

# How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)

**Burkert Pieske<sup>1,2,3,4\*</sup>, Carsten Tschöpe<sup>1,2,5</sup>, Rudolf A. de Boer<sup>6</sup>, Alan G. Fraser<sup>7</sup>, Stefan D. Anker<sup>1,2,5,8</sup>, Erwan Donal<sup>9</sup>, Frank Edelmann<sup>1,2</sup>, Michael Fu<sup>10</sup>, Marco Guazzi<sup>11,12</sup>, Carolyn S.P. Lam<sup>13,14</sup>, Patrizio Lancellotti<sup>15</sup>, Vojtech Melenovsky<sup>16</sup>, Daniel A. Morris<sup>1</sup>, Eike Nagel<sup>17,18</sup>, Elisabeth Pieske-Kraigher<sup>1</sup>, Piotr Ponikowski<sup>19</sup>, Scott D. Solomon<sup>20</sup>, Ramachandran S. Vasan<sup>21</sup>, Frans H. Rutten<sup>22</sup>, Adriaan A. Voors<sup>6</sup>, Frank Ruschitzka<sup>23</sup>, Walter J. Paulus<sup>24</sup>, Petar Seferovic<sup>25</sup> and Gerasimos Filippatos<sup>26,27</sup>**

<sup>1</sup>Department of Internal Medicine and Cardiology, Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum; <sup>2</sup>German Center for Cardiovascular Research (DZHK), Berlin, Partner Site, Germany; <sup>3</sup>Department of Internal Medicine and Cardiology, German Heart Institute, Berlin, Germany; <sup>4</sup>Berlin Institute of Health (BIH), Germany; <sup>5</sup>Berlin Institute of Health (BIH) Center for Regenerative Therapies (BCRT), Charite, Berlin, Germany; <sup>6</sup>University Medical Centre Groningen, University of Groningen, Department of Cardiology, Groningen, the Netherlands; <sup>7</sup>School of Medicine, Cardiff University, Cardiff, UK; <sup>8</sup>Department of Cardiology and Pneumology, University Medicine Göttingen (UMG), Germany; <sup>9</sup>Cardiology and CIC, IT1414, CHU de Rennes LTSI, Université Rennes-1, INSERM 1099, Rennes, France; <sup>10</sup>Section of Cardiology, Department of Medicine, Sahlgrenska University Hospital/Ostra, Göteborg, Sweden; <sup>11</sup>Department of Biomedical Sciences for Health, University of Milan, IRCCS, Milan, Italy; <sup>12</sup>Department of Cardiology, IRCCS Policlinico, San Donato Milanese, Milan, Italy; <sup>13</sup>National Heart Centre, Singapore & Duke-National University of Singapore; <sup>14</sup>University Medical Centre Groningen, The Netherlands; <sup>15</sup>Department of Cardiology, Heart Valve Clinic, University of Liège Hospital, GIGA Cardiovascular Sciences, CHU Sart Tilman, Liège, Belgium; <sup>16</sup>Institute for Clinical and Experimental Medicine - IKEM, Prague, Czech Republic; <sup>17</sup>Institute for Experimental and Translational Cardiovascular Imaging, University Hospital Frankfurt; <sup>18</sup>German Centre for Cardiovascular Research (DZHK), Partner Site Frankfurt, Germany; <sup>19</sup>Medical University, Clinical Military Hospital, Wrocław, Poland; <sup>20</sup>Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; <sup>21</sup>Section of Preventive Medicine and Epidemiology and Cardiovascular Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA; <sup>22</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; <sup>23</sup>University Heart Centre, University Hospital Zurich, Switzerland; <sup>24</sup>Department of Physiology and Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, The Netherlands; <sup>25</sup>University of Belgrade School of Medicine, Belgrade University Medical Center, Serbia; <sup>26</sup>Department of Cardiology, National and Kapodistrian University of Athens Medical School; University Hospital "Attikon", Athens, Greece; and <sup>27</sup>University of Cyprus, School of Medicine, Nicosia, Cyprus

Received 16 May 2018; revised 30 October 2018; editorial decision 16 August 2019; accepted 26 August 2019

Making a firm diagnosis of chronic heart failure with preserved ejection fraction (HFpEF) remains a challenge. We recommend a new step-wise diagnostic process, the 'HFA–PEFF diagnostic algorithm'. Step 1 (*P*=Pre-test assessment) is typically performed in the ambulatory setting and includes assessment for HF symptoms and signs, typical clinical demographics (obesity, hypertension, diabetes mellitus, elderly, atrial fibrillation), and diagnostic laboratory tests, electrocardiogram, and echocardiography. In the absence of overt non-cardiac causes of breathlessness, HFpEF can be suspected if there is a normal left ventricular ejection fraction, no significant heart valve disease or cardiac ischaemia, and at least one typical risk factor. Elevated natriuretic peptides support, but normal levels do not exclude a diagnosis of HFpEF. The second step (*E*: Echocardiography and Natriuretic Peptide Score) requires comprehensive echocardiography and is typically performed by a cardiologist. Measures include mitral annular early diastolic velocity (*e'*), left ventricular (LV) filling pressure estimated using *E/e'*, left atrial volume index, LV mass index, LV relative wall thickness, tricuspid regurgitation velocity, LV global longitudinal systolic

\* Corresponding author. Tel: +49 30 450 553702, Fax: +49 30 450 7 553702, Email: [burkert.pieske@charite.de](mailto:burkert.pieske@charite.de)

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author(s) 2019. For permissions, please email: [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

strain, and serum natriuretic peptide levels. Major (2 points) and Minor (1 point) criteria were defined from these measures. A score  $\geq 5$  points implies definite HFpEF;  $\leq 1$  point makes HFpEF unlikely. An intermediate score (2–4 points) implies diagnostic uncertainty, in which case Step 3 ( $F_1$ : Functional testing) is recommended with echocardiographic or invasive haemodynamic exercise stress tests. Step 4 ( $F_2$ : Final aetiology) is recommended to establish a possible specific cause of HFpEF or alternative explanations. Further research is needed for a better classification of HFpEF.

## Keywords

Heart failure • HFpEF • diagnosis • echocardiography • biomarkers • natriuretic peptides • exercise echocardiography

## Introduction

In the general population aged  $\geq 60$  years, 4.9% were identified to have heart failure with preserved ejection fraction (HFpEF),<sup>1</sup> implying several millions of affected individuals in Europe. This number is expected to increase further as people live longer and obesity and diabetes become more common.<sup>1–3</sup> Heart failure with preserved ejection fraction already accounts for more than half of all heart failure (HF) hospital admissions.<sup>1</sup> Providing effective management is a major unmet clinical need that will depend on a clear diagnosis.

The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) published a consensus statement in 2007 on 'How to diagnose diastolic heart failure'.<sup>4</sup> Since then, terminology has evolved through HF with normal ejection fraction (HFneEF) to the current definition as 'HF with preserved ejection fraction'.<sup>4</sup>

Additional diagnostic criteria for HFpEF have been published, including one scoring system,<sup>5</sup> but they differ in echocardiographic cut-off values, the role of comorbidities, the inclusion of biomarkers, the role of invasive haemodynamic assessment, and the role of exercise stress testing.<sup>3,4,6–8</sup> Understanding of the pathophysiology of HFpEF has advanced,<sup>9–13</sup> diagnostic options have evolved,<sup>14–17</sup> and this novel information needs to be integrated into a new comprehensive diagnostic algorithm for suspected HFpEF.

A writing committee initiated by the HFA of the ESC has therefore produced an updated consensus recommendation—the HFA–PEFF diagnostic algorithm (Figure 1). Its key elements are (i) the concept that identification of HFpEF involves all levels of care, including general practitioners, internists, general cardiologists, HF specialists, and invasive cardiologists; (ii) a stepwise diagnostic approach from initial clinical assessment to more specialized tests will therefore be useful; (iii) the diagnosis is not always straightforward, so the integration of distinct parameters from complementary diagnostic domains into a new diagnostic score is recommended; (iv) for the subset of patients with an inconclusive score, definitive diagnosis (or exclusion) will require invasive haemodynamics and/or non-invasive or invasive exercise stress tests; and (v) underlying pathophysiological alterations (such as chronotropic incompetence, reduced LV compliance) and specific aetiologies (such as amyloidosis<sup>18</sup>) have to be considered. A precise diagnosis is increasingly important since new targeted therapies are becoming available for defined subsets of HFpEF patients.

## Why new diagnostic recommendations for heart failure with preserved ejection fraction?

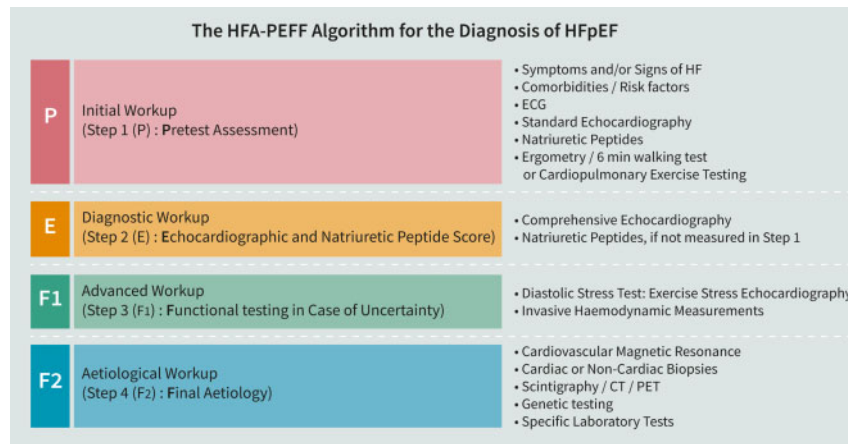
The key criteria in the previous HFA recommendations were: (i) symptoms and/or signs of HF, (ii) normal or only mildly abnormal LV systolic function, and (iii) LV diastolic dysfunction.<sup>4</sup> Diagnostic parameters were invasive measurements, echocardiographic indices of LV diastolic function and filling pressures, LV hypertrophy (LVH), left atrial (LA) enlargement, serum natriuretic peptides (NP), and atrial fibrillation (AF).<sup>4</sup> Over time, both advantages and disadvantages of this approach have been reported.

Cut-offs for key non-invasive parameters are often based on limited data, and may fall in a non-diagnostic intermediate range. The non-invasive diagnosis or exclusion of HFpEF will not depend on a single parameter above or below a certain cut-off, but on a combination of parameters derived from clinical, laboratory, and imaging tests that together will give a probability for the diagnosis. A recent example of such an approach was a composite HFpEF diagnostic score, derived retrospectively from clinical characteristics (age  $>60$  years, obesity, atrial fibrillation, treatment with  $\geq 2$  antihypertensive drugs) and echocardiographic measurements [ $E/e'$   $>9$ , pulmonary artery systolic pressure (PASP)  $>35$  mmHg].<sup>5</sup>

## Echocardiographic criteria for diagnosing heart failure with preserved ejection fraction

Left ventricular ejection fraction (LVEF) estimates global function but does not indicate LV volume or stroke volume. Despite a preserved LVEF, patients with HFpEF have impaired LV long-axis systolic function, which can be measured using mitral annular systolic excursion or systolic velocities or LV global longitudinal strain (GLS).<sup>19</sup> As well as global diastolic dysfunction, they have long-axis diastolic dysfunction which can be measured from the velocity of long-axis lengthening of the LV in early diastole (from mitral annular velocity,  $e'$ ). These were not considered in the previous HFA recommendations.<sup>4</sup>

A mean  $E/e'$  index  $\geq 15$  at rest has good diagnostic value for identifying a high mean pulmonary capillary wedge pressure (mPCWP), supporting the likelihood of HFpEF,<sup>20,21</sup> but an  $E/e'$  ratio within the intermediate range (9–14) is less sensitive.<sup>22</sup> The  $E/e'$  ratio has limitations that are relevant in routine clinical practice<sup>23–29</sup> and its use as a



**Figure 1** HFA-PEFF diagnostic algorithm. Overview of the diagnostic heart failure with preserved ejection fraction steps 1–4 (P–F). CT, computed tomography; PET, positron emission tomography.

single diagnostic index above all other non-invasive measures of filling pressures (such as retrograde pulmonary venous flow) cannot be recommended. In consequence, HFpEF cannot be diagnosed from a single echocardiographic measure, and inclusion of recently validated functional and structural parameters into a diagnostic score may better define this heterogeneous disorder.

### Usefulness of natriuretic peptides

In general, NP levels are higher in patients presenting with acute shortness of breath for cardiac reason or in acute HF, than in patients who have chronic HF.<sup>30,31</sup> Of note, our recommendations target stable symptomatic HFpEF, and natriuretic peptide levels can be normal in these patients even with invasively confirmed HFpEF. In consequence, normal NP levels do not exclude HFpEF, especially in the presence of obesity.<sup>32,33</sup> Interpretation depends also on whether the patient is in sinus rhythm (SR) or has AF, which itself is associated with increased NP levels even in the absence of HF.<sup>34,35</sup>

Besides obesity, sex, age, and renal function affect NP levels,<sup>36,37</sup> but using stratified cut-points only marginally improves diagnostic accuracy (net reclassification index 3%),<sup>38</sup> at the expense of less everyday utility. The variability of repeated measurements in individual patients is up to 100%, so a rise or fall of  $\leq 100\%$  may not necessarily indicate recovery or progression of disease.<sup>39,40</sup>

### Diagnostic algorithms for heart failure with preserved ejection fraction

The concept of a diagnostic algorithm that incorporates imaging and biomarkers (NPs) was recommended by the HFA in 2007,<sup>4</sup> and adapted by others.<sup>41</sup> It allowed parallel diagnostic pathways starting from haemodynamic measurements, echocardiography, or NPs,<sup>4</sup> that could yield different results for the same patients. In addition, the proportion of non-classifiable patients was substantial. Thus, our revised algorithm (see below) proposes a novel stepwise diagnostic approach that has only one entry point, and all patients will be classifiable.

## Defining aetiology and pathophysiology

Heart failure with preserved ejection fraction typically evolves from a combination of risk factors and comorbidities, including advanced age, female sex, obesity, systemic arterial hypertension, diabetes mellitus, renal dysfunction, anaemia, iron deficiency, sleep disorders, and chronic obstructive pulmonary disease.<sup>1,2,11,42–44</sup> Heart failure with preserved ejection fraction ‘masqueraders’ such as heart valve disease, arrhythmias, and pericardial constriction need to be excluded. Similarly, a patient with a normal LVEF and HF-like symptoms caused by significant coronary artery disease (CAD) is also not considered to have HFpEF.

Similar to current practice for heart failure with reduced ejection fraction (HFrEF), we recommend applying the descriptive term HFpEF for both the classical form with typical risk factors and comorbidities, and for rarer cases with a specific aetiology, provided that the key diagnostic criteria are met. Specific aetiologies that may be treatable include inherited or acquired infiltrative, restrictive, inflammatory, or genetic cardiomyopathies<sup>45–48</sup> (Table 2). They should always be considered once a diagnosis of HFpEF has been made (Table 2, Supplementary material online, S2–S4). It has been suggested that patients with HFrEF share a common mechanism that responds to common treatment (inhibition of the renin-angiotensin system)<sup>3</sup> but there are other treatments for subsets of patients with HFrEF that are specific (such as treating ischaemia when there is hibernating myocardium, using targeted antiviral therapy or immune modulation in inflammatory HFrEF, and corticosteroid therapy in sarcoidosis-related HFrEF); in that respect, our proposed use of the generic term HFpEF is similar and should include specific myocardial aetiologies.

Basic mechanisms affecting the myocardium in HFpEF include myocyte hypertrophy, systolic and diastolic dysfunction, energetic abnormalities, interstitial fibrosis, inflammation, increased oxidative stress, endothelial dysfunction, and impaired density and autoregulation of the microcirculation.<sup>9,10,12,45–48,154,155</sup> Cardiovascular pathophysiological processes include increased systemic vascular

resistance, increased conduit arterial stiffness, abnormal ventricular-arterial coupling, reduced LV long-axis systolic function, slowed early diastolic relaxation, reduced LV compliance with increased end-diastolic stiffness, reduced LA reservoir and contractile function, impaired right ventricular (RV) function, and chronotropic incompetence.<sup>52,156–164</sup> Patients often have reduced reserve of stroke volume, heart rate, and cardiac output (CO), and the increase in CO relative to oxygen consumption is blunted.<sup>165</sup> Heart failure with preserved ejection fraction patients typically have high LV filling pressures, whether at rest and/or on exercise, and they may develop fluid retention and an expanded plasma volume.<sup>28,159,164,166,167</sup> All these mechanisms might be targets for treatment.

In a meta-analysis, exercise capacity in HFpEF was related to chronotropic incompetence, high mPCWP, blunted augmentation of arteriovenous oxygen-content difference (implying inadequate perfusion of exercising skeletal muscles), reduced stroke volume reserve, and pulmonary hypertension.<sup>168</sup> Changes in pulmonary artery pressure (PAP) on exercise are determined by the interplay between CO, PA compliance, pulmonary vascular resistance, and mPCWP. The increase in PAP is flow-dependent so it is best reported in relation to the increase in CO; the upper limit of normal is +3 mmHg/L/min.<sup>169</sup> There are haemodynamic differences between patients with pre- and post-capillary pulmonary hypertension.<sup>164</sup>

We recommend that the pathophysiological phenotype(s) prevailing in an individual HFpEF patient are determined, as that may allow the selection of specific therapies (see diagnostic Step 4 below).

