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HFA CONSENSUS RECOMMENDATION

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)

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Making a firm diagnosis of chronic heart failure with preserved ejection fraction (HFpEF) remains a challenge. We recommend a new stepwise diagnostic process, the 'HFA–PEFF diagnostic algorithm'. Step 1 (*P*=Pre-test assessment) is typically performed in the ambulatory setting and includes assessment for heart failure 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

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breathlessness, HFpEF can be suspected if there is a normal left ventricular (LV) 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′), 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 strain, and serum natriuretic peptide levels. Major (2 points) and Minor (1 point) criteria were defined from these measures. A score ≥5 points implies definite HFpEF; ≤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 ≥60 years, 4.9% were identified to have heart failure with preserved ejection fraction (HFpEF),[1] 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.[1–3] Heart failure with preserved ejection fraction already accounts for more than half of all heart failure (HF) hospital admissions.[1] 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'.[4] Since then, terminology has evolved through HF with normal ejection fraction to the current definition as 'HF with preserved ejection fraction'.[4]

Additional diagnostic criteria for HFpEF have been published, including one scoring system,[5] 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.[3,4,6–8] Understanding of the pathophysiology of HFpEF has advanced,[9–13] diagnostic options have evolved,[14–17] 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 left ventricular (LV) compliance] and specific aetiologies (such as amyloidosis[18]) 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.[4] 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).[4] 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, AF, treatment with ≥2 antihypertensive drugs) and echocardiographic measurements [*E*/e′ >9, pulmonary artery systolic pressure (PASP) >35 mmHg].[5]

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

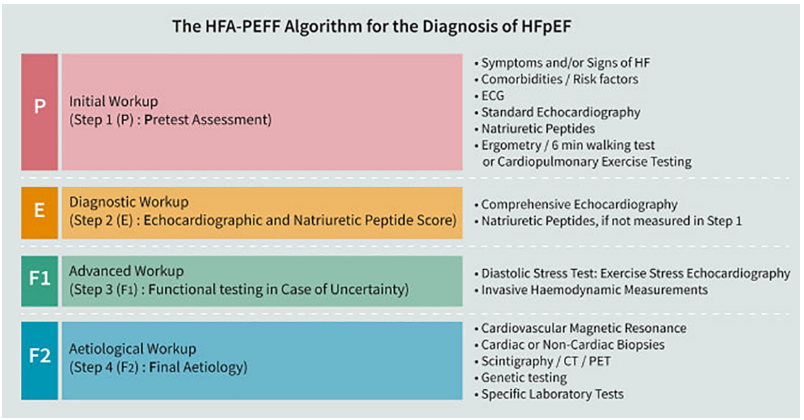

Figure 1 HFA–PEFF diagnostic algorithm. Overview of the diagnostic heart failure with preserved ejection fraction (HFpEF) steps 1–4 (P–F). CT, computed tomography; PET, positron emission tomography.

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).[19] 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.[4]

A mean *E*/*e′* index ≥15 at rest has good diagnostic value for identifying a high mean pulmonary capillary wedge pressure (mPCWP), supporting the likelihood of HFpEF,[20,21] but an *E*/*e′* ratio within the intermediate range (9–14) is less sensitive.[22] The *E*/*e′* ratio has limitations that are relevant in routine clinical practice[23–29] and its use as a 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.[30,31] Of note, our recommendations target stable symptomatic HFpEF, and NP 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.[32,33] 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.[34,35]

Besides obesity, sex, age, and renal function affect NP levels,[36,37] but using stratified cut-points only marginally improves diagnostic accuracy (net reclassification index 3%),[38] 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 ≤100% may not necessarily indicate recovery or progression of disease.[39,40]

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,[4] and adapted by others.[41] It allowed parallel diagnostic pathways starting from haemodynamic measurements, echocardiography, or NPs,[4] 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.[1,2,11,42–44] 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[45–48] (*Table 2*). They should always be considered once a diagnosis of HFpEF has been made (*Table 2*; online supplementary *Appendix S1*). It has been suggested that patients with HFrEF share a common mechanism that responds to common treatment (inhibition of the

renin–angiotensin system)[3] 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.[9,10,12,45–48,154,155] 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.[52,156–164] 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.[165] 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.[28,159,164,166,167] 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.[168] Changes in pulmonary artery pressure (PAP) on exercise are determined by the interplay between CO, pulmonary artery 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.[169] There are haemodynamic differences between patients with pre- and post-capillary pulmonary hypertension.[164]

