction and an independent risk factor for cardiac death.\textsuperscript{90,92,93} Impaired peripheral vasodilation has been documented in exercised HFpEF patients using MRI.\textsuperscript{94} Borlaug et al\textsuperscript{95} examined cardiac systolic reserve in exercising HFpEF 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 HFpEF, 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.\textsuperscript{95} However, in 2 subsequent HFpEF studies, LV function with incremental pacing increased contractility compared with controls or showed no difference,\textsuperscript{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.\textsuperscript{90} Thus, the HFpEF response was more consistent with normal physiology. Preload reserve limitations were not observed in several HFpEF exercise hemodynamic studies\textsuperscript{16,94}, whether diastolic filling is truly restricted in HFpEF during tachycardia remains uncertain.

**Myocardial Energetics and Skeletal Muscle Metabolism**

Among potential mechanisms for limited cardiac systolic reserve with HFpEF are abnormalities of myocardial energetics, including adenosine triphosphate (ATP) generation and shuttling between phosphocreatine and ATP by the creatine kinase reaction. Smith et al\textsuperscript{17} used NMR spectroscopy to assess patients with non-HFrEF (few technically had HFpEF) 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 HFpEF found a significant decline in phosphocreatine/ATP compared with controls.\textsuperscript{98} In a recent study to evaluate whether skeletal muscle abnormalities contribute to decreased peak exercise VO\textsubscript{2} (peak VO\textsubscript{2}) in HFpEF, Kitzman et al\textsuperscript{99} performed cardiopulmonary exercise testing and needle biopsies of the vastus lateralis muscle to assess muscle fiber type distribution, capillary density, and peak VO\textsubscript{2}. HFpEF 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 HFpEF. The type I fibers and capillary-to-fiber ratio was significantly associated with peak VO\textsubscript{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 HFpEF, several studies have found that limited cardiac reserve fails to explain exertional intolerance and have highlighted abnormal skeletal muscle performance as likely contributors.\textsuperscript{100,101}

**Role of Inflammation**

Results from LV endomyocardial biopsy\textsuperscript{70} and analyses of inflammatory cell markers\textsuperscript{63} suggest that increased oxidative stress and depressed NO signaling resulting in inflammation play a key role in HFpEF.\textsuperscript{66,67} The multitude of HFpEF comorbidities may contribute to a proinflammatory state\textsuperscript{102}; circulating inflammatory cytokines such as interleukin 6, tumor necrosis factor α, soluble ST2, and pentraxin 3 are elevated in HFpEF.\textsuperscript{103–106} Systemic inflammation could lead to endothelial dysfunction supported by higher expression of vascular cell adhesion molecules such as VCAM-1, E-selectin, and ROS.\textsuperscript{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. TGFβ signaling may also be increased in HFpEF myocardium,\textsuperscript{66} although data remain limited. The complex and cell-specific signaling linked to this cytokine suggests that therapeutic targeting could prove difficult.\textsuperscript{107,108}

**Biomarkers in HFpEF: 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 HFpEF to aid in diagnosis and prognosis and to help better understand mechanisms of disease. The natriuretic peptides are perhaps the best characterized biomarkers in HFpEF. B-type natriuretic peptide (BNP) is typically higher in HFpEF than in non-HF patients, but lower than in HFrEF.\textsuperscript{109,110} BNP linearly correlates with LV diastolic pressure and with LV diastolic wall stress in HFpEF; the smaller LV cavity size and thicker walls with resultant lower end-diastolic wall stress may account for lower BNP levels.\textsuperscript{111} Biomarkers of extracellular matrix turnover and fibrosis in HFpEF have recently been reviewed, including soluble ST2, galectin-3; collagen propeptides (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.\textsuperscript{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 HFpEF.\textsuperscript{112} Although nearly all of these biomarkers support the diagnosis of HFpEF 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 HFpEF.

**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 HFpEF 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 hypervolemia and HFrEF; however, after adjusting for PCWP, pulmonary systolic pressure is still higher in HFpEF. 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. 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. has demonstrated that many HFpEF 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 HFpEF), which is manifested more under conditions of exertion or volume loading.

