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The Role of Echocardiography in Heart Failure with Preserved Ejection Fraction: What Do We Want from Imaging?

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Abstract

Non-invasive imaging, particularly echocardiography, plays a central role in the evaluation for heart failure with preserved ejection fraction (HFpEF). Echocardiography helps to rule in HFpEF among patients with unexplained dyspnea when the diagnosis is uncertain. In established HFpEF, echocardiography provides important insights into pathophysiology and phenotyping, such as isolated left ventricular diastolic dysfunction, left atrial dysfunction, abnormal right ventricular-pulmonary artery coupling, ischemia, or obesity phenotypes. Finally, imaging enables risk stratification for HFpEF. In this review, we will provide a critical appraisal of the role of echocardiography in the diagnosis and evaluation of HFpEF.

Keywords

diagnosis; diastolic function; echocardiography; filling pressure; heart failure; phenotyping; risk stratification

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a common clinical syndrome that is increasing in prevalence coupled with the growing population burden of aging and comorbidities.[1, 2] Over half of patients with unexplained exertional dyspnea referred for invasive evaluation are ultimately found to have HFpEF, and over 70% of patients with prevalent HF above the age of 65 years have normal EF.[3, 4] Cardiovascular imaging plays a key role in the evaluation and management of HFpEF, particularly echocardiography.[5]

Echocardiography provides essential information on cardiac structure, function, and hemodynamics and is performed in essentially all patients where there is clinical suspicion for HFpEF.[6] From a practical standpoint, the most important questions that can be addressed

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center on 1) diagnosis, determining whether a patient with unexplained dyspnea truly has HFpEF or an alternate cardiac or non-cardiac cause of dyspnea, and 2) management, where imaging can be used to evaluate hemodynamic status, determine underlying pathophysiologic phenotypes and 3) risk stratification for outcomes. In this review, we will provide a critical appraisal of the role of echocardiography crossing these 3 categories involved in the care of patients with or suspected of having HFpEF.

Case

A 72-year-old man was referred for evaluation of a two-year history of progressive exertional dyspnea with fatigue. He was obese (body mass index [BMI]: 36.2 kg/m^2) and had chronic systemic hypertension treated with lisinopril and chlorthalidone. Jugular venous pressure was 8 cm, and there was no lower edema. N-terminal pro-B-type natriuretic peptide was 80pg/ml. Transthoracic echocardiography revealed normal left ventricular (LV) EF (62%), LV size (LV end-diastolic dimension 51 mm), left atrial (LA) volume (LA volume index [LAVI], 22 ml/m^2), and right ventricular (RV) size, with normal systolic function. Transmitral inflow Doppler showed an E/A ratio of 1.0 with medial E/e' of 12.9 and estimated right ventricular systolic pressure (RVSP) was 36 mmHg (peak tricuspid regurgitation [TR] velocity 2.8 m/sec). LV global longitudinal strain (GLS) was mildly reduced at −16.8%. A prominent epicardial fat pad was seen on echocardiography.

This common clinical presentation should raise clinical suspicion for HFpEF, and if present, it raises the question of what the underlying drivers of this patient's HFpEF syndrome are. In the text below, we shall use this to frame what we seek from echocardiography in the evaluation of suspected HFpEF.

Diastolic Dysfunction and HFpEF—While the two terms are often used interchangeably, it is important to remember that diastolic dysfunction is not equivalent to HFpEF. HFpEF by definition requires the presence of elevated filling pressures either at rest or with exertion without which systemic perfusion cannot be maintained.[7] Although diastolic dysfunction is a central feature in HFpEF, the pathophysiology is complex with variable contributions from diastolic dysfunction, impaired contractile reserve, impaired atrial function, relative pericardial restraint and abnormal ventricular vascular coupling which all contribute to the elevation in pulmonary venous and left sided filling pressures.[8–10] Increases in LV filling pressures promote symptoms of dyspnea,[11] impair exercise capacity,[11, 12] and increase risk for HF hospitalization and mortality in HFpEF.[1314] Thus diastolic dysfunction is considered to be the cornerstone of HFpEF pathophysiology.[8]

Diastolic dysfunction is defined by prolongation of relaxation in early diastole, an increase in viscoelastic LV diastolic chamber stiffness, or some combination of the two.[15] Declines in LV relaxation and compliance are part of normal aging, and accordingly not all patients with diastolic dysfunction have or will develop go on to develop clinical HFpEF.[16–18] In one prospective cohort study, only 12% of subjects with severe diastolic dysfunction at initial evaluation developed clinical HFpEF over 6 years of follow up.[19] Approximately one-third of patients with HFpEF enrolled in clinical trials lack echocardiographic evidence of diastolic dysfunction.[20–22] Thus, while echocardiographic categorization of diastolic

dysfunction is prognostic[23] and useful to predict incident HFpEF,[19] recent studies have suggested that they should not be used in isolation for diagnostic purposes[3, 24].

Echocardiography to Identify Elevated Filling Pressure—The ultimate expression of abnormalities in diastolic function is an elevation in LV filling pressures. There are a number of echocardiographic indices that have been applied for the estimation of filling pressures, but the most studied (by far) is the ratio of early diastolic transmitral inflow velocity to mitral annular tissue velocity (E/e').[24–28] The diagnostic accuracy of the E/e' ratio in HFpEF has recently been questioned, as a recent meta-analysis reported only a modest correlation between E/e' and invasively-obtained resting filling pressures across studies (pooled r=0.56).[5] Correlations between E/e' and invasive filling pressure in subjects with preserved EF have been reported in 30 studies and vary widely in the strength of correlation (r=0.02 to 0.87) (Table 1). Despite its variable and often modest correlation with filling pressure, E/e' has been reported to have prognostic value in patients with HFpEF.[5, 21, 29]

Transmitral flow (TMF) is driven by the LA-LV pressure gradient during diastole and can be used for identification of elevated filling pressure in subjects with normal sinus rhythm. TMF is often graded as normal, impaired relaxation, pseudo-normal, and restrictive filling patterns. Since TMF is influenced by LA pressure, E/A ratio displays a U-shape relationship with LV filling pressure. The biphasic relationship of E/A ratio makes it difficult to differentiate normal and pseudo-normal patterns, and one must rely on other echocardiographic indices such as indexing E wave velocity to e' septal tissue Doppler velocity.[6]

Other indices have also been related to LV filling pressures.[6] Pulmonary vein (PV) Doppler flow reversals during atrial contraction provide a measure of end diastolic LV operative compliance and LVEDP. With increased impedance to end-diastolic atrial contraction, there is a prolongation of flow reversal into the PV relative to the duration of forward flow. Differences in these durations exceeding 20–30ms have been correlated with increased LVEDP,[30–33] with a diagnostic sensitivity of 87% and specificity of 85%.[34] Six studies have reported reasonable correlations between backward and forward PV flow duration and invasively-measured LV filling pressure in patients with preserved EF (r=0.39–0.70).[27, 34–38] While these data appear favorable, diagnostic-quality recordings of the PV are often not technically feasible, and other PV parameters such as systolic and diastolic flow velocities are less robust.[25, 27, 35] As such, PV Doppler indices have not gained substantial traction as indicators of filling pressure.