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

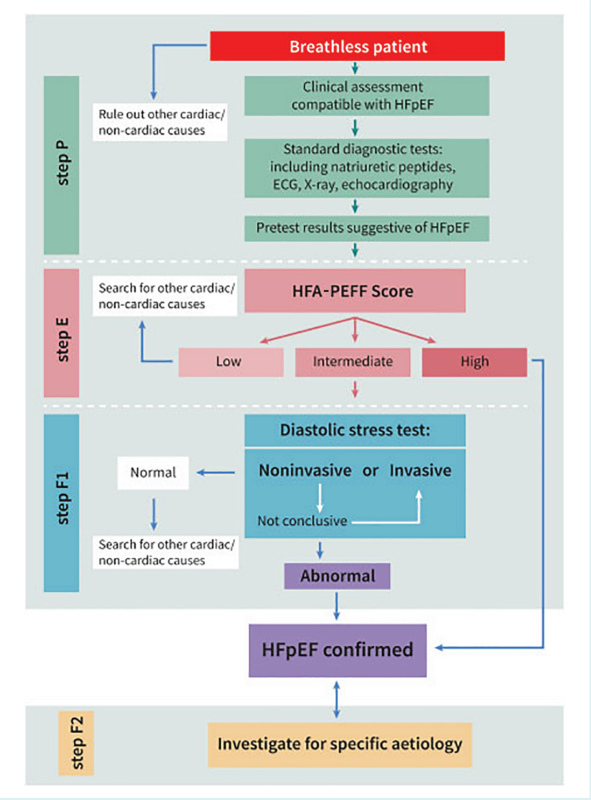

Figure 2 Flowchart of the HFA–PEFF diagnostic algorithm. Step P is meant to identify patients with the potential diagnosis of heart failure with preserved ejection fraction (HFpEF), and exclude or identify other specific causes for their heart failure-like symptoms. Patients likely to have HFpEF are 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_1 should be done, if Step E is inconclusive. Depended 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_2 is designed to identify a specific aetiology, if appropriate, when HFpEF has been diagnosed. For details of steps 2–4, see *Figures 3–5*.

HFpEF. Step 1(P) mirrors the 2016 ESC HF guidelines concerning initial HF diagnostic workup.[3]

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.[170] 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.

Electrocardiographic abnormalities

Patients may have electrocardiographic features of LVH (such as a Sokolov-Lyon index ≥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.[5] The most important indication is to detect AF, which is highly predictive of underlying HFpEF.[5,148]

Laboratory tests

Several tests are recommended, including: sodium, potassium, urea, and creatinine (with an estimated glomerular filtration rate); liver function tests; glycated haemoglobin (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.[171,172]

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 HF.[39,40,121,173–177] 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,[28,178–180] 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.[28,178–180]

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.[181,182]

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

Advanced age (age ≥ 70 in men or ≥ 75 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 ≥ 35 pg/mL or NT-proBNP ≥ 125 pg/mL)

BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Left ventricular ejection fraction should be measured, not estimated, ideally from biplane or three-dimensional images. Only small variations in normal ranges for ejection fraction by age, gender, and ethnic group have been reported, so it is recommended that a single cut-point of ≥50% is applied to define a 'preserved' ejection fraction. 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 ejection fraction, concentric remodelling or LVH, and LA 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.[183,184] 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); online supplementary *Appendix 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 CAD in patients with HFpEF impacts on mortality and should be detected and treated.[133] Coronary microvascular dysfunction is part of the HFpEF pathophysiology,[134] so non-invasive stress testing can give false-positive results.[134,186] Nonetheless, a bicycle or treadmill exercise test, or tests with higher sensitivity to detect ischaemia such as dobutamine stress echocardiography, cardiac magnetic resonance (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.[187]

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,[188,189] and defined as the failure to reach 70–80%[188–190] of the predicted maximal heart rate. Reduced heart rate recovery after exercise has prognostic value.[191–193] Reduced exercise capacity can be defined as a peak workload ≤75% of the value predicted for age. In elderly patients with suspected HFpEF a 6-minute walk test (6MWT)

