Diagnostic role of echocardiography for patients with heart failure symptoms and preserved left ventricular ejection fraction

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Abstract

The syndrome heart failure with preserved ejection fraction (HFpEF) represents patients with different comorbidities and specific etiologies, but with a key and common alteration: an elevation in left ventricular (LV) filling pressure or pulmonary capillary wedge pressure (PCWP). Expert consensuses, society guidelines, and diagnostic scores have been stated to diagnose HFpEF syndrome based mainly on the determination of elevated LV filling pressure or PCWP by transthoracic echocardiography (TTE). Echocardiographic parameters such as early (E) and late diastolic mitral inflow velocity (mitral E/A ratio), septal and lateral mitral annular early diastolic velocity (E′), ratio of the early diastolic mitral inflow and annular velocity (E/E′-ratio), maximal left atrial volume index (LAVI$_{max}$), and tricuspid regurgitation peak velocity (V$_{TR}$) constitute the pivotal parameters for determining elevated LV filling pressure or PCWP in patients with suspected HFpEF symptoms. Notwithstanding this, taking into consideration the heterogeneity of patients with HFpEF symptoms, the term "HFpEF" should be considered as a syndrome rather than an entity since HFpEF results from different pathological entities that should and can be characterized by echocardiography and multimodality imaging. Comprehensive TTE might help diagnose specific diseases and etiologies by characterization of specific cardiac phenotypes.

Keywords
HFpEF · Ventricular elasticity · Myocardial work · Speckle tracking · Diagnostic algorithm

The syndrome of "heart failure with preserved ejection fraction" (HFpEF) represents patients with different comorbidities and specific etiologies, but with a key and common alteration, that is, an elevation of left ventricular (LV) filling pressure or pulmonary capillary wedge pressure (PCWP). Expert consensus, society guidelines, and diagnostic scores have been put forward to diagnose the syndrome of HFpEF based mainly on the determination of elevated LV filling pressure or PCWP by transthoracic echocardiography. Echocardiographic parameters—such as early (E) and late (A) diastolic mitral inflow velocity as well as transmitral E/A ratio, septal and lateral mitral annular early diastolic velocity (E′), ratio of the early diastolic mitral inflow and annular velocity (E/E′ ratio), maximal left atrial volume index (LAVI$_{max}$), and tricuspid regurgitation peak velocity (V$_{TR}$)—are pivotal to determine elevated LV filling pres-
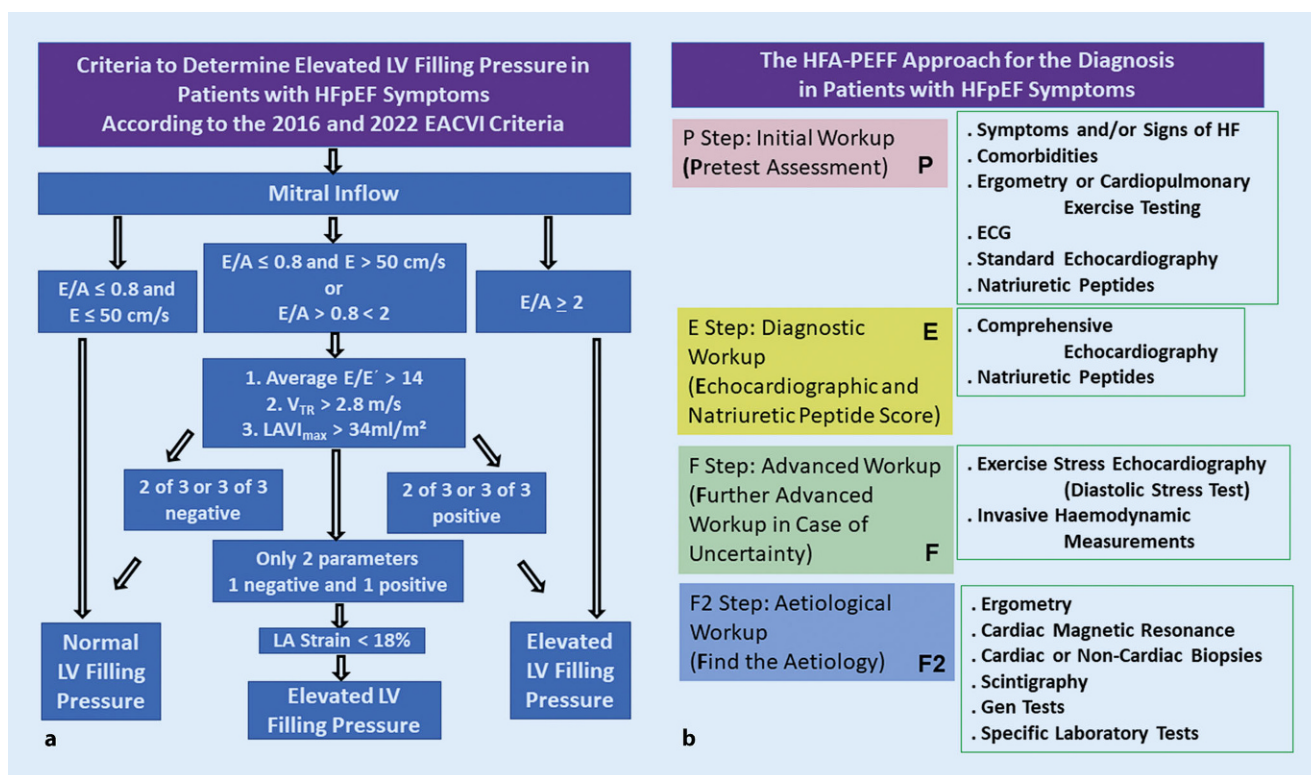
Fig. 1 ▲ Schemes illustrating the diagnostic workflow to estimate left ventricular (*LV*) filling pressures in patients with HFpEF symptoms according to the diagnostic EACVI criteria (**a**) and the HFA-PEFF approach (**b**). *E* early diastolic mitral inflow velocity, *A* late diastolic mitral inflow velocity, *E/A* transmitral E/A ratio, *E'* septal and lateral mitral annular early diastolic velocity, E/E' ratio of early diastolic mitral inflow and annular velocity, *LA* left atrial, *LAVI$_{max}$* left atrial volume index, *V$_{TR}$* tricuspid regurgitation peak velocity