## The new Heart Failure Association diagnostic recommendations

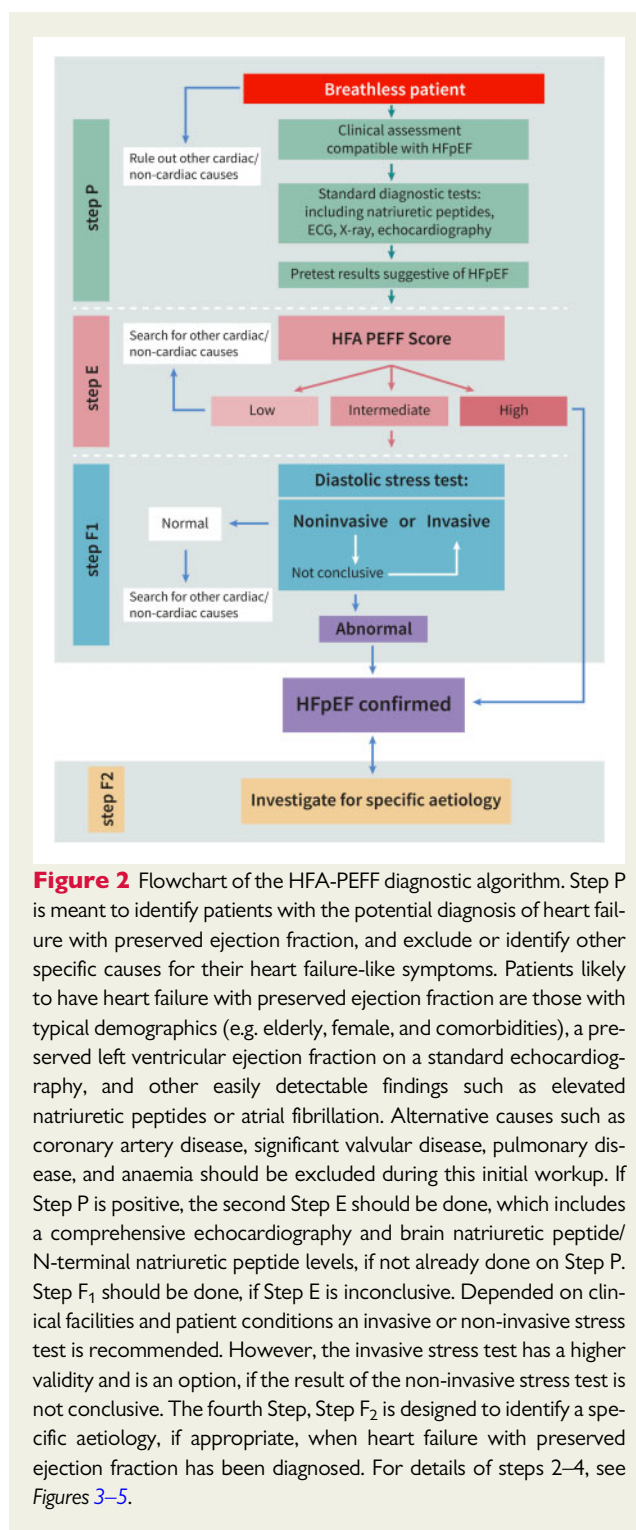
The flowchart (Figure 2) provides an overview of the new diagnostic algorithm.

### Step 1(P): Pre-test assessment

Step 1(P) should be performed in any patient who presents with symptoms and/or signs compatible with a diagnosis of HF. It requires a detailed clinical and demographic history; an electrocardiogram (ECG); blood tests; standard echocardiography to exclude other causes such as HFrEF or heart valve disease; and investigations for ischaemia, arrhythmias, anaemia, or pulmonary disease (Figure 2). NP levels can be obtained if the assay is available; elevated levels suggest heart disease but normal levels do not exclude HFpEF. Step 1(P) mirrors the 2016 ESC HF guidelines concerning initial HF diagnostic workup.<sup>3</sup>

### Symptoms and signs

Breathlessness on exertion (New York Heart Association Class II or III) is highly sensitive for a diagnosis of HF but only moderately specific (about 50%) for a cardiac cause.<sup>170</sup> Orthopnoea is quite specific but relatively insensitive. Patients with HFpEF often report reduced exercise capacity and fatigue, out of proportion to cardiac abnormalities at rest. In elderly, overweight and deconditioned persons, poor exercise capacity, dyspnoea on exertion, and peripheral oedema may also have a non-cardiac origin.



**Figure 2** Flowchart of the HFA-PEFF diagnostic algorithm. Step P is meant to identify patients with the potential diagnosis of heart failure with preserved ejection fraction, and exclude or identify other specific causes for their heart failure-like symptoms. Patients likely to have heart failure with preserved ejection fraction are those with typical demographics (e.g. elderly, female, and comorbidities), a preserved left ventricular ejection fraction on a standard echocardiography, and other easily detectable findings such as elevated natriuretic peptides or atrial fibrillation. Alternative causes such as coronary artery disease, significant valvular disease, pulmonary disease, and anaemia should be excluded during this initial workup. If Step P is positive, the second Step E should be done, which includes a comprehensive echocardiography and brain natriuretic peptide/N-terminal natriuretic peptide levels, if not already done on Step P. Step F<sub>1</sub> should be done, if Step E is inconclusive. Depending on clinical facilities and patient conditions an invasive or non-invasive stress test is recommended. However, the invasive stress test has a higher validity and is an option, if the result of the non-invasive stress test is not conclusive. The fourth Step, Step F<sub>2</sub> is designed to identify a specific aetiology, if appropriate, when heart failure with preserved ejection fraction has been diagnosed. For details of steps 2–4, see Figures 3–5.

### Electrocardiographic abnormalities

Patients may have electrocardiographic features of LVH (such as a Sokolov-Lyon Index  $\geq 3.5$  mV; abnormal repolarisation) and/or LA enlargement, but there are no pathognomonic signs and the diagnostic value of an ECG to identify HFpEF is poor.<sup>5</sup> The most important indication is to detect atrial fibrillation (AF), which is highly predictive of underlying HFpEF.<sup>5,148</sup>

### Laboratory tests

Several tests are recommended, including: sodium, potassium, urea, and creatinine (with an estimated glomerular filtration rate); liver function tests; HbA1c (metabolic syndrome and type 2 diabetes are common comorbidities); thyroid stimulating hormone; and full blood count, ferritin, transferrin saturation, and for anaemia. Anaemia associated with HFpEF aggravates symptoms and exercise intolerance.<sup>171,172</sup>

### Natriuretic peptides

Multiple studies in primary care have shown that serum levels <125 pg/mL (or ng/L) for N-terminal pro-brain natriuretic peptide (NT-proBNP) or <35 pg/mL for BNP, have high negative predictive values (NPV; 95–99%) for excluding any heart failure.<sup>39,40,121,173–177</sup>

The main trigger for release of NPs is high LV end-diastolic wall stress, which is inversely proportional to wall thickness. It is therefore understandable that the excellent NPV of NPs is true particularly for HFrEF with a dilated LV, but not necessarily for HFpEF where LVH tends to normalize wall stress. In consequence, it has become clear that up to 20% of patients with invasively proven HFpEF have NPs below these diagnostic thresholds,<sup>28,178–180</sup> which represents a limitation to the use of NPs. Therefore, it is important to understand that with our SCORE approach HFpEF can still be diagnosed even, if NP cut-offs (stratified by SR vs. AF) are below the given thresholds.<sup>28,178–180</sup>

### Echocardiography

Standard echocardiography should be performed in every breathless patient in whom there is clinical suspicion of HF, unless all the factors listed in *Table 1* are absent or negative. Echocardiography may exclude alternative causes of dyspnoea such as HFrEF, valve disease, primary pulmonary hypertension, or pericardial effusion.<sup>181,182</sup>

Left ventricular ejection fraction should be measured, not estimated, ideally from biplane or three-dimensional images. Only small variations in normal ranges for EF by age, gender, and ethnic group have been reported, so it is recommended that a single cut-point of  $\geq 50\%$  is applied to define a 'preserved' EF. Left ventricular diameters and volumes should also be recorded. A diagnosis of HFpEF is suggested if there is a non-dilated LV with a normal EF, concentric remodelling or LVH, and left atrial enlargement. Echocardiographic findings at rest compatible with this HFpEF phenotype are often found in asymptomatic patients, who are at risk of progressing to overt HFpEF.<sup>183,184</sup> Of note, the presence of structural alterations on echocardiography supports, but its absence does not exclude HFpEF. A more detailed or advanced echocardiographic study (see Step 2(E); [Supplementary material online, S1](#)) is not necessary at this step, but if it can be performed then only one examination will be needed.

### Exercise tests

Coexisting epicardial stenotic coronary artery disease in patients with HFpEF impacts on mortality and should be detected and treated.<sup>133</sup> Coronary microvascular dysfunction is part of the HFpEF pathophysiology<sup>134</sup> so non-invasive stress testing can give false-positive results.<sup>134,186</sup> Nonetheless, a bicycle or treadmill exercise test, or tests with higher sensitivity to detect ischaemia such as dobutamine stress echocardiography, cardiac magnetic resonance

**Table 1 Risk factors and findings consistent with heart failure with preserved ejection fraction in a symptomatic patient**

Early (age $\geq 70$ in men or $\geq$ in women)
Overweight/obesity
Metabolic syndrome/diabetes mellitus
Physical inactivity/deconditioning
Arterial hypertension
Atrial fibrillation
ECG abnormalities (beyond atrial fibrillation)
Elevated natriuretic peptide levels (if available, BNP $\geq 35$ pg/mL or NT-proBNP $\geq 125$ pg/mL)

(CMR) imaging, or myocardial scintigraphy, or an anatomical approach using coronary computed tomography (CT) angiography or invasive angiography, should be considered if CAD is suspected.<sup>187</sup>

A stress test provides information about exercise capacity, the blood pressure response to exercise (which may be hypertensive), and the heart rate response. Chronotropic incompetence is present in 33–77% of HFpEF patients,<sup>188,189</sup> and defined as the failure to reach 70–80%<sup>188–190</sup> of the predicted maximal heart rate. Reduced heart rate recovery after exercise has prognostic value.<sup>191–193</sup> Reduced exercise capacity can be defined as a peak workload  $\leq 75\%$  of the value predicted for age. In elderly patients with suspected HFpEF a 6-minute walk test (6MWT) distance  $\leq 300$  m can be considered abnormal<sup>193</sup> but 6MWT performance is affected by non-cardiac as well as cardiopulmonary conditions.<sup>193,194</sup>

In selected cases, advanced cardiopulmonary exercise testing (CPET) with spiro-ergometry may be performed. Reduced exercise capacity is defined as a peak oxygen consumption ( $VO_2$  max)  $\leq 20$  mL/kg/min, and ventilatory inefficiency as a  $VE/VCO_2$  slope  $\geq 30$ .<sup>166,195</sup> Cardiopulmonary exercise testing provides objective evidence of exercise capacity and may differentiate between cardiac and non-cardiac causes (pulmonary, peripheral) for dyspnoea,<sup>157,166,196–200</sup> but its value to distinguish between HFpEF and non-cardiac causes may be limited.<sup>166</sup> Cardiopulmonary exercise testing is not a typical element in the initial HFpEF workup (see below).

If HFpEF is suspected after Step 1(P), a more specific assessment may confirm or exclude the diagnosis (Step 2(E)).

## Step 2(E): Echocardiographic and natriuretic peptide heart failure with preserved ejection fraction diagnostic score

There is no single non-invasive diagnostic criterion for HFpEF so we recommend a combination of echocardiographic measurements of cardiac structure and function, and NP levels. Some may already be available from Step 1(P).

Many of these measurements are continuously distributed within a population, from normal to possibly abnormal and to overtly abnormal values. Diagnostic cut-points may vary according to age, gender, body weight, renal function, and the presence of atrial fibrillation.

**Table 2** Potential specific aetiologies underlying heart failure with preserved ejection fraction-like syndromes in Step 4 (F<sub>2</sub>)

Abnormalities of the myocardium		
Ischaemic		Myocardial post-infarction/scar <sup>49</sup> Myocardial stunning <sup>50</sup> Epicardial coronary artery disease <sup>51</sup> Microvascular and endothelial dysfunction <sup>52,53–55</sup>
Toxic	Recreational substance abuse	Such as alcohol, <sup>56</sup> cocaine, <sup>57</sup> and anabolic steroids <sup>58</sup>
	Heavy metals	Such as iron, <sup>59</sup> lead, <sup>60</sup> cadmium, <sup>60</sup> cobalt, <sup>61</sup> copper (M. Wilson) <sup>62</sup>
	Medications	Such as chloroquine, <sup>63</sup> ergotamine, <sup>64</sup> cytostatic drugs (e.g. anthracyclines), <sup>64</sup> immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab) <sup>64</sup>
Immune and inflammatory	Radiation	Mean cardiac radiation doses > 3 Gy <sup>65,66</sup>
	Related to infection	Such as cardiotropic viruses, <sup>67,68</sup> HIV, <sup>69–71</sup> hepatitis, <sup>72</sup> helminths, <sup>73</sup> parasites (e.g. Chagas' disease <sup>74</sup> )
	Not related to infection	Lymphocytic myocarditis, <sup>75–79</sup> autoimmune diseases (e.g. rheumatoid arthritis, <sup>80</sup> connective tissue disorders like scleroderma, <sup>81</sup> M. Raynaud, <sup>55</sup> systemic lupus erythematosus, <sup>82</sup> dermatomyositis, <sup>83</sup> and hypersensitivity and eosinophilic myocarditis <sup>73,84–87</sup>
Infiltrative	Related to malignancy	Direct infiltrations and metastases <sup>88–90</sup>
	Not related to malignancy	Amyloidosis, <sup>19,91</sup> sarcoidosis, <sup>92,93</sup> primarily and secondary haemochromatosis, <sup>94–96</sup> storage diseases <sup>97</sup> (e.g. Fabry disease, <sup>98,99</sup> Danon disease, <sup>100–102</sup> Pompe disease, <sup>99,102</sup> PRKAG2 deficiency, <sup>99</sup> Gaucher's disease <sup>99,103,104,105,106</sup> )
Metabolic	Hormonal	Such as thyroid diseases, <sup>107,108</sup> parathyroid diseases, <sup>109</sup> acromegaly, <sup>110</sup> GH deficiency, <sup>111</sup> Cushing disease, <sup>112</sup> Conn's disease, <sup>113</sup> Addison disease, <sup>114</sup> pheochromocytoma, <sup>115</sup> pathologies related to pregnancy and peripartum <sup>116,117</sup>
	Nutritional	Such as deficiencies in thiamine, <sup>118</sup> L-carnitine, <sup>119</sup> selenium, <sup>120</sup> (functional) iron, <sup>121,122</sup> complex malnutrition (e.g. AIDS, infections, <sup>73</sup> anorexia nervosa <sup>73,123,124</sup> )
Genetic	Diverse forms	Such as HCM, <sup>97,125,126</sup> restrictive cardiomyopathies, <sup>103,104,106</sup> hypertrophic form of non-compaction cardiomyopathy, <sup>127,128</sup> early forms of muscular dystrophies (Duchenne/Becker disease <sup>129</sup> ).
Endomyocardial		HES, <sup>84</sup> EMF, <sup>71,127</sup> endocardial fibroelastosis, <sup>128</sup> carcinoid, <sup>130,131</sup> endocardial calcification (Paget's disease <sup>132</sup> )
Abnormalities of loading conditions		
Hypertension		Primary and secondary forms of hypertension <sup>112,113,115,130,131</sup>
Valvular and structural defects	Acquired	Heart valve diseases <sup>133,134</sup>
	Congenital	Septal defects <sup>132,135,136</sup>
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis and pericardial effusion <sup>137,138</sup>
	Endomyocardial	HES, <sup>86</sup> EMF, <sup>73,139</sup> endocardial fibroelastosis, <sup>140</sup> carcinoid, <sup>141,142</sup> endocardial calcification (Paget's disease <sup>143</sup> )
High output states		Severe anaemia, <sup>144</sup> sepsis, <sup>145</sup> thyrotoxicosis, <sup>105</sup> arteriovenous fistula, <sup>146</sup> and pregnancy <sup>147</sup>
Volume overload		Renal failure and fluid overload <sup>148,149,150</sup>
Abnormalities of the cardiac rhythm		
Rhythm disorders		Atrial/ventricular arrhythmias, pacing, conduction disorders <sup>38,151–153</sup>

EMF, endomyocardial fibrosis; GH, growth hormone; HCM, hypertrophic cardiomyopathy; HES, hypereosinophilic syndrome (formerly known as Löffler's endocarditis); HIV/AIDS, human immunodeficiency virus/acquired immune deficiency; LV, left ventricular; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma 2.

