

Frontiers in cardiovascular medicine

# Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment

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Half of patients with heart failure (HF) have a preserved left ventricular ejection fraction (HFpEF). Morbidity and mortality in HFpEF are similar to values observed in patients with HF and reduced EF, yet no effective treatment has been identified. While early research focused on the importance of diastolic dysfunction in the pathophysiology of HFpEF, recent studies have revealed that multiple non-diastolic abnormalities in cardiovascular function also contribute. Diagnosis of HFpEF is frequently challenging and relies upon careful clinical evaluation, echo-Doppler cardiography, and invasive haemodynamic assessment. In this review, the principal mechanisms, diagnostic approaches, and clinical trials are reviewed, along with a discussion of novel treatment strategies that are currently under investigation or hold promise for the future.

**Keywords** Heart failure • Diastolic • Systolic • Ejection fraction • Preserved ejection fraction • Pathophysiology • Diagnosis • Treatment

## Introduction

Clinical interest in heart failure (HF) with preserved ejection fraction (HFpEF) emerged from the confluence of two research areas dealing, respectively, with diastolic left ventricular (LV) dysfunction in hypertrophied hearts and with LV remodelling after small myocardial infarctions. In the late seventies, the first studies appeared that showed diastolic LV dysfunction to importantly contribute to HF in hypertrophic cardiomyopathy,<sup>1,2</sup> aortic stenosis,<sup>2,3</sup> and hypertensive heart disease.<sup>4</sup> Shortly after this inroad from the small niche of diastolic LV dysfunction in hypertrophied hearts, HFpEF was also identified and addressed in studies, which were a 'by-product' of the large HF trials investigating the use of angiotensin converting enzyme inhibitors (ACEIs) in HF with reduced EF (HFrEF) and in post-infarct LV remodelling.<sup>5–7</sup> The HFpEF populations derived from the latter studies were, however, clearly different, as they consisted of patients with limited myocardial infarction at risk for unfavourable eccentric LV remodelling. This ambiguous origin of HFpEF contributed to the confusion surrounding HFpEF as a distinct diagnosis<sup>8–10</sup> and the neutral outcome of many large HFpEF trials.<sup>11,12</sup>

Cardiac hypertrophy indeed has little in common with limited myocardial infarction, and in both conditions, mechanisms driving LV remodelling are likely to be dissimilar and react differently to pharmacological treatment. Recently, stringent criteria have been proposed for the diagnosis of HFpEF consisting not only of signs or symptoms of fluid overload and a preserved LVEF but also of evidence of diastolic LV dysfunction.<sup>13,14</sup> This caused most HFpEF patients to currently present with a concentrically remodelled left ventricle because of arterial hypertension, obesity, and diabetes, without evidence of coronary artery disease. A low prevalence of coronary artery disease has indeed recently been proposed as a measure for correct patient enrolment in HFpEF trials.<sup>15</sup>

In the past, HFpEF was frequently referred to as 'diastolic' HF (DHF) in opposition to 'systolic' HF (SHF), which corresponded with HFrEF. Because diastolic LV dysfunction was not unique to HFpEF but also observed in patients with HFrEF, the term DHF was abandoned and replaced by HFpEF<sup>16,17</sup> or by HF with normal LVEF (HFnEF).<sup>17</sup> The terms HFpEF and HFnEF, however, also have their shortcomings. The notion of a preserved LVEF implies knowledge of a pre-existing EF, which is almost always absent, and

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the exact range of a 'normal' LVEF is hard to define.<sup>18,19</sup> It is not established whether HFpEF and HFrEF represent distinct forms of HF or exist as part of one 'HF spectrum',<sup>13</sup> although the distinct patterns of chamber and myocellular remodelling observed coupled with disparate responses to medical therapies would all suggest that they are two discrete disease processes. Heart failure with preserved ejection fraction is currently observed in 50% of HF patients, and outcomes are similar to those seen in HFrEF.<sup>20</sup> The dismal prognosis is likely a reflection of the complex multisystem involvement characteristic of all HF, regardless of EF—including skeletal muscle and vascular dysfunction, pulmonary hypertension, renal failure, anaemia, and atrial fibrillation.<sup>21</sup> The prevalence of HFpEF relative to HFrEF is rising at an alarming rate of ~1% per year, thereby rapidly turning HFpEF into the most prevalent HF phenotype over the next decennium; yet in contrast to HFrEF, no improvements in outcome have been realized over the past two decades.<sup>20</sup> Despite these worrisome epidemiological trends, pathophysiological mechanisms underlying HFpEF and diagnostic or therapeutic strategies remain uncertain<sup>21,22</sup> and will therefore be addressed in the current review, which spans transatlantic views on this subject as part of the Frontiers in Cardiovascular Medicine Series of the European Heart Journal.

## Pathophysiology

The seminal studies on HFpEF explained HF in the presence of normal systolic LV performance by diastolic LV dysfunction, which consisted of prolonged isovolumic LV relaxation, slow LV filling, and increased diastolic LV stiffness.<sup>1–4</sup> With the advent of Doppler echocardiography, diastolic LV dysfunction could easily be appreciated from mitral or pulmonary vein flow velocity recordings.<sup>23</sup> Abnormal mitral flow velocity recordings suggestive of

diastolic LV dysfunction were, however, non-specific for HFpEF, as they also occurred in the elderly<sup>24</sup> and in patients with HFrEF.<sup>25</sup> The importance of diastolic LV dysfunction for HFpEF was recently reappraised by invasive studies, which showed uniform presence at rest of slow LV relaxation and elevated diastolic LV stiffness<sup>26</sup> and which demonstrated that elevated diastolic LV stiffness limited cardiac performance during atrial pacing and exercise.<sup>27,28</sup> This reappraisal was also evident from the recent issuing of guidelines for the diagnosis of diastolic LV dysfunction by both the European and American Echocardiography Associations.<sup>13,14</sup>