sure or PCWP in patients with suspected HFpEF symptoms [1–5].

However, there is an ongoing discussion about whether HFpEF should be regarded as a single diagnosis or as a symptom complex or a syndrome [3, 4]. Patients with HFpEF symptoms obviously form a cohort of different diseases with the same clinical phenotype. As a consequence, the underlying varying individual diagnoses combined with further comorbidities need different specific treatment. Depending on the specific diagnosis, individual outcomes can significantly vary [6]. Consequently, the single diagnosis of HFpEF should be discarded because the clinical phenotype characterized by HFpEF symptoms is due to heterogeneous syndromes with different etiologies [7]. Thus, diagnostic procedures for patients with HFpEF symptoms should focus on the detection of specific underlying diseases. Between 1998 and 2021, recommendations regarding heart failure (HF) were published to characterize patients with HFpEF symptoms [2–5,

8–12] centering on the question of "how to diagnose HFpEF" [1–5, 8–12]. The initial terminology or definition of diastolic HF as "an increased resistance to filling one or both ventricles, leading to symptoms of congestion due to an inappropriate upward shift of the diastolic pressure–volume relation" [13] was later replaced by the term "heart failure with normal ejection fraction" (HFnEF), and finally by the term "HFpEF" [9] presupposing cardiac causes of the HFpEF symptoms.

Patients with diastolic HF or with HFpEF symptoms were originally characterized by the presence of signs or symptoms of congestive HF with a normal or mildly reduced LV systolic function and by the evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness. In the past, functional parameters—such as LV relaxation and stiffness—were measured via invasive investigations [8, 9]. However, over time, noninvasive techniques—especially Doppler echocardiography—have been

increasingly used to characterize LV diastolic function and elevated LV filling pressure (▣ Fig. 1; [1, 14]).