To take account of these factors, we recommend the use of major and minor diagnostic criteria according to the severity of an abnormality and the presence of modifiers. Major criteria (and cut-points) have been selected for their high specificity, while minor criteria should be more sensitive. Cut-points were derived particularly from studies that compared echocardiographic parameters against invasive haemodynamic data.<sup>5,28,166</sup>

In one cohort with 64% prevalence of HFpEF determined by invasive measurements, the univariable sensitivity of septal  $e'$  velocity  $<7$  cm/s to diagnose HFpEF, without adjusting for age or other variables, was 46%, while its specificity was 76%.<sup>5</sup> The sensitivity and specificity of an  $E/e'$  ratio  $>9$  were 78% and 59%, compared with 46% and 86% for  $E/e' >13$ . The sensitivity and specificity of LA volume index  $>30$  mL/m<sup>2</sup> were about 70%. Measurements of LV mass had low sensitivity (26%) for HFpEF but high specificity (86%) if LVH was present. PAP  $>35$  mmHg [derived from tricuspid regurgitation (TR) velocity] was 46% sensitive and 86% specific for HFpEF,<sup>5</sup> which makes it an important diagnostic criterion. The utility of GLS  $<16\%$  was moderate (sensitivity 62% and specificity 56%).<sup>5, 201</sup>

The utility of NP levels varies according to several factors including cardiac rhythm. For NT-proBNP  $>275$  pg/mL, a sensitivity of 59% and a specificity of 77% were reported (accuracy 68%).<sup>5</sup> Sensitivity decreased to 46% while specificity increased to 85% if the cut-off was increased to  $>450$  pg/mL (accuracy 66%). At our lowest recommended cut-off of 125 pg/mL (minor criterion, if the patient is in sinus rhythm), the sensitivity reported in that study was 77% and the specificity 53% (accuracy 65%). Of note, 39% of patients in that study were in AF or had a history of paroxysmal AF.<sup>5</sup> Combining the results of  $E/e'$  and NT-proBNP can increase their predictive value, notably their sensitivity to diagnose HFpEF.<sup>202</sup>

### Echocardiographic measurements of function and morphology

In Step 1(P) we recommend standard echocardiography, at least to assess LVEF and LV diameter. In Step 2(E) we recommend more detailed echocardiographic measurements (Supplementary material online, S1). These could all be obtained during a single study. The echocardiographic criteria in the HFA-PEFF score, listed below, mirror consensus recommendations for the diagnosis of LV diastolic function.<sup>41</sup>

*Septal and lateral mitral annular peak early diastolic velocity ( $e'$ )*

*Major criterion:* septal  $e' <7$  cm/s, or lateral  $e' <10$  cm/s

[subjects aged  $<75$  years]

*Major criterion:* septal  $e' <5$  cm/s, or lateral  $e' <7$  cm/s

[subjects aged  $\geq 75$  years]

The main determinant of  $e'$ , the early diastolic velocity of mitral annular motion, is LV relaxation. It reflects LV lengthening and is influenced by preload.<sup>203,204</sup> Left ventricular longitudinal  $e'$  velocity declines with age,<sup>205</sup> normative ranges reported from elderly participants were found to be lower than those given in the 2007 HFA consensus.<sup>206</sup> We include age-specific  $e'$  criteria in the HFA-PEFF score, measured as recommended.<sup>41</sup>

### Average septal-lateral $E/e'$ ratio

*Major criterion:* average septal-lateral  $E/e'$  ratio  $\geq 15$

*Minor criterion:* average septal-lateral  $E/e'$  ratio 9-14

The ratio of the peak velocity of mitral inflow during early diastole ( $E$ ), recorded by pulsed Doppler between the tips of the mitral leaflets, over the average of septal and lateral mitral annular early diastolic peak velocities ( $e'$ ) recorded by pulsed tissue Doppler, reflects the mPCWP.<sup>41</sup> The mitral  $E/e'$  index correlates with LV stiffness and fibrosis<sup>20,21</sup> and is less age-dependent than  $e'$ .<sup>206</sup> It also has diagnostic value during exercise.<sup>28,158</sup> The  $E/e'$  index is little influenced by changes in volume but it is influenced by the severity of LVH.<sup>23,24</sup>

### Tricuspid regurgitation peak velocity or pulmonary arterial systolic pressure

*Major criterion:* TR peak velocity  $>2.8$  m/s

*Major criterion:* Pulmonary artery systolic pressure  $>35$  mmHg

Pulmonary arterial systolic pressure is calculated from the modified Bernoulli equation as  $4 \times$  peak TR velocity plus estimated right atrial pressure. Elevated PASP and reduced RV function are important predictors of mortality in HFpEF.<sup>207-211</sup> Even a moderate increase in PASP can lead to increased ventricular interaction since a leftward shift of the ventricular septum impedes LV filling.<sup>212</sup> A PASP  $>35$  mmHg discriminates HFpEF from hypertensives and controls.<sup>207</sup> A TR peak velocity  $>2.8$  m/s indicates increased PASP<sup>41,213</sup> and is an indirect marker of LV diastolic dysfunction.<sup>41</sup>

### Left ventricular global longitudinal systolic strain

*Minor criterion:* GLS  $< 16\%$

Left ventricular peak systolic GLS is not angle-dependent, unlike myocardial velocities recorded by tissue Doppler.<sup>186</sup> It is measured using speckle-tracking echocardiography as the average of systolic strain obtained from all LV segments in the apical 4-chamber, apical 2-chamber, and apical long-axis views.<sup>214</sup>

Reduced LV longitudinal systolic strain and LV early diastolic strain rate have both been identified in HFpEF.<sup>19,215,216</sup> Impaired GLS predicts HF hospitalization, cardiovascular death, or cardiac arrest.<sup>216,217</sup> It correlates with invasive measurements of LV stiffness and with NP levels.<sup>19,204,218</sup> All strain values are dimensionless and are expressed as percentages. For ease of use in these recommendations, we suggest a cut-point of 16% in absolute values,<sup>219-222</sup> and a value below 16% (e.g. 14%) is recommended as a minor criterion.

### Left atrial volume index

*Major criterion:*  $>34$  mL/m<sup>2</sup> [in sinus rhythm]

*Major criterion:*  $>40$  mL/m<sup>2</sup> [in atrial fibrillation]

*Minor criterion:* 29-34 mL/m<sup>2</sup> [in sinus rhythm]

*Minor criterion:* 34-40 mL/m<sup>2</sup> [in atrial fibrillation]

The maximal volume of the LA, measured at end-systole from bi-plane or three-dimensional images and indexed to body surface area [left atrial volume index (LAVI)] is an indirect correlate of LV filling pressures.<sup>41</sup> It is more accurate as a marker of chronic LA remodeling than either LA area or diameter<sup>223–225</sup> and it correlates with other echocardiographic indices of LV diastolic function.<sup>226</sup> A LAVI of 29–34 mL/m<sup>2</sup> is considered as a minor criterion since it represents the upper limit in healthy subjects.<sup>227,228</sup>

In patients without AF or heart valve disease, LAVI >34 mL/m<sup>2</sup> independently predicts death, heart failure, AF, and ischaemic stroke.<sup>229–231</sup> In patients with HFpEF and permanent AF, LAVI was 35% more enlarged than it was in HFpEF patients in SR.<sup>34</sup> Patients with permanent AF may have a large LAVI even if they have no LV diastolic dysfunction.<sup>34,41</sup> We therefore recommend separate cut-offs for LAVI in SR vs. AF.

## Left ventricular mass index and relative wall thickness

*Major criterion:* LVMI  $\geq 149$  g/m<sup>2</sup> in men or  $\geq 122$  g/m<sup>2</sup> in women and RWT >0.42

*Minor criterion:* LVMI  $\geq 115$  g/m<sup>2</sup> in men or  $\geq 95$  g/m<sup>2</sup> in women or RWT >0.42 or LV end-diastolic wall thickness  $\geq 12$  mm

Increased LV diastolic wall thickness in a non-dilated heart implies that the patient has LVH. It develops first in the basal segments of the ventricular septum,<sup>232</sup> and a wall thickness  $\geq 12$  mm at that site is common in elderly people. Localized septal hypertrophy may be a consequence of abnormal ventricular–arterial coupling but it is not sufficient to indicate that there is significant global LV remodelling or hypertrophy.

Left ventricular geometry is often classified using relative wall thickness (RWT), calculated as twice the LV posterior wall thickness divided by the LV internal diameter at end-diastole (LVPW  $\times$  2/ LVIDD), and using left ventricular mass index (LVMI) normalized to body surface area or height. Four patterns are described: normal (normal LVMI, RWT  $\leq 0.42$ ), concentric remodelling (normal LVMI, RWT >0.42), concentric hypertrophy (increased LVMI, RWT >0.42), and eccentric hypertrophy (increased LVMI, RWT  $\leq 0.42$ ).<sup>41,233,234</sup> In patients with HFpEF, both concentric LVH and concentric remodelling can be observed.<sup>235</sup>

The absence of LVH on echocardiography does not exclude HFpEF.<sup>5</sup> We therefore recommend the finding of concentric hypertrophy (increased LVMI and increased RWT) as a major criterion, or any one of a lesser degree of LVH, RWT, and LV end-diastolic wall thickness as a minor criterion.<sup>227,234,236</sup>

## Natriuretic peptides

*Major criterion:* NT-proBNP >220 pg/mL, or BNP >80 pg/mL [in sinus rhythm]

*Major criterion:* NT-proBNP >660 pg/mL or BNP >240 pg/mL [in atrial fibrillation]

*Minor criterion:* NT-proBNP 125–220 pg/mL, or BNP 35–80 pg/mL [in sinus rhythm]

*Minor criterion:* NT-proBNP 375–660 pg/mL, or BNP 105–240 pg/mL [in atrial fibrillation]

In Step 1(P), a single low cut-point was recommended in order to have a sensitive marker for cardiac abnormalities. In this step, in order to increase specificity, a higher cut-off value is recommended as a major criterion, in agreement with ESC guidelines.<sup>3</sup> Cut-offs are also stratified for the presence of SR or AF.

Natriuretic peptide levels should always be interpreted in context.<sup>180</sup> Definitive cut-offs to diagnose HFpEF in patients with SR or in AF are not well established, and trials have used different values.<sup>237,238</sup> In the setting of screening, average NPs have been reported to be 3–3.5 fold higher in patients with AF than in patients in SR.<sup>239</sup> Average NPs were found to be threefold higher in patients with AF than in patients in SR.<sup>34,35,240</sup> In prevalent symptomatic HFpEF with AF, levels tend to be even higher.<sup>241</sup> For diagnosing HFpEF, we hence recommend values in patients with AF that are three times higher than used for patients in SR.

## Calculating and interpreting the HFA-PEFF score

The score has functional, morphological, and biomarker domains. Within each domain, a major criterion scores 2 points or a minor criterion 1 point (*Figure 3; Supplementary material online, Table S1*). Each domain can contribute maximally 2 points, if any major criterion from this domain is positive, or 1 point if no major but any minor criterion is positive. If several major criteria within a single domain are positive, this domain still contributes 2 points; and if no major but several minor criteria are positive the contribution still is 1 point. Major and minor criteria are not additive in a single domain. Points are added only when they come from different domains.

For example, 2 major ( $E/e' > 15$ , and TR >2.8 m/s) and 1 minor (GLS <16) criteria, all in the functional domain, will lead to a total score from that domain of 2 points. The total score would be 5, if at least one minor criterion (LAVI <34 mL/m<sup>2</sup>; LV wall thickness >12 mm) and one major criterion (BNP in SR >80 pg/mL) would be present coming from the morphological and biomarker domains, respectively. It is important to understand that not all parameters from each domain need to be recordable (which is typically the case). The HFA-PEFF score can be calculated even if not all parameters are obtained, which adds to the practical utility of the score.

A total score  $\geq 5$  points is considered to be diagnostic of HFpEF, while a score of  $\leq 1$  point is considered to make a diagnosis of HFpEF very unlikely and to mandate investigations for alternative causes. Patients with an intermediate score (2–4 points, *Figures 2 and 3*) need further evaluation (Step 3(F<sub>1</sub>); *Figures 4A,B*).

If LAVI, LVMI, or wall thickness cannot be assessed by echocardiography, we recommend using measurements obtained from CMR imaging instead. Of note, there are some systematic differences in measurements of LV volumes and LVEF between imaging



	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal $e' < 7$ cm/s or lateral $e' < 10$ cm/s or Average $E/e' \geq 15$ or TR velocity $> 2.8$ m/s (PASP $> 35$ mmHg)	LAVI $> 34$ ml/m <sup>2</sup> or LVMI $\geq 149/122$ g/m <sup>2</sup> (m/w) and RWT $> 0,42$ #	NT-proBNP $> 220$ pg/ml or BNP $> 80$ pg/ml	NT-proBNP $> 660$ pg/ml or BNP $> 240$ pg/ml
Minor	Average $E/e' 9-14$ or GLS $< 16\%$	LAVI 29-34 ml/m <sup>2</sup> or LVMI $> 115/95$ g/m <sup>2</sup> (m/w) or RWT $> 0,42$ or LV wall thickness $\geq 12$ mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml
Major Criteria: 2 points		<b><math>\geq 5</math> points: HFpEF</b>		
Minor Criteria: 1 point		<b>2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements</b>		

**Figure 3** Step 2 (E): Echocardiographic and natriuretic peptide heart failure with preserved ejection fraction workup and scoring system (diagnostic workup).

modalities.<sup>242</sup> In one comparative study, LV volumes were larger and LVEF was lower but not statistically different with CMR compared with other imaging modalities.<sup>243</sup>

### Step 3 (F1): Functional testing

Symptoms compatible with HF can be confirmed to originate from the heart if haemodynamic abnormalities such as reduced stroke volume, reduced CO, and elevated LV filling pressures are detected either at rest or during exercise. In a typical elderly patient with multiple comorbidities, the presence or absence of isolated cardiac structural and/or functional abnormalities at rest does not always establish or exclude the diagnosis of HFpEF. If invasive testing demonstrates a high LV filling pressure [left ventricular end-diastolic pressure (LVEDP)  $\geq 16$  mmHg, PCWP  $\geq 15$  mmHg] at rest, then the diagnosis may be confirmed; otherwise, assessment during exercise is recommended, either by non-invasive exercise stress echocardiography or by invasive haemodynamics (Figures 2 and 4A,B).

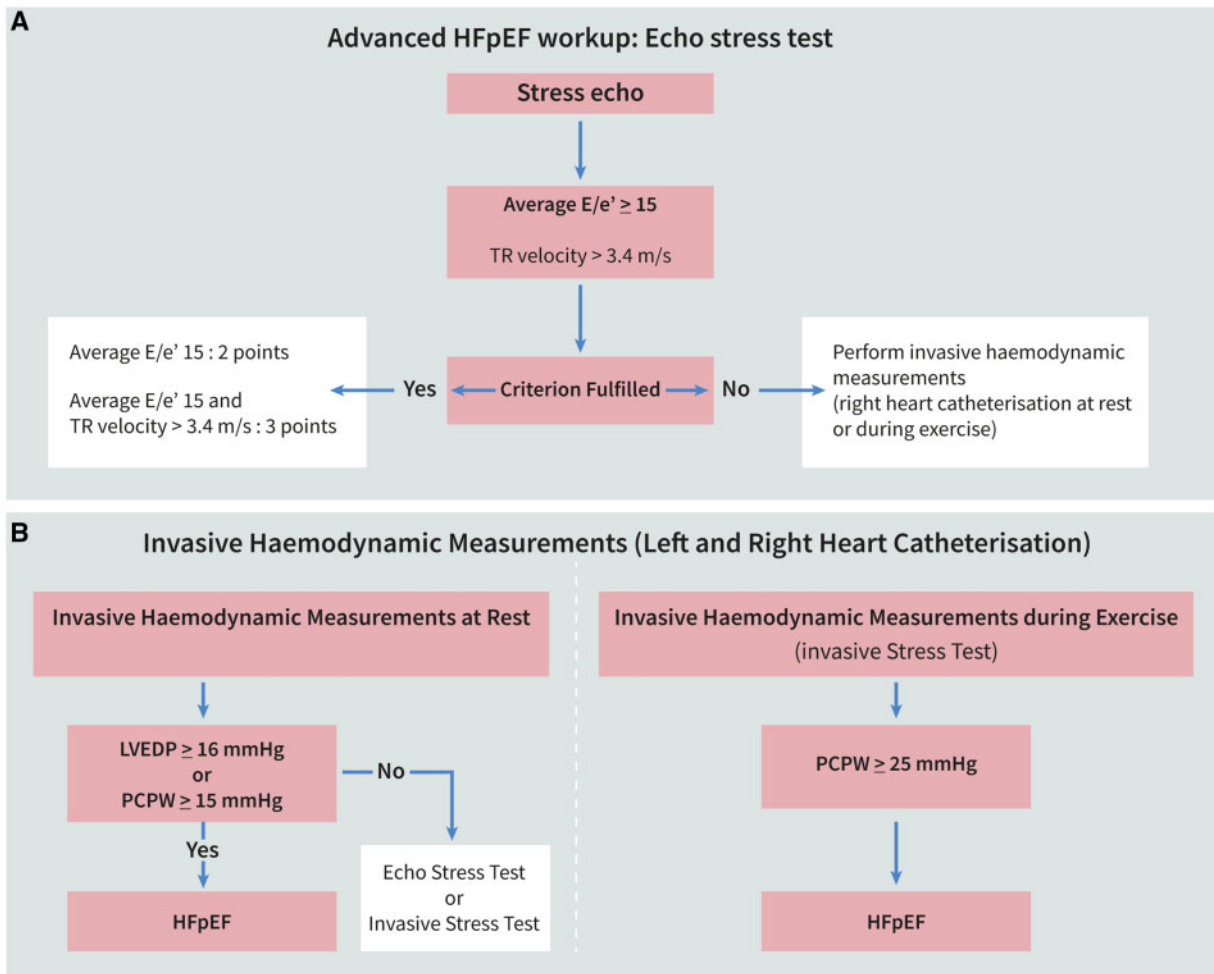
#### Exercise stress echocardiography: the diastolic stress test

During exercise in healthy people, enhanced LV untwisting and early diastolic suction maintain or increase stroke volume despite shortening of the filling time and without increasing LV filling pressures. In patients with HFpEF, impaired early diastolic relaxation, reduced increments in suction, and poor LV compliance lead to inadequate increases in stroke volume and CO on exercise, increased LV filling pressures, and increased PASP.<sup>28,41,244–248</sup> High LV filling pressures and inadequate CO responses during exercise can also impair RV reserve.<sup>52</sup>

Many patients with HFpEF have symptoms mainly on exertion that are usually attributed to the increase in LV filling pressures which is needed to maintain adequate filling and stroke volume.<sup>159,249</sup> Acquiring echocardiographic data during exercise can unmask LV diastolic and systolic dysfunction. The parameters that have been studied most often, during or immediately after exercise, are the mitral  $E/e'$  ratio and the TR peak velocity, which indicate increases in mPCWP and PASP, respectively.<sup>28,41,244–248,250</sup>

Ideally a semi-supine bicycle test with imaging during exercise, or else a treadmill or upright bicycle exercise protocol with imaging at or immediately after peak stress, is recommended<sup>41,244</sup> but there are no universally adopted protocols. The European Association of Cardiovascular Imaging and the American Society of Echocardiography recommend a stepped protocol, starting at 25 W at 60 r.p.m. with the load increasing by 25 W every 3 min until the patient has reached his maximal predicted workload and/or maximal predicted heart rate ( $220 - \text{age in years}$ ) and/or developed limiting symptoms.<sup>244</sup> Some patients cannot perform that protocol, and a ramped exercise test on a semi-supine bicycle at 60 r.p.m. starting at 15 W and with increments of 5 W every minute has also been proposed, to a submaximal target heart rate of 100–110/min or until the patient develops limiting symptoms.<sup>245</sup> None of these protocols have been shown to be superior to others.

The mitral  $E/e'$  ratio and peak TR velocity should be acquired at baseline, during each stage including peak exercise, and during a submaximal stage before fusion of the mitral  $E$  and  $A$  velocities<sup>213</sup> or during the first 2 min of the recovery phase when mitral  $E$  and  $A$  velocities are no longer fused and LV filling pressures remain



**Figure 4** Step 3 (F): Functional tests in cases of diagnostic uncertainty. (A, upper panel) It shows the diastolic stress test workup with exercise echocardiography is shown. If key haemodynamic abnormalities are identified, a definite heart failure with preserved ejection fraction diagnosis can be made. (B, lower panel) It shows the invasive haemodynamic measurements at rest (left) or during exercise (right) that may complement stress echocardiography and are recommended in cases with remaining diagnostic uncertainty.

elevated.<sup>41,244</sup> Changes in CO can be assessed by measuring the velocity integral of flow in the LV outflow tract, multiplied by the HR.