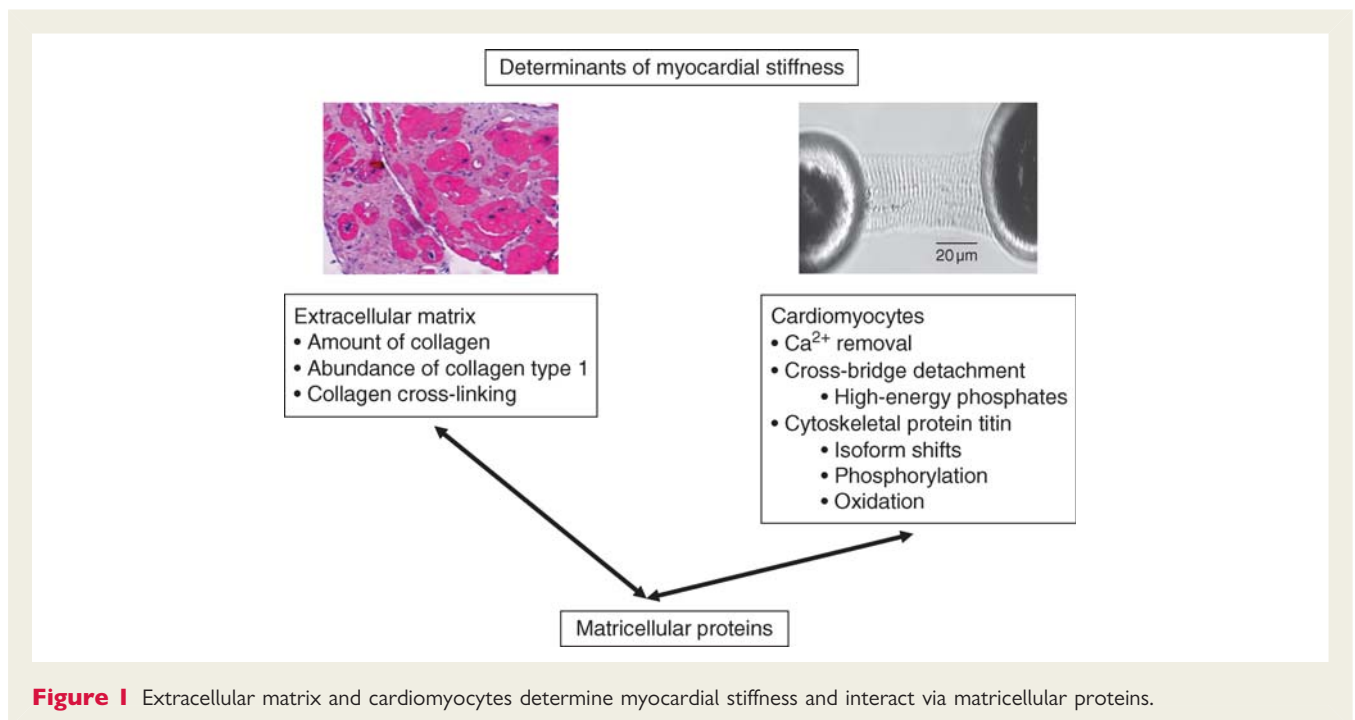
The reappraisal of diastolic LV dysfunction as an important mechanism underlying HFpEF does not imply that the latter represents the sole contributor to disease pathophysiology. Numerous other mechanisms have indeed recently been identified and play important roles. These include resting and exercise-exacerbated systolic dysfunction,<sup>29–35</sup> impaired ventricular–vascular coupling,<sup>33,34,36,37</sup> abnormal exercise-induced and flow mediated vasodilation,<sup>28,31–33</sup> chronotropic incompetence,<sup>31,33,34,38</sup> and pulmonary arterial hypertension.<sup>39,40</sup>

## Diastolic left ventricular dysfunction

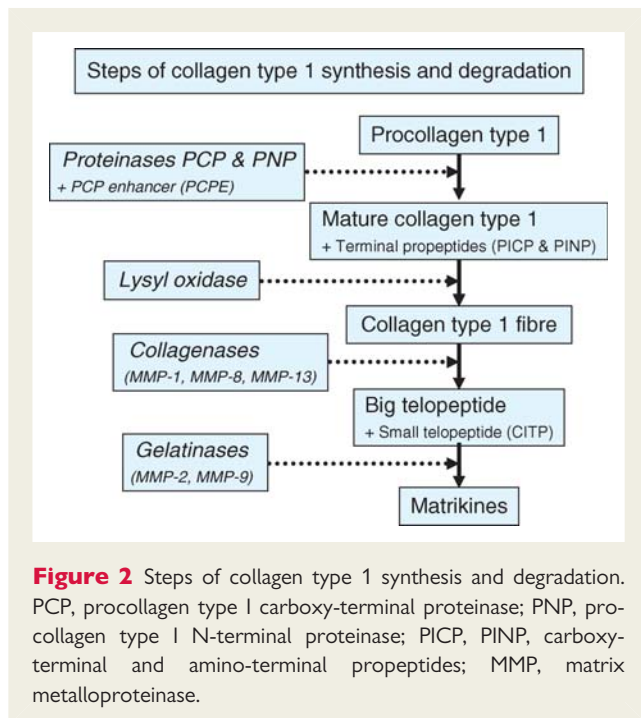
In the absence of endocardial or pericardial disease, diastolic LV dysfunction results from increased myocardial stiffness. Two compartments within the myocardium regulate its diastolic stiffness. These compartments are the extracellular matrix and the cardiomyocytes. A stiffness change within one compartment is also transmitted to the other compartment via matricellular proteins (Figure 1).

### Extracellular matrix

Stiffness of the extracellular matrix is largely determined by collagen through regulation of its total amount, relative abundance



**Figure 1** Extracellular matrix and cardiomyocytes determine myocardial stiffness and interact via matricellular proteins.



of collagen type I, and degree of collagen cross-linking. In HFpEF patients, all three mechanisms appear to be involved. Excessive collagen type I deposition results from an imbalance between an exaggerated synthesis and a depressed degradation.<sup>41</sup> Several steps are involved in the process of the collagen type I synthesis (Figure 2). Of clinical relevance is the observation that pro-collagen type I carboxy-terminal pro-peptide, which is cleaved by PCP from pro-collagen type I, is released into the bloodstream and therefore a potential biomarker of activity of the PCP-PCPE system.<sup>42,43</sup> Excessive collagen type I deposition can result not only from an exaggerated synthesis of collagen type I but also from a depressed collagen type I degradation. In hypertensive patients with HFpEF<sup>44</sup> and in patients with aortic stenosis,<sup>45</sup> there is decreased matrix degradation because of downregulation of matrix metalloproteinases (MMPs) and upregulation of tissue inhibitors of matrix metalloproteinases (TIMPs). Plasma levels of TIMP-1 have recently been proposed as a potential biomarker of HFpEF development in patients with arterial hypertension.<sup>46</sup> Conversely, in patients with dilated cardiomyopathy, there is increased matrix degradation because of upregulation of MMPs.<sup>47</sup> These distinct expression profiles of MMPs and TIMPs also correspond with unequal patterns of myocardial collagen deposition with mainly interstitial fibrosis in DHF and both replacement and interstitial fibrosis in dilated cardiomyopathy.<sup>48</sup> In patients with aortic stenosis, who develop a depressed LVEF, there is reversal of the balance between collagen antiproteolysis and proteolysis.<sup>49</sup>

### Cardiomyocytes

In LV endomyocardial biopsies, one-third of the patients presenting with HFpEF have a normal collagen volume fraction.<sup>50</sup> Their LVEDP, LV end-systolic wall stress, and LV stiffness modulus were, however, comparable with patients presenting with a

raised collagen volume fraction. This finding suggests that in addition to collagen deposition, intrinsic cardiomyocyte stiffness also contributes to diastolic LV dysfunction in HFpEF.<sup>50</sup> Intrinsic cardiomyocyte stiffness is indeed elevated in patients with HFpEF<sup>48,50,51</sup> and in patients with right or LV hypertrophy because of congenital heart disease.<sup>52</sup> This elevation of cardiomyocyte stiffness has been related to the cytoskeletal protein titin.