With respect to the HFpEF definition and the diagnostic procedures in patients with HFpEF symptoms, two important aspects must be mentioned:

First, the 2021 recommendation describes only three criteria for evaluating HFpEF syndrome: symptoms, LVEF ≥ 50%, and LV diastolic dysfunction (DD; [4]). The importance of normal LV size as a prerequisite for diastolic HF was highlighted in the recommendations until 2012 [8–11] and has not been emphasized since 2016 [1, 8, 9] introducing obliviscence of basic pathophysiological principles that normal LV relaxation depends on normal end-systolic LV load and LV volume [15]. Thus, eccentric LV hypertrophy is an exclusion criterion for diastolic HF. Consequently, the proper assessment of LV diameters and LV volumes by transthoracic echocardiography (TTE) as a prerequisite to characterize a pathophysiological state is an essential

Table 1 Structure of the HFA-PEFF score: measurements, criteria, and points to determine the score (0–2 points can be formed per domain)

Measurement	Criterion	Points	Score (from 0 to maximal 2 points per domain)
A. Functional measurement domain			
E′ Peak early diastolic velocity of mitral annular motion (cm/s)	*Age < 75 years*: Septal e′ < 7 *or* lateral e′ < 10	2	–
	Age ≥ 75 years: Septal e′ < 5 *or* lateral e′ < 7	2	
E/E′ as *major* criterion Peak early diastolic velocity of mitral inflow, divided by the mean value of e′ recorded at the septal and lateral mitral annulus	E/e′ ratio ≥ 15	2	
Tricuspid regurgitation velocity (m/s)	Peak velocity > 2.8	2	
E/E′ as *minor* criterion	E/e′ ratio 9–14	1	
Global longitudinal strain (GLS) of the LV in systole (%, as positive value)	GLS < 16	1	
B. Morphological measurement domain			
Left atrial volume index (ml/m²) as *major* criterion	*Patient in sinus rhythm*: > 34	2	–
	Patient in atrial fibrillation: > 40	2	
Left ventricular hypertrophy *(major)* LV mass index (LVMI) in g/m² LV relative wall thickness (RWT)	*Male patient*: LVMI ≥ 149 *and* RWT > 0.42	2	
	Female patient: LVMI ≥ 122 *and* RWT > 0.42	2	
Left atrial volume index (ml/m²) as *minor* criterion	*Patient in sinus rhythm*: 29–34	1	–
	Patient in atrial fibrillation: 34–40	1	
Left ventricular hypertrophy *Minor* criteria: LV mass index (LVMI) in g/m² LV relative wall thickness (RWT) LV wall thickness (mm)	*Male patient*: LVMI ≥ 115 RWT > 0.42 LV wall thickness ≥ 12		
	– Any 1 criterion positive	1	
	– 2 or 3 positive	1	
	Female patient: LVMI ≥ 95 RWT > 0.42 LV wall thickness ≥ 12		
	– Any 1 criterion positive	1	
	– 2 or 3 positive	1	
C. Natriuretic peptide domain			
Serum concentration of brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) (pg/ml or ng/l)	*Patient in sinus rhythm*:		–
	BNP > 80	2	
	BNP 35–80	1	
	NT-proBNP > 220	2	
	NT-proBNP 125–220	1	
	Patient in atrial fibrillation:		
	BNP > 240	2	
	BNP 105–240	1	
	NT-proBNP > 660	2	
	NT-proBNP 375–660	1	

Table 1 (Continued)			
Measurement	**Criterion**	**Points**	**Score (from 0 to maximal 2 points per domain)**
Select only 1 score from each domain (A, B, C)		TOTAL	–
Unlikely		≤ 1	
Intermediate		2–4	
Probable		≥ 5	

focus of attention [16]. Therefore, comprehensive TTE must satisfy methodological requirements to assess proper LV volumes. The accuracy of LV volume assessment by TTE is highly debated in clinical routine [17].

Second, the switch from invasive to noninvasive diagnostics to define HFpEF syndrome is mandatory because pathological LV filling patterns and elevated LV end-diastolic pressure (LVEDP) are hallmarks in these patients and measurable by TTE. Hence, both aspects have implications on diagnostic algorithms to characterize cardiac diagnoses in patients with HFpEF symptoms (◘ Fig. 1). In addition, pathological LV filling patterns are not necessarily linked to increased E/E' ratio [18, 19] and to increased N-terminal pro-brain natriuretic peptide (pro-NT-BNP) levels [20].