An alternative method of assessing the impact of elevated left sided filling pressures chronically is to determine their downstream effects on the LA. Atrial operating compliance and atrial volume are linked to LV diastolic function through atrioventricular coupling; whereby chronic impedance to LA emptying secondary to LV diastolic dysfunction causes LA remodeling and dysfunction.[39–42] LA volume is believed to reflect the chronic effects of LV filling pressure elevation over time, rather than instantaneous pressures.

Because this is a chronic marker, correlations between LA volume index and ambient LV filling pressures are lower than what has been reported for other indices such as E/e' and PV Doppler (r=0.10 to 0.49).[28, 43–46] In contrast to E/e', LA volume index is not strongly associated with outcome in HFpEF.[21, 47–49] This does not mean that cumulative effects of filling pressure does not contribute to outcome in HFpEF, but rather emphasizes the need for an alternative parameter to evaluate LA burden such as LA reservoir strain, which we will be discuss below.

Earlier studies suggested that patients with HFpEF display concentric hypertrophy, which leads to increased passive chamber stiffness and thus elevated filling pressure.[50] Indeed, LV mass index has been reported to be modestly correlated with invasively-measured LV filling pressure (r=0.41–0.48, p<0.001).[43, 44] Current ESC guidelines include increased LV mass index as one of the criteria for the diagnosis of HFpEF.[51] However, community-based studies, as well as trial ancillary studies, have shown that many patients with HFpEF have either concentric remodeling in the absence of hypertrophy, or even normal LV geometry.[22, 52, 53]

Consistent with this observation, it was recently demonstrated that LV hypertrophy was highly specific (88%) but poorly sensitive (26%) for the diagnosis of HFpEF and therefore its absence cannot be used to rule out the diagnosis.[3] When evaluating LV morphology, care should be taken to exclude other differential diagnoses that mimic HFpEF (Table 2). Whenever significant LV hypertrophy is identified, the diagnosis of amyloidosis must be considered, particularly in the presence of a pericardial effusion or apical sparing pattern of LV strain.[54] In a series of consecutive patients with LVH≥12 mm, amyloidosis represented 13% of hospitalized "HFpEF".[55] This distinction from HFpEF is particularly important now that new treatments are becoming available for cardiac amyloid.[56]

Strain and strain rate imaging have also been evaluated to estimate LV filling pressure. The ratio of mitral E velocity to longitudinal diastolic strain rate during early diastole (E/SR_E) correlated moderately with invasively-obtained filling pressure, with high sensitivity and specificity (E/SR_E >11.5, 91% and 78%, respectively).[57–59] One study reported that E/SR_E predicted cardiovascular outcomes better than E/e'.[60] Smaller studies have demonstrated correlations between LV GLS and filling pressures.[57, 61, 62] Left atrial longitudinal strain during ventricular systole represents atrial reservoir function and is reduced in HFpEF.[63] One study has demonstrated a high correlation between LA reservoir strain and invasive filling pressure (r=−0.79) in patients with preserved EF,[45] but its discriminatory ability to diagnose HFpEF from non-cardiac dyspnea remains unexplored. On the other hand, decreased GLS (>−16%) has been reported to be associated with adverse outcomes in HFpEF.[29]

Optimal Use of Echocardiography in Diagnosis of HFpEF—The diagnosis of HFpEF is obvious in the patient with overt congestion at rest, where jugular vein distention, peripheral edema and pulmonary congestion are present, and echocardiography is not necessary to establish the clinical diagnosis. In contrast, evaluation of the euvolemic patient with exertional dyspnea presents a greater diagnostic challenge.[3, 24, 64] Correlative analyses are important to demonstrate strength of association between two variables, and as described

above, numerous echocardiographic indices are correlated with filling pressures. However, from a diagnostic perspective, it is more important to consider the ability of a test to discriminate cases from controls rather than simple correlative analyses.

In this regard, an elevated E/e' ratio has been reported to have excellent specificity for identifying high LV filling pressure (77–100%), suggesting that it may be useful to 'rule in' the diagnosis of HFpEF when elevated.[3, 24, 37, 38, 44, 46, 58, 65–68] However, the E/e' ratio displays poor sensitivity (range 0–73%), meaning it is not an effective test to exclude HFpEF.[24, 37, 38, 44, 46, 65–67] Because impaired relaxation is expected to accompany high filling pressures, it has been proposed that elevation in E/e' be coupled with an impairment in the e' velocity.[51] This more stringent requirement may improve specificity, but will only further compromise sensitivity.[24]

Expert consensus guidelines have recommended use of an elevated LA volume index at a cutpoint of >34 ml/m^2 as another indicator of diastolic dysfunction.[69–71] When prospectively evaluated, an enlarged LA volume index (>34ml/m^2) is indeed specific (83%) for HFpEF, but like E/e', it is poorly sensitive (49%).[3, 46] One potential concern is the appropriate method of allometrically scaling LA volume to body size in obese patients, who represent the majority of the HFpEF population.[72] With obesity, a linear adjustment of LA volume index to body surface area may result in underestimation of LA remodeling, because the quotient will be lower as body mass increases. Another complicating issue in the evaluation of LA volume is the presence of atrial fibrillation.[73] Despite this, recent data have shown that the presence of atrial fibrillation in the patient with dyspnea is highly predictive of the presence of underlying HFpEF, making this less of an issue, at least as it pertains to diagnosis.[3, 74]

The current guidelines have recommended a combination of different indices of diastolic function to diagnose HFpEF. While these approaches have been found to display high specificity, sensitivity is poor.[3, 24] We recently developed a simple score to predict the presence of HFpEF among more than 500 patients with unexplained dyspnea.[3] While many echocardiographic variables were predictive of HFpEF diagnosis in isolation (Table 3), we found that the combination of elevated E/e' (>9) and RVSP (>35 mmHg) were additive to clinical characteristics, including older age, larger body mass index, number of antihypertensive drugs, and history of atrial fibrillation in multivariable analyses (H_2FPEF score, Figure 1).[3] This scheme was then validated in an independent test cohort where it retained excellent discriminatory capacity (AUC 0.886; $p<0.0001$). Thus, while numerous echocardiographic indicators are related to the presence or absence of HFpEF (Table 2), it appears that the combination of E/e' and RVSP is optimal to inform the noninvasive diagnosis.