Exercise echocardiography should be considered abnormal if average  $E/e'$  ratio at peak stress increases to  $\geq 15$ , with or without a peak TR velocity  $> 3.4$  m/s.<sup>28,41,244</sup> An increase only in TR velocity should not be used to diagnose HFpEF because it might be caused simply by a normal hyperdynamic response to exercise (with increased pulmonary blood flow) in the absence of LV diastolic dysfunction.<sup>251</sup>

An average  $E/e'$  ratio during exercise  $\geq 15$  adds 2 points to the HFA-PEFF score. An average  $E/e'$  ratio  $\geq 15$  with a peak TR velocity  $> 3.4$  m/s adds 3 points to the previous score from Step 2(E). If the combined score from Step 2(E) and Step 3(F1) is  $\geq 5$  points, then the diagnosis of HFpEF can be confirmed.

However, echocardiographic stress tests also have limitations. It was reported that  $E/e'$  was not measurable in about 10% of subjects

during submaximal exercise (20 W) and in about 20% of HFpEF patients during peak exercise, and that TR velocity was measurable in only 50%; about 20% of controls were considered to have false-positive tests.<sup>28</sup> Data from stress echocardiography are not sufficient to substitute for invasive haemodynamic data under all circumstances. If the score remains  $< 5$  points or if exercise echocardiography cannot be performed, we recommend an invasive haemodynamic stress test in any case of doubt, especially if a therapeutic decision depends on the results.

#### **Invasive haemodynamic tests at rest and with exercise**

Left ventricular end-diastolic pressure LVEDP in the resting supine position is typically obtained in the context of left heart catheterization and bears important diagnostic information in the workup of unexplained dyspnoea. In selected patients, LV compliance and stiffness can be determined directly by using a multiple-loop conductance

catheter to record the end-diastolic pressure–volume relationship (EDPVR) during preload reduction, giving a volume-independent parameter for LV stiffness (constant of chamber stiffness,  $b$ , normal  $<0.27^{252}$ ,  $21,159,253–255$ ). Invasive demonstration of impaired LV relaxation at rest, measured by high-fidelity pressure catheters as the time constant of LV relaxation ( $\tau > 48 \text{ ms}^4$ ) or of elevated LV filling pressures at rest (LVEDP  $\geq 16 \text{ mmHg}$ ) confirms definite evidence of HFpEF.

Right heart catheterization should be considered for the structured workup of suspected HFpEF, especially when left heart pressures are not available. When resting mPCWP, measured using a Swan-Ganz catheter, is elevated in the presence of a normal LV end-diastolic volume index, then usually LV end-diastolic distensibility is reduced. A resting mPCWP  $\geq 15 \text{ mmHg}^3$  confirms definite evidence of HFpEF.

However, normal LVEDP or mPCWP levels at rest do not exclude HFpEF. In compensated HFpEF, haemodynamic alterations may be detected only during exercise or when the patient deteriorates.<sup>28,179,230,256,257</sup> Also, volume depletion or intensified diuretic treatment may shift the diastolic pressure–volume relationship to the left, without changing LV compliance ( $dV/dP$ ; the inverse of LV stiffness<sup>252</sup>). If resting filling pressures are normal, exercise right heart catheterization is recommended for the definite workup of unexplained exertional dyspnoea,<sup>179</sup> especially if the patient has an intermediate Score in Step 2(E) or if exercise echocardiography is inconclusive or not feasible (Figures 2 and 4B). Specialized centres may perform exercise right heart catheterization upfront in the absence of exercise echocardiography, depending on the individual experience of the site.

During supine exercise in healthy control subjects, cut-offs for peak PCWP and LVEDP are  $<20–23 \text{ mmHg}^{258,259}$  and  $<25 \text{ mmHg}^{260,261}$  respectively. Patients with values  $<25 \text{ mmHg}$  during peak exercise are classified as having non-cardiac dyspnoea. A steep increase in PCWP during exercise is a typical haemodynamic response in HFpEF,<sup>256,262</sup> indicating that the dyspnoea on exertion is mainly of cardiac origin. Patients with peak exercise PCWP  $\geq 25 \text{ mmHg}$  are classified as having HFpEF (Supplementary material online, S2). An increase in LV filling pressure during exercise that is not accompanied by increases in end-diastolic volume, indicates limitation to LV filling or the development of pericardial constraint.<sup>256</sup>

A high resting mPCWP and a pathological increase in mPCWP during exercise predict poor outcomes from HFpEF.<sup>168,249,263</sup> Patients with a normal mPCWP at rest ( $<12 \text{ mmHg}$ ) but a steep increase during exercise (to  $\geq 25 \text{ mmHg}$ ) have a two-fold increase in mortality.<sup>263</sup> Ten-year mortality was 6.6% if resting mPCWP was  $\leq 12 \text{ mmHg}$  and peak exercise mPCWP was  $<25 \text{ mmHg}$ ; 28.2% in patients with low mPCWP at rest and high exercise mPCWP; and 35.2% in those with high resting mPCWP and high peak exercise mPCWP ( $\geq 25 \text{ mmHg}$ ).<sup>263</sup>

Exercise mPCWP reclassifies patients with a normal resting mPCWP and stratifies risk. If other investigations have been inconclusive, invasive measurement of mPCWP or LVEDP is considered as the clinical reference investigation for diagnosing HFpEF<sup>28</sup> (see Supplementary material online, S7 about how to perform an invasive stress test). Other causes such as significant CAD, mitral stenosis, or pericardial constriction must be excluded.

## Step 4(F2): Final aetiology

Most cases of HFpEF are related to common risk factors and comorbidities, but the possibility of a specific underlying aetiology should always be considered (Table 2, Supplementary material online, Tables S2–S4; Figure 5A,B). We postulate that identification of specific HFpEF aetiologies will advance the field of targeted therapies.

Specific heart muscle diseases that may present with the HFpEF phenotype include hypertrophic cardiomyopathies,<sup>125,264–266</sup> myocarditis and chronic inflammatory cardiomyopathy,<sup>67,75–77,97,137,267,268</sup> autoimmune diseases,<sup>78,79</sup> non-infiltrative and infiltrative cardiomyopathies,<sup>83,125</sup> idiopathic or acquired endomyocardial fibrosis,<sup>269</sup> storage diseases,<sup>125,269</sup> and other genetic disorders including early stages of cardiomyopathies associated with muscular dystrophy.<sup>103</sup> Rare causes such as toxicity from drugs or heavy metals, radiation, and metabolic causes related to hormonal or nutritional disease, should also be considered (Table 2). The trigger may occur long before the onset of symptoms. For instance radiation-induced HFpEF develops after 10–15 years, even when low mean cardiac radiation doses of 3.3 Gy are used.<sup>104,129</sup>

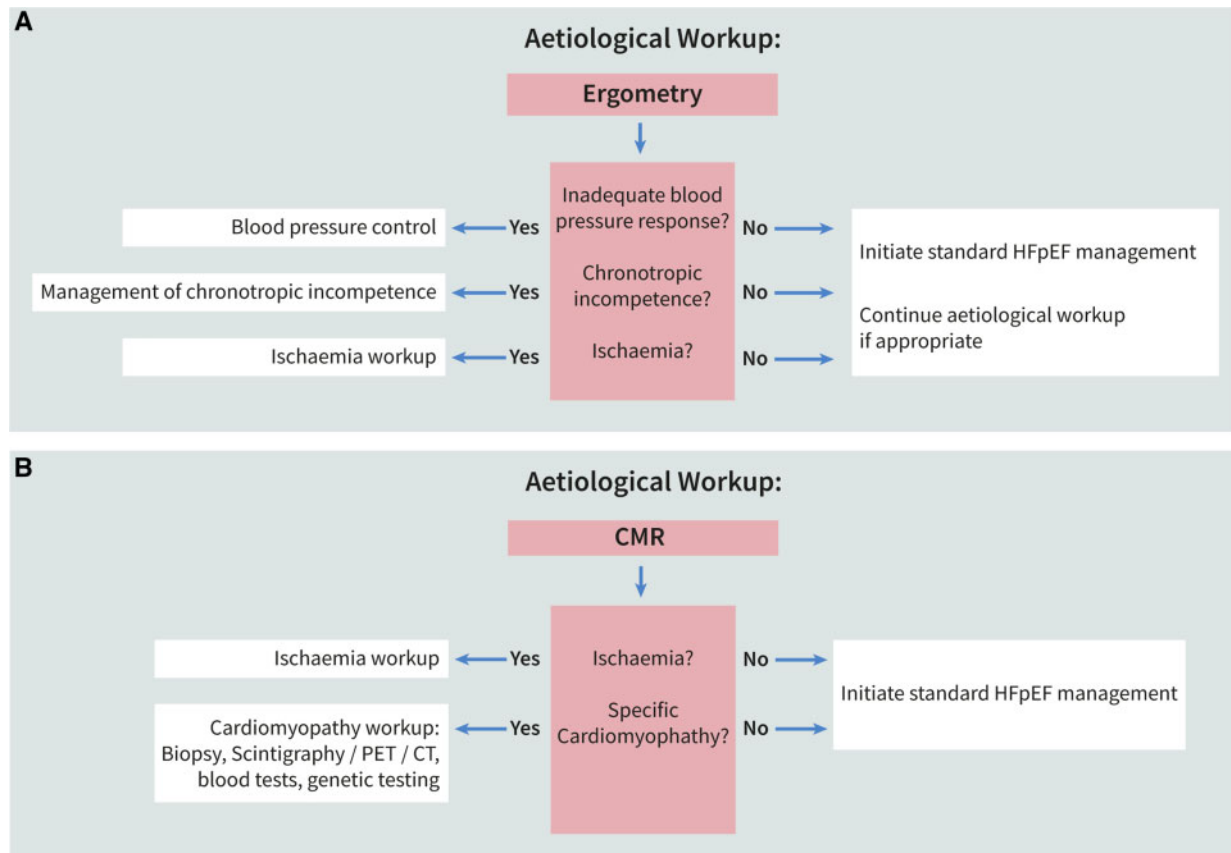
Aetiological workup may include a standard exercise stress test that may identify myocardial ischaemia, an abnormal blood pressure response to exercise, chronotropic incompetence, or supraventricular and ventricular arrhythmias (Figure 5A; Supplementary material online, S2). These findings can immediately translate into management strategies, such as anti-ischaemic therapy, improved blood pressure control, removal of bradycardic agents (such as beta-blockers often prescribed for hypertension), and control of exercise-induced cardiac arrhythmias.

More sophisticated tools for aetiological workup include CMR which is most accurate for determining LA and LV volumes and mass,<sup>270</sup> detects scar and myocardial ischaemia due to epicardial coronary disease or microvascular dysfunction,<sup>65</sup> and stress perfusion imaging to reveal diffuse subendocardial defects. Regional and diffuse myocardial oedema (T2-imaging) and infiltration or fibrosis are quantified using late gadolinium enhancement [LGE; for extracellular volume fraction (ECV)] or T1-mapping<sup>137,267,271–274</sup> (Supplementary material online, Table S3). Right or left ventricular myocardial biopsy, <sup>(99m)Tc</sup>-DPD scintigraphy to identify cardiac amyloidosis, positron emission tomography (PET)-CT, as well as specific genetic and laboratory tests (Figure 5B) should be considered in selected cases where a specific aetiology is suspected.

Of note, we do not intend to lump together all causes of the clinical syndrome of heart failure with a normal ejection fraction under the term 'HFpEF', but instead to stress the importance to always consider specific aetiologies if the clinical diagnosis of HFpEF is made. It is also important to understand that non-myocardial aetiologies (Table 2) that may mimic HFpEF, such as constrictive pericarditis, primary valvular heart disease, or high output failure should not be considered part of the HFpEF syndrome.

## Limitations, gaps in evidence, and unanswered questions

Heart failure with preserved ejection fraction is a clinical syndrome with multiple contributing factors, aetiologies, and pathophysiological expressions.<sup>168,275</sup> It is a limitation that we suggest an algorithm that reduces it to a single clinical diagnosis. Future studies should evaluate



**Figure 5** Step 4 (F<sub>2</sub>): Final aetiological workup. (A) It shows the role of ergometry to detect underlying causes such as inadequate blood pressure response, chronotropic incompetence, or myocardial ischaemia during exercise. (B) It shows the aetiological workup using cardiac magnetic resonance (CMR). CT, computed tomography; PET, positron emission tomography.

and refine the recommended diagnostic algorithm and classify HFpEF patients into specific subgroups. Ideally, a large and unselected sample of breathless patients, and age-matched controls, would undergo all tests including echocardiography and the 'gold standard' invasive haemodynamic assessment.

The stage and severity of HFpEF may impact on the accuracy of a specific diagnostic parameter. In a recent trial 45% of patients had 'early' HFpEF with normal filling pressures at rest, and elevated filling pressures only during invasive haemodynamic exercise testing.<sup>5</sup> Because of the intermittent diastolic pressure overload in early HFpEF, LAVI may be smaller (and less diagnostic), and functional indices such as global LA strain or LA conduit strain might be more appropriate diagnostic parameters.<sup>276</sup> In consequence, the patient mix under investigation may affect the test results. Prospective testing and retesting in distinct HFpEF patients populations is needed to sort this out.

The diagnosis of HF is still based on LVEF, partly for historical reasons and despite its limitations<sup>277</sup> for predicting cardiac functional reserve and symptoms. Exercise capacity correlates better with long-axis functional reserve of the LV<sup>52,278–281</sup> and with peripheral blood flow<sup>282</sup> than with LVEF. In fact, a preserved LVEF has no diagnostic role for HFpEF except to exclude HF with reduced LVEF. In future,

real-time non-invasive assessments of chamber volumes, stroke volumes, and CO, as well as filling pressures, in combination with innovative markers of systolic and diastolic function, will markedly reduce the significance of LVEF in characterizing HF.

We have recommended exercise testing as a component of the diagnostic workflow in cases of uncertainty, but there is no consensus yet about which stress protocol should be used or which measurements are most important. It is uncertain if a simple parameter such as the 6MWT distance could be as useful as detailed cardiopulmonary stress testing, which can be difficult to perform in breathless elderly subjects.<sup>193</sup>

Besides increases in filling pressures, HFpEF patients may be haemodynamically limited by their inability to adequately enhance stroke volume during exercise,<sup>165,278,279,283</sup> but no cut-points have been published to diagnose the resulting impaired reserve of CO. Unfortunately, reliable data on LV diastolic properties, stroke volume, and CO can currently only be obtained invasively, ideally by conductance catheterization. 3D echocardiography and CMR is now reaching a state where pressure–volume loops and stroke volumes can be obtained non-invasively,<sup>20,284</sup> but these measurements still await validation in broader HFpEF cohorts.

It will be important not just to confirm the diagnosis using the scoring system that we propose, but to document which specific abnormalities correlate with individual responses to treatment, in order to dissect out specific pathophysiological mechanisms that need different treatments.<sup>285,286</sup> We recommend that future HFpEF studies and registries should collect, record, and analyse the detailed components that are included in the HF-PEFF Score.

There is a close relationship between HFpEF and AF. There is overlap in symptoms, signs, echocardiographic findings, and NP levels between the two conditions, and a substantial proportion of patients in HFpEF registries and trials have AF. We have provided distinct diagnostic thresholds for NP and LAVI in SR vs. AF, based on existing literature and consensus. These thresholds need more prospective research for their validation. In addition, other functional measures are also likely to be affected by concomitant AF. Of note, we did not adopt the alternative view that AF *per se* could be used as a stand-alone indicator of HFpEF, but we again emphasize the close association between AF and HFpEF.

There is controversy about the best non-invasive indicators of elevated LV filling pressures and mPCWP.<sup>287</sup> The  $E/e'$  index has gained a supremacy in clinical practice that is not fully supported by all clinical investigations.<sup>288,289</sup> The diagnostic utility of alternative indices such as retrograde pulmonary venous flow,<sup>290,291</sup> estimated LV stiffness (diastolic pressure–volume quotient),<sup>284</sup> and left atrial strain rate during atrial contraction<sup>74,161,276,292</sup> in patients in sinus rhythm, and the L wave of mitral inflow<sup>293</sup> and left atrial strain during reservoir function<sup>160,294</sup> in patients in AF, merit further investigation.

Modern imaging methods generate a huge quantity of digital data about global and regional left ventricular morphology and function throughout the cardiac cycle, and about arterial and endothelial function and myocardial perfusion, which can be coupled with comprehensive demographic data including traditional risk factors and new biomarkers and with proteomic, metabolomic, and genomic data. Making sense of all this information is a challenge that can likely be met by machine learning. Recent studies suggest that it may be useful for diagnosis and for defining pathophysiology,<sup>15,295,296</sup> but long-term studies in large populations are needed to unravel which features best predict clinical outcomes and responses to treatment. Molecular phenotyping for a better identification of distinct HFpEF phenotypes is emerging and may also help to develop targeted therapies.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Acknowledgements

We acknowledge the continuous support of the Heart Failure Association (HFA) for this manuscript. Members of this Task Force were selected by the HFA Board and HFA HFpEF Committee to represent professionals involved with the medical care of patients with HFpEF. Selected experts in the field undertook a comprehensive review of the published evidence for diagnosis of HFpEF according to the ESC Committee for Practice Guidelines (CPG) and HFA policy. A critical evaluation of suggested procedures was done by all authors and accepted after consensus. The experts of the writing and

reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Figures were drawn by Medical Visuals, Maartje Kunen.