Diagnostic scores for patients with HFpEF symptoms

In addition to the conventional diagnostic assessment of patients with HFpEF symptoms [9–12], scores have been introduced to improve the diagnostic accuracy: the H_2FPEF score [2, 21] and the HFA-PEFF score [3]. The main principle of these scores is the attempt to increase the probability of detecting cardiac causes of HFpEF symptoms due to multifactorial considerations. The H_2FPEF score is based on weight, age, LV filing pressure measured with the E/E' ratio, and the history of hypertensive heart disease, atrial fibrillation, and pulmonary hypertension. The H_2FPEF score might overestimate atrial fibrillation in patients with HFpEF symptoms in comparison with the HFA-PEFF score. The HFA-PEFF score (◘ Fig. 1; ◘ Table 1) is based on a stepwise approach with an initial workup characterizing HF symptoms, comorbidities, and risk factors by ECG, TTE,

and natriuretic peptides; a special diagnostic workup by comprehensive TTE; an advanced workup by functional testing using diastolic stress echocardiography or invasive measurements; and finally by an etiological workup to clarify the final etiology using cardiac magnetic resonance imaging (MRI), cardiac or noncardiac biopsies, scintigraphy, computed tomography (CT), and positron emission tomography (PET), genetic testing, and/or specific laboratory tests. The HFA-PEFF score eliminated the E/A ratio as a criterion of DD.

The problems of these scores are obviously that the factors contributing to the points of the H_2FPEF score are interrelated (e.g., obesity is linked to LV hypertrophy, increased E/E'-ratio, and pulmonary hypertension), and that the most important target—the specific underlying diagnosis responsible for the HF symptoms—is addressed in the last step of the HFA-PEFF score. Thus, both scores largely disagree in classifying patients with HFpEF symptoms due to diastolic HF [22, 23].

Consequently, there are still ongoing diagnostic challenges in managing patients with HFpEF symptoms. Firstly, how to improve the detection of noncardiac causes of symptoms. And how to distinguish between early subclinical stages of diseases due to risk factors and comorbidities.

Secondly, how to characterize the "masqueraders" [3] such as coronary artery disease (CAD), valvular heart disease (VHD), arrhythmias, and pericardial constriction. And how to handle specific pathological entities that are recently not integrated into the masqueraders described here. Systemic inflammatory diseases and coronary microvascular endothelial inflammation play an important role as the cause of myocardial structural and functional alterations that can be commonly observed in obesity, diabetes, consuming neoplasms, and rheumato-

logical diseases at subclinical stages [24, 25].

Thirdly, how to deal with atrial fibrillation (AF) in patients with HFpEF symptoms. If arrhythmias are described as masqueraders, why is AF not integrated as a masquerader to exclude patients with HFpEF symptoms in the scores? Normally, AF is a symptom of pathophysiological circumstances or an underlying cardiac diagnosis.

Fourthly, the simplification of echocardiographic analysis of diastolic dysfunction by solely determining the E/E' ratio raises the fundamental question of why comprehensive TTE should not focus directly on specific diagnoses instead of describing a multifactorial HFpEF hodgepodge.

In summary, the so-called HFpEF diagnosis according to the scores merges a cohort of patients with HFpEF symptoms, in which patients with chronic hypertensive heart disease and storage diseases are mixed with patients of unknown, unclear, or undetected specific cardiac or noncardiac diagnoses. Thus, the diagnostic HFpEF mishmash of similar, but still heterogeneous, clinical phenogroups with extremely varying disease outcome is presumably the reason of treatment failure in several HFpEF trials [26–28].