According to the approach,[3] the findings in this case on echocardiography (elevated E/e' and RVSP) along with older age, obesity, and use of 2 antihypertensive drugs indicate HFpEF is the likely cause of exertional dyspnea with 92% probability.

In contrast, patients with very low probability can be excluded and work-up for other causes will be required. Dynamic stress testing to evaluate abnormal elevation in filling pressure

will be required to establish the cause of exertional dyspnea, as will be discussed in the later section (Fig. 2).[24] In this case, exercise catheterization study demonstrated a normal PCWP at rest (11 mmHg) but markedly increased filling pressures during exertion (30 mmHg) which confirmed the diagnosis of HFpEF.

Diastolic Stress Echocardiography for the Diagnosis of HFpEF—Part of the difficulty in diagnosing HFpEF is related to the fact that filling pressures are often normal at rest, but become elevated only during the stress of exercise.[3, 24, 64] Because of this fact, invasive cardiopulmonary exercise testing has emerged as the gold standard to definitively identify or exclude HFpEF as the cause of dyspnea.[3, 24, 64, 75, 76] Recent studies have evaluated whether similar data can be obtained non-invasively using diastolic stress echocardiography (Fig. 3).[24]

A recent study using simultaneous catheterization-echocardiographic evaluation at rest and during exercise in patients being evaluated for exertional dyspnea (EF≥50%) demonstrated that addition of E/e' during exercise improved sensitivity for diagnosis of HFpEF compared to resting assessment alone, but at the cost of a decreased specificity.[24] However, only 74 patients were enrolled in this single-center study, and other groups have not observed as favorable results in HFpEF with exercise echocardiography.[67, 77–79] Some studies have raised questions with the ability of E/e' to track changes in filling pressure during exercise, particularly since E/e' increases far less than directly measured filling pressures.[24, 67, 79] Given the discrepant results in the totality of studies published to date and lack of reproducibility, additional validation, preferably using multicenter designs, are required to clarify the role for noninvasive diastolic stress echocardiography in the evaluation of HFpEF.[80]

Abnormal LV systolic and diastolic responses to exercise assessed by LV longitudinal strain or strain rate and E/e' have been reported to improve risk prediction over clinical and resting measurements in HFpEF, though this usage also requires additional confirmation in larger, multicenter studies.[81, 82]

Echocardiography to Identify HFpEF Phenotypes—It has recently been recognized that HFpEF is a heterogeneous syndrome, and treatments applying the "one size fits all" approach have uniformly failed to date when tested in clinical trials.[83] Accordingly, there is an unmet need to categorize different phenotypes within the broader spectrum of HFpEF into pathophysiologically homogenous groups, and cardiac imaging may be a very useful tool to enable this characterization. Candidate phenotypes that might be used for deeper characterization by echocardiography in HFpEF are described below.

Left Atrial Dysfunction Phenotype—Left atrial remodeling and dysfunction secondary to increased LV filling pressure are associated with worse symptoms of dyspnea, more pulmonary vascular disease, greater RV dysfunction, depressed exercise capacity, and adverse outcomes in HFpEF.[39, 42, 84, 85] Thus, LA hypertension/dysfunction can be a potential sub-phenotype of HFpEF. Multiple recent studies have shown the utility of LA reservoir strain assessed by speckle-tracking echocardiography to identify LA dysfunction, help diagnosis, and predict outcomes in HFpEF[42, 63, 85, 86]

Pulmonary Hypertension and Pulmonary Vascular Disease Phenotype—PH is common in patients with HFpEF, and is associated with worse exercise capacity and clinical outcomes.[48, 87, 88] While PH is predominantly related to left atrial hypertension in the majority of HFpEF patients, a number of patients develop pulmonary vascular disease, manifest by elevation in pulmonary vascular resistance and reduction in pulmonary arterial compliance.[89] HFpEF patients with pulmonary vascular disease is associated with reduced exercise capacity, impaired RV systolic reserve, and worse outcomes, suggesting a different phenotype in the HFpEF spectrum.[90] The presence of pulmonary vascular disease can be suspected from mid systolic notching in the RV outflow Doppler profile, along with a short acceleration time caused by increased pulmonary arterial impedance with enhanced early wave reflection.[91, 92] There is increasing recognition of the importance of RV and pulmonary vascular coupling (RV-PA coupling) and a recent study has reported that RV-PA coupling assessed by tricuspid annular plane systolic excursion (TAPSE) to RVSP (<0.36 mm/mmHg) predicts the pulmonary vascular disease in HFpEF.[93]

Right Ventricular Dysfunction Phenotype—The presence of PH causes RV systolic dysfunction in HFpEF, but recent data have shown that RV-PA coupling is even more important.[87, 88] TAPSE, RV fractional area change, free wall strain, tricuspid annular s' velocity, and RV index of myocardial performance can be measured as indices of RV systolic function.[94, 95] RV-PA coupling can then be assessed by the ratio of RV function to RVSP,[94, 95] and lower TAPSE/RVSP ratio (<0.36 mm/mmHg) is associated with adverse outcomes in HFpEF.[93, 94, 96]

RV dysfunction is associated with RV remodeling. Echocardiography allows for assessments of RV dilation (RV basal, mid, and longitudinal dimensions and areas), RV hypertrophy, as well as right atrial (RA) dilation. Increased RV diameter, area, and RV wall thickness have been shown to predict adverse outcome in HFpEF.[47, 87] RV and RA dilatation lead to tricuspid annular dilation and resultant tricuspid insufficiency, which may further promote systemic venous congestion and impair left heart filling, particularly during exercise.[97] Thus, the severity of tricuspid insufficiency should be assessed in all patients with HFpEF.