**Conflict of interest:** Dr B.P. has received research funds from Bayer Healthcare, Servier, and Astra-Zeneca, as well as speakers honoraria/committee membership fees from Novartis, Bayer Healthcare, Daiichi-Sankyo, MSD, Stealth Peptides, Astra-Zeneca, Sanofi, Vifor, and Servier. Dr R.A.d.B. is supported by the Netherlands Heart Foundation (CVON DOSIS, grant 2014-40, CVON SHE-PREDICTS-HF, grant 2017-21, and CVON RED-CVD, grant 2017-11); and the Innovational Research Incentives Scheme program of the Netherlands Organization for Scientific Research (NWO VIDI, grant 917.13.350). The UMCG, which employs Dr De Boer has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Roche, Trevena, and ThermoFisher GmbH. Dr R.A.d.B. received personal fees from MandalMed Inc., Novartis, and Servier. Dr A.A.V. has received consultancy fees and/or research grants from Amgen, Bayer, Boehringer Ingelheim, Merck/Merck Sharp & Dohme, Novartis, Roche Diagnostics, Sanofi Aventis, Servier, Stealth Peptides, Singulex, Sphingotec, Trevena, and Vifor. Dr C.T. received research grants from Novartis and speaker fees from Astra Zeneca, Berlin Chemie, Akcea, Impulse Dynamics, Servier, Bayer, Pfizer, Abbott, Boston Scientific. Dr S.D.A. has received consultancy fees and/or research grants from Abbott Vascular, Bayer, Boehringer Ingelheim, Brahms, Novartis, Servier, Stealth Peptides, and Vifor. Dr C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, WebMD Global LLC, Radcliffe Group Ltd and Corpus. Patent pending: PCT/SG2016/050217. Co-founder & non-executive director: eKo.a; Dr W.J.P. is supported by grants from CardioVasculair Onderzoek Nederland (CVON), Dutch Heart Foundation, The Hague, The Netherlands (RECONNECT, EARLY-HFPEF). Dr E.N. has received research grants from Bayer AG and fees/speaker honoraria from Bayer AG and Siemens Healthiness. Dr F.E. reports personal fees from Novartis, grants and personal fees from Boehringer Ingelheim, personal fees from CVRx, Pfizer, Medtronic, Resmed, grants and personal fees from Servier, from MSD, Bayer, Vifor, Berlin Chemie. Dr E.P.-K. reports research grants and consulting fees from Bayer Healthcare and MSD. Dr G.F. received research grants from the European Union and is Committee member of trials and registries sponsored by Novartis, Medtronic, BI, Vifor, Servier, Bayer. The remaining authors have no conflicts of interest to declare.

## References

- van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016; **18**:242–252.

2. Seferovic PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, Paulus WJ, Komajda M, Cosentino F, de Boer RA, Farmakis D, Doehner W, Lambrinou E, Lopatin Y, Piepoli MF, Theodorakis MJ, Wiggers H, Lekakis J, Mebazaa A, Mamas MA, Tschope C, Hoes AW, Seferovic JP, Logue J, McDonagh T, Riley JP, Milinkovic I, Polovina M, van Veldhuisen DJ, Lainscak M, Maggioni AP, Ruschitzka F, McMurray J. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:853–872.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M, Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
4. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;**28**:2539–2550.
5. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;**138**:861.
6. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441–1446.
7. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation* 2000;**101**:2118–2121.
8. Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. *Prog Cardiovasc Dis* 2005;**47**:314–319.
9. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263–271.
10. Tschope C, Van Linthout S. New insights in (inter)cellular mechanisms by heart failure with preserved ejection fraction. *Curr Heart Fail Rep* 2014;**11**:436–444.
11. Little WC, Zile MR. HFpEF: cardiovascular abnormalities not just comorbidities. *Circ Heart Dis* 2012;**5**:669–671.
12. Franssen C, Chen S, Hamdani N, Paulus WJ. From comorbidities to heart failure with preserved ejection fraction: a story of oxidative stress. *Heart* 2016;**102**:320–330.
13. Tromp J, Westenbrink BD, Ouwkerk W, van Veldhuisen DJ, Samani NJ, Ponikowski P, Metra M, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Lang CC, Ng LL, Zannad F, Zwinderman AH, Hillege HL, van der Meer P, Voors AA. Identifying pathophysiological mechanisms in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2018;**72**:1081–1090.
14. Sengupta PP, Kramer CM, Narula J, Dilsizian V. The potential of clinical phenotyping of heart failure with imaging biomarkers for guiding therapies: a focused update. *JACC Cardiovasc Imaging* 2017;**10**:1056–1071.
15. Omar AMS, Narula S, Abdel Rahman MA, Pedrizzetti G, Raslan H, Rifaie O, Narula J, Sengupta PP. Precision phenotyping in heart failure and pattern clustering of ultrasound data for the assessment of diastolic dysfunction. *JACC Cardiovasc Imaging* 2017;**10**:1291–1303.
16. Tabassian M, Sunderji I, Erdei T, Sanchez-Martinez S, Degiovanni A, Marino P, Fraser AG, D'Hooge J. Diagnosis of heart failure with preserved ejection fraction: machine learning of spatiotemporal variations in left ventricular deformation. *J Am Soc Echocardiogr* 2018;**31**:1272–1284.
17. Trippel TD, Van Linthout S, Westermann D, Lindhorst R, Sandek A, Ernst S, Bobenko A, Kasner M, Spillmann F, González A, López B, Ravassa S, Pieske B, Paulus WJ, Díez J, Edelmann F, Tschope C. Investigating a biomarker-driven approach to target collagen turnover in diabetic heart failure with preserved ejection fraction patients. Effect of torasemide versus furosemide on serum C-terminal propeptide of procollagen type I (DROP-PIP trial). *Eur J Heart Fail* 2018;**20**:460–470.
18. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;**36**:2585–2594.
19. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD, Investigators P. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2014;**63**:447–456.
20. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschope C. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation* 2007;**116**:637–647.
21. Kasner M, Westermann D, Lopez B, Gaub R, Escher F, Kuhl U, Schultheiss HP, Tschope C. Diastolic tissue Doppler indexes correlate with the degree of collagen expression and cross-linking in heart failure and normal ejection fraction. *J Am Coll Cardiol* 2011;**57**:977–985.
22. Sharifov OF, Schiros CG, Aban I, Denney TS, Gupta H. Diagnostic accuracy of tissue Doppler index E/e' for evaluating left ventricular filling pressure and diastolic dysfunction/heart failure with preserved ejection fraction: a systematic review and meta-analysis. *J Am Heart Assoc* 2016;**5**:e002530.
23. Donal E, Galli E, Fraser AG. Non-invasive estimation of left heart filling pressures: another nail in the coffin for E/e'? *Eur J Heart Fail* 2017;**19**:1661–1663.
24. Mitter SS, Shah SJ, Thomas JD. A test in context: E/A and E/e' to assess diastolic dysfunction and LV filling pressure. *J Am Coll Cardiol* 2017;**69**:1451–1464.
25. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliaš G, Cardim N, Magne J, Laginha S, Hagendorff A, Haland TF, Abergel L, Martinez C, Rapaciuolo A, Santoro C, Ilardi F, Postolache A, Dulgheru R, Mateescu AD, Beladan CC, Deleanu D, Marchetta S, Auffret V, Schwammenthal E, Habib G, Popescu BA. Echo-Doppler estimation of left ventricular filling pressure: results of the multi-centre EACVI Euro-Filling study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:961–968.
26. Andersen OS, Smiseth OA, Dokainish H, Abudiyab MM, Schutt RC, Kumar A, Sato K, Harb S, Gude E, Remme EW, Andreassen AK, Ha JW, Xu J, Klein AL, Nagueh SF. Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol* 2017;**69**:1937–1948.
27. Sharifov OF, Schiros CG, Aban I, Perry GJ, Dell'italia LJ, Lloyd SG, Denney TS, Jr, Gupta H. Left ventricular torsion shear angle volume approach for noninvasive evaluation of diastolic dysfunction in preserved ejection fraction. *J Am Heart Assoc* 2017;**7**:e007039.
28. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation* 2017;**135**:825–838.
29. Obokata M, Borlaug BA. The strengths and limitations of E/e' in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2018;**20**:1312–1314.
30. Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P, Omland T, Storrow AB, Krishnaswamy P, Abraham WT, Clopton P, Steg G, Aumont MC, Westheim A, Knudsen CW, Perez A, Kamin R, Kazanegra R, Herrmann HC, McCullough PA; Breathing Not Properly Multinational Study Investigators. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. *J Am Coll Cardiol* 2003;**41**:2010–2017.
31. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS; Breathing Not Properly Multinational Study Investigators. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003;**41**:571–579.
32. Buckley LF, Canada JM, Del Buono MG, Carbone S, Trankle CR, Billingsley H, Kadariya D, Arena R, Van Tassel BW, Abbate A. Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction. *ESC Heart Fail* 2018;**5**:372–378.
33. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6–19.
34. Lam CS, Rienstra M, Tay WT, Liu LC, Hummel YM, van der Meer P, de Boer RA, Van Gelder IC, van Veldhuisen DJ, Voors AA, Hoendermis ES. Atrial fibrillation in heart failure with preserved ejection fraction: association with exercise capacity, left ventricular filling pressures, natriuretic peptides, and left atrial volume. *JACC Heart Fail* 2017;**5**:92–98.
35. McKelvie RS, Komajda M, McMurray J, Zile M, Ptaszynska A, Donovan M, Carson P, Massie BM, Investigators IP. Baseline plasma NT-proBNP and clinical characteristics: results from the irbesartan in heart failure with preserved ejection fraction trial. *J Card Fail* 2010;**16**:128–134.
36. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;**40**:976–982.
37. Suthahar N, Meijers WC, Ho JE, Gansevoort RT, Voors AA, van der Meer P, Bakker SJL, Heymans S, van Empel V, Schroen B, van der Harst P, van

- Veldhuisen DJ, de Boer RA. Sex-specific associations of obesity and N-terminal pro-B-type natriuretic peptide levels in the general population. *Eur J Heart Fail* 2018;**20**:1205–1214.
38. Rogers RK, Stoddard GJ, Greene T, Michaels AD, Fernandez G, Freeman A, Nord J, Stehlik J. Usefulness of adjusting for clinical covariates to improve the ability of B-type natriuretic peptide to distinguish cardiac from noncardiac dyspnea. *Am J Cardiol* 2009;**104**:689–694.
  39. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, Hardman SM, Dargie HJ, Cowie MR. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 2005;**7**:537–541.
  40. Fuat A, Murphy JJ, Hungin AP, Curry J, Mehrzad AA, Hetherington A, Johnston JJ, Smellie WS, Duffy V, Cawley P. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *Br J Gen Pract* 2006;**56**:327–333.
  41. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston T, Oslo N, Phoenix A, Nashville T, Hamilton OC, Uppsala S, Ghent Liege B, Cleveland O, Novara I, Rochester M, Bucharest R, St. Louis M. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1321–1360.
  42. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferrari R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585.
  43. Triposkiadis F, Giamouzis G, Parissis J, Starling RC, Boudoulas H, Skoularigis J, Butler J, Filippatos G. Reframing the association and significance of comorbidities in heart failure. *Eur J Heart Fail* 2016;**18**:744–758.
  44. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. *Circulation* 2018;**138**:198–205.
  45. Mohammed SF, Hussain S, Mirzoyev SA, Edwards VWD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation* 2015;**131**:550–559.
  46. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, von Schlippenbach J, Skurk C, Steendijk P, Riad A, Poller W, Schultheiss H-P, Tschöpe C. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. *Circ Heart Fail* 2011;**4**:44–52.
  47. Wang C, Fan F, Cao Q, Shen C, Zhu H, Wang P, Zhao X, Sun X, Dong Z, Ma X, Liu X, Han S, Wu C, Zou Y, Hu K, Ge J, Sun A. Mitochondrial aldehyde dehydrogenase 2 deficiency aggravates energy metabolism disturbance and diastolic dysfunction in diabetic mice. *J Mol Med (Berl)* 2016;**94**:1229–1240.
  48. Perseghin G, Ntali G, De Cobelli F, Lattuada G, Esposito A, Belloni E, Canu T, Costantino F, Ragogna F, Scifo P, Del Maschio A, Luzi L. Abnormal left ventricular energy metabolism in obese men with preserved systolic and diastolic functions is associated with insulin resistance. *Diabetes Care* 2007;**30**:1520–1526.
  49. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, Bartz TM, Santhanakrishnan R, Lee DS, Chan C, Liu K, Blaha MJ, Hillege HL, van der Harst P, van Gilst WH, Kop WJ, Gansevoort RT, Vasan RS, Gardin JM, Levy D, Gottdiener JS, de Boer RA, Larson MG. Predicting heart failure with preserved and reduced ejection fraction: the international collaboration on heart failure subtypes. *Circ Heart Fail* 2016;**9**:e003116.
  50. Pernot M, Lee WN, Bel A, Mateo P, Couade M, Tanter M, Crozatier B, Messas E. Shear wave imaging of passive diastolic myocardial stiffness: stunned versus infarcted myocardium. *JACC Cardiovasc Imaging* 2016;**9**:1023–1030.
  51. Konerman MC, Greenberg JC, Kolas TJ, Corbett JR, Shah RV, Murthy VL, Hummel SL. Reduced myocardial flow reserve is associated with diastolic dysfunction and decreased left atrial strain in patients with normal ejection fraction and epicardial perfusion. *J Card Fail* 2018;**24**:90–100.
  52. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J* 2016;**37**:3293–3302.
  53. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, Hainer J, Bibbo CF, Dorbala S, Blankstein R, Di Carli MF. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J* 2018;**39**:840–849.
  54. Elesber AA, Redfield MM, Rihal CS, Prasad A, Lavi S, Lennon R, Mathew V, Lerman LO, Lerman A. Coronary endothelial dysfunction and hyperlipidemia are independently associated with diastolic dysfunction in humans. *Am Heart J* 2007;**153**:1081–1087.
  55. Tschope C, Westermann D, Steendijk P, Kasner M, Rudwaleit M, Schwimmbeck PL, Poller WC, Schultheiss HP. Coronary vasospasm-induced acute diastolic dysfunction in a patient with Raynaud's phenomenon. *Clin Res Cardiol* 2006;**95**:344–348.
  56. Catena C, Colussi G, Verheyen ND, Novello M, Fagotto V, Soardo G, Sechi LA. Moderate alcohol consumption is associated with left ventricular diastolic dysfunction in nonalcoholic hypertensive patients. *Hypertension* 2016;**68**:1208–1216.
  57. Tong W, Lima JA, Meng Q, Flynn E, Lai S. Long-term cocaine use is related to cardiac diastolic dysfunction in an African-American population in Baltimore, Maryland. *Int J Cardiol* 2004;**97**:25–28.
  58. Baggish AL, Weiner RB, Kanayama G, Hudson JJ, Picard MH, Hutter AM Jr, Pope HG Jr. Long-term anabolic-androgenic steroid use is associated with left ventricular dysfunction. *Circ Heart Fail* 2010;**3**:472–476.
  59. Seldrum S, Pierard S, Moniotte S, Vermeylen C, Vancraeynest D, Pasquet A, Vanoverschelde JL, Gerber BL. Iron overload in polytransfused patients without heart failure is associated with subclinical alterations of systolic left ventricular function using cardiovascular magnetic resonance tagging. *J Cardiovasc Magn Reson* 2011;**13**:23.
  60. Yang WY, Zhang ZY, Thijs L, Cauwenberghs N, Wei FF, Jacobs L, Lutun A, Verhamme P, Kuznetsova T, Nawrot TS, Staessen JA. Left ventricular structure and function in relation to environmental exposure to lead and cadmium. *J Am Heart Assoc* 2017;**6**.
  61. Linna A, Oksa P, Groundstroem K, Halkosaari M, Palmroos P, Huikko S, Uitti J. Exposure to cobalt in the production of cobalt and cobalt compounds and its effect on the heart. *Occup Environ Med* 2004;**61**:877–885.
  62. Grandis DJ, Nah G, Whitman IR, Vittinghoff E, Dewland TA, Olgin JE, Marcus GM. Wilson's disease and cardiac myopathy. *Am J Cardiol* 2017;**120**:2056–2060.
  63. Tonnesmann E, Kandolf R, Lewalter T. Chloroquine cardiomyopathy—a review of the literature. *Immunopharmacol Immunotoxicol* 2013;**35**:434–442.
  64. Slordal L, Spigset O. Heart failure induced by non-cardiac drugs. *Drug Safety* 2006;**29**:567–586.
  65. Hendel RC, Friedrich MG, Schulz-Menger J, Zemmerich C, Bengel F, Berman DS, Camici PG, Flamm SD, Le Guludec D, Kim R, Lombardi M, Mahmarian J, Sechtem U, Nagel E. CMR first-pass perfusion for suspected inducible myocardial ischemia. *JACC Cardiovasc Imaging* 2016;**9**:1338–1348.
  66. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, Cosyns B, Coucke P, Dulgheru R, Edvardsen T, Gaemperli O, Galderisi M, Griffin B, Heidenreich PA, Nieman K, Plana JC, Port SC, Scherrer-Crosbie M, Schwartz RG, Sebag IA, Voigt JU, Wann S, Yang PC; European Society of Cardiology Working Groups on Nuclear Cardiology and Cardiac Computed Tomography and Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, Society of Cardiovascular Computed Tomography. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2013;**14**:721–740.
  67. Escher F, Kasner M, Kuhl U, Heymer J, Wilkenshoff U, Tschope C, Schultheiss HP. New echocardiographic findings correlate with intramyocardial inflammation in endomyocardial biopsies of patients with acute myocarditis and inflammatory cardiomyopathy. *Mediators Inflamm* 2013;**2013**:1.
  68. Wessely R, Vorpahl M, Schomig A, Klingel K. Late constrictive involvement of the pericardium in a case of previous myocarditis. *Cardiovasc Pathol* 2004;**13**:327–329.
  69. Fontes-Carvalho R, Mancio J, Marcos A, Sampaio F, Mota M, Rocha Gonçalves F, Gama V, Azevedo A, Leite-Moreira A. HIV patients have impaired diastolic function that is not aggravated by anti-retroviral treatment. *Cardiovasc Drugs Ther* 2015;**29**:31–39.
  70. Ntusi N, O'Dwyer E, Dorrell L, Wainwright E, Piechnik S, Clutton G, Hancock G, Ferreira V, Cox P, Badri M, Karamitsos T, Emmanuel S, Clarke K, Neubauer S, Holloway C. HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. *Circ Cardiovasc Imaging* 2016;**9**:e004430.
  71. Freiberg MS, Chang CH, Skanderson M, Patterson OV, DuVall SL, Brandt CA, So-Armah KA, Vasan RS, Oursler KA, Gottdiener J, Gottlieb S, Leaf D, Rodriguez-Barradas M, Tracy RP, Gibert CL, Rimland D, Bedimo RJ, Brown ST, Goetz MB, Warner A, Crothers K, Tindle HA, Alcorn C, Bachmann JM, Justice AC, Butt AA. Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: results from the Veterans Aging Cohort Study. *JAMA Cardiol* 2017;**2**:536–546.
  72. Che W, Liu W, Wei Y, Xu Y, Hou L, Matsumori A, Hu D. Increased serum N-terminal pro-B-type natriuretic peptide and left ventricle diastolic dysfunction in patients with hepatitis C virus infection. *J Viral Hepat* 2012;**19**:327–331.