Titin is a giant elastic protein expressed in cardiomyocytes in two main isoforms, N2B (stiffer spring) and N2BA (more compliant spring).<sup>53</sup> Earlier work showed that the N2BA:N2B isoform expression ratio is increased in eccentrically remodelled explanted hearts from dilated cardiomyopathy patients when compared with control donor hearts.<sup>54–56</sup> Although titin-isoform switching is a confirmed mechanism for adjusting myocardial passive stiffness, recent studies suggested that the increased passive stiffness of failing myocardium can also arise from alterations in the phosphorylation state of titin<sup>57–59</sup> or from the oxidative stress-induced formation of disulfide bridges within the titin molecule.<sup>60</sup>

A characteristic feature of HFpEF is slow LV relaxation, which may reduce LV stroke volume, especially at high heart rates.<sup>61,62</sup> This finding is in contrast to the normal heart, which accelerates LV relaxation at high heart rates. Left ventricular relaxation is dependent on both cross-bridge detachment and sarcoplasmic reticular Ca<sup>2+</sup> reuptake.<sup>63</sup> Nitric oxide (NO) signalling is involved as well. Its downstream mediator cyclic guanosine monophosphate (cGMP) reduces myofilamentary Ca<sup>2+</sup> sensitivity and thereby facilitates cross-bridge detachment.<sup>64</sup> This involvement of NO was also recently reappraised because of close correlations between asymmetric dimethylarginine and diastolic LV dysfunction in failing human hearts<sup>65,66</sup> and because of uncoupling of NO synthase-1 inducing HFpEF in an animal model.<sup>67</sup> As cross-bridge detachment is an energy-consuming process, slow LV relaxation can also result from a myocardial energy deficit. Recent studies using myocardial phosphorus magnetic resonance spectroscopy indeed showed lower myocardial creatine phosphate/adenosine triphosphate ratio in HFpEF patients compared with normal controls,<sup>34,68</sup> consistent with reduced myocardial energy reserve.

### Matricellular proteins

The mechanosensitive induction of matricellular proteins affects fibroblast function and regulates cardiomyocyte hypertrophy and survival.<sup>69</sup> By binding to collagen, cell surface receptors, and MMPs, matricellular proteins improve both matrix quality and cardiomyocyte function.<sup>70</sup> Their role in HFpEF remains unexplored.

### Systolic dysfunction

Ejection fraction is preserved in HFpEF, but EF is more accurately regarded as a measure of ventricular–arterial coupling than contractility alone.<sup>30</sup> In 2002, two seminal studies reported that regional measures of systolic function, assessed by Tissue Doppler imaging, are impaired in HFpEF, despite a normal EF.<sup>29,71</sup> Numerous subsequent studies have similarly shown depressed longitudinal<sup>72,73</sup> and radial systolic function in HFpEF.<sup>74</sup> However, the significance of these abnormalities has been questioned,<sup>75</sup> because global measures of systolic function appeared preserved in HFpEF.<sup>76</sup> Recently, a large population-based study demonstrated that both the chamber level and myocardial

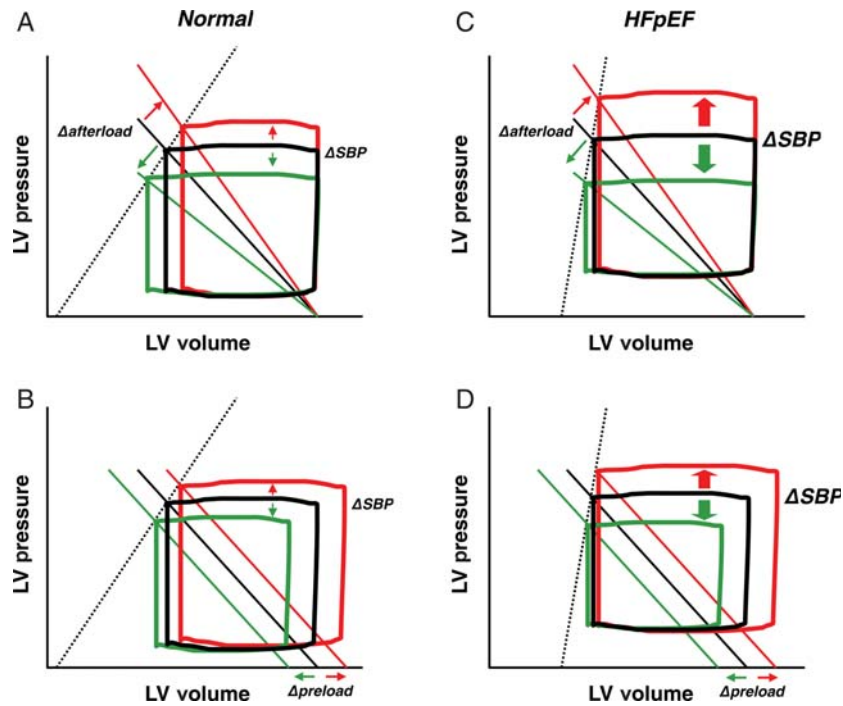
contractility are subtly but significantly depressed in HFpEF, compared with hypertensive and healthy controls.<sup>30</sup> Importantly, the extent of myocardial contractile dysfunction in HFpEF was associated with increased mortality, suggesting that it may be a mediator or nominally a marker of more severe disease.<sup>30</sup>

End-systolic elastance (Ees), defined by the slope and intercept of the end-systolic pressure–volume relationship, is a gold standard measure of chamber contractility that, in contrast to other measures, is elevated in HFpEF,<sup>30,36,76,77</sup> suggesting enhanced contractility. The coexistence of elevated Ees and reduced systolic function by other indices has been difficult to reconcile. However, in addition to being sensitive to contractility, Ees is also influenced by chamber geometry—being increased with concentric remodelling and passive ventricular stiffening—processes commonly observed in HFpEF. Ees is elevated in HFpEF despite depressed contractility, measured using other contractile indices, across each pattern of ventricular chamber geometry.<sup>30</sup> It is speculated that the same processes that promote diastolic ventricular stiffening in HFpEF also increase systolic stiffening (Ees) and contribute to reduced myocardial contractility and limited systolic reserve. Systolic function is clearly not as impaired in HFpEF as in HFrEF,<sup>73</sup> but recent studies have shown that even mild limitations in basal contractility in HFpEF may become more problematic in the setting of exercise stress,<sup>31–35</sup> where an inability to enhance contractility may be associated with impaired cardiac output reserve, more severe symptoms of exercise intolerance, and reduced aerobic capacity.