Obesity Phenotype—Obesity is now recognized as an important phenotype of HFpEF.[72] As compared to patients with non-obese HFpEF, patients with the obese phenotype display a number of key differences, including greater relationships between body weight and cardiac filling pressures, greater plasma volume expansion, more ventricular remodeling, more adverse hemodynamics, altered right ventricular-pulmonary artery coupling, worse exercise capacity, and enhanced pericardial restraint.[72] Assessments of septal configuration in the short axis can provide non-invasive estimates of the degree of relative pericardial restraint which contributes to the PCWP elevation in HFpEF obese phenotype as well as patients with pulmonary vascular phenotype and those with severe tricuspid insufficiency (Fig. 4).[72, 97, 98]

Visceral adiposity and ectopic fat deposit can contribute to the obesity phenotype by altering hemodynamics, inducing systemic and local inflammation, and causing mechanistic compression exaggerating pericardial restraint. Abdominal obesity is associated with epicardial fat and has recently been found to be associated with increased mortality in

HFpEF.[99] Measurements of epicardial thickness are feasible by echocardiography (Fig. 5), but are more accurately performed using other modalities such as CT and MRI.

Ischemia/Microvascular Dysfunction Phenotype—The presence of epicardial coronary artery disease identifies a distinct HFpEF phenotype in view of its high prevalence, worse prognosis, and importantly a possibility of improving outcomes through revascularization.[100] Stress imaging, including echocardiography has been shown to be less accurate in patients with HFpEF, with high rates of false positive and false negative tests.[100] This may reflect the fact that subendocardial ischemia may also develop in the absence of epicardial coronary stenosis in HFpEF, caused by the combination of coronary microvascular dysfunction and hemodynamic derangements that compromise subendocardial perfusion.[101]

Patients with HFpEF developing greater myocardial injury during exercise in tandem with myocardial supply-demand mismatch, and those with greater burden of ischemia and injury display the most profound limitations in LV systolic and diastolic reserve, higher filling pressures during exercise, and more impaired exercise capacity.[101] A recent study has shown that adenosine stress echocardiography can be used to assess coronary flow reserve in these patients, and this may be an important non-invasive phenotyping tool, particularly if new treatments are developed targeting microvascular function.[102] Other groups have used nuclear and MRI-based imaging to evaluate for coronary microvascular dysfunction in HFpEF,[103] and there is hope that novel therapies targeted to microvascular dysfunction may be properly targeted to the right patients using the different imaging modalities.

Conclusions and Future Directions

Echocardiography is clearly essential in the evaluation for HFpEF and provides valuable information to estimate LV filling pressure and understand pathophysiology and improve both evaluation for both diagnosis and prognosis (Summary Figure). Together with clinical characteristics, echocardiography can help determine the likelihood that HFpEF is present, and allow for more informed decision making regarding the need for more advanced testing. However, echocardiography alone is often insufficient to make or refute the diagnosis of HFpEF, and in many cases, invasive hemodynamic exercise testing is required. Categorizing HFpEF patients based upon underlying pathophysiological phenotypes represents a key next step providing individualized medicine in this field, and echocardiography plays a crucial role in this regard, though the optimal ways to categorize patients remain unknown. Finally, echocardiographic parameters provide prognostic information reflecting specific pathophysiologic abnormalities in HFpEF. Further study is required to standardize diagnostic criteria for HFpEF, determine roles for different modalities in its evaluation, establish the potential value for diastolic stress echocardiography, and identify the optimal roles of noninvasive imaging along with other clinical markers for HFpEF phenotyping.

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KEY POINTS:

- Heart failure with preserved ejection fraction (HFpEF) is a common clinical syndrome that is increasing in prevalence coupled with the growing population burden of aging and comorbidities.
- Cardio-vascular imaging plays a key role in the evaluation and management of HFpEF, particularly echocardiography.
- Echocardiography provides essential information on cardiac structure, function, and hemodynamics and is performed in essentially all patients where there is clinical suspicion for HFpEF.
- From a practical standpoint, the most important questions that can be addressed center on 1) diagnosis, determining whether a patient with unexplained dyspnea truly has HFpEF or an alternate cardiac or non-cardiac cause of dyspnea, and 2) management, where imaging can be used to evaluate hemodynamic status, determine underlying pathophysiologic phenotypes and 3) risk stratification for outcomes.

	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or persistent	3
P	**P**ulmonary Hypertension	Doppler echocardiographic estimated right ventricular systolic pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)

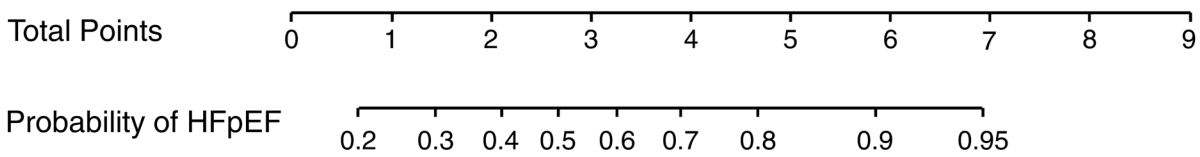

Figure 1. The H_2FPEF score to Aide in Diagnosis HFpEF

In this score, the echocardiographic parameters that were independently predictive for heart failure with preserved ejection fraction (HFpEF) (E/e' >9 and right ventricular systolic pressure >35mmHg) are incorporated in tandem with clinical characteristics to determine the probability that HFpEF is present in patients presenting with unexplained dyspnea. (*Adapted from* Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation. 2018;138(9): 861–870; with permission.)