An additional role of PCWP from LV disease to PAH was revealed by Tedford et al., who studied the inverse relation between total pulmonary arterial compliance ($C_p$) and resistance ($R_p$) in patients with varying levels of PAH and PCWP elevation. The $C_p-R_p$ relation is hyperbolic with a tight interdependence between the 2 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 $C_p-R_p$ relation was remarkably invariant, but it did change with a rise in PCWP, with $C_p$ declining at the same $R_p$. This indicates that PCWP affects pulmonary arterial pulsatile load and thus right ventricular (RV) systolic load and likely has implications for HFpEF and PH. As with PH, RV dysfunction is a well-established predictor of poor outcomes in increased mortality in HFpEF, and this may apply to HFpEF in that RV wall thickening was predictive of worse outcomes.

**Renal Dysfunction**

Chronic kidney disease occurs in 26% to 53% of HFpEF and is associated with poor prognosis. Beyond baseline impairment, worsening renal function during HFpEF 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 HFpEF 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 HFrEF, 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 HFpEF, 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 HFpEF? Does HFpEF 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 transient receptor potential channel 6, a Gq-receptor–and ROS-activated nonselective 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 HFpEF patients.

**Abdominal Contributions**

In many HFpEF 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 HFpEF, it does likely play a role in fluid homeostasis, and is an area deserving attention. The splanchnic vasculature normally contains $\approx 25\%$ of total blood volume in capacitance veins. This capacitance function is impaired in HF, with increased neurohormonal activation resulting in venoconstriction 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; splanchnic bed congestion, which creates a false state of hypovolemia; and nonocclusive bowel ischemia, which may eventually result in circulating endotoxin.

