Echocardiographic diagnosis of heart failure with preserved ejection fraction in elderly patients with hypertension

Magnus C. Johanssona,b, Annika Rosengrenb and Michael Fub

aDepartment of Clinical Physiology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden; bDepartment of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

ABSTRACT

Objectives. The aim of this study is to evaluate the diagnostic performance of echocardiography for the diagnosis of heart failure with preserved ejection fraction (HFpEF) in the elderly and to validate the Heart Failure Association diagnostic algorithm (HFA-PEFF). Design. A case–control study was conducted in patients with hypertension with or without HFpEF who were matched for age (n = 33; 78.4 ± 5.3 years) and sex. Participants underwent echocardiography including assessment of left atrial (LA) volume index (LAVI), early mitral filling to early diastolic mitral annulus velocity ratio (E/e'), LA reservoir strain (LASeq), tissue Doppler LA contraction (a'), right ventricular isovolumic relaxation time (RVIVRT), and a 6-minute walk test (6-MWT). The filling pressure algorithm from the European association of cardiovascular imaging (EACVI) 2021 was applied. The HFA-PEFF score was also applied, using echocardiography parameters and the value of NT pro-BNP, without considering symptomatic status. Results. Echocardiographic parameters identified patients with HFpEF with an area under the curve (AUC) >0.9 for E/e', RVIVRT, LASr, a', and the ratio of LAVI/a'. LASr correlated with 6-MWT (r = 0.59, p = .0003). The EACVI filling pressure algorithm, RVIVRT, LASr, and the ratio LAVI/a' were accurate for diagnosing HFpEF in elderly patients with hypertension. The HFA-PEFF score had high sensitivity but limited ability to exclude HFpEF.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome that occurs at a mean age of 78 years in the United States, affects 1/10 of the population >65 years, and constitutes ≥70% of all heart failure in the elderly [1,2]. The diagnosis is complex and often challenging because of its non-specific symptoms and because exercise capacity decreases to less than half from 20–80 years of age in healthy persons, as part of the ageing process [3]. Relying on high N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels may be misleading, considering that normal levels can be found in a proportion of HFpEF (NT-proBNP) levels may be misleading, considering that normal levels can be found in a proportion of HFpEF patients, especially among obese patients with HFpEF [4,5]. In contrast, increased levels may occur in the elderly or in patients with reduced renal function without heart failure [6]. Previous studies often included younger patients with fewer comorbidities, unlike real-world patients with HFpEF who are often elderly and have multiple associated comorbidities [1,7,8]. Taken together, these considerations make the diagnostic approach to HFpEF uncertain. The current reference method for diagnosing HFpEF is complex,

requiring invasive measurement of left ventricular (LV) filling pressure at rest and during exercise, but such an approach is impractical for routine use.

Echocardiography is an essential diagnostic method with published recommendations for the classification of LV diastolic function and the semiquantitative estimation of LV filling pressure [9], helping distinguish between cardiac and non-cardiac causes of dyspnoea, fatigue, and oedema. However, the diagnostic value of echocardiography in HFpEF remains controversial. Reduced LV diastolic function with low tissue Doppler relaxation velocity (e') is considered a sign of HFpEF, but cut-off limits may be ambiguous since normal values decrease significantly with age [9]. Although left atrial (LA) enlargement is considered to be a marker of HFpEF and an estimate of the chronic effect of elevated filling pressure, enlarged LA may be found in normal controls and more frequently in patients with hypertension [1,10,11]. Additionally, the correlation between LAVI and LV filling pressure is weak, with r = 0.23 in one report [10]. Even though such diastolic abnormalities are common in the elderly and are associated with lower exercise capacity, most are not affected by clinical heart failure [1].
A non-invasive scoring system, ‘Heart Failure Association Pretest assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology’ (HFA-PEFF) diagnostic algorithm, has been developed by the Heart Failure Association of the European Society of Cardiology in order to integrate clinical and echocardiographic characteristics with NT-proBNP for predicting HFpEF probability [12]. This scoring system has not yet been adequately validated in hypertensive patients with a mean age >70 years and with age-matched controls [6,7,13–15]. Furthermore, symptoms and signs may be unspecific and NT-proBNP increased in the elderly even without heart failure [6]. The accuracy of echocardiographic parameters varies with age, heart rhythm, and chosen cut-off limits [1,6,10]. There is therefore a need for updated echocardiographic methods with data on diagnostic accuracy in the elderly phenotype.