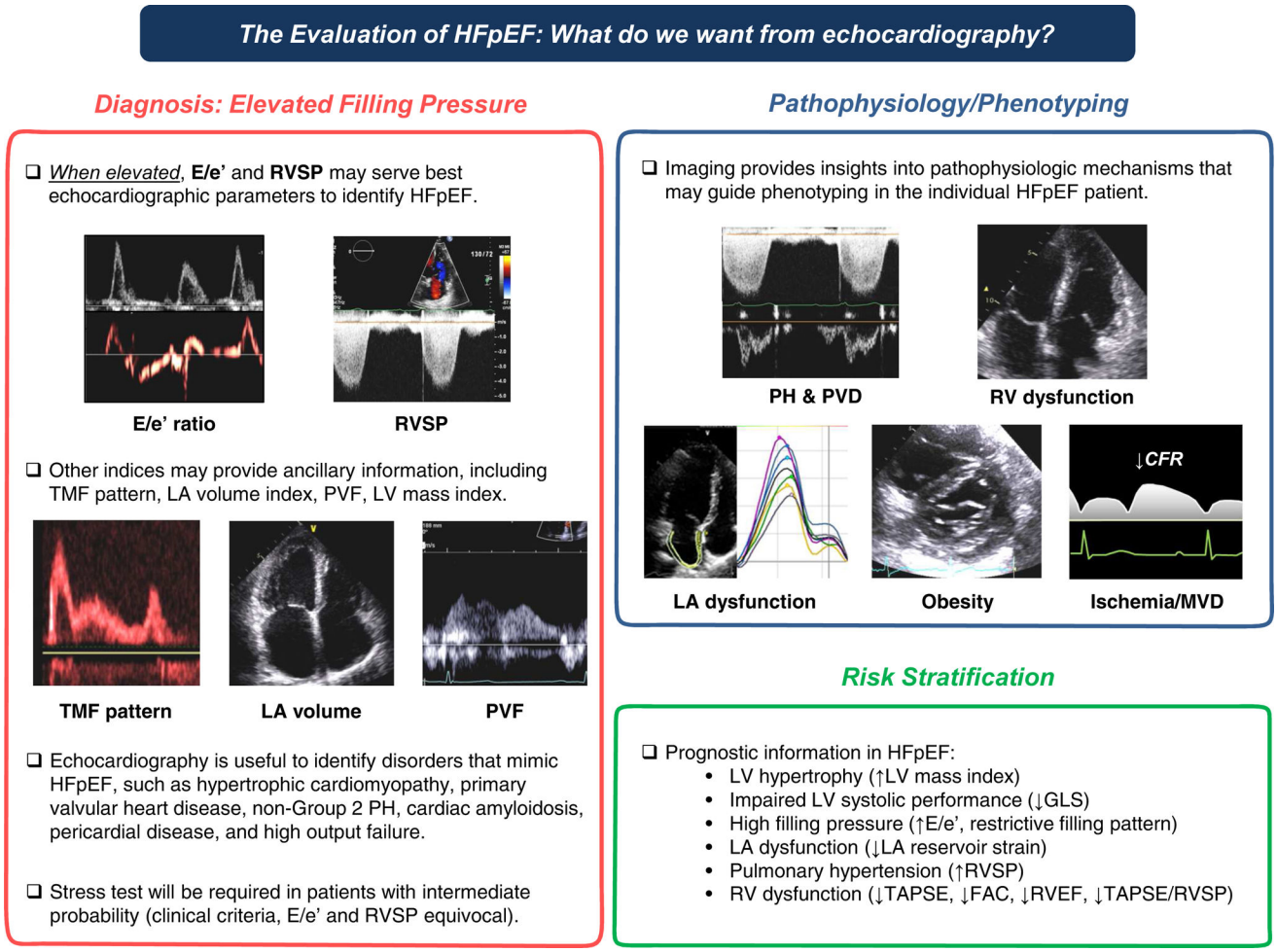

Figure 2. Summary of the Role of Non-Invasive Imaging in the Evaluation of Heart Failure with Preserved Ejection Fraction

E/e', the ratio of early diastolic mitral inflow to mitral annular tissue velocities; FAC, right ventricular fractional area change; GLS, left ventricular global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; MVD, microvascular dysfunction; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVF, pulmonary venous flow; and RV, right ventricular; RVEF, right ventricular ejection fraction; RVSP, estimated right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; and TMF, transmitral flow.