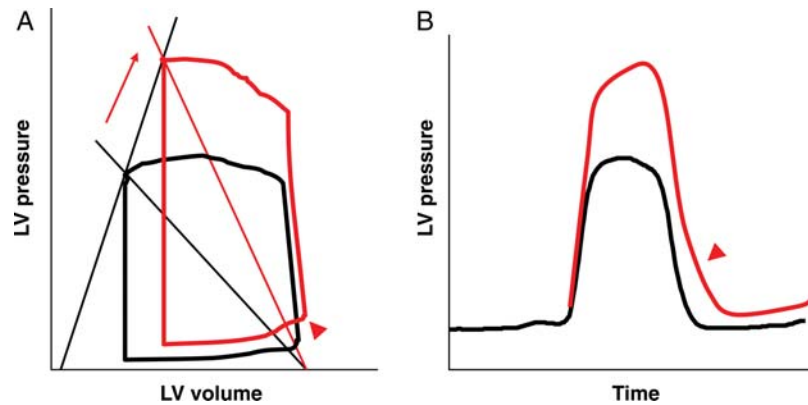
## Ventricular-arterial coupling and vascular dysfunction

Ventricular and vascular stiffening increase with ageing, hypertension, and diabetes, and are abnormally elevated in patients with HFpEF.<sup>20,77</sup> Reduced aortic distensibility in HFpEF is strongly associated with impaired exercise capacity.<sup>78</sup> Kawaguchi *et al.*<sup>36</sup> showed that both arterial elastance (Ea) and Ees are elevated in tandem in HFpEF, explaining the labile blood pressure swings commonly seen in HFpEF.<sup>79</sup> Combined ventricular-arterial stiffening leads to greater blood pressure lability, by creating a ‘high gain’ system—with amplified blood pressure changes for any alteration in preload or afterload (*Figure 3*).<sup>37</sup> Acute afterload elevation in the setting of ventricular-arterial stiffening causes greater increase in blood pressure, which may then feedback to further impair diastolic relaxation<sup>80,81</sup>—leading to dramatic increases in filling pressures during stress (*Figure 4*). Recent studies have also highlighted the importance of abnormal ventricular-arterial coupling during exercise in HFpEF<sup>33,34</sup>—where blunted increases in contractility and impaired reductions in arterial afterload with stress each contribute to exertional intolerance.<sup>82</sup> Therapies targeting combined ventricular-arterial stiffening improve exercise capacity in elderly hypertensive patients,<sup>83</sup> suggesting a possible role in HFpEF.

Systemic vasorelaxation with exercise is attenuated in HFpEF,<sup>31–33</sup> promoting impaired delivery of blood flow to skeletal muscle. Vascular dysfunction in HFpEF may be due in part to endothelial dysfunction, as a recent study demonstrated impaired flow-mediated



**Figure 3** Compared with normal controls (A and B), the slope of the end-systolic pressure–volume relationship (end-systolic elastance; Ees, dotted lines) is increased in heart failure with preserved ejection fraction (HFpEF) (C and D). This leads to exaggerated increases and decreases in blood pressure for the same change in afterload (A and C) or preload (B and D) in HFpEF, accounting for the greater predilection for hypertensive crisis and/or hypotension and azotemia with over-diuresis or overly vigorous vasodilation.



**Figure 4** (A) Combined ventricular–arterial stiffening in heart failure with preserved ejection fraction may lead to dramatic elevations in blood pressure with afterload increase (red arrow). This feeds back to increase LV end-diastolic pressures (arrowhead), by altering the slope or position of the diastolic pressure–volume relation, and/or (B) by prolonging LV pressure decay during isovolumic relaxation (arrowhead).

vasodilation in HFpEF compared with healthy age-matched controls.<sup>33</sup> Symptoms of dyspnoea and fatigue in HF may be related to pathologic ergoreflex activation, which is also related to NO bioavailability.<sup>84</sup> Intriguingly, the extent of flow-mediated vasodilation (a biomarker of endothelial function) is related to the severity of symptoms of effort intolerance during low-level exercise in HFpEF,<sup>33</sup> emphasizing the complex cross-talk between peripheral processes and perception of symptoms in HF.<sup>85</sup> These data provide further rationale for therapies targeting NO in HFpEF.

Vascular dysfunction is not confined to the systemic circulation in HFpEF, as pulmonary hypertension is frequently observed as well.<sup>40</sup> Among elderly patients with normal EF and high pulmonary artery pressure, HFpEF may be the most common aetiology.<sup>86</sup> Pulmonary pressures increase with ageing and are correlated with systemic vascular stiffening—both common risk factors for HFpEF.<sup>87</sup> Pulmonary hypertension in HFpEF appears to be due to both elevated left heart pressures and high pulmonary vascular resistance, which may develop in response to the former.<sup>40</sup> In early-stage HFpEF, pulmonary vasodilation with exercise is preserved, and exertional pulmonary hypertension is passive and secondary primarily to high left heart pressures.<sup>28</sup> Elevated pulmonary artery pressures predict increased mortality in HFpEF<sup>40</sup> and may represent a novel therapeutic target, although unbalanced pulmonary arterial vasodilation in such patients may lead to pathologic elevations in left heart pressures or even frank pulmonary oedema, and further study is required to define the possible role of pulmonary vasodilators in HFpEF.<sup>88</sup>