73. Andy JJ, Ogunowo PO, Akpan NA, Odigwe CO, Ekanem IA, Esin RA. Helminth associated hypereosinophilia and tropical endomyocardial fibrosis (EMF) in Nigeria. *Acta Trop* 1998;**69**:127–140.
74. Barros MV, Machado FS, Ribeiro AL, Rocha MO. Diastolic function in Chagas' disease: an echo and tissue Doppler imaging study. *Eur J Echocardiogr* 2004;**5**:182–188.
75. Lurz P, Luecke C, Eitel I, Fahrenbach F, Frank C, Grothoff M, de Waha S, Rommel KP, Lurz JA, Klingel K, Kandolf R, Schuler G, Thiele H, Gutberlet M. Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-trial. *J Am Coll Cardiol* 2016;**67**:1800–1811.
76. Kasner M, Sinning D, Escher F, Lassner D, Kuhl U, Schultheiss HP, Tschöpe C. The utility of speckle tracking imaging in the diagnostic of acute myocarditis, as proven by endomyocardial biopsy. *Int J Cardiol* 2013;**168**:3023–3024.
77. Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. *Circ Res* 2019;**124**:1568–1583.
78. Plazak W, Kopec G, Tomkiewicz-Pajak L, Rubis P, Dziedzic H, Suchon E, Kostkiewicz M, Olszowska M, Musial J, Podolec P. Heart structure and function in patients with generalized autoimmune diseases: echocardiography with tissue Doppler study. *Acta Cardiol* 2011;**66**:159–165.
79. Puntmann VO, D'Cruz D, Smith Z, Pastor A, Choong P, Voigt T, Carr-White G, Sangle S, Schaeffter T, Nagel E. Native myocardial T1 mapping by cardiovascular magnetic resonance imaging in subclinical cardiomyopathy in patients with systemic lupus erythematosus. *Circ Cardiovasc Imaging* 2013;**6**:295–301.
80. Aslam F, Bandeaali SJ, Khan NA, Alam M. Diastolic dysfunction in rheumatoid arthritis: a meta-analysis and systematic review. *Arthritis Care Res (Hoboken)* 2013;**65**:534–543.
81. Vemulapalli S, Cohen L, Hsu V. Prevalence and risk factors for left ventricular diastolic dysfunction in a scleroderma cohort. *Scand J Rheumatol* 2017;**46**:281–287.
82. Chen JZ, Tang Y, Zhu MS, Xu AP. Heart involvement in systemic lupus erythematosus: a systemic review and meta-analysis. *Clin Rheumatol* 2016;**35**:2437–2448.
83. Pereira NL, Grogan M, Dec GW. Spectrum of Restrictive and infiltrative cardiomyopathies: part 1 of a 2-part series. *J Am Coll Cardiol* 2018;**71**:1130–1148.
84. Seguela PE, Iriart X, Acar P, Montaudon M, Roudaut R, Thambo JB. Eosinophilic cardiac disease: molecular, clinical and imaging aspects. *Arch Cardiovasc Dis* 2015;**108**:258–268.
85. Crane MM, Chang CM, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. *J Allergy Clin Immunol* 2010;**126**:179–181.
86. Weller PF, Buble GJ. The idiopathic hypereosinophilic syndrome. *Blood* 1994;**83**:2759–2779.
87. Ommen SR, Seward JB, Tajik AJ. Clinical and echocardiographic features of hypereosinophilic syndromes. *Am J Cardiol* 2000;**86**:110–113.
88. Tunçkale A, Ilerigelen B, Aktuğlu G. Evaluation of the left ventricular systolic and diastolic functions by echocardiography in patients with acute leukemia. *Acta Haematol* 1999;**102**:38–41.
89. Palaskas N, Thompson K, Gladish G, Agha AM, Hassan S, Ilescu C, Kim P, Durand JB, Lopez-Mattei JC. Evaluation and management of cardiac tumors. *Curr Treat Options Cardiovasc Med* 2018;**20**:29.
90. Pazos-Lopez P, Pozo E, Siqueira ME, Garcia-Lunar I, Cham M, Jacobi A, Macaluso F, Fuster V, Narula J, Sanz J. Value of CMR for the differential diagnosis of cardiac masses. *JACC Cardiovasc Imaging* 2014;**7**:896–905.
91. Mohammed SF, Mirzoyev SA, Edwards WD, Dogan A, Grogan DR, Dunlay SM, Roger VL, Gertz MA, Dispenzieri A, Zeldenrust SR, Redfield MM. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail* 2014;**2**:113–122.
92. Murtagh G, Laffin LJ, Beshai JF, Maffessanti F, Bonham CA, Patel AV, Yu Z, Addetia K, Mor-Avi V, Moss JD, Hogarth DK, Sweiss NJ, Lang RM, Patel AR. Prognosis of myocardial damage in sarcoidosis patients with preserved left ventricular ejection fraction: risk stratification using cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2016;**9**:e003738.
93. Murtagh G, Laffin LJ, Patel KV, Patel AV, Bonham CA, Yu Z, Addetia K, El-Hangouche N, Maffessanti F, Mor-Avi V, Hogarth DK, Sweiss NJ, Beshai JF, Lang RM, Patel AR. Improved detection of myocardial damage in sarcoidosis using longitudinal strain in patients with preserved left ventricular ejection fraction. *Echocardiography* 2016;**33**:1344–1352.
94. Liu P, Olivieri N. Iron overload cardiomyopathies: new insights into an old disease. *Cardiovasc Drugs Ther* 1994;**8**:101–110.
95. Spirito P, Lupi G, Melevendi C, Vecchio C. Restrictive diastolic abnormalities identified by Doppler echocardiography in patients with thalassemia major. *Circulation* 1990;**82**:88–94.
96. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. *J Card Fail* 2010;**16**:888–900.
97. Tschöpe C, Bock CT, Kasner M, Noutsias M, Westermann D, Schwimmbeck PL, Pauschinger M, Poller WC, Kuhl U, Kandolf R, Schultheiss HP. High prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. *Circulation* 2005;**111**:879–886.
98. Pieroni M, Chimenti C, Ricci R, Sale P, Russo MA, Frustaci A. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. *Circulation* 2003;**107**:1978–1984.
99. Nagueh SF. Anderson-Fabry disease and other lysosomal storage disorders. *Circulation* 2014;**130**:1081–1090.
100. Cheng Z, Cui Q, Tian Z, Xie H, Chen L, Fang L, Zhu K, Fang Q. Danon disease as a cause of concentric left ventricular hypertrophy in patients who underwent endomyocardial biopsy. *Eur Heart J* 2012;**33**:649–656.
101. Cheng Z, Fang Q. Danon disease: focusing on heart. *J Hum Genet* 2012;**57**:407–410.
102. Chen CA, Chien YH, Hwu WL, Lee NC, Wang JK, Chen LR, Lu CW, Lin MT, Chiu SN, Chiu HH, Wu MH. Left ventricular geometry, global function, and dyssynchrony in infants and children with pompe cardiomyopathy undergoing enzyme replacement therapy. *J Card Fail* 2011;**17**:930–936.
103. Kamdar F, Garry DJ. Dystrophin-deficient cardiomyopathy. *J Am Coll Cardiol* 2016;**67**:2533–2546.
104. Andratschke N, Maurer J, Molls M, Trott KR. Late radiation-induced heart disease after radiotherapy. Clinical importance, radiobiological mechanisms and strategies of prevention. *Radiother Oncol* 2011;**100**:160–166.
105. Linhart A, Cecchi F. Common presentation of rare diseases: left ventricular hypertrophy and diastolic dysfunction. *Int J Cardiol* 2018;**257**:344–350.
106. Mughtar E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017;**121**:819–837.
107. Selvaraj S, Klein I, Danzi S, Akhter N, Bonow RO, Shah SJ. Association of serum triiodothyronine with B-type natriuretic peptide and severe left ventricular diastolic dysfunction in heart failure with preserved ejection fraction. *Am J Cardiol* 2012;**110**:234–239.
108. Thomas MR, McGregor AM, Jewitt DE. Left ventricle filling abnormalities prior to and following treatment of thyrotoxicosis—is diastolic dysfunction implicated in thyrotoxic cardiomyopathy? *Eur Heart J* 1993;**14**:662–668.
109. Altay H, Colkesen Y. Parathyroid hormone and heart failure: novel biomarker strategy. *Endocr Metab Immune Disord Drug Targets* 2013;**13**:100–104.
110. Akdeniz B, Gedik A, Turan O, Ozpelit E, Ilkiz AO, Itil O, Badak O, Baris N, Comlekci A. Evaluation of left ventricular diastolic function according to new criteria and determinants in acromegaly. *Int Heart J* 2012;**53**:299–305.
111. Arcopinto M, Salzano A, Giallauria F, Bossone E, Isgaard J, Marra AM, Bobbio E, Vriz O, Aberg DN, Masarone D, De Paulis A, Saldamarco L, Vigorito C, Formisano P, Niola M, Perticone F, Bonaduce D, Sacca L, Colao A, Cittadini A, Investigators T. Growth hormone deficiency is associated with worse cardiac function, physical performance, and outcome in chronic heart failure: insights from the T.O.S.C.A. GHD Study. *PLoS One* 2017;**12**:e0170058.
112. Kamenicky P, Redheuil A, Roux C, Salenave S, Kachenoura N, Raissouni Z, Macron L, Guignat L, Jublanc C, Azarine A, Brailly S, Young J, Mousseaux E, Chanson P. Cardiac structure and function in Cushing's syndrome: a cardiac magnetic resonance imaging study. *J Clin Endocrinol Metab* 2014;**99**:E2144–53.
113. Kurisu S, Iwasaki T, Mitsuba N, Ishibashi K, Dohi Y, Nishioka K, Utsunomiya H, Hidaka T, Kihara Y. Effects of serum potassium level on left ventricular diastolic function in patients with primary aldosteronism. *Int J Cardiol* 2012;**160**:68–70.
114. Schumaecker MM, Larsen TR, Sane DC. Cardiac manifestations of adrenal insufficiency. *Rev Cardiovasc Med* 2016;**17**:131–136.
115. Ferreira VM, Marcelino M, Piechnik SK, Marini C, Karamitsos TD, Ntusi NAB, Francis JM, Robson MD, Arnold JR, Mihai R, Thomas JDJ, Herincs M, Hassan-Smith ZK, Greiser A, Arlt W, Korbonits M, Karavitaki N, Grossman AB, Wass JAH, Neubauer S. Pheochromocytoma is characterized by catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction. *J Am Coll Cardiol* 2016;**67**:2364–2374.
116. Wells GL, Little WC. Peripartum cardiomyopathy presenting as diastolic heart failure. *Congest Heart Fail* 2008;**14**:52–54.
117. Alma LJ, Bokslag A, Maas A, Franx A, Paulus WJ, de Groot C. Shared biomarkers between female diastolic heart failure and pre-eclampsia: a systematic review and meta-analysis. *ESC Heart Fail* 2017;**4**:88–98.
118. Al-Daghri NM, Al-Attas OS, Alkharfy KM, Alokail MS, Abd-Alrahman SH, Sabico S. Thiamine and its phosphate esters in relation to cardiometabolic risk factors in Saudi Arabs. *Eur J Med Res* 2013;**18**:32.
119. Yoshihisa A, Watanabe S, Yokokawa T, Misaka T, Sato T, Suzuki S, Oikawa M, Kobayashi A, Takeishi Y. Associations between acylcarnitine to free carnitine ratio and adverse prognosis in heart failure patients with reduced or preserved ejection fraction. *ESC Heart Fail* 2017;**4**:360–364.



120. Saito Y, Hashimoto T, Sasaki M, Hanaoka S, Sugai K. Effect of selenium deficiency on cardiac function of individuals with severe disabilities under long-term tube feeding. *Dev Med Child Neurol* 2008;**40**:743–748.
121. Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. *Arch Intern Med* 2004;**164**:1978–1984.
122. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol* 2018;**73**:115–123.
123. Hammer S, van der Meer RW, Lamb HJ, Schär M, de Roos A, Smit JWA, Romijn JA. Progressive caloric restriction induces dose-dependent changes in myocardial triglyceride content and diastolic function in healthy men. *J Clin Endocrinol Metab* 2008;**93**:497–503.
124. Escudero CA, Potts JE, Lam PY, De Souza AM, Mugford GJ, Sandor GG. An echocardiographic study of left ventricular size and cardiac function in adolescent females with anorexia nervosa. *Eur Eat Disord Rev* 2016;**24**:26–33.
125. Seferovic PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, Felix SB, Arbutini E, Caforio ALP, Farmakis D, Filippatos GS, Gialafos A, Kanjuh V, Krljanac G, Limongelli G, Linhart A, Lyon AR, Maksimovic R, Milicic D, Milinkovic I, Noutsias M, Oto A, Oto O, Pavlovic SU, Piepoli MF, Ristic AD, Rosano GMC, Seggewiss H, Asanin M, Seferovic JP, Ruschitzka F, Celutkiene J, Jaarsma T, Mueller C, Moura B, Hill L, Volterrani M, Lopatin Y, Metra M, Backs J, Mullens W, Chioncel O, de Boer RA, Anker S, Rapezzi C, Coats AJS, Tschope C. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:553–576.
126. Westphal JG, Rigopoulos AG, Bakogiannis C, Ludwig SE, Mavrogeni S, Bigalke B, Doenst T, Pauschinger M, Tschope C, Schulze PC, Noutsias M. The MOGE(S) classification for cardiomyopathies: current status and future outlook. *Heart Fail Rev* 2017;**22**:743–752.
127. Brescia ST, Rossano JW, Pignatelli R, Jefferies JL, Price JF, Decker JA, Denfield SW, Dreyer WJ, Smith O, Towbin JA, Kim JJ. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. *Circulation* 2013;**127**:2202–2208.
128. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet* 2015;**386**:813–825.
129. Saiki H, Petersen IA, Scott CG, Bailey KR, Dunlay SM, Finley RR, Ruddy KJ, Yan E, Redfield MM. Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. *Circulation* 2017;**135**:1388–1396.
130. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. *JACC Heart Fail* 2017;**5**:543–551.
131. Herrscher TE, Akre H, Overland B, Sandvik L, Westheim AS. High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function. *J Card Fail* 2011;**17**:420–425.
132. Cossio-Aranda J, Zamora KD, Nanda NC, Uzendu A, Keirns C, Verdejo-Paris J, Martinez-Rios MA, Espinola-Zavaleta N. Echocardiographic correlates of severe pulmonary hypertension in adult patients with ostium secundum atrial septal defect. *Echocardiography* 2016;**33**:1891–1896.
133. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2014;**63**(25 Pt A):2817–2827.
134. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan R-S, Beussink-Nelson L, Ljung Faxén U, Fermer ML, Broberg MA, Gan L-M, Lund LH. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J* 2018;**39**:3439–3450.
135. Gorter TM, Willems TP, van Melle JP. Ventricular interdependence in pulmonary arterial hypertension: providing small pieces of a complex puzzle. *Eur J Heart Fail* 2015;**17**:1–2.
136. Abdelkarim A, Levi DS, Tran B, Ghobrial J, Aboulhosn J. Fenestrated transcatheter ASD closure in adults with diastolic dysfunction and/or pulmonary hypertension: case series and review of the literature. *Congenit Heart Dis* 2016;**11**:663–671.
137. Aquaro GD, Perfetti M, Camastra G, Monti L, Dellegrottaglie S, Moro C, Pepe A, Todiere G, Lanzillo C, Scatteia A, Di Roma M, Pontone G, Perazzolo Marra M, Barison A, Di Bella G; Cardiac Magnetic Resonance Working Group of the Italian Society of Cardiology. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. *J Am Coll Cardiol* 2017;**70**:1977–1987.
138. Adler Y, Charron P, Imazio M, Badano L, Baron-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Maisch B, Mayosi B, Pavie A, Ristic AD, Sabate Tenas M, Seferovic P, Swedberg K, Tomkowski W, Achenbach S, Agewall S, Al-Attar N, Angel Ferrer J, Arad M, Asteggiano R, Bueno H, Caforio AL, Cerej S, Cecconi C, Evangelista A, Flachskampf F, Giannakoulas G, Gielen S, Habib G, Kolh P, Lambrinou E, Lancellotti P, Lazaros G, Linhart A, Meurin P, Nieman K, Piepoli MF, Price S, Roos-Hesselink J, Roubille F, Ruschitzka F, Sagrista Sauleda J, Sousa-Uva M, Uwe Voigt J, Luis Zamorano J; European Society of Cardiology. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2015;**36**:2921–2964.
139. Grimaldi A, Mocumbi AO, Freers J, Lachaud M, Mirabel M, Ferreira B, Narayanan K, Celermajer DS, Sidi D, Jouven X, Marijon E. tropical endomyocardial fibrosis: natural history, challenges, and perspectives. *Circulation* 2016;**133**:2503–2515.
140. Ino T, Benson LN, Freedom RM, Rowe RD. Natural history and prognostic risk factors in endocardial fibroelastosis. *Am J Cardiol* 1988;**62**:431–434.
141. Mansencal N, McKenna WJ, Mitry E, Beauchet A, Pellerin D, Rougier P, Dubourg O. Comparison of prognostic value of tissue Doppler imaging in carcinoid heart disease versus the value in patients with the carcinoid syndrome but without carcinoid heart disease. *Am J Cardiol* 2010;**105**:527–531.
142. Hassan SA, Banchs J, Ilescu C, Dasari A, Lopez-Mattei J, Yusuf SW. Carcinoid heart disease. *Heart* 2017;**103**:1488–1495.
143. Shaker JL. Paget's disease of bone: a review of epidemiology, pathophysiology and management. *Ther Adv Musculoskelet Dis* 2009;**1**:107–125.
144. Caughey MC, Avery CL, Ni H, Solomon SD, Matsushita K, Wruck LM, Rosamond WD, Loefer LR. Outcomes of patients with anemia and acute decompensated heart failure with preserved versus reduced ejection fraction (from the ARIC study community surveillance). *Am J Cardiol* 2014;**114**:1850–1854.
145. Vallabhajosyula S, Pruthi S, Shah S, Wiley BM, Mankad SV, Jentzer JC. Basic and advanced echocardiographic evaluation of myocardial dysfunction in sepsis and septic shock. *Anaesth Intensive Care* 2018;**46**:13–24.
146. Zamboli P, Luca S, Borrelli S, Garofalo C, Liberti ME, Pacilio M, Luca S, Palladino G, Punzi M. High-flow arteriovenous fistula and heart failure: could the indexation of blood flow rate and echocardiography have a role in the identification of patients at higher risk? *J Nephrol* 2018;**31**:975.
147. Aggarwal SR, Herrington DM, Vladutiu CJ, Newman JC, Swett K, Gonzalez F, Kizer JR, Kominarek MA, Tabb KM, Gallo LC, Talavera GA, Hurwitz BE, Rodriguez CJ. Higher number of live births is associated with left ventricular diastolic dysfunction and adverse cardiac remodeling among US Hispanic/Latina women: results from the Echocardiographic Study of Latinos. *Open Heart* 2017;**4**:e000530.
148. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. *Circulation* 2018;**137**:534–535.
149. Nijst P, Martens P, Dupont M, Tang WHW, Mullens W. Intrarenal flow alterations during transition from euolemia to intravascular volume expansion in heart failure patients. *JACC Heart Fail* 2017;**5**:672–681.
150. Koell B, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S, Dalos D, Antlanger M, Hecking M, Saemann M, Mascherbauer J, Bonderman D. Fluid status and outcome in patients with heart failure and preserved ejection fraction. *Int J Cardiol* 2017;**230**:476–481.
151. Vaduganathan M, Patel RB, Shah SJ, Butler J. Sudden cardiac death in heart failure with preserved ejection fraction: a target for therapy? *Heart Fail Rev* 2016;**21**:455–462.
152. Fang F, Zhang Q, Chan JY, Xie JM, Fung JW, Yip GW, Lam YY, Chan A, Yu CM. Deleterious effect of right ventricular apical pacing on left ventricular diastolic function and the impact of pre-existing diastolic disease. *Eur Heart J* 2011;**32**:1891–1899.
153. Joseph J, Claggett BC, Anand IS, Fleg JL, Huynh T, Desai AS, Solomon SD, O'Meara E, Mckinlay S, Pitt B, Pfeffer MA, Lewis EF. QRS duration is a predictor of adverse outcomes in heart failure with preserved ejection fraction. *JACC Heart Fail* 2016;**4**:477–486.
154. Franssen C, Chen S, Unger A, Korkmaz HI, De Keulenaer GW, Tschope C, Leite-Moreira AF, Musters R, Niessen HW, Linke WA, Paulus WJ, Hamdani N. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. *JACC Heart Fail* 2016;**4**:312–324.
155. Hamdani N, Paulus WJ. Myocardial titin and collagen in cardiac diastolic dysfunction: partners in crime. *Circulation* 2013;**128**:5–8.
156. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2014;**11**:507–515.
157. Sinning D, Kasner M, Westermann D, Schulze K, Schultheiss HP, Tschope C. Increased left ventricular stiffness impairs exercise capacity in patients with heart failure symptoms despite normal left ventricular ejection fraction. *Cardiol Res Pract* 2011;**2011**:1.
158. Kasner M, Sinning D, Lober J, Post H, Fraser AG, Pieske B, Burkhoff D, Tschope C. Heterogeneous responses of systolic and diastolic left ventricular function to exercise in patients with heart failure and preserved ejection fraction. *ESC Heart Fail* 2015;**2**:121–132.
159. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, Tschope C. Role of left