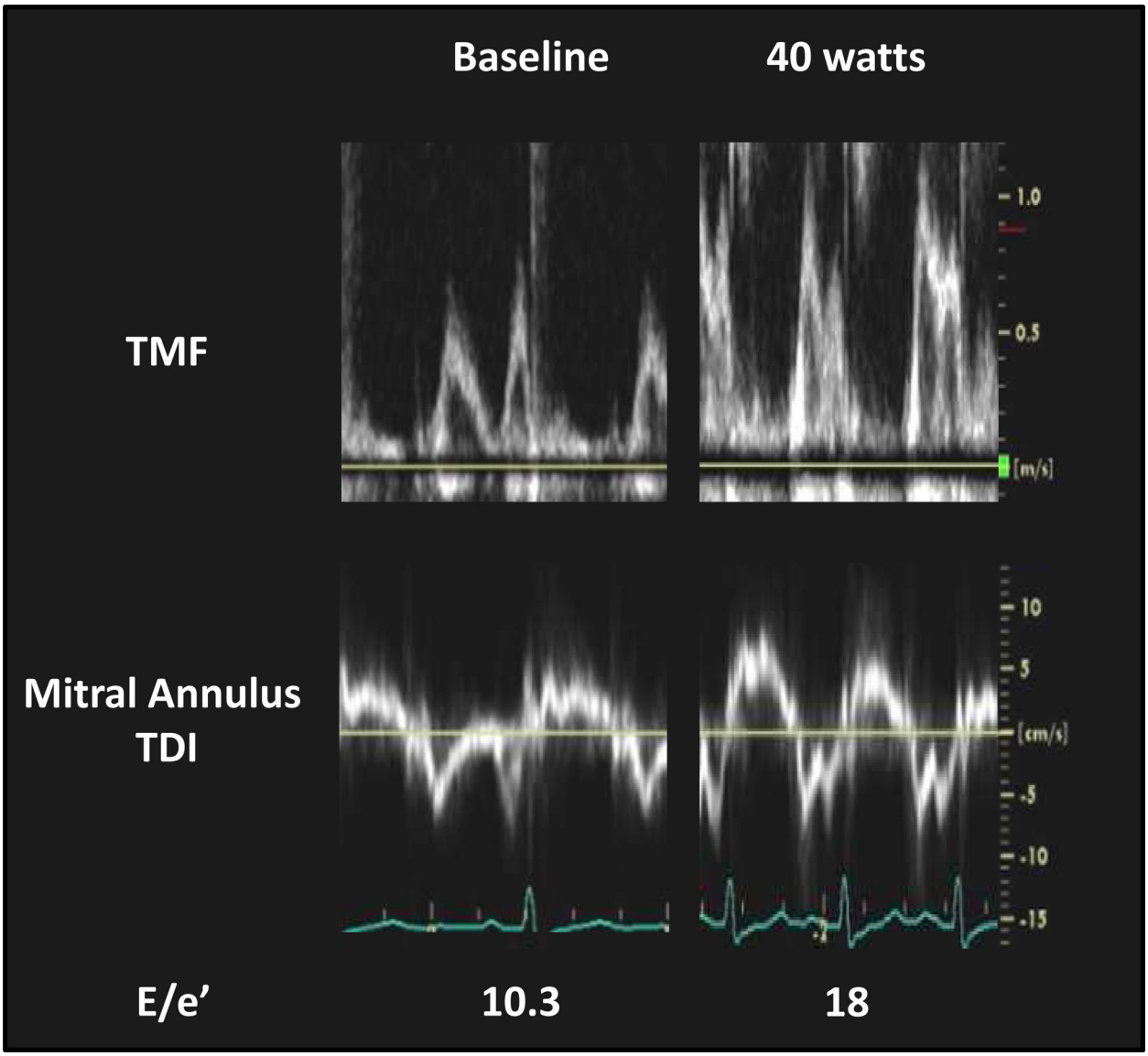

Figure 3. Typical Case of Diastolic Stress Echocardiography

Transmitral inflow velocities (TMF) and mitral annular tissue Doppler velocities at rest and during 40 watts supine ergometer exercise in an invasively-proven HFpEF patient (pulmonary capillary wedge pressure during exercise 27 mmHg). At baseline, transthoracic echocardiography demonstrates normal EF (70%), left atrial volume index (30 ml/m^2), normal E/e' (average 10.3), and an estimated right ventricular systolic pressure of 28 mmHg. With exercise up to 40 watts, mitral E increases dramatically without significant change in e', resulting in an increase E/e' ratio. Tricuspid regurgitant velocity increases from 2.5 to 3.5 m/sec during exercise. TDI, tissue Doppler imaging and other abbreviations as in Figure 1.

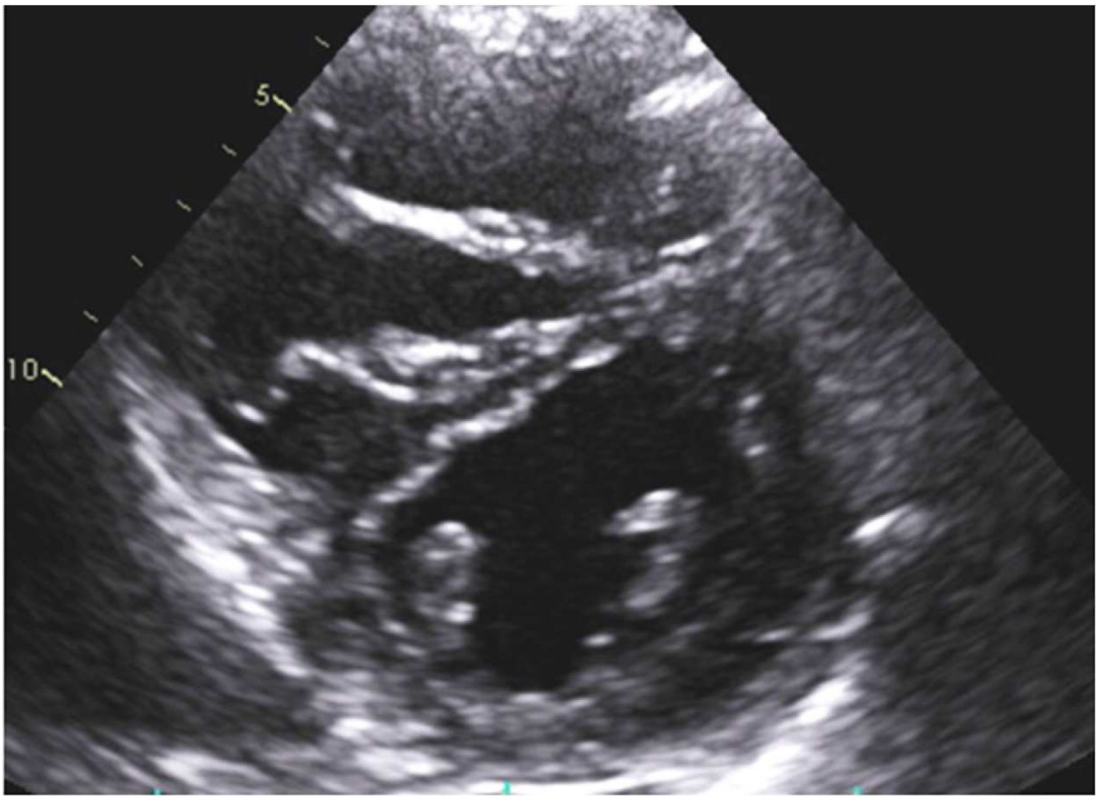

Figure 4. Typical Case of Obese HFpEF

An echocardiographic parasternal short-axis view at end-diastole demonstrates the Dshaped septum in a patient with obese HFpEF (body mass index [BMI] 44 kg/m^2).Cardiac catheterization reveals severely elevated right atrial pressure (17 mmHg) relative to pulmonary capillary wedge pressure (21 mmHg). Abbreviations as in Figure 1.