### Chronotropic incompetence and cardiovascular reserve dysfunction

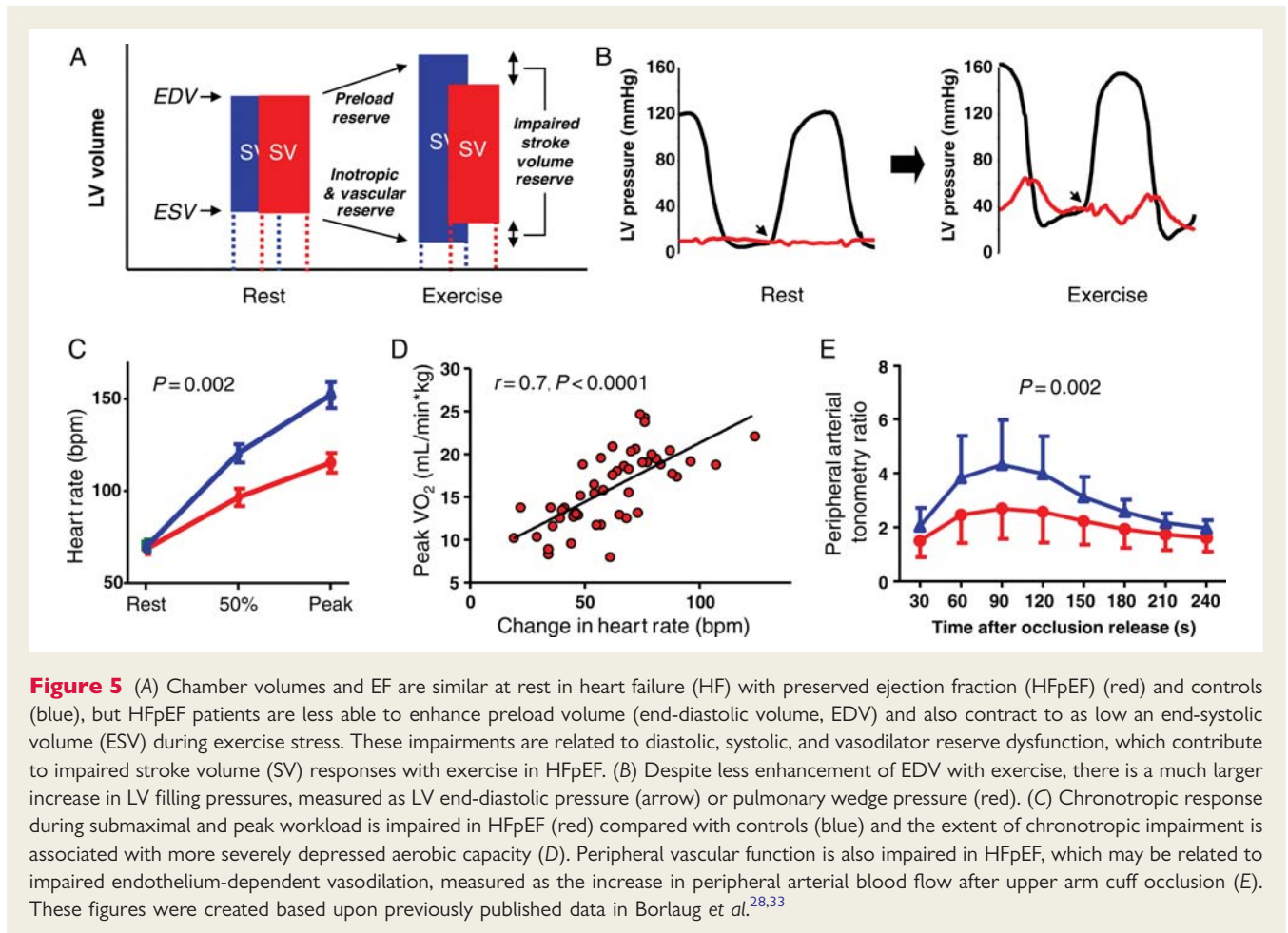
Most patients with HF do not complain of symptoms at rest, but rather with physical exertion. A number of recent studies have highlighted the importance of abnormalities in cardiovascular reserve function with exercise stress in the pathophysiology of HFpEF.<sup>31–35,38</sup> During physical exertion, cardiac output increases

through integrated enhancements in venous return, contractility, heart rate, and peripheral vasodilation.<sup>89</sup> Abnormalities in each of these components of normal exercise reserve function have been identified in HFpEF and all may contribute to pathophysiology in individual patients (Figure 5).

Normal diastolic reserve with exercise allows the ventricle to fill to a larger preload volume, in a shorter amount of time, with no increase in filling pressures.<sup>90</sup> Indeed, the normal aged heart is more reliant upon enhanced preload reserve to compensate for age-related reductions in contractile and chronotropic reserve.<sup>91</sup> Just as diastolic function is impaired in HFpEF, diastolic reserve is also reduced—patients display blunted increases in preload volume with exertion, despite marked elevations in filling pressure.<sup>28,92</sup> This is likely related to increased chamber stiffness<sup>27</sup> and inadequate enhancement of early relaxation,<sup>61,62</sup> although pericardial restraint and enhanced ventricular interaction may also contribute.<sup>93</sup>

Systolic reserve with exercise is also impaired in HFpEF—with blunted increases in EF, contractility, and longitudinal systolic shortening velocities during exercise.<sup>31–35</sup> Exercise stress may ‘unmask’ mild deficits in resting systolic function, and the inability to reduce end-systolic volume, combined with less increase in end-diastolic volume, greatly limits stroke volume responses during exercise. The causes of systolic and diastolic reserve dysfunction in HFpEF remain unclear, but may be related to myocardial ischaemia (epicardial/microvascular coronary disease or vascular rarefaction), impaired  $\beta$ -adrenergic signalling,<sup>94</sup> myocardial energetics,<sup>34,68</sup> or abnormal calcium handling.<sup>95</sup>

Chronotropic reserve is depressed in HFpEF,<sup>31,33,34,38,96</sup> even compared with older, age-matched controls and independent of rate-slowing medication use. Similar to HFrEF,<sup>97</sup> this is likely related to downstream deficits in  $\beta$ -adrenergic stimulation, because the increase in plasma catecholamines with exercise is similar in HFpEF and healthy controls.<sup>31</sup> Autonomic dysfunction may contribute to chronotropic incompetence, as baroreflex sensitivity<sup>31</sup> is reduced and heart rate recovery impaired in HFpEF.<sup>31,96</sup>



Patients with HFpEF display attenuated exercise-mediated reductions in mean vascular resistance and arterial elastance, coupled with abnormalities in endothelial function and dynamic ventricular–arterial coupling.<sup>31–33</sup> Many of these abnormalities are noted with normal ageing and are simply more markedly abnormal in HFpEF, consistent with the notion that HFpEF develops as a progressive and pathologic form of exaggerated hypertensive ageing.<sup>82</sup> Patients with HFpEF are more likely to display a greater number of discrete individual abnormalities in ventricular–vascular reserve, and recent evidence suggests that acquisition of a sufficient number of individual abnormalities in reserve promotes the transition from asymptomatic hypertensive diastolic dysfunction to symptomatic HFpEF.<sup>33</sup> In this way, HFpEF may be conceived as a fundamental disorder of cardiovascular reserve function—diastolic, systolic, chronotropic, and vascular. Future research is required to determine how these abnormalities may be effectively treated.

## Diagnosis

### Diagnostic algorithms

In contrast to HFREF, the diagnosis of HFpEF is cumbersome, especially in patients presenting in an out-patient clinic with

exertional dyspnoea and multiple comorbidities but without obvious physical signs of fluid overload. To avoid a low specificity when diagnosing HFpEF, exertional dyspnoea and a normal LVEF need to be coupled with objective measures of diastolic LV dysfunction, LV hypertrophy, left atrial (LA) enlargement, or plasma levels of natriuretic peptides (NP), as recommended by all hitherto published guidelines for the diagnosis of HFpEF.