**Treatment of HFpEF**

*A Brief History of Neutral Trials*

Targeting the RAAS and β-adrenergic stimulation pathways has long been considered reasonable for HFpEF, 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 HFpEF. 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]),46 Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction [RAA-MPEF],131 and Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist [TOPCAT]),45, digoxin (Digitalis Intervention Group-Preserved Ejection Fraction [DIG-PEF]),46 and sildenafil (RELAX).35 Despite broad acceptance of diastolic impairment as a contributor to HFpEF, 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 HFpEF. 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, HFpEF 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 HFpEF 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 HFpEF 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 HFpEF 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 HFpEF 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 HFpEF.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, HFpEF patients have low myocardial cGMP, 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 HFpEF. First, our fixation on RAAS signaling may indeed be misplaced. It seems unlikely that neurohormonal stimulation is not involved in HFpEF, but it may not be as sustained, with less impact cleansed by its blockade. Perhaps HFpEF 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, who described the concept of matchmaking 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. 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_F) channel blocker, ivabradine, which slows sinus rate but has no impact on contractility or the peripheral vasculature, unlike β-blockade. Experimental data in mice with obesity and diabetes mellitus found reduced aortic stiffness and fibrosis and improvement in LV function from 4 weeks of ivabradine therapy. Kosmala et al 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 of 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. Largely-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. Natriuretic peptides can promote myocardial relaxation, reduce hypertrophy, and are integral to diuresis, natriuresis, and modest vasodilation. Clinical data for all of these effects are less well documented, but benefits have been observed. A recent randomized clinical trial compared LCZ696, which combines a neprilysin inhibitor prodrug AHU377 and the AT1 receptor blocker (valsartan), to valsartan alone in 266 HFpEF patients. 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. Exercise training provides cardioprotection against ischemia-reperfusion injury (see excellent recent review by Powers et al.), in part by suppressing ROS-mediated cellular damage, decreasing cystolic 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>First Author/Trial</th>
<th>Japanese-DHF127</th>
<th>ELANDD128</th>
<th>I-PRESERVE130</th>
<th>DIG-PEF45</th>
<th>ALDO-DHF36</th>
<th>RAAM-PEF131</th>
<th>RELAX35</th>
<th>TOPCAT34,118</th>
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<td>Intervention</td>
<td>Carvedilol</td>
<td>Nebivolol</td>
<td>Irbesartan</td>
<td>Digoxin</td>
<td>Spironolactone</td>
<td>Eplerenone</td>
<td>Sildenafil</td>
<td>Spironolactone</td>
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<tr>
<td>Sample size</td>
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<td>4128</td>
<td>988</td>
<td>422</td>
<td>44</td>
<td>216</td>
<td>3445</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>LVEF &gt;40%</td>
<td>LVEF &gt;45% diastolic dysfunction by Doppler echo, NYHA class II–III</td>
<td>LVEF &gt;45%; NYHA II–IV; hospitalization for HF within past 6 mo</td>
<td>LVEF &gt;45%; clinical signs/ symptoms of HF; normal sinus rhythm</td>
<td>LVEF &gt;50%; NYHA II–III; evidence of diastolic dysfunction</td>
<td>LVEF &gt;50%, elevated NT-proBNP; reduced exercise capacity</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></td>
</tr>
<tr>
<td>Primary end point</td>
<td>Composite cardiovascular death and unplanned hospitalization for HF</td>
<td>Change in 6MWT</td>
<td>Composite cardiovascular death from any cause or hospitalization for cardiovascular cause</td>
<td>Combined HF hospitalization or HF mortality</td>
<td>Changes in diastolic function (E/e′) and maximum exercise capacity (peak VO2)</td>
<td>Change in 6MWT</td>
<td>Change in peak VO2</td>
<td>Composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF</td>
</tr>
<tr>
<td>Outcome</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Improved diastolic function; did not improve exercise capacity</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative; lower hospitalization for HF in Spironolactone group</td>
</tr>
<tr>
<td>1-y survival, %</td>
<td>Placebo 90%; treatment 90*</td>
<td>Placebo 90%; treatment 90*</td>
<td>Placebo 77%; treatment 77</td>
<td>Placebo 100%; treatment &gt;99</td>
<td>6-mo survival: placebo 100%; treatment 97</td>
<td>Placebo &gt;90; treatment &gt;90</td>
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<tr>
<td>Patient characteristics, means or %</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>73</td>
<td>67</td>
<td>72</td>
<td>67</td>
<td>67</td>
<td>72</td>
<td>68</td>
<td>69</td>
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<tr>
<td>Women, %</td>
<td>43</td>
<td>65</td>
<td>59</td>
<td>42</td>
<td>52</td>
<td>5</td>
<td>43</td>
<td>52</td>
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<tr>
<td>White, %</td>
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<td>86</td>
<td></td>
<td></td>
<td></td>
<td>90</td>
<td>89</td>
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<tr>
<td>Black, %</td>
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<td>NYHA class, %</td>
<td>I (18), II (69), III (11), IV (2)</td>
<td>II (77), III (21)</td>
<td>II (21), III (77), IV (3)</td>
<td>I (19), II (59), III (20), IV (1)</td>
<td>II (85), III (15)</td>
<td>II (67), III (33)</td>
<td>II (49), III (51)</td>
<td>I (3), II (63), III (33), IV (0.4)</td>
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<tr>
<td>Comorbidities</td>
<td>Hypertension, %</td>
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<td>86</td>
<td>89</td>
<td>62</td>
<td>92</td>
<td>100</td>
<td>80</td>
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<tr>
<td></td>
<td>CAD, %</td>
<td>28</td>
<td>17</td>
<td>38</td>
<td>50</td>
<td>43</td>
<td>67</td>
<td>42</td>
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<tr>
<td></td>
<td>Diabetes mellitus, %</td>
<td>28</td>
<td>21</td>
<td>28</td>
<td>27</td>
<td>61</td>
<td>62</td>
<td>42</td>
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<tr>
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<td>CKD, %</td>
<td>31</td>
<td></td>
<td>48</td>
<td></td>
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<td></td>
<td>Left ventricular hypertrophy, %</td>
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<td>48</td>
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<td>Vital signs</td>
<td>SBP, mm Hg</td>
<td>134</td>
<td>134</td>
<td>137</td>
<td>135</td>
<td>130</td>
<td>124 (median)</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>DBP, mm Hg</td>
<td>75</td>
<td>81</td>
<td>79</td>
<td>79</td>
<td>71</td>
<td>76</td>
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<td></td>
<td>Body mass index, kg/m²</td>
<td>24</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>30</td>
<td>33 (median)</td>
<td>32</td>
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<tr>
<td>Admission data</td>
<td>BNP, pg/mL</td>
<td>219</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>234 (median)</td>
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<tr>
<td></td>
<td>NT-proBNP, pg/mL</td>
<td>360</td>
<td>179 (median)</td>
<td>757 (median)</td>
<td>950 (median)</td>
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<tr>
<td></td>
<td>Serum creatinine, mg/dL</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.6</td>
<td>1.3</td>
<td>1.1</td>
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<tr>
<td></td>
<td>LV mass, g/m²; or LVMI, g/m²</td>
<td>126 g/m²</td>
<td>108 g/m²</td>
<td>49 g/m²</td>
<td>77 g/m²</td>
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<td>Medications</td>
<td>(Continued)</td>
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Targeting Neural Reflex Arcs: Renal Denervation and Nerve Stimulation