Comprehensive echocardiography for specific diagnosis in HFpEF

One of the cornerstones of the diagnostic HFpEF scores is to perform TTE [1–12]. Pathological TTE findings in patients with HFpEF symptoms are characterized by the parameters LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), E', E/E' ratio, E/A ratio, transmitral deceleration time (DT), the time duration of ArD – AD (ArD, = duration of reverse pulmonary vein atrial systole flow; AD = duration of mitral valve atrial wave flow), the maximum left atrial (LA) volume index ($LAVI_{max}$), and the LV
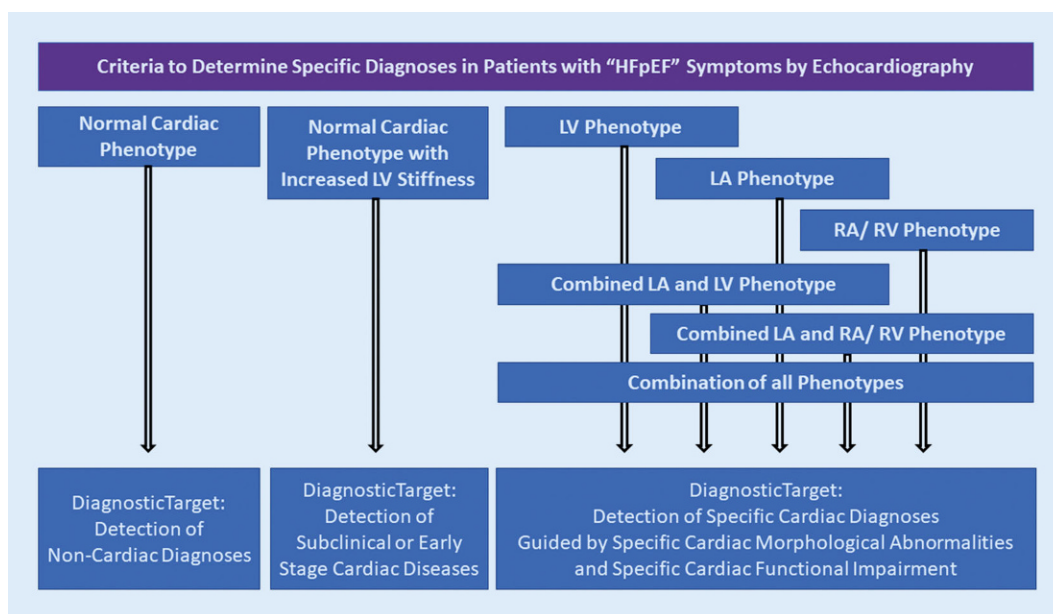
Fig. 2 ◀ Scheme of the echocardiographic phenotyping of patients with HFpEF symptoms to detect specific underlying diseases. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

mass index (LVMI; [8, 9]). Recently, the maximum tricuspid regurgitant velocity (V_{TR}), calculated systolic pulmonary artery pressure (sPAP), and LV global longitudinal strain (GLS) have been added [3, 4]. However, the accuracy of these pivotal parameters to characterize diastolic HF is limited due to a sensitivity between 26 and 70% and a specificity between 56 and 86% [2]. Thus, the diagnostic approach of comprehensive TTE must be improved to detect specific cardiac or noncardiac diagnoses through specific echocardiographic findings in patients with HFpEF symptoms. Generally, TTE imaging can be completed by additional imaging modalities [5, 29–32].

An advanced diagnostic TTE workflow includes a systematic morphological and functional classification with additional conventional as well as modern echocardiographic parameters [1, 16, 33–35]. It is obvious that the masqueraders VHD, CAD, and pericardial constriction as well as eccentric LV hypertrophy must be detected as specific diagnoses [3]. Hereafter, the echocardiographic characterization might focus on the proper detection of echocardiographic cardiac phenotypes, which are indicative of specific diagnoses (◻ **Fig. 2**). Echocardiographic phenotypes are determined by isolated morphological and functional abnormalities of the left ventricle, the left atrium, and the right cardiac chambers as well as by

their combination (◻ **Fig. 2**). This conventional echocardiographic phenotyping using a "human intelligence approach" corresponds to current methodological developments of machine learning-derived echocardiographic phenotyping [36].

Alterations of LV wall size and consecutive LV geometry can be easily detected by conventional TTE assessing the LV wall, LV mass, LV volume, and LV geometry. The parameters that are necessary for characterizing this echocardiographic LV phenotype are LV wall thickness, relative wall thickness (RWT), LVMI, LV end-diastolic and end-systolic diameter (LVEDD, LVESD) as well as volume (LVEDV, LVESV), LVEF, LVLV remodeling index (LVRI), and LV sphericity ratio and index [16]. In addition, mitral annular plane systolic excursion (MAPSE) and LV strain assessment are also established in the clinical scenario.

Alterations in LA size and function are commonly detectable by LA planimetry and Doppler echocardiography. Parameters to characterize this echocardiographic LA phenotype are LAVI, E/A ratio, DC, and ArD-AD [1]. However, parameters such as minimum LA volume index ($LAVI_{min}$), LA emptying fraction, LA strain including the compounds of reservoir, conduit, and contraction LA strain as well as E′, E/E′ ratio, isovolumetric relaxation time (IVRT), V_{TR}, and sPAP to characterize DD should be added [34, 35].