Four sets of guidelines for the diagnosis of HFpEF have so far been published.<sup>13,98–100</sup> They all require the simultaneous and obligatory presence of signs and/or symptoms of HF, evidence of normal systolic LV function, and evidence of diastolic LV dysfunction or of surrogate markers of diastolic LV dysfunction such as LV hypertrophy, LA enlargement, atrial fibrillation, or elevated plasma NP levels. The first set of guidelines was provided by the Working Group on Myocardial Function of the European Society of Cardiology.<sup>98</sup> A second set of guidelines was provided by the NHLBI Framingham Heart Study and combined signs and symptoms of HF, normal LVEF (>50%), and invasive evidence of diastolic LV dysfunction.<sup>99</sup> A third set of guidelines was proposed by Yturralde and Gaasch from the Lahey Clinic.<sup>100</sup> They implement their assessment with a scoring system of major and minor criteria and use LV hypertrophy and LA enlargement as surrogate markers of diastolic LV dysfunction. Finally, the last set of guidelines was provided by the Heart Failure and Echocardiography Associations

of the European Society of Cardiology.<sup>13</sup> In accordance to this last set of guidelines, the diagnosis of HFpEF required signs or symptoms of HF, a LVEF >50%, a LVEDVI <97 mL/m<sup>2</sup>, and evidence of diastolic LV dysfunction. LVEDP >16 mmHg, PCW >12 mmHg and/or E/E' >15 provided stand-alone evidence of diastolic LV dysfunction, whereas NP always needed to be associated with an E/E' >8, a mitral flow velocity Doppler signal showing a E/A ratio <0.5 + deceleration time (DT) >280 ms, a pulmonary vein flow velocity signal showing a Ard-Ad >30 ms (Ard: duration of reverse pulmonary vein atrial systole flow; Ad: duration of mitral valve atrial wave flow), a LA size >40 mL/m<sup>2</sup>, or a LV mass >149 g/m<sup>2</sup> (men) or >122 g/m<sup>2</sup> (women).

Validation of these diagnostic guidelines for HFpEF is urgently needed.<sup>101</sup> Valuable validation efforts of the last set of guidelines provided by the Heart Failure and Echocardiography Associations of the European Society of Cardiology have to some extent been addressed, including: (i) the diagnostic value of E/E' against a LV stiffness modulus calculated from multiple LV end-diastolic pressure–volume points observed during balloon caval occlusion;<sup>102</sup> (ii) the diagnostic value of LA size >40 mL/m<sup>2</sup>, LV mass >149 g/m<sup>2</sup> (men) or >122 g/m<sup>2</sup> (women), Ard-Ad >30 ms, and E/A ratio <0.5 + DT >280 ms against E/E';<sup>103</sup> (iii) the diagnostic value of NTproBNP >220 pg/mL against E/E'.<sup>104</sup> In contrast to recent critiques on the validity of E/E' as a measure of LV filling pressures in acutely decompensated HFrEF patients,<sup>105</sup> a direct comparison of E/E' against conductance catheter-derived diastolic LV stiffness moduli yielded a 83% sensitivity, a 92% specificity, and an area under the ROC curve of 0.907 for E/E' >8 as a measure of high-stiffness modulus in HFpEF patients.<sup>102</sup> These findings suggested E/E' >8 may be able to provide stand-alone evidence of diastolic LV dysfunction without further need of serial non-invasive tests in patients presenting with a  $8 < E/E' < 15$ .<sup>106</sup> Early diastolic LV load, which is high in HFrEF but normal in HFpEF, may account for the dissimilar value of E/E' as a measure of LV filling pressures in HFrEF and HFpEF.<sup>107</sup> A direct comparison between the diagnostic values of E/E' and mitral or pulmonary flow velocity-derived indices showed the latter to be unreliable for the diagnosis of diastolic LV dysfunction.<sup>103</sup> In contrast, however, LA size >40 mL/m<sup>2</sup> provided both a high sensitivity and a high specificity to detect E/E' >15. Left ventricular mass >149 g/m<sup>2</sup> (men) or >122 g/m<sup>2</sup> (women) provided a low sensitivity but a high specificity for E/E' >15.<sup>103</sup> Finally, the diagnostic value of NTproBNP >220 pg/mL is currently being evaluated against E/E' in the Aldo-DHF trial.<sup>104</sup> In analogy to LV mass indices, it is expected to have a low sensitivity but a high specificity for the TDI diagnosis of HFpEF.

## Role of exercise testing

Heart failure with reduced EF is characterized by chamber dilation and reduced EF—both readily detectable by echocardiography. In HFpEF, chamber size and EF are normal, and the principal haemodynamic derangement is an elevation in filling pressures.<sup>26</sup> When pressures are high and congestion is present at rest, HFpEF is readily diagnosed based upon history, physical examination, radiography, NP levels, and echocardiography.<sup>13</sup> However, many patients with early-stage HFpEF have significant symptoms of exertional intolerance in the absence of apparent volume overload.