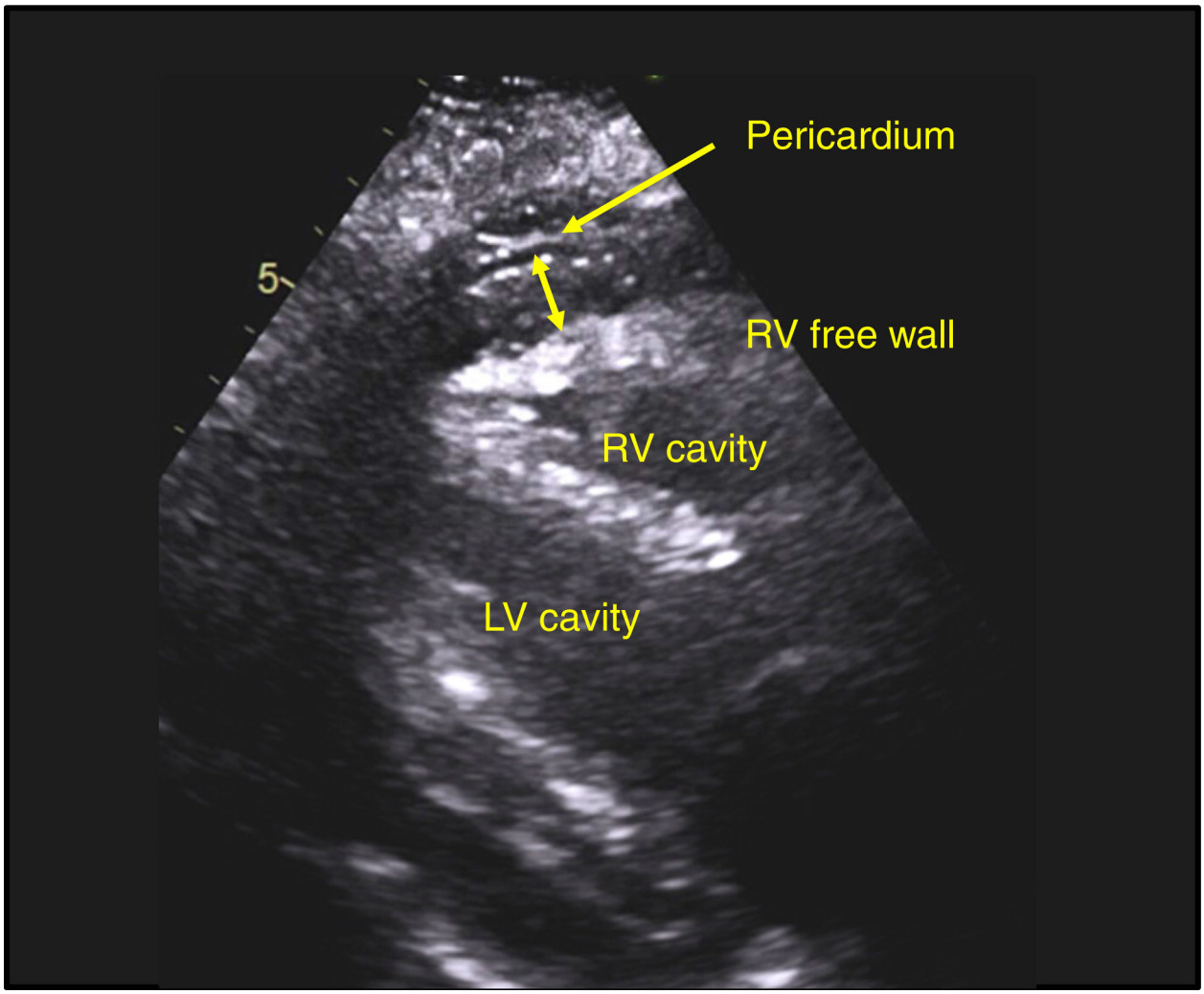

Figure 5. Example of Prominent Epicardial Fat in Obese HFpEF

Parasternal long-axis view at end-systole in an obese HFpEF patient (BMI 38 kg/m^2). Note the increased epicardial fat thickness (14 mm) identified between the right ventricular (RV) free wall and the pericardium. LV, left ventricular; and other abbreviations as in Figures 1 and 4.

Table 1:

Correlations between E/e' and invasive filling pressure in subjects with preserved EF

Study	n	Subjects' Characteristics	Timeframe	Echo	Invasive	r	p	Cutoff Cath	Cutoff Echo	Sens	Spec	Feasibility	Reproducibility*
Nagueh 1997[1]	60	45 ICU, 15 Cath lab	Simultaneous	E/e' (sep)	PCWP	0.87	<0.001	>15 mmHg	>10	97	78		Intra/Inter 5±4/6±5%
Ommen 2000[2]	64	73% suspicious CAD	Simultaneous	E/e' (avg)	MDP	0.45						100%	
				E/e' (sep)	MDP	0.47		>12 mmHg	>15	22%	100%	100%	
Poerner 2003[3]	85	Subjects referred to CAG and E/A>0.9	Mean 3 hours	E/e' (sep)	EDP	0.40	<0.01						
				E/e' (lat)	EDP	0.49	<0.01						
				E/e' (avg)	EDP	0.57	<0.01						
Mansencal 2004[4]	20	CAD	<1 hour	E/e' (lat)	Pre-A	0.18		>15 mmHg	>12	0%	100%	100%	
Hadano 2005[5]	65	UA 6%, AS 5%	<3 hours	E/e' (lat)	PCWP	0.54	<0.001	>15 mmHg	>12	42%	92%		
Kidawa 2005[6]	50	Subjects referred to CAG	Simultaneous	E/e' (lat)	EDP	0.58	<0.01	>15 mmHg	>11	28%	92%		
				E/e' (sep)	EDP	0.29	NS						
Kasner 2007[7]	55	43 HFpEF and 12 controls	3–5 hours	E/e' (lat)	EDP	0.71	0.001						
Min 2007[8]	55	Subjects referred to cath and E/e' 8–15	Simultaneous	E/e' (sep)	EDP	0.03	0.8						
Dokanish 2008[9]	32	Patients with dyspnea	Immediately after cath	E/e' (avg)	Pre-A	0.39	<0.001	>15 mmHg	>15	73%	77%		
Rudko 2008[10]	39	Elevated filling pressure or DD (77% CAD)	Simultaneous	E/e' (sep)	EDP	0.47	<0.001						
Dokanish 2010[11]	122	Subjects referred to CAG	<20min	E/e' (avg)	Pre-A	0.63	<0.001	>15m mHg	>13	70%	93%		
Kasner 2010[12]	33	21 HFpEF and 11 controls	Simultaneous	E/e' (avg)	EDP	0.57	<0.001						
Maeder 2010[13]	22	14 HFpEF and 8 controls	Simultaneous	E/e' (sep)	PCWP	0.19	0.39						
				E/e' (lat)	PCWP	0.04	0.87						
				E/e' (avg)	PCWP	0.12	0.59						
Hsiao 2011[14]	100	Stable CAD	Immediately after cath	E/e' (sep)	Pre-A	0.31	0.002						
				E/e' (lat)	Pre-A	0.23	0.02						
Maeder 2011[15]	36	15 HFpEF, 11 PAH, 10 healthy controls	Immediately after cath	E/e' (sep)	PCWP	0.23	0.2						
				E/e' (lat)	PCWP	−0.04	0.8						
				E/e' (avg)	PCWP	0.13	0.5						
Bhella 2011[16]	11	11 HFpEF	Simultaneous	E/e' (avg)	PCWP	0.64	0.04			59%	92%		
Previtali 2012[17]	57	Subjects referred toCAG	<1 hour	E/e' (lat)	EDP	0.1	0.4						Intra/Inter <10/20%
				E/e' (avg)	EDP		NS	>15 mmHg	>12.1 (optim al)	44%	71%		Intra/Inter <10/20%