Tissue deformation imaging, strain, is a promising new echocardiographic technique that has shed light on the importance of LA function in HFpEF, both as a booster pump in end-diastole and as a compliant reservoir during ventricular systole [8]. A reduced LA reservoir strain (LASr) may be a more reliable marker of HFpEF than the mitral inflow (E) to e’ ratio (E/e’) and seems to be correlated not only to filling pressure at rest but also during exercise [8,16]. This is interesting because many patients with HFpEF are symptomatic only during exertion, and pulmonary capillary wedge pressure (PCWP) may be normal at rest but increased during exercise [8].

This study sought to compare elderly patients with HFpEF in sinus rhythm with controls free from heart failure and matched for age, sex, and hypertension. The aims were to evaluate the diagnostic performance of echocardiography including LASr, tissue Doppler, and stress echocardiography, determine optimal cut-off limits for key echocardiographic parameters in the elderly, and validate the recommended echocardiographic algorithms and the HFA-PEFF diagnostic algorithm for HFpEF diagnosis.

Materials and methods

Population

HFpEF population
Patients with validated chronic HFpEF aged 65–89 years were recruited from the ‘Optimizing the Management of Heart Failure with Preserved Ejection Fraction in the Elderly by Targeting Comorbidities’ (OPTIMIZE-HFPEF) study, as previously described [17]. Inclusion criteria were established HFpEF according to the available guideline of the European Society of Cardiology 2012 with at least one hospitalization or equivalent (increased oral furosemide to 80 mg/day or need of intra-venous diuretics) in the prior year, and optimal treatment for at least 4 weeks prior to inclusion. Exclusion criteria were: estimated glomerular filtration rate <30 ml/min/m², (Modification on Diet in renal Disease GFR equation) significant COPD with FEV1.0 < 30% within 4 weeks before randomisation. Patients included in the OPTIMIZE-HFPEF at Sahlgrenska University Hospital were consecutively recruited for the current study. Only patients with sinus rhythm at recruitment and echocardiography were included in the study.

Control population
The controls were selected from a population-based study of the combined Intergene-ADONIX (Adult-onset asthma and nitric oxide) cohort (3614 participants out of 8626 invited) from a random sample in western Sweden aged 25–77 years at baseline in 2001–2004, as previously described [18]. Of the participants from the Goteborg area who survived until 2018, consecutive controls were selected and matched by age and sex in a 1:1 ratio to patients with HFpEF. Selected controls were contacted by telephone and excluded if they had known cardiovascular disease or another exclusion criterion, and another control was invited instead. A total of 47 controls were interviewed via telephone, and 35 controls visited. Exclusion criteria regarding GFR and COPD were the same as in the HFpEF group. To be eligible as a control, additional criteria had to be met during a subsequent assessment. They had to be able to walk without a walking aid; be in sinus rhythm, have established hypertension without any evidence of significant valvular heart disease, ischaemic heart disease, and heart failure upon physical examination; and have undergone electrocardiography, laboratory assessment, and echocardiography prior to the study. The presence of hypertension is one of the key matching criteria, since most patients with HFpEF have underlying hypertension. Sixteen controls were included in the study.

Examinations
A 6-minute walk test (6 MWT) was performed, as it is closely associated with peak oxygen consumption in patients with heart failure [19]. Blood samples were collected for NT-proBNP analysis at the Sahlgrenska University laboratory.