Long-standing, resistant hypertension is common in HFrEF patients, and alternatives to traditional pharmacological therapies are being sought. Renal sympathetic denervation is an approach that has shown some utility in HF patients.164 A HFrEF device therapy has made enormous inroads into HFrEF with pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy. The role of each in HFrEF is undefined; some patients with symptomatic chronotropic incompetence receive pacemakers, and those with a history of sudden death receive a defibrillator. Dyssynchrony in HFrEF can occur although it seems more rare than with HFrEF, and the efficacy of cardiac resynchronization therapy has not yet been demonstrated in HFrEF. 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, lasting (9 days), with multiple proposed mechanisms of benefit, including improved coronary circulation, stimulation of cytosolic antioxidants, increased heat shock proteins, increase in sarcoclemmal- and mitochondrial-ATP–sensitive K channels, increase in cyclooxygenase 2, increased NO signaling, and altered mitochondrial phenotype (increased antioxidant capacity). Many of these mechanisms have been implicated in the development of HF, including HfPEF.

Kitzman et al155 reported findings from the first randomized, controlled study of exercise training in older patients with HfPEF during a 16-week period. The primary outcome of peak exercise oxygen uptake significantly improved in the exercise therapy group compared with controls. Improvements were also noted in exercise time, 6-minute walk distance, ventilatory anaerobic threshold, peak power output, and the physical component of quality of life score. Interestingly, exercise training did not seem to improve endothelial function or arterial stiffness in a study of exercise training evaluating flow-mediated arterial dilation and carotid artery stiffness.156 These initial studies of exercise training are promising and suggest that exercise training should be considered part of the management of HFpEF. Effective translation in a population that is notably sedentary and often morbidly obese will undoubtedly pose challenges, however.

Table 2. Continued

<table>
<thead>
<tr>
<th>First Author/Trial</th>
<th>Japanese-DHF137</th>
<th>ELANDD129</th>
<th>I-PRESERVE134</th>
<th>DIG-PEF46</th>
<th>ALDO-DHF36</th>
<th>RAAM-PEF131</th>
<th>RELAX35</th>
<th>TOPCAT34,118</th>
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<tr>
<td>Diuretic, %</td>
<td>63</td>
<td>49</td>
<td>82</td>
<td>82</td>
<td>55</td>
<td>95</td>
<td>88</td>
<td>65</td>
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<tr>
<td>ACE-I, %</td>
<td>24</td>
<td>75 (ACE-I or ARB)</td>
<td>26</td>
<td>86</td>
<td>78</td>
<td>95 (ACE-I or ARB)</td>
<td>65 (ACE-I or ARB)</td>
<td>82</td>
</tr>
<tr>
<td>ARB, %</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>β-blocker, %</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78</td>
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<tr>
<td>Digoxin, %</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Aldosterone antagonist, %</td>
<td>21</td>
<td>46</td>
<td>32</td>
<td>53</td>
<td>63</td>
<td>53</td>
<td></td>
<td></td>
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<tr>
<td>Statin, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

6MWT indicates 6-min walk test; ACE-I, angiotensin-converting enzyme inhibitor; ALDO-DHF, Effect of Spironolactone on Diastolic Function and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DIG-PEF, Digitalis Intervention Group-Preserved Ejection Fraction; ELANDD, Effects of Nebivolol on Clinical Symptoms, Exercise Capacity, and Left Ventricular Function in Diastolic Dysfunction; HF, heart failure; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction; Japanese-DHF, Japanese Diastolic Heart Failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index (LV mass/body surface area); NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAAM-PEF, Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction; RELAX, Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction; SBP, systolic blood pressure; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; and VO2, oxygen consumption.

*Estimated survival based on Kaplan–Meier curves.
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,168 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,169 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,170 pulmonary artery pressure sensors (CardioMEMS Heart Sensor),169 and left atrial pressure monitors (sensor system implanted transvenously into the atrial septum, oriented toward the left atrium).171 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-RAAS 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.
The hope is that as we better focus on each of these issues, and gain new insights into how HFpEF works as a disease, we should finally be able to move it off the unmet need shelf where it has remained for some time, and onto one with our successful HF managements.

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Disclosures

None.

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Sharma and Kass

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Kavita Sharma and David A. Kass

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