Table 2 Potential specific aetiologies underlying heart failure with preserved ejection fraction-like syndromes in Step 4 (F_2)

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

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 syndrome; LV, left ventricular; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma 2.

distance ≤300 m can be considered abnormal[193] but 6MWT performance is affected by non-cardiac as well as cardiopulmonary conditions.[193,194]

In selected cases, advanced cardiopulmonary exercise testing with spiro-ergometry may be performed. Reduced exercise capacity is defined as a peak oxygen consumption (VO_2 max) ≤20 mL/kg/min, and ventilatory inefficiency as a VE/VCO_2 slope ≥30.[166,195] Cardiopulmonary exercise testing provides objective evidence of exercise capacity and may differentiate between cardiac and non-cardiac causes (pulmonary, peripheral) for dyspnoea,[157,166,196–200] but its value to distinguish between HFpEF and non-cardiac causes may be limited.[166] 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 AF. 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.[5,28,166]

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%.[5] 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^2 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,[5] which makes it an important diagnostic criterion. The utility of GLS <16% was moderate (sensitivity 62% and specificity 56%[5]).[201]

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%).[5] 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 SR), 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.[5] Combining the results of *E*/*e′* and NT-proBNP can increase their predictive value, notably their sensitivity to diagnose HFpEF.[202]

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 (online supplementary *Appendix 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.[41]

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 ≥ 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.[203,204] Left ventricular longitudinal *e′* velocity declines with age;[205] normative ranges reported from elderly participants were found to be lower than those given in the 2007 HFA consensus.[206] We include age-specific *e′* criteria in the HFA–PEFF score, measured as recommended.[41]

Average septal-lateral E/e′ *ratio.*

Major criterion: average septal-lateral E/e' ratio ≥ 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.[41] The mitral *E*/*e′* index correlates with LV stiffness and fibrosis[20,21] and is less age-dependent than *e′*.[206] It also has diagnostic value during exercise.[28,158] The E/e′ index is little influenced by changes in volume but it is influenced by the severity of LVH.[23,24]

Tricuspid regurgitation peak velocity or pulmonary arterial systolic pressure.

Major criterion: TR peak velocity > 2.8 m/s

Major criterion: PASP > 35 mmHg

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

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.[186] 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.[214]

Reduced LV longitudinal systolic strain and LV early diastolic strain rate have both been identified in HFpEF.[19,215,216] Impaired GLS predicts HF hospitalization, cardiovascular death, or cardiac arrest.[216,217] It correlates with invasive measurements of LV stiffness and with NP levels.[19,204,218] 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;[219–222] and a value below 16% (e.g. 14%) is recommended as a minor criterion.

Left atrial volume index.

Major criterion: $> 34\,mL/m^2$ [in SR]

Major criterion: $> 40\,mL/m^2$ [in AF]

Minor criterion: $29 - 34\,mL/m^2$ [in SR]

Minor criterion: $34 - 40\,mL/m^2$ [in AF]

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

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

Left ventricular mass index and relative wall thickness.

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

Minor criterion: LVMI $\geq 115\,g/m^2$ in men or $\geq 95\,g/m^2$ in women or RWT > 0.42 or LV end-diastolic wall thickness ≥ 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,[232] and a wall thickness ≥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 × 2/LVIDD), and using left ventricular mass index (LVMI) normalized to body surface area or height. Four patterns are described: normal (normal LVMI, RWT ≤0.42), concentric remodelling (normal LVMI, RWT >0.42), concentric hypertrophy (increased LVMI, RWT >0.42), and eccentric hypertrophy (increased LVMI, RWT ≤0.42).[41,233,234] In patients with HFpEF, both concentric LVH and concentric remodelling can be observed.[235]

The absence of LVH on echocardiography does not exclude HFpEF.[5] 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.[227,234,236]

Natriuretic peptides.

Major criterion: NT-proBNP $> 220\,pg/mL$, or BNP $> 80\,pg/mL$ [in SR]

Major criterion: NT-proBNP $> 660\,pg/mL$ or BNP $> 240\,pg/mL$ [in AF]

Minor criterion: NT-proBNP $125 - 220\,pg/mL$, or BNP $35 - 80\,pg/mL$ [in SR]

Minor criterion: NT-proBNP $375 - 660\,pg/mL$, or BNP $105 - 240\,pg/mL$ [in AF]

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.[3] Cut-offs are also stratified for the presence of SR or AF.