- ventricular stiffness in heart failure with normal ejection fraction. *Circulation* 2008;**117**:2051–2060.
160. Singh A, Addetia K, Maffessanti F, Mor-Avi V, Lang RM. LA strain for categorization of LV diastolic dysfunction. *JACC Cardiovasc Imaging* 2017;**10**:735–743.
  161. Sanchis L, Andrea R, Falces C, Lopez-Sobrinho T, Montserrat S, Perez-Villa F, Bijns B, Sitges M. Prognostic value of left atrial strain in outpatients with de novo heart failure. *J Am Soc Echocardiogr* 2016;**29**:1035–1042 e1.
  162. Andersen MJ, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail* 2015;**8**:41–48.
  163. Reddy YNV, Andersen MJ, Obokata M, Koeppe KE, Kane GC, Melenovsky V, Olson TP, Borlaug BA. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2017;**70**:136–148.
  164. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J* 2018;**39**:2825–2835.
  165. Abudlab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2013;**15**:776–785.
  166. Reddy YNV, Olson TP, Obokata M, Melenovsky V, Borlaug BA. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *JACC Heart Fail* 2018;**6**:665–675.
  167. Miller WL, Mullan BP. Volume overload profiles in patients with preserved and reduced ejection fraction chronic heart failure: are there differences? A pilot study. *JACC Heart Fail* 2016;**4**:453–459.
  168. Pandey A, Khara R, Park B, Haykowsky M, Borlaug BA, Lewis GD, Kitzman DW, Butler J, Berry JD. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. *JACC Heart Fail* 2018;**6**:117–126.
  169. Naeije R, Vanderpool R, Dhakal BP, Saggarr R, Saggarr R, Vachieri JL, Lewis GD. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med* 2013;**187**:576–583.
  170. Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, Mant D, McManus RJ, Holder R, Deeks J, Fletcher K, Qume M, Sohanpal S, Sanders S, Hobbs FD. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. *Health Technol Assess* 2009;**13**:1-207.
  171. Kasner M, Aleksandrov AS, Westermann D, Lassner D, Gross M, von Haehling S, Anker SD, Schultheiss H-P, Tschöpe C. Functional iron deficiency and diastolic function in heart failure with preserved ejection fraction. *Int J Cardiol* 2013;**168**:4652–4657.
  172. Bekfani T, Pellicori P, Morris D, Ebner N, Valentova M, Sandek A, Doehner W, Cleland JG, Lainscak M, Schulze PC, Anker SD, von Haehling S. Iron deficiency in patients with heart failure with preserved ejection fraction and its association with reduced exercise capacity, muscle strength and quality of life. *Clin Res Cardiol* 2018.
  173. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;**350**:1349–1353.
  174. Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazanegra R, Wanner E, Gardetto N, Garcia A, DeMaria A, Maisel AS. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. *Am J Med* 2001;**111**:274–279.
  175. Gustafsson F, Steensgaard-Hansen F, Badskaer J, Poulsen AH, Corell P, Hildebrandt P. Diagnostic and prognostic performance of N-terminal ProBNP in primary care patients with suspected heart failure. *J Card Fail* 2005;**11**(5 Suppl):S15–20.
  176. Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, Fonarow GC, Greenberg B, Januzzi JL Jr, Kiernan MS, Liu PP, Wang TJ, Yancy CW, Zile MR; American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology, Council on Basic Cardiovascular Sciences, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Cardiopulmonary Critical Care, Perioperative and Resuscitation, Council on Epidemiology and Prevention, Council on Functional Genomics and Translational Biology, Council on Quality of Care and Outcomes Research. Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. *Circulation* 2017;**135**:e1054–e1091.
  177. Tschöpe C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. *Eur Heart J* 2005;**26**:2277–2284.
  178. Anjan VY, Loftus TM, Burke MA, Akhter N, Fonarow GC, Gheorghide M, Shah SJ. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. *Am J Cardiol* 2012;**110**:870–876.
  179. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;**3**:588–595.
  180. Meijers WC, Hoekstra T, Jaarsma T, van Veldhuisen DJ, de Boer RA. Patients with heart failure with preserved ejection fraction and low levels of natriuretic peptides. *Neth Heart J* 2016;**24**:287–295.
  181. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, Roffi M, Alfieri O, Agewall S, Ahlsson A, Barbato E, Bueno H, Collet J-P, Coman IM, Czerny M, Delgado V, Fitzsimons D, Folliquet T, Gaemperli O, Habib G, Harringer W, Haude M, Hindricks G, Katus HA, Knuuti J, Kolh P, Leclercq C, McDonagh TA, Piepoli MF, Pierard LA, Ponikowski P, Rosano GMC, Ruschitzka F, Shlyakhto E, Simpson IA, Sousa-Uva M, Stepinska J, Tarantini G, Tchétché D, Aboyans V, Windecker S, Aboyans V, Agewall S, Barbato E, Bueno H, Coca A, Collet J-P, Coman IM, Dean V, Delgado V, Fitzsimons D, Gaemperli O, Hindricks G, Iung B, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, McDonagh T, Piepoli MF, Ponikowski P, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Zamorano JL, Zhdryan HK, Mascherbauer J, Samadov F, Shumavets V, Camp GV, Lončar D, Lovric D, Georgiou GM, Linhartova K, Ihlmann N, Abdelhamid M, Pern T, Turpeinen A, Srbinska-Kostovska E, Cohen A, Bakhtushvili Z, Ince H, Vavuranakis M, Temesvári A, Gudnason T, Mylotte D, Kuperstein R, Indolfi C, Pyy Y, Bajraktari G, Kerimkulova A, Rudzitis A, Mizariene V, Lebrun F, Demarco DC, Oukerraj L, Bouma BJ, Steigen TK, Komar M, De Moura Branco LM, Popescu BA, Uspenskiy V, Foscoli M, Jovicic L, Simkova I, Bunc M, de Prada JAV, Stagmo M, Kaufmann BA, Mahdhaoui A, Bozkurt E, Nesukay E, Brecker SJD; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791.
  182. Hwang JW, Park SJ, Cho EJ, Kim EK, Lee GY, Chang SA, Choi JO, Lee SC, Park SW. Relation of N-terminal Pro-B-type natriuretic peptide and left ventricular diastolic function to exercise tolerance in patients with significant valvular heart disease and normal left ventricular systolic function. *Am J Cardiol* 2017;**119**:1846–1853.
  183. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. *J Am Coll Cardiol* 2014;**63**:407–416.
  184. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction: a population-based study. *J Am Coll Cardiol* 2010;**55**:300–305.
  185. Obokata M, Borlaug BA. Stress imaging in heart failure: physiologic, diagnostic, and therapeutic insights. *Circ Cardiovasc Imaging* 2018;**11**:e007785.
  186. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreiro JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, Guidelines E, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hämilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirim A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
  187. Phan TT, Shivu GN, Abozguia K, Davies C, Nassimzadeh M, Jimenez D, Weaver R, Ahmed I, Frenneaux M. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;**3**:29–34.
  188. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E, Relax Trial FT. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013;**309**:1268–1277.
  189. Bangalore S, Yao SS, Chaudhry FA. Comparison of heart rate reserve versus 85% of age-predicted maximum heart rate as a measure of chronotropic response in patients undergoing dobutamine stress echocardiography. *Am J Cardiol* 2006;**97**:742–747.

190. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol* 2001;**37**:153–156.
191. Cahalin LP, Arena R, Labate V, Bandera F, Lavie CJ, Guazzi M. Heart rate recovery after the 6 min walk test rather than distance ambulated is a powerful prognostic indicator in heart failure with reduced and preserved ejection fraction: a comparison with cardiopulmonary exercise testing. *Eur J Heart Fail* 2013;**15**:519–527.
192. Ahmeti A, Henein MY, Ibrahim P, Elezi S, Haliti E, Poniku A, Batalli A, Bajraktari G. Quality of life questionnaire predicts poor exercise capacity only in HFpEF and not in HFrEF. *BMC Cardiovasc Disord* 2017;**17**:268.
193. Wolsk E, Kaye D, Borlaug BA, Burkhoff D, Kitzman DW, Komtebedde J, Lam CSP, Ponikowski P, Shah SJ, Gustafsson F. Resting and exercise haemodynamics in relation to six-minute walk test in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2018;**20**:715–722.
194. Gary RA, Suetta CA, Rosenberg B, Cheek D. Use of the 6-minute walk test for women with diastolic heart failure. *J Cardiopulm Rehabil* 2004;**24**:264–268.
195. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. *JACC Heart Fail* 2016;**4**:607–616.
196. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2018;**39**:1144–1161.
197. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B, Aldo D. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013;**309**:781–791.
198. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Löffler M, Hasenfuss G, Halle M, Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol* 2011;**58**:1780–1791.
199. Guazzi M, Bandera F, Ozemek C, Systrom D, Arena R. Cardiopulmonary exercise testing: what is its value? *J Am Coll Cardiol* 2017;**70**:1618–1636.
200. Corra U, Agostoni PG, Anker SD, Coats AJS, Crespo Leiro MG, de Boer RA, Hairola VP, Hill L, Lainscak M, Lund LH, Metra M, Ponikowski P, Riley J, Seferovic PM, Piepoli MF. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:3–15.
201. Kasner M, Gaub R, Sinning D, Westermann D, Steendijk P, Hoffmann W, Schultheiss HP, Tschope C. Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume loop analysis. *Eur J Echocardiogr* 2010;**11**:743–751.
202. Kasner M, Gaub R, Westermann D, Kaplan H, Akpulat S, Steendijk P, Schultheiss HP, Tschope C. Simultaneous estimation of NT-proBNP on top to mitral flow Doppler echocardiography as an accurate strategy to diagnose diastolic dysfunction in HFNEF. *Int J Cardiol* 2011;**149**:23–29.
203. Opdahl A, Remme EW, Helle-Valle T, Lyseggen E, Vartdal T, Pettersen E, Edvardsen T, Smiseth OA. Determinants of left ventricular early-diastolic lengthening velocity: independent contributions from left ventricular relaxation, restoring forces, and lengthening load. *Circulation* 2009;**119**:2578–2586.
204. Graham RJ, Gelman JS, Donelan L, Mottram PM, Peverill RE. Effect of preload reduction by haemodialysis on new indices of diastolic function. *Clin Sci (Lond)* 2003;**105**:499–506.
205. von Bibra H, Paulus WJ, St John Sutton M, Leclercq C, Schuster T, Schumm-Draeger PM. Quantification of diastolic dysfunction via the age dependence of diastolic function—impact of insulin resistance with and without type 2 diabetes. *Int J Cardiol* 2015;**182**:368–374.
206. Shah AM, Claggett B, Kitzman D, Biering-Sorensen T, Jensen JS, Cheng S, Matsushita K, Konety S, Folsom AR, Mosley TH, Wright JD, Heiss G, Solomon SD. Contemporary assessment of left ventricular diastolic function in older adults: the atherosclerosis risk in communities study. *Circulation* 2017;**135**:426–439.
207. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol* 2009;**53**:1119–1126.
208. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. *JACC Heart Fail* 2015;**3**:467–474.
209. Rosenkranz S, Gibbs JSR, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry J-L. Left ventricular heart failure and pulmonary hypertension. *Eur Heart J* 2016;**37**:942–954.
210. Aschauer S, Zotter-Tufaro C, Duca F, Kammerlander A, Dalos D, Mascherbauer J, Bonderman D. Modes of death in patients with heart failure and preserved ejection fraction. *Int J Cardiol* 2017;**228**:422–426.
211. Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, Crespo-Leiro MG, Guazzi M, Harjola VP, Heymans S, Hill L, Lainscak M, Lam CSP, Lund LH, Lyon AR, Mebazaa A, Mueller C, Paulus WJ, Pieske B, Piepoli MF, Ruschitzka F, Rutten FH, Seferovic PM, Solomon SD, Shah SJ, Triposkiadis F, Wachter R, Tschope C, de Boer RA. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:16–37.
212. Kasner M, Westermann D, Steendijk P, Drose S, Poller W, Schultheiss HP, Tschope C. Left ventricular dysfunction induced by nonsevere idiopathic pulmonary arterial hypertension: a pressure-volume relationship study. *Am J Respir Crit Care Med* 2012;**186**:181–189.
213. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;**23**:685–713; quiz 786–768.
214. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, Song JH, Hamilton J, Sengupta PP, Koliaas TJ, d'Hooge J, Aurigemma GP, Thomas JD, Badano LP. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:1–11.
215. Morris DA, Boldt LH, Eichstadt H, Ozcelik C, Haverkamp W. Myocardial systolic and diastolic performance derived by 2-dimensional speckle tracking echocardiography in heart failure with normal left ventricular ejection fraction. *Circ Heart Fail* 2012;**5**:610–620.
216. Morris DA, Ma XX, Belyavskiy B, Aravind Kumar R, Kropf M, Kraft R, Frydas A, Osmanoglou E, Marquez E, Donal E, Edelmann F, Tschope C, Pieske B, Pieske-Kraigher E. Left ventricular longitudinal systolic function analyzed by 2d speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis. *Open Heart* 2017;**4**:e000630.
217. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L, Pitt B, Pfeffer MA, Solomon SD. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circulation* 2015;**132**:402–414.
218. Carluccio E, Biagioli P, Alunni G, Murrone A, Leonelli V, Pantano P, Biscottini E, Paulus WJ, Ambrosio G. Advantages of deformation indices over systolic velocities in assessment of longitudinal systolic function in patients with heart failure and normal ejection fraction. *Eur J Heart Fail* 2011;**13**:292–302.
219. Morris DA, Otani K, Bekfani T, Takigiku K, Izumi C, Yuda S, Sakata K, Ohte N, Tanabe K, Friedrich K, Kuhnle Y, Nakatani S, Otsuji Y, Haverkamp W, Boldt LH, Takeuchi M. Multidirectional global left ventricular systolic function in normal subjects and patients with hypertension: multicenter evaluation. *J Am Soc Echocardiogr* 2014;**27**:493–500.
220. Menting ME, McGhie JS, Koopman LP, Vletter WB, Helbing WA, van den Bosch AE, Roos-Hesselink JW. Normal myocardial strain values using 2D speckle tracking echocardiography in healthy adults aged 20 to 72 years. *Echocardiography* 2016;**33**:1665–1675.
221. Sugimoto T, Dulgheru R, Bernard A, Ilardi F, Contu L, Addetia K, Caballero L, Akhaladze N, Athanassopoulos GD, Barone D, Baroni M, Cardim N, Hagendorff A, Hristova K, Lopez T, de la Morena G, Popescu BA, Moonen M, Penicka M, Ozyigit T, Rodrigo Carbonero JD, van de Veire N, von Bardeleben RS, Vinereanu D, Zamorano JL, Go YY, Rosca M, Calin A, Magne J, Cosyns B, Marchetta S, Donal E, Habib G, Galderisi M, Badano LP, Lang RM, Lancellotti P. Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:833–840.
222. Kocabay G, Muraru D, Peluso D, Cucchini U, Mihaila S, Padayattil-Jose S, Gentian D, Iliceto S, Vinereanu D, Badano LP. Normal left ventricular mechanics by two-dimensional speckle-tracking echocardiography. Reference values in healthy adults. *Rev Esp Cardiol (Engl Ed)* 2014;**67**:651–658.
223. Stefano GT, Zhao H, Schluchter M, Hoit BD. Assessment of echocardiographic left atrial size: accuracy of M-mode and two-dimensional methods and prediction of diastolic dysfunction. *Echocardiography* 2012;**29**:379–384.
224. Moya-Mur J-L, García-Martin A, García-Lledó A, Ruiz-Leria S, Jiménez-Nacher JJ, Megias-Sanz A, Taboada D, Muriel A. Indexed left atrial volume is a more sensitive indicator of filling pressures and left heart function than is anteroposterior left atrial diameter. *Echocardiography* 2010;**27**:1049–1055.
225. Marchese P, Malavasi V, Rossi L, Nikolskaya N, Donne GD, Becirovic M, Colantoni A, Luciani A, Modena MG. Indexed left atrial volume is superior to