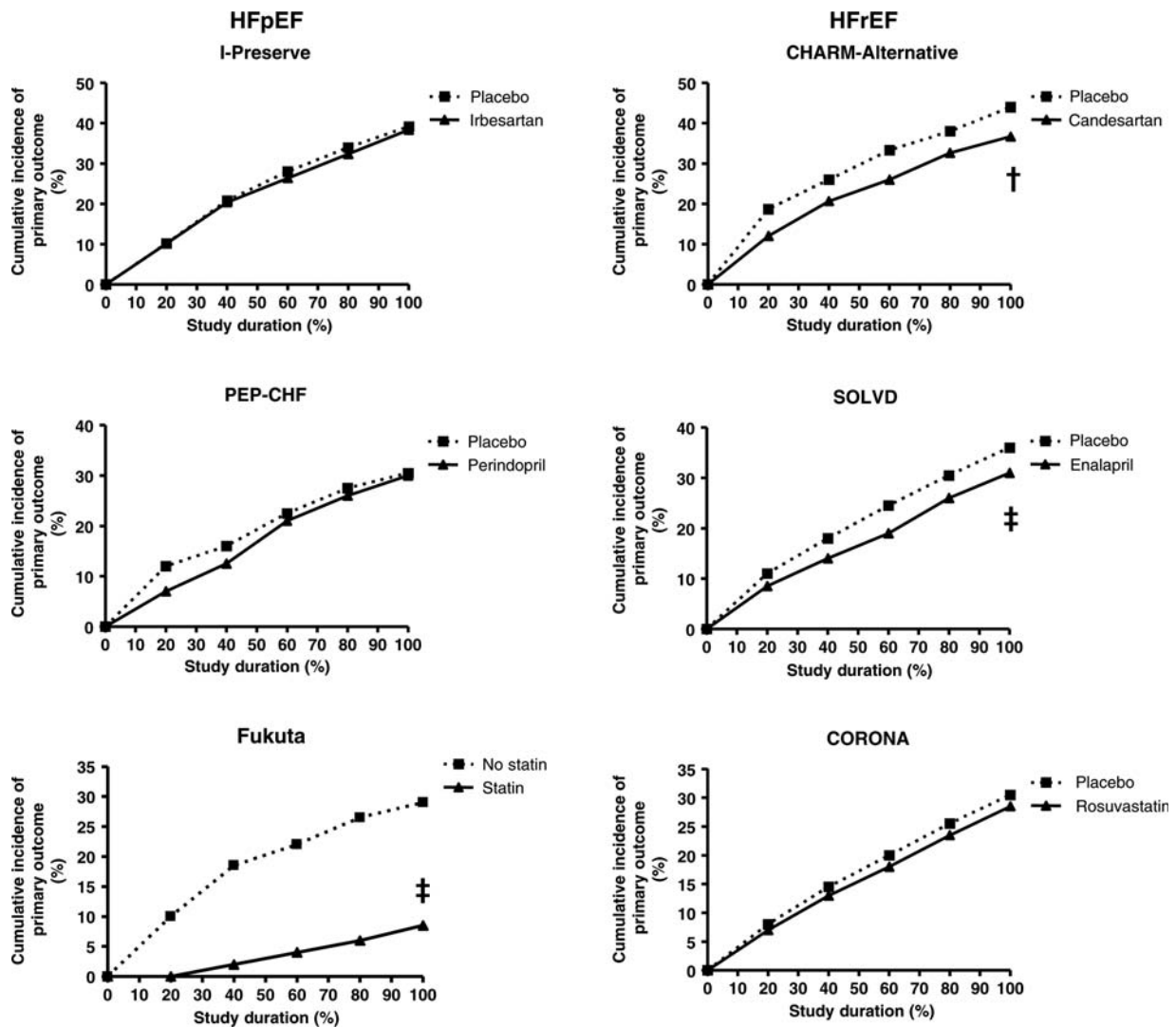
Invasive assessment in some patients may reveal pathologic elevation in filling pressures that had not been previously suspected,<sup>108</sup> and a recent study found that even among patients with normal exam, echocardiography, NP, and normal resting haemodynamics, many patients may still develop pathologic elevations in filling pressures characteristic of HFpEF during the stress of exercise.<sup>28</sup> The diagnosis of HFpEF could only be made using exercise haemodynamic evaluation in such patients, although an abnormal increase in left heart pressures with leg raise (a marker of reduced diastolic reserve) was also a strong predictor of HFpEF. Pulmonary artery pressures track very closely with left heart filling pressures in early-stage HFpEF,<sup>28</sup> suggesting that if the former could be accurately estimated by echocardiography during exercise, this may serve as a useful non-invasive screen among patients with normal EF and exertional dyspnoea.

The E/E' ratio is a cornerstone in the non-invasive evaluation of diastolic function at rest,<sup>13,14</sup> and some groups have begun to apply TDI-based evaluations during exercise, with early studies showing reasonable correlations with invasive measures.<sup>109</sup> However, E/E' may be less robust in the setting of tachycardia, hyperventilation, and fusion of early and late transmitral filling velocities, as the variability in both numerator and denominator will be summed. The role of non-invasive diastolic stress testing in the evaluation of early HFpEF merits further study and validation, but at this time invasive evaluation provides more reliable diagnostic information. In patients who do not meet established criteria for positive diagnosis of HFpEF<sup>13</sup> but in whom there is reasonably strong clinical suspicion, invasive evaluation should be strongly considered, with exercise stress if available and resting measurements are unremarkable.<sup>28</sup>

## Treatment

### Trial data

An extensive overview of all HFpEF trials performed so far was recently published.<sup>22</sup> Diverging efficacy of comparable pharmacological agents in HFrEF and HFpEF was evident for ACEIs, angiotensin receptor blockers (ARB), beta-blockers, and statins (Figure 6). The PEP-CHF study was the first major randomized controlled trial on the use of ACEI in HFpEF patients.<sup>110</sup> It compared perindopril 4 mg daily to placebo in elderly patients (≥70 years old) with a diagnosis of HF, LVEF >40%, minimal impairment of segmental LV wall motion, echocardiographic evidence of LA dilatation or LV hypertrophy, and abnormal LV filling kinetics on mitral flow velocity Doppler. The results of the PEP-CHF study contrasted sharply with earlier reports on the use of ACEI in HFrEF,<sup>111</sup> as it showed no overall difference in mortality and or need for HF hospitalizations. A neutral outcome in HFpEF and a positive outcome in HFrEF were also repeatedly observed for ARBs. The first major trial investigating cardiovascular mortality and HF hospitalizations in HFpEF was the CHARM-preserved trial, which randomized 3023 patients between candesartan and placebo.<sup>11</sup> CHARM-preserved failed to demonstrate a significant effect on cardiovascular death but observed fewer HF hospitalizations in the candesartan-treated patients. I-PRESERVE was so far the largest reported trial for HFpEF as it enrolled 4128 patients and randomly



**Figure 6** Contrasting outcomes of trials using similar compounds in HFpEF and HFrEF. For ARB and ACEI, a neutral outcome is observed in HFpEF but a positive in HFrEF. Conversely, for statins, a positive outcome is observed in HFrEF but a neutral in HFpEF. † $P < 0.0001$ ; ‡ $P < 0.01$ .

assigned them to irbesartan or placebo.<sup>12</sup> Mortality or rates of hospitalizations for cardiovascular causes were again not improved by treatment with an ARB. Outcomes of both CHARM-preserved and I-PRESERVE are at odds with the positive results of the CHARM-Alternative trial,<sup>112</sup> which assigned ACEI-intolerant HFrEF patients to the ARB candesartan or placebo.

Some information on the outcome of chronic use of beta-blockers is available in the OPTIMIZE-HF registry, which contains both HFrEF and HFpEF patients. In the OPTIMIZE-HF registry,<sup>113</sup> discharge use of beta-blockers exerted no effect on 1 year mortality or hospitalization rates of HFpEF patients, but significantly improved both endpoints in HFrEF patients. Finally, the reverse situation with a positive outcome in HFpEF and a neutral outcome in HFrEF has also been observed. A preliminary report suggested statin therapy to be beneficial in HFpEF<sup>114</sup> with lower mortality rates. This positive outcome of statin therapy in HFpEF

patients contrasted with the recently reported neutral outcome of statin therapy in the HFrEF patients of the CORONA trial.<sup>115</sup> A neutral outcome in HFpEF compared with a positive outcome in HFrEF, as occurred with ACEIs, ARBs, and beta-blockers, could be compatible with flawed HFpEF trial design, but a positive outcome in HFpEF compared with a neutral outcome in HFrEF, as occurred with statins, can no longer be attributed to trial conception but supports different signal transduction cascades driving myocardial remodelling in HFpEF and HFrEF.<sup>22</sup>