Natriuretic peptide levels should always be interpreted in context.[180] Definitive cut-offs to diagnose HFpEF in patients with

SR or in AF are not well established, and trials have used different values.[237,238] 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.[239] Average NPs were found to be threefold higher in patients with AF than in patients in SR.[34,35,240] In prevalent symptomatic HFpEF with AF, levels tend to be even higher.[241] 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*; online supplementary *Appendix 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^2; 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 ≥5 points is considered to be diagnostic of HFpEF, while a score of ≤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_1); *Figure*].

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

Step 3(F_1): *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) ≥16 mmHg, PCWP ≥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 *4*).

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.[28,41,244–248] High LV filling pressures and inadequate CO responses during exercise can also impair RV reserve.[52]

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.[159,249] 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.[28,41,244–248,250]

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[41,244] 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—age in years) and/or developed limiting symptoms.[244] 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.[245] 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[213] 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 elevated.[41,244] Changes in CO can be assessed by measuring the velocity integral of flow in the LV outflow tract, multiplied by the heart rate.

Exercise echocardiography should be considered abnormal if average E/e' ratio at peak stress increases to ≥15, with or without a peak TR velocity >3.4 m/s.[28,41,244] 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

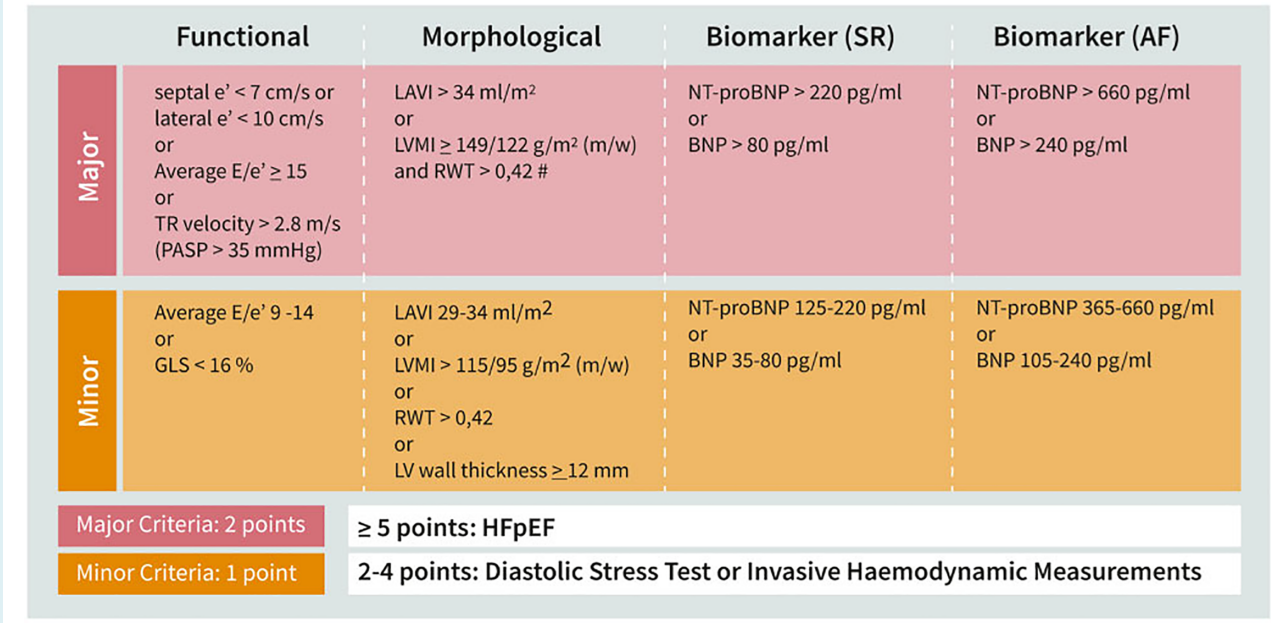

Figure 3 Step 2(E): Echocardiographic and natriuretic peptide heart failure with preserved ejection fraction (HFpEF) workup and scoring system (diagnostic workup). AF, atrial fibrillation; BNP, brain natriuretic peptide; LAVI, left atrial volume index; LV, left ventricular; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; PASP, pulmonary artery systolic pressure; RWT, relative wall thickness; SR, sinus rhythm; TR, tricuspid regurgitation.