Alterations in right chamber morphology and function can be primarily detected by right atrial and right ventricular (RA, RV) volume assessment. Due to the bipyramidal RV shape, three-dimensional RV volume assessment is necessary with respect to objectification and accuracy. In general, the volumes of the cardiac chambers can be assessed more precisely by three-dimensional or triplane datasets [33]. In addition, diastolic RV wall thickness, radial RV thickening, RV eccentricity index, tricuspid annular plane systolic excursion (TAPSE), and RV as well as RA strain can be added to assess the RA/RV phenotype.

The main problem with TTE is the detection of subclinical or early disease stages in patients with a normal echocardiographic phenotype if abnormal LV relaxation, LV filling, LV diastolic distensibility, and LV diastolic stiffness only are present. Additional parameters such as end-systolic elastance (Ees) and arterial elastance (Ea) might be added to the proposed echocardiographic parameters E′, E/E′ ratio, IVRT, E/A ratio, DC, and ArD-AR. The estimation of increased LV chamber stiffness through the invasive analysis of the LV pressure–volume relationship is the gold standard for characterizing LV distensibility [18, 19]. Ees is determined by the slope of the end-systolic pressure volume relationship (ESPVR), while Ea is reflected by the negative slope between ESPVR and the LVEDV at zero LV
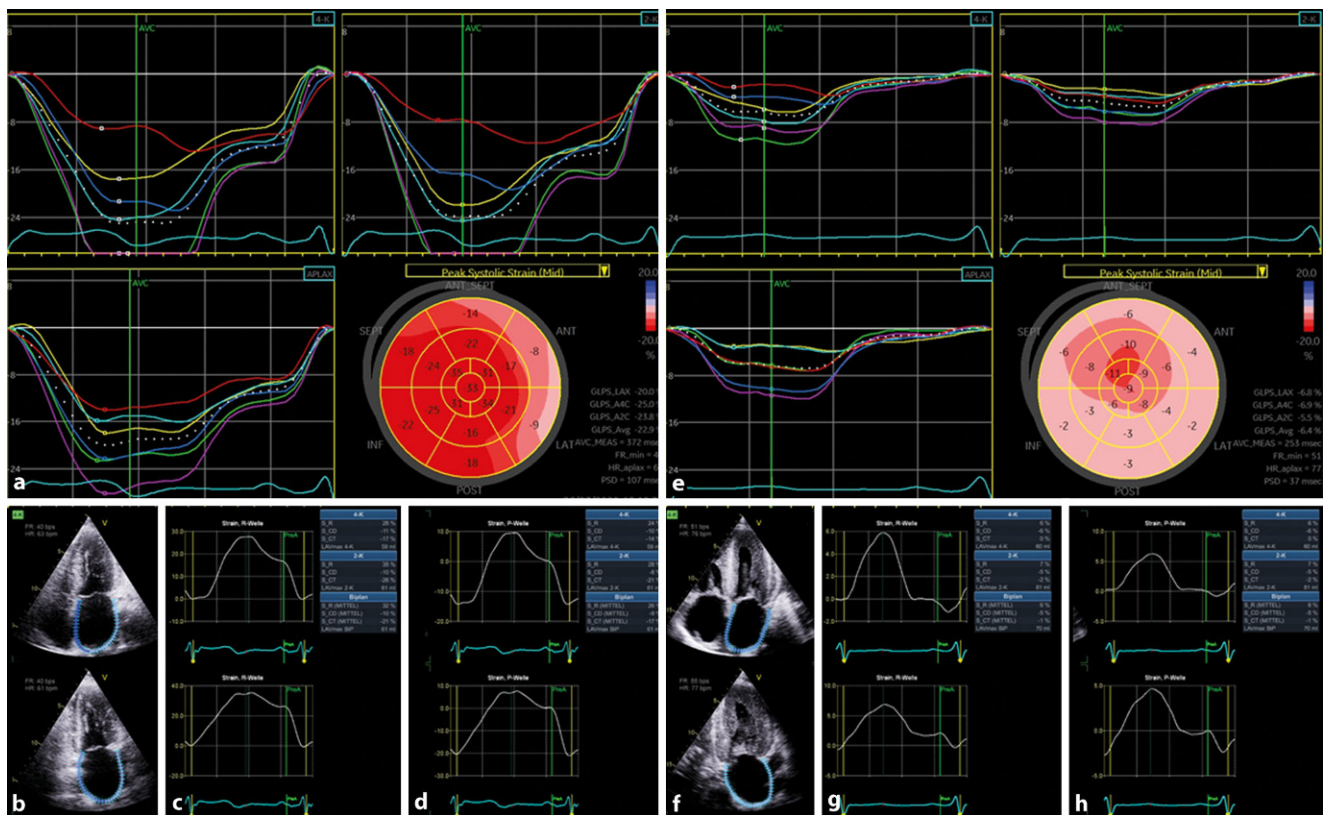
Fig. 3 ◀ Comprehensive echocardiography in patients with HFpEF symptoms. **a–d** Strain imaging in a patient with hypertensive heart disease (combined LA and LV phenotype). **a** Regional longitudinal LV strain graphs and the LV strain pattern; **b** tracking area of the biplane atrial strain assessment; **c** atrial strain curves adjusted to the r-wave, and **d** adjusted to the p-wave. **e–h** Corresponding strain imaging in a patient with amyloidosis (combined LA, LV, and RA/RV phenotype). The reduced LV as well as LA deformation in storage disease in comparison with hypertensive heart disease is objectively shown. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