## Novel therapies

Recent advances in pathophysiologic understanding of HFpEF have suggested roles for novel treatment strategies. Among the most exciting are agents that enhance cellular cGMP signalling.<sup>116</sup> Natriuretic peptides and NO both increase cGMP synthesis, activating cGMP-dependent protein kinases (PKG). Several



key transcription factors and sarcomeric proteins involved in hypertrophy signalling, diastolic relaxation and stiffness, and vasorelaxation are modified favourably by PKG-dependent phosphorylation, suggesting these agents may be beneficial in HFpEF.<sup>57,58,64,116,117</sup>

Phosphodiesterase 5 inhibitors (PDE5I) increase cGMP levels by blocking their catabolism. PDE5I attenuate adrenergic stimulation,<sup>118</sup> reduce ventricular–vascular stiffening,<sup>119</sup> antagonize maladaptive chamber remodelling,<sup>117</sup> improve endothelial function,<sup>120</sup> reduce pulmonary vascular resistance,<sup>121</sup> and may enhance renal responsiveness to NP.<sup>122</sup> The PDE5I sildenafil is currently being tested in the ongoing RELAX trial,<sup>123</sup> which will evaluate the effects of PDE5I on exercise capacity, functional status, and ventricular form and function.

Uncoupling of nitric oxide synthase (NOS) has emerged as an important contributor to pathologic concentric chamber remodelling and diastolic dysfunction in animal models of HF, in addition to promoting endothelial dysfunction.<sup>67,124</sup> Nitric oxide synthase uncoupling is due in part to oxidative depletion of its cofactor, tetrahydrobiopterin (BH4). Pre-clinical studies have shown that administration of BH4 in animal models reduces pressure-overload hypertrophy, fibrosis, NOS uncoupling, and oxidative stress, while improving systolic and diastolic function.<sup>67,124</sup> Enhancement of cGMP function with NP<sup>125</sup> or nitroglycerin<sup>126</sup> also may mitigate pathologic increases in LV filling pressures during exercise.

Aldosterone plays an important role in the pathogenesis of vascular stiffening and endothelial dysfunction.<sup>127</sup> A preliminary open label, non-placebo controlled study documented improvements in exercise capacity and the E/E' ratio in HFpEF patients treated with spironolactone,<sup>128</sup> and aldosterone antagonists are currently being actively investigated for HFpEF in the USA and Europe. Rho-kinase inhibitors such as fasudil and Y-27632 have vasorelaxation properties and have demonstrated the ability to blunt progression of hypertrophic remodelling in animal models of HF.<sup>129</sup> Intriguingly, 3-hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) also inhibit rho-kinase signalling, and a case series reported that statin use was associated with the improved outcome in HFpEF, whereas other conventional HF therapies such as ACEI or BB were not.<sup>114</sup>

Negative chronotropic medications have traditionally been recommended in HFpEF to increase the diastolic filling period, but slowing the rate in the absence of tachycardia tends to only prolong diastasis, where transmitral flow is minimal or absent.<sup>130</sup> More importantly, recent studies have repeatedly shown that chronotropic incompetence is highly prevalent and associated with exercise disability in HFpEF.<sup>31,33,38,96</sup> Indeed, in the setting of reduced systolic and diastolic reserve, chronotropic reserve may represent the only mechanism to augment cardiac output during exercise, although there is concern that inadequate ability to enhance relaxation with tachycardia may limit stroke volume responses.<sup>27,61,62</sup> These questions require further study. The effect of rate adaptive atrial pacing in HFpEF was being evaluated in the RESET trial,<sup>131</sup> but enrolment was below goal and the study has since been terminated by the sponsor. In contrast, another trial is testing the efficacy of the If channel blocker ivabradine in HFpEF,<sup>132</sup> an agent that slows heart rate. The role of beta-

blockade remains unresolved. The SENIORS trial suggested benefit in HF regardless of EF,<sup>133</sup> but there was not a large number of patients with truly 'normal' EF (>50–55%). Autonomic dysfunction is prevalent in HFpEF,<sup>31</sup> and enhancement in parasympathetic tone via carotid sinus stimulation has been proposed as a treatment,<sup>134</sup> but data are not available. Dyssynchrony is common in HFpEF,<sup>135</sup> but in contrast to HFrEF, electrical conduction delay is not,<sup>136,137</sup> and it remains unknown whether resynchronization therapy may play a role in HFpEF.

The macromolecule titin is the principal determinant of passive cardiomyocyte tension.<sup>138</sup> As discussed, the stiffness of titin may be modified based upon the expression of alternative isoforms,<sup>55,56,139</sup> but recent studies have produced great enthusiasm that acute modification of titin PKG phosphorylation sites may dynamically modulate titin stiffness.<sup>57–59</sup> Chamber stiffness is also altered by the extracellular matrix—including both quantitative and qualitative changes in collagen. Alagebrium chloride (ALT-711) is a novel compound that breaks glucose cross-links and improves ventricular and arterial compliance in animals<sup>140</sup> and reduces blood pressure and vascular stiffness in human hypertension.<sup>141</sup> A small open-label study found that ALT-711 was associated with reduced LV mass and improved diastolic filling.<sup>142</sup> Transforming growth factor-beta (TGF- $\beta$ ) is a pro-fibrotic cytokine, and infusion of TGF- $\beta$  neutralizing antibody in a rat model of pressure overload was found to reduce fibrosis and development of diastolic dysfunction.<sup>143</sup> New advances in cardiac MRI now allow visualization and quantification of myocardial fibrosis associated with diastolic dysfunction,<sup>144</sup> providing a potential outcome measure in therapeutic trials targeting fibrosis.

Systolic and diastolic reserve dysfunction in HFpEF may be related to abnormalities in cardiomyocyte energy availability or utilization.<sup>31,34,92</sup> Smith *et al.*<sup>68</sup> demonstrated abnormal ATP phosphocreatine shuttle kinetics in HFpEF, and similar results were recently reported by Phan *et al.*<sup>34</sup> Novel therapies targeting energy substrate utilization are currently under active investigation.<sup>145</sup> The anti-anginal drug ranolazine blocks inward sodium current, thereby reducing intracellular calcium, and it has also been suggested as a potential treatment for HFpEF,<sup>146</sup> although human HFpEF data are currently unavailable.

## Conclusions

Heart failure with preserved ejection fraction is a major and growing public health problem in Europe and the USA, currently representing half of all patients with HF. Despite improvements in disease understanding, there are no treatments of proven benefit. Advances in diagnostic algorithms, imaging, and invasive assessment will allow for more accurate and earlier diagnosis, so that therapies may be implemented earlier in disease progression, where potential for benefit may be higher. While important advances have been made in our understanding of the haemodynamic and cellular pathophysiology of diastolic and non-diastolic mechanisms of disease, further research is urgently required to determine how to better target these abnormalities to reduce the substantial burden of morbidity and mortality in this form of HF, which is reaching epidemic proportions.

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