increased pulmonary blood flow) in the absence of LV diastolic dysfunction.[251]

An average *E*/*e*′ ratio during exercise ≥15 adds 2 points to the HFA–PEFF score. An average *E*/*e*′ ratio ≥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(F_1) is ≥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.[28] 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 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, $\tau > 48$ ms[4]) or of elevated LV filling pressures at rest (LVEDP ≥16 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 ≥15 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.[28,179,230,256,257] 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[252]) If resting filling pressures are normal, exercise right heart catheterization is recommended for the definite workup of unexplained exertional dyspnoea,[179] 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.

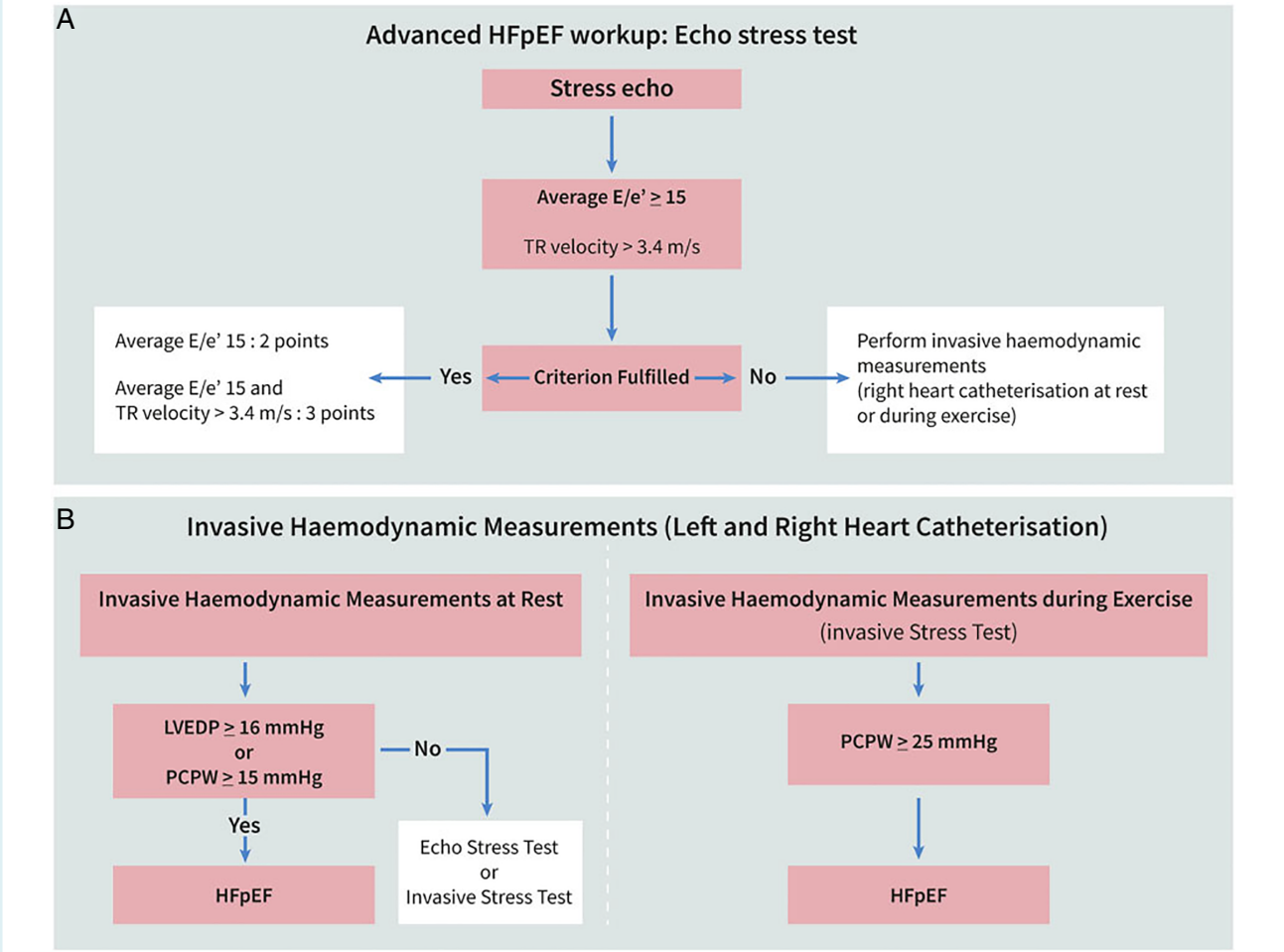

Figure 4 Step 3(F): Functional tests in cases of diagnostic uncertainty. (*A*) It shows the diastolic stress test workup with exercise echocardiography. If key haemodynamic abnormalities are identified, a definite heart failure with preserved ejection fraction (HFpEF) diagnosis can be made. (*B*) It 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. LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; TR, tricuspid regurgitation.

During supine exercise in healthy control subjects, cut-offs for peak PCWP and LVEDP are <20–23 mmHg[258,259] and <25 mmHg,[260,261] respectively. Patients with values <25 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,[256,262] indicating that the dyspnoea on exertion is mainly of cardiac origin. Patients with peak exercise PCWP ≥25 mmHg are classified as having HFpEF (online supplementary *Appendix S1*). 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.[256]

A high resting mPCWP and a pathological increase in mPCWP during exercise predict poor outcomes from HFpEF.[168,249,263] Patients with a normal mPCWP at rest (<12 mmHg) but a steep increase during exercise (to ≥25 mmHg) have a two-fold increase in mortality.[263] Ten-year mortality was 6.6% if resting mPCWP was ≤12 mmHg and peak exercise mPCWP was <25 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 (≥25 mmHg).[263]

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[28] (see online supplementary *Appendix S1* about how to perform an invasive stress test). Other causes such as significant CAD, mitral stenosis, or pericardial constriction must be excluded.

Step 4(F_2): 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*, *Figure 5*; online