pressure and estimates global myocardial afterload [37–39]. Compared to LVEF or GLS, Ees, Ea, and global myocardial work are load-independent parameters of LV systolic function [40–42]. The single-beat noninvasive echocardiographic approach for calculating Ees and Ea requires the measurement of noninvasive blood pressure recordings as well as the systolic time interval, defined by pre-ejection period and systolic ejection time derived from pulsed-waved Doppler recordings in the LV outflow tract with simultaneous ECG recordings. Noninvasive assessment of myocardial work requires LV strain analysis and noninvasive blood pressure recordings. The complex equations for calculating Ees, Ea, and myocardial work must be facilitated by automated software to establish these measurements in the clinical scenario.

Thus, the detailed characterization of echocardiographic phenotypes and their combinations by an advanced TTE approach might improve the direct detection of specific underlying diagnoses in patients with HFpEF symptoms (◘ Figs. 2 and 3).

Diastolic stress echocardiography to unmask diastolic dysfunction in HFpEF

If advanced echocardiographic assessment at rest in patients with HFpEF symptoms is limited in determining cardiac causes due to DD, machine learning-derived echocardiographic phenotypes might help identify subclinical asymptomatic HF patients at rest [36] or diastolic stress echocardiography might help unmask DD by inducing pathological changes of diastolic filling properties due to structural cardiac findings at stress [43]. However, physical diastolic stress echocardiography [3, 43] is a methodological challenge. Standardiza-

tion of image acquisition at the respective stress levels is a prerequisite to gain verifiable results. In particular, the sample volume position of the pulsed wave Doppler spectra of the transmitral flow velocities and of the basal myocardial tissue velocities must be comparable between rest and stress. In addition, the fusion of E and A wave with increasing heart rate is often observed at low stress levels, limiting the value of stress testing. Therefore, DD detection should be confirmed by invasive hemodynamic exercise testing if the diagnosis with diastolic stress echocardiography is uncertain [44, 45]. Despite high methodological standards, diastolic stress echocardiography has the potential to distinguish between cardiac and noncardiac causes of HFpEF symptoms and to increase the sensitivity to detect DD.

Conclusion

Patients with symptoms of heart failure with preserved ejection fraction (HFpEF) form a heterogeneous cohort with different underlying diseases. The diagnostic approach for characterizing HF patients with normal or preserved LVEF is challenging because HFpEF symptoms can be induced by cardiac as well as noncardiac underlying diagnoses. Algorithms for HFpEF describe a cohort of patients with hypertensive heart disease, storage diseases, and unknown, unclear, or undetected specific cardiac or noncardiac pathologies. Thus, a more detailed echocardiographic approach including stress echocardiography might be helpful for detecting specific diagnoses, because the outcome of the underlying diseases in patients with HFpEF symptoms can vary extremely. Thus, the term "HFpEF" as a diagnosis may be misleading; HFpEF symptoms form a syndrome resulting from different pathological entities. The detection of the specific underlying diagnosis is possible by advanced echocardiography and multimodality imaging.

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Declarations

Conflict of interest. A. Hagendorff, S. Stöbe, J. Kandels, R. de Boer and C. Tschöpe declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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