- left atrial diameter in predicting nonvalvular atrial fibrillation recurrence after successful cardioversion: a prospective study. *Echocardiography* 2012;**29**:276–284.
226. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol* 2005;**45**:87–92.
227. Lang RM, Nanda N, Franke A, Collins KA. Live three-dimensional transthoracic echocardiography: case study world atlas. *Echocardiography* 2005;**22**:95–98.
228. Kou S, Caballero L, Dulgheru R, Voilliot D, De Sousa C, Kacharava G, Athanassopoulos GD, Barone D, Baroni M, Cardim N, Gomez De Diego JJ, Hagendorff A, Henri C, Hristova K, Lopez T, Magne J, De La Morena G, Popescu BA, Penicka M, Ozyigit T, Rodrigo Carbonero JD, Salustri A, Van De Veire N, Von Bardeleben RS, Vinereanu D, Voigt JU, Zamorano JL, Donal E, Lang RM, Badano LP, Lancellotti P. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. *Eur Heart J Cardiovasc Imaging* 2014;**15**:680–690.
229. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006;**47**:2357–2363.
230. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail* 2015;**8**:295–303.
231. Almeida P, Rodrigues J, Lourenco P, Maciel MJ, Bettencourt P. Left atrial volume index is critical for the diagnosis of heart failure with preserved ejection fraction. *J Cardiovasc Med (Hagerstown)* 2018.
232. Baltabaeva A, Marciniak M, Bijmens B, Moggridge J, He FJ, Antonios TF, MacGregor GA, Sutherland GR. Regional left ventricular deformation and geometry analysis provides insights in myocardial remodelling in mild to moderate hypertension. *Eur J Echocardiogr* 2008;**9**:501–508.
233. D'Andrea A, Radmilovic J, Ballo P, Mele D, Agricola E, Cameli M, Rossi A, Esposito R, Novo G, Mondillo S, Montisci R, Gallina S, Bossone E, Galderisi M; Working Group on Echocardiography of the Italian Society of Cardiology. Left ventricular hypertrophy or storage disease? The incremental value of speckle tracking strain bull's-eye. *Echocardiography* 2017;**34**:746–759.
234. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W; American Society of Echocardiography's Nomenclature and Standards Committee, Task Force on Chamber Quantification, American College of Cardiology Echocardiography Committee, American Heart Association, European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
235. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, O'Meara E, Desai AS, Heitner JF, Li G, Fang J, Rouleau J, Zile MR, Markov V, Ryabov V, Reis G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail* 2014;**7**:740–751.
236. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270.
237. Pieske B, Butler J, Filippatos G, Lam C, Maggioni AP, Ponikowski P, Shah S, Solomon S, Kraigher-Krainer E, Samano ET, Scalise AV, Müller K, Roessig L, Gheorghiane M; SOCRATES Investigators and Coordinators. Rationale and design of the SOLuble guanylate Cyclase stimulator in heArT failurE Studies (SOCRATES). *Eur J Heart Fail* 2014;**16**:1026–1038.
238. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;**380**:1387–1395.
239. van Doorn S, Geersing GJ, Kievit RF, van Mourik Y, Bertens LC, van Riet EES, Boonman-de Winter LJ, Moons KGM, Hoes AW, Rutten FH. Opportunistic screening for heart failure with natriuretic peptides in patients with atrial fibrillation: a meta-analysis of individual participant data of four screening studies. *Heart* 2018;**104**:1236–1237.
240. Filippatos G, Maggioni AP, Lam CSP, Pieske-Kraigher E, Butler J, Spertus J, Ponikowski P, Shah SJ, Solomon SD, Scalise AV, Mueller K, Roessig L, Bamber L, Gheorghiane M, Pieske B. Patient-reported outcomes in the SOLuble guanylate Cyclase stimulator in heArT failurE patientS with PRESERVED ejection fraction (SOCRATES-PRESERVED) study. *Eur J Heart Fail* 2017;**19**:782–791.
241. Kristensen SL, Mogensen UM, Jhund PS, Rorth R, Anand IS, Carson PE, Desai AS, Pitt B, Pfeffer MA, Solomon SD, Zile MR, Kober L, McMurray J. N-terminal Pro-B-type natriuretic peptide levels for risk prediction in patients with heart failure and preserved ejection fraction according to atrial fibrillation status. *Circ Heart Fail* 2019;**12**:e005766.
242. Wood PW, Choy JB, Nanda NC, Becher H. Left ventricular ejection fraction and volumes: it depends on the imaging method. *Echocardiography* 2014;**31**:87–100.
243. Hoffmann R, Barletta G, von Bardeleben S, Vanoverschelde JL, Kasprzak J, Greis C, Becher H. Analysis of left ventricular volumes and function: a multicenter comparison of cardiac magnetic resonance imaging, cine ventriculography, and unenhanced and contrast-enhanced two-dimensional and three-dimensional echocardiography. *J Am Soc Echocardiogr* 2014;**27**:292–301.
244. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, Edvardsen T, Garbi M, Ha JW, Kane GC, Kreeger J, Mertens L, Pibarot P, Picano E, Ryan T, Tsutsui JM, Varga A. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2016;**17**:1191–1229.
245. Erdei T, Smiseth OA, Marino P, Fraser AG. A systematic review of diastolic stress tests in heart failure with preserved ejection fraction, with proposals from the EU-FP7 MEDIA study group. *Eur J Heart Fail* 2014;**16**:1345–1361.
246. Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. *J Am Coll Cardiol* 2006;**47**:1891–1900.
247. Holland DJ, Prasad SB, Marwick TH. Contribution of exercise echocardiography to the diagnosis of heart failure with preserved ejection fraction (HFpEF). *Heart* 2010;**96**:1024–1028.
248. van Riel AC, Opatowsky AR, Santos M, Rivero JM, Dhimitri A, Mulder BJ, Bouma BJ, Landzberg MJ, Waxman AB, Systrom DM, Shah AM. Accuracy of echocardiography to estimate pulmonary artery pressures with exercise: a simultaneous invasive-noninvasive comparison. *Circ Cardiovasc Imaging* 2017;**10**:e005711.
249. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. *Eur Heart J* 2018;**39**:2810–2821.
250. Belyavskiy E, Morris DA, Url-Michitsch M, Verheyen N, Meinert A, Radhakrishnan AK, Kropf M, Frydas A, Ovchinnikov AG, Schmidt A, Tadic M, Genger M, Lindhorst R, Bobenko A, Tschöpe C, Edelmann F, Pieske-Kraigher E, Pieske B. Diastolic stress test echocardiography in patients with suspected heart failure with preserved ejection fraction: a pilot study. *ESC Heart Fail* 2019;**6**:146–153.
251. Nagueh SF, Chang SM, Nabi F, Shah DJ, Estep JD. Cardiac imaging in patients with heart failure and preserved ejection fraction. *Circ Cardiovasc Imaging* 2017;**10**:e006547.
252. Kraysenbuehl HH, Ritter M, Schneider J, Monrad ES, Grimm J. *Influence of Pressure and Volume Overload on Diastolic Compliance*. Boston: Martinus Nijhoff;1987. p143–150.
253. Perez Del Villar C, Savvatis K, Lopez B, Kasner M, Martinez-Legazpi P, Yotti R, Gonzalez A, Diez J, Fernandez-Aviles F, Tschöpe C, Bermejo J. Impact of acute hypertension transients on diastolic function in patients with heart failure with preserved ejection fraction. *Cardiovasc Res* 2017;**113**:906–914.
254. Borlaug BA, Kass DA. Invasive hemodynamic assessment in heart failure. *Heart Fail Clin* 2009;**5**:217–228.
255. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;**350**:1953–1959.
256. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;**17**:1065–1072.
257. Paulus WJ. H2FPEF score. At last, a properly validated diagnostic algorithm for heart failure with preserved ejection fraction. *Circulation* 2018;**138**:871–873.
258. Thadani U, Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. *Am J Cardiol* 1978;**41**:52–59.
259. Yoshida A, Kadota K, Kambara H, Tamaki S, Suzuki Y, Kawai C, Tamaki N, Torizuka K. Left ventricular responses to supine bicycle exercise assessed by radionuclide angiography and a Swan-Ganz catheter. *Jpn Circ J* 1985;**49**:661–671.
260. Parker JO, Thadani U. Cardiac performance at rest and during exercise in normal subjects. *Bull Eur Physiopathol Respir* 1979;**15**:935–949.
261. McCallister BD, Yipintsoi T, Hallermann FJ, Wallace RB, Frye RL. Left ventricular performance during mild supine leg exercise in coronary artery disease. *Circulation* 1968;**37**:922–931.
262. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol* 2010;**56**:855–863.

263. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B, Neumann FJ. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J* 2014;**35**:3103–3112.
264. Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, Tendera M, Maupain C, Laroche C, Rubis P, Jurcut R, Calo L, Helio TM, Sinagra G, Zdravkovic M, Kavaliuniene A, Felix SB, Grzybowski J, Losi MA, Asselbergs FW, Garcia-Pinilla JM, Salazar-Mendiguchia J, Mizia-Stec K, Maggioni AP, Investigators E. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. *Eur Heart J* 2018.
265. Chan RH, Maron BJ, Olivetto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation* 2014;**130**:484–495.
266. Hinojar R, Varma N, Child N, Goodman B, Jabbour A, Yu CY, Gebker R, Doltra A, Kelle S, Khan S, Rogers T, Arroyo Ucar E, Cummins C, Carr-White G, Nagel E, Puntmann VO. T1 Mapping in discrimination of hypertrophic phenotypes: hypertensive heart disease and hypertrophic cardiomyopathy: findings from the international T1 multicenter cardiovascular magnetic resonance study. *Circ Cardiovasc Imaging* 2015;**8**:e003285.
267. Kasner M, Aleksandrov A, Escher F, Al-Saadi N, Makowski M, Spillmann F, Genger M, Schultheiss H-P, Kühl U, Pieske B, Morris DA, Noutsias M, Tschöpe C. Multimodality imaging approach in the diagnosis of chronic myocarditis with preserved left ventricular ejection fraction (MCPeEF): the role of 2D speckle-tracking echocardiography. *Int J Cardiol* 2017;**243**:374–378.
268. Escher F, Westermann D, Gaub R, Pronk J, Bock T, Al-Saadi N, Kuhl U, Schultheiss HP, Tschope C. Development of diastolic heart failure in a 6-year follow-up study in patients after acute myocarditis. *Heart* 2011;**97**:709–714.
269. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative cardiomyopathies: part 2 of a 2-part series. *J Am Coll Cardiol* 2018;**71**:1149–1166.
270. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002;**90**:29–34.
271. Leong DP, De Pasquale CG, Selvanayagam JB. Heart failure with normal ejection fraction: the complementary roles of echocardiography and CMR imaging. *JACC Cardiovasc Imaging* 2010;**3**:409–420.
272. Rommel KP, von Roeder M, Latuscynski K, Oberueck C, Blazek S, Fengler K, Besler C, Sandri M, Lucke C, Gutberlet M, Linke A, Schuler G, Lurz P. Extracellular volume fraction for characterization of patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2016;**67**:1815–1825.
273. Puntmann VO, Pekar E, Chandrasekhar Y, Nagel E. T1 mapping in characterizing myocardial disease: a comprehensive review. *Circ Res* 2016;**119**:277–299.
274. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018;**72**:3158–3176.
275. Fraser AG. What limits functional capacity in heart failure with preserved ejection fraction? Unravelling the knots of an enigma. *JACC Heart Fail* 2018;**6**:127–129.
276. Morris DA, Belyavskiy E, Aravind-Kumar R, Kropf M, Frydas A, Braunauer K, Marquez E, Krisper M, Lindhorst R, Osmanoglu E, Boldt LH, Blaschke F, Haverkamp W, Tschope C, Edelmann F, Pieske B, Pieske-Kraigher E. Potential usefulness and clinical relevance of adding left atrial strain to left atrial volume index in the detection of left ventricular diastolic dysfunction. *JACC Cardiovasc Imaging* 2018;**11**:1405–1415.
277. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, Backs J, Bauersachs J, Burkhardt D, Bonow RO, Chopra VK, de Boer RA, de Windt L, Hamdani N, Hasenfuss G, Heymans S, Hulot JS, Konstam M, Lee RT, Linke WA, Lunde IG, Lyon AR, Maaack C, Mann DL, Mebazaa A, Mentz RJ, Nihoyannopoulos P, Papp Z, Parissis J, Pedrazzini T, Rosano G, Rouleau J, Seferovic PM, Shah AM, Starling RC, Tocchetti CG, Trochu JN, Thum T, Zannad F, Brutsaert DL, Segers VF, De Keulenaer GW. The continuous heart failure spectrum: moving beyond an ejection fraction classification. *Eur Heart J* 2019.
278. Tan YT, Wenzelburger F, Lee E, Heatlie G, Frenneaux M, Sanderson JE. Abnormal left ventricular function occurs on exercise in well-treated hypertensive subjects with normal resting echocardiography. *Heart* 2010;**96**:948–955.
279. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. *J Am Coll Cardiol* 2009;**54**:36–46.
280. Wenzelburger FW, Tan YT, Choudhary FJ, Lee ES, Leyva F, Sanderson JE. Mitral annular plane systolic excursion on exercise: a simple diagnostic tool for heart failure with preserved ejection fraction. *Eur J Heart Fail* 2011;**13**:953–960.
281. Mordi IR, Singh S, Rudd A, Srinivasan J, Frenneaux M, Tzemos N, Dawson DK. Comprehensive echocardiographic and cardiac magnetic resonance evaluation differentiates among heart failure with preserved ejection fraction patients, hypertensive patients, and healthy control subjects. *JACC Cardiovasc Imaging* 2018;**11**:577–585.
282. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail* 2015;**8**:286–294.
283. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A, Frenneaux M. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. *J Am Coll Cardiol* 2009;**54**:402–409.
284. Kasner M, Sinning D, Burkhardt D, Tschope C. Diastolic pressure-volume quotient (DPVQ) as a novel echocardiographic index for estimation of LV stiffness in HFpEF. *Clin Res Cardiol* 2015;**104**:955–963.
285. Lourenco AP, Leite-Moreira AF, Balligand JL, Bauersachs J, Dawson D, de Boer RA, de Windt LJ, Falcao-Pires I, Fontes-Carvalho R, Franz S, Giacca M, Hilfiker-Kleiner D, Hirsch E, Maaack C, Mayr M, Pieske B, Thum T, Tocchetti CG, Brutsaert DL, Heymans S. An integrative translational approach to study heart failure with preserved ejection fraction: a position paper from the Working Group on Myocardial Function of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:216–227.
286. Tschope C, Birner C, Bohm M, Bruder O, Frantz S, Luchner A, Maier L, Stork S, Kherad B, Laufs U. Heart failure with preserved ejection fraction: current management and future strategies: expert opinion on the behalf of the nucleus of the “Heart Failure Working Group” of the German Society of Cardiology (DKG). *Clin Res Cardiol* 2018;**107**:1–19.
287. Sharifov OF, Gupta H. What is the evidence that the tissue Doppler index E/e' reflects left ventricular filling pressure changes after exercise or pharmacological intervention for evaluating diastolic function? A systematic review. *J Am Heart Assoc* 2017;**6**:e004766.
288. Santos M, Rivero J, McCullough SD, West E, Opatowsky AR, Waxman AB, Systrom DM, Shah AM. E/e' ratio in patients with unexplained dyspnea: lack of accuracy in estimating left ventricular filling pressure. *Circ Heart Fail* 2015;**8**:749–756.
289. Hummel YM, Liu LCY, Lam CSP, Fonseca-Munoz DF, Damman K, Rienstra M, van der Meer P, Rosenkranz S, van Velthuisen DJ, Voors AA, Hoendermis ES. Echocardiographic estimation of left ventricular and pulmonary pressures in patients with heart failure and preserved ejection fraction: a study utilizing simultaneous echocardiography and invasive measurements. *Eur J Heart Fail* 2017;**19**:1651–1660.
290. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993;**21**:1687–1696.
291. Hadano Y, Murata K, Liu J, Oyama R, Harada N, Okuda S, Hamada Y, Tanaka N, Matsuzaki M. Can transthoracic Doppler echocardiography predict the discrepancy between left ventricular end-diastolic pressure and mean pulmonary capillary wedge pressure in patients with heart failure? *Circ J* 2005;**69**:432–438.
292. Braunauer K, Pieske-Kraigher E, Belyavskiy E, Aravind-Kumar R, Kropf M, Kraft R, Frydas A, Marquez E, Osmanoglu E, Tschöpe C, Edelmann F, Pieske B, Dungen H-D, Morris DA. Early detection of cardiac alterations by left atrial strain in patients with risk for cardiac abnormalities with preserved left ventricular systolic and diastolic function. *Int J Cardiovasc Imaging* 2018;**34**:701–711.
293. Nakai H, Takeuchi M, Nishikage T, Nagakura T, Otani S. The mitral L wave: a marker of advanced diastolic dysfunction in patients with atrial fibrillation. *Circ J* 2007;**71**:1244–1249.
294. Cameli M, Sparla S, Losito M, Righini FM, Menci D, Lisi M, D'Ascenzi F, Focardi M, Favilli R, Pierli C, Fineschi M, Mondillo S. Correlation of left atrial strain and Doppler measurements with invasive measurement of left ventricular end-diastolic pressure in patients stratified for different values of ejection fraction. *Echocardiography* 2016;**33**:398–405.
295. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghide M, Bonow RO, Huang CC, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* 2015;**131**:269–279.
296. Sanchez-Martinez S, Duchateau N, Erdei T, Kunszt G, Aakhus S, Degiovanni A, Marino P, Carluccio E, Piella G, Fraser AG, Bijns BH. Machine learning analysis of left ventricular function to characterize heart failure with preserved ejection fraction. *Circ Cardiovasc Imaging* 2018;**11**:e007138.