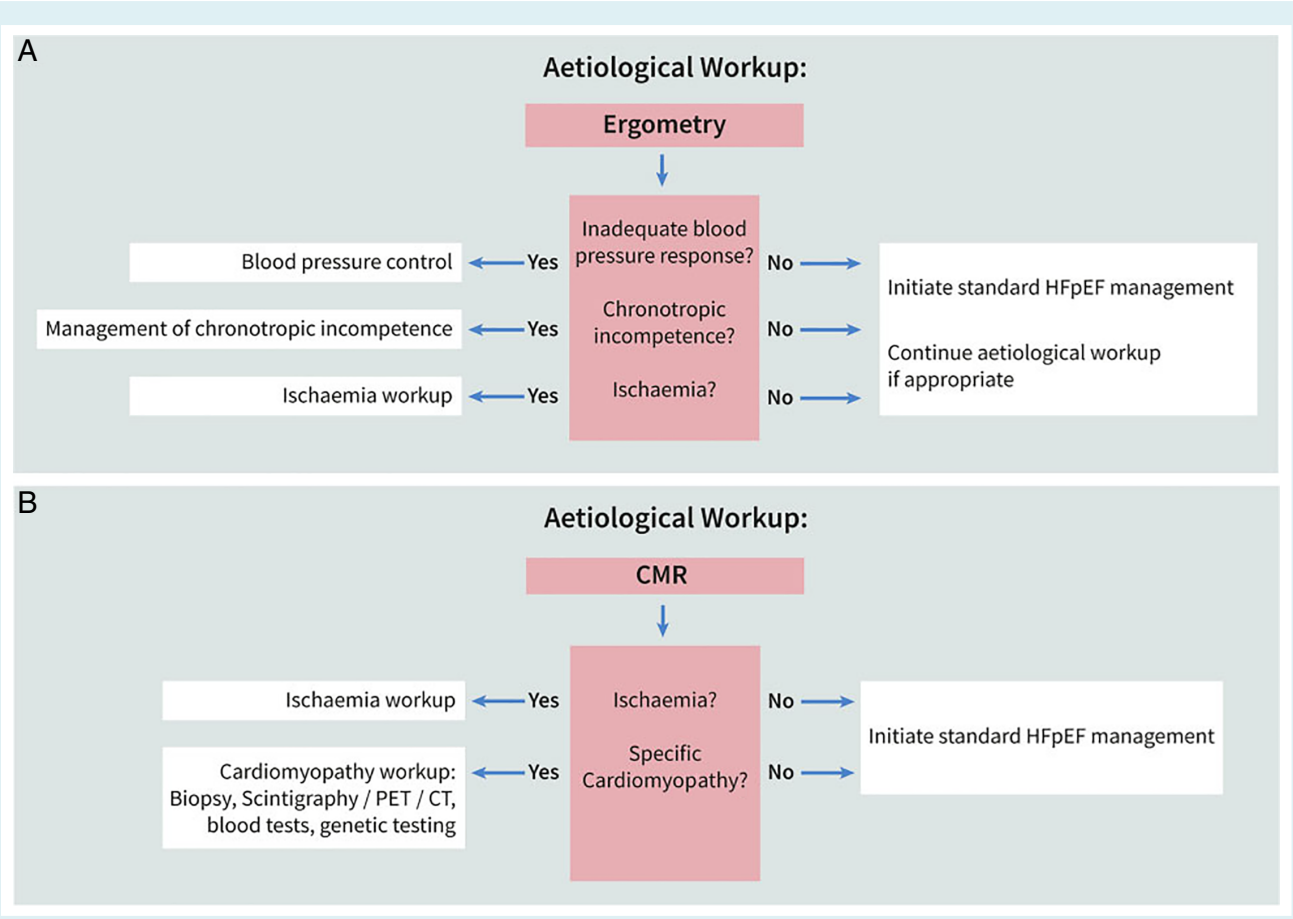

Figure 5 Step 4(F_2): Final aetiological workup. (*A*) It shows the role of ergometry to detect underlying causes such as inadequate blood pressure response, chronotropic incompetence, or myocardial ischaemia during exercise. (*B*) It shows the aetiological workup using cardiac magnetic resonance (CMR). CT, computed tomography; HFpEF, heart failure with preserved ejection fraction; PET, positron emission tomography.

supplementary *Appendix S1*). 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,[125,264–266] myocarditis and chronic inflammatory cardiomyopathy,[67,75–77,97,137,267,268] autoimmune diseases,[78,79] non-infiltrative and infiltrative cardiomyopathies,[83,125] idiopathic or acquired endomyocardial fibrosis,[269] storage diseases,[125,269] and other genetic disorders including early stages of cardiomyopathies associated with muscular dystrophy.[103] 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.[104,129]

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*; online supplementary *Appendix S1*). 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,[270] detects scar and myocardial ischaemia due to epicardial coronary disease or microvascular dysfunction,[65] 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[137,267,271–274] (online supplementary *Appendix S1*). Right or left ventricular myocardial biopsy, $^{(99m)}$Tc-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 HF 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.[168,275] It is a limitation that we suggest an algorithm that reduces it to a single clinical diagnosis. Future studies should evaluate 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.[5] 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.[276] 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[277] for predicting cardiac functional reserve and symptoms. Exercise capacity correlates better with long-axis functional reserve of the LV[52,278–281] and with peripheral blood flow[282] than with LVEF. In fact, a preserved LVEF has no diagnostic role for HFpEF except to exclude HFrEF, 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.[193]

Besides increases in filling pressures, HFpEF patients may be haemodynamically limited by their inability to adequately enhance stroke volume during exercise,[165,278,279,283] 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,[20,284] 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.[285,286] We recommend that future HFpEF studies and registries should collect, record, and analyse the detailed components that are included in the HFA–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.[287] The *E*/*e*′ index has gained a supremacy in clinical practice that is not fully supported by all clinical investigations.[288,289] The diagnostic utility of alternative indices such as retrograde pulmonary venous flow,[290,291] estimated LV stiffness (diastolic pressure–volume quotient),[284] and LA strain rate during atrial contraction[74,161,276,292] in patients in SR, and the L wave of mitral inflow[293] and LA strain during reservoir function[160,294] in patients in AF, merit further investigation.

Modern imaging methods generate a huge quantity of digital data about global and regional LV 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,[15,295,296] 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 Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Appendix S1. Supplementary materials.

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