Study	n	Subjects' Characteristics	Timeframe	Echo	Invasive	r	p	Cutoff Cath	Cutoff Echo	Sens	Spec	Feasibility	Reproducibility*
Manouras 2013[18]	38	Subjects with angina/dyspnea	Simultaneous	E/e' (sep)	Pre-A	0.02	NS						
				E/e' (lat)	Pre-A	0.40	<0.05						
				E/e' (avg)	Pre-A	0.21	<0.05	>12 mmHg	>13	8%	91%		
Tatsumi 2014[19]	22	Subjects underwent 3D echo and cath	0.1 ± 5.8 days	E/e' (sep)	PCWP	0.64	0.001						
Kasner 2015[20]	23	HFpEF	Simultaneous	E/e' (avg)	EDP	0.84	<0.001						
Matsushita 2015[21]	16	Inpatient HFpEF	Same hospitalization	E/e' (avg)	PCWP	0.56	0.01	>15 mmHg	>10	71%	56%		
Ma 2015[22]	114	84 CAD and 30 controls	< 24 hours	E/e' (sep)	EDP	0.60	<0.01						
Santos 2015[23]	118	Subjects with dyspnea	Immediately after cath	E/e' (sep)	PCWP	0.41	<0.001	>15 mmHg	≥15	6%	92%	79%	
				E/e' (lat)	PCWP	0.30	<0.001	>15 mmHg	≥12	13%	92%	75%	
				E/e' (avg)	PCWP	0.36	<0.001	>15 mmHg	≥13	6%	90%	75%	
Cameli 2016[24]	20	39% UA, 25% angina with positive stress test	1 hour	E/e' (avg)	EDP	0.72	<0.001					100%	
Rommel 2016[25]	36	24 HFpEFand 12 controls	N/R	E/e' (N/R)	EDP	0.63	<0.001						
Ma 2016[26]	114	84 CAD and 30 controls		E/e' (sep)	EDP	0.60	<0.01	>15 mmHg	>10.9	91%	68%		
				E/e' (lat)	EDP	0.29	<0.01						
				E/e' (avg)	EDP	0.41	<0.01						
Hayashi 2016[27]	47	Cardiac diseases (CAD, OMI, HCM, HFpEF, etc)	<3 hours	E/e' (avg)	MDP	0.56	<0.001						
Obokata 2016[28]	74	50 HFpEF and 24 controls	Simultaneous	E/e' (sep)	PCWP	0.63	<0.001					99%	
				E/e' (lat)	PCWP	0.58	<0.001					95%	
Lancellotti 2017[29]	120	Suspicious CAD	Simultaneous	E/e' (avg)	EDP	0.17	0.07	≥15 mmHg	≥14	2.4%	96%		
				E/e' (sep)	EDP	0.08	0.36	≥15 mmHg	≥15	4.8%	96%		
Andersen 2017[30†]	450	Subjects referred to right or left cath (EF<50% n=209)	Simultaneous or immediately after cath	E/e' (avg)	PCWP	0.65	<0.001						

*Reproducibility represents percent variability, intra-class correlation coefficient, or mean difference. 3D, 3-dimentional; A, late diastolic mitral inflow velocity; AS, aortic stenosis; Avg, average; CAD, coronary artery disease; CAG, coronary angiography; cath, catheterization; DD, diastolic dysfunction; E, early diastolic mitral inflow velocity; e', early diastolic mitral annular tissue velocity; Echo, echocardiography; EDP, left ventricular end-diastolic pressure; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; ICU, intensive care unit; lat, lateral; MDP, left ventricular mean diastolic pressure; N/R, not reported; NS, not significant; OMI, old myocardial infarction; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; Pre-A, left ventricular pressure during pre-atrial contraction; Sens, sensitivity; sep, septal; Spec, specificity; and UA, unstable angina.

†This study pooled together both HFpEF and HFrEF patients.

Table 2.

Differential Diagnoses of HFpEF and Their Echocardiographic Clues

Differential Diagnosis	Echocardiographic Clues
Hypertrophic cardiomyopathy	Asymmetric hypertrophy, ↑↑LV wall thickness, LVOT obstruction, SAM
Restrictive cardiomyopathy	Small LV cavity, ↑LV wall thickness, Sparkling myocardium, Apical sparing, Severely reduced tissue Doppler, PE
Pulmonary arterial hypertension	↑RVSP with no sign of elevated LV filling pressure, Isolated right heart dilation, PA dilation, RVOT Doppler midsystolic notch
Constrictive pericarditis	Pericardial thickening, Septal bounce, annulus paradoxus and annulus reversus, ↑Respiratory variation in mitral/tricuspid flow, Absence of IVC collapse
Valvular heart disease	Morphological valvular abnormalities, Color Doppler
Coronary artery disease	Regional wall motion abnormality and thinning
Chronic thromboembolic pulmonary hypertension	↑RVSP with no sign of elevated LV filling pressure, Isolated right heart dilation, PA dilation, RVOT Doppler midsystolic notch
High output heart failure	↑Doppler-derived cardiac output

IVC, inferior vena cava; LV, left ventricular; LVOT, left ventricular outflow obstruction; PA, pulmonary artery; RVSP, estimated right ventricular systolic pressure; PE, pericardial effusion; RVOT, right ventricular outflow; SAM, systolic anterior motion of the mitral valve; and other abbreviations as in Table 1.

Table 3:

Operating Characteristics of Echocardiographic Parameters for the Diagnosis of HFpEF

Data from Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation. 2018;138(9):861–870.

	AUC	P	Sensitivity	Specificity
Ejection fraction <55%	0.52	0.09	8%	96%
LV hypertrophy	0.57	0.0006	26%	88%
LA volume Index >34 ml/m2	0.66	<0.0001	49%	83%
E/e' ratio (septal) >9	0.69	<0.0001	78%	59%
E/e' ratio (septal) >13	0.66	<0.0001	46%	86%
Septal e' velocity <7 cm/s	0.62	<0.0001	48%	76%
Right atrial pressure >10 mmHq	0.56	<0.0001	16%	97%
RV systolic pressure >35mmHq	0.66	<0.0001	46%	86%
RV fractional area change <48%	0.64	<0.0001	39%	88%
Tricuspid annular plane systolic excursion <16 mm	0.54	0.0008	9%	99%
Visual RV dysfunction	0.58	<0.0001	22%	94%
Visual RV dilation	0.60	<0.0001	32%	88%

AUC, area under the curve; LA, left atrial; RV, right ventricular; and other abbreviations as in Tables 1 and 2.