Echocardiography
Comprehensive examinations were performed by an experienced echo technician using Vivid E9 (General Electric Fairfield, CT, USA). Blinded measurements were performed offline using EchoPAC 201 (General Electric), according to current recommendations, by another trained echo technician [20]. LV mass index (LVMI) was calculated using linear measurements in the parasternal long-axis view with indexation for body surface area (BSA). The modified Simpson method was used to measure the volumes, and the LV ejection fraction (EF) was calculated. In atrial-focused apical two- and four-chamber views, LA volume was measured in end-systole and indexed for BSA (LAVI). The thickness of the epicardial adipose tissue was measured on the free wall of the right ventricle (RV) at end-systole. This adipose tissue is a paracrine organ that shares microcirculation with the RV and seems to be associated with an ‘inflammatory-metabolic phenotype’ of HFpEF [21].

Tissue Doppler was recorded at the medial and lateral sides of the mitral annulus, and the early diastolic (e’) and
medial late diastolic (a') velocities were measured (Figure 1). The ratio of LAVI/a' was calculated since it may be a feasible measure of LV diastolic function [22]. The E/e' ratio was calculated using the mean of the medial and lateral e'. When mitral annulus calcification >4 mm was present, the lateral e' and the E/e' ratio were considered missing [9]. The deceleration time (DT) of the E wave was measured, and the deceleration rate (E/DT) was calculated.

Myocardial deformation was analysed by speckle tracking echocardiography using EchoPAC 201 (General Electric) according to the standard consensus, and absolute values were reported [23]. LV global longitudinal strain (GLS) was analysed in apical four—chamber, apical two—chamber, and apical long axis views. LA strain was measured in LA—focused apical four—chamber view using a mean of two consecutive beats with the QRS as the reference point, and was reported as the LA reservoir strain (LASr) and LA strain during contraction (LASct). The ratio of LA strain to E/e' was calculated as a measure of LA compliance, which may have pathophysiological importance in HFrEF to dampen the phasic inflow to the LA [24].

Classification of diastolic function
Diastolic function was classified using the algorithm recommended by the American Society of Echocardiography/ European Association of Cardiovascular Imaging 2016 (ASE/EACVI), and classification of filling pressure was done in all patients [9]. When the initial classification was indeterminate, the difference in duration between pulmonary vein atrial reversal (PV-A) and the mitral atrial-wave (MV-A) was used in an additional step, with a cut—off of at least 30 ms [9]. Two blinded independent observers analysed this additional step with no disparities. A post hoc analysis was also performed according to the 2021 EACVI consensus on HFrEF imaging with LASr <18% indicating increased filling pressure in the indeterminate situation [10].

Measures of the right ventricle
The RV area was measured in end—diastole and end—systole in the RV focused apical four—chamber view, indexed for BSA (RVADI and RVASI, respectively), and the fractional area shortening (FAC) was calculated. In the focused RV apical view, RV free wall longitudinal strain (RVFWS) was measured using a mean of two consecutive beats. Using tissue Doppler, RV systolic velocity (RV-s') was measured. The right ventricular isovolumetric relaxation time (RVIVRT) was measured to test it as a diagnostic parameter because it may be a semiquantitative estimate of tricuspid regurgitation (TR) velocity (Figure 2(A,B)) [25]. The TR velocity was measured in modified apical four—chamber views. The right atrial pressure (RAP) was estimated by the variation in inferior vena cava (IVC) diameter during a brief sniff, and RV systolic pressure (RVSP) was calculated. The RAP was estimated as normal (3 mmHg) if the IVC diameter was <21 mm with >50% collapse; the RAP was considered to be increased to 15 mmHg if the IVC diameter was >21 mm with <50% collapse. When this paradigm did not fit, the RAP was considered to be 8 mmHg [20]. The tricuspid...
annular plane systolic excursion (TAPSE) was measured in the apical view using anatomic M-mode. The ratio TAPSE/RVSP was calculated as a measure of RV-pulmonary artery coupling [26]. RV dysfunction was defined as at least two of the following: increased RVADI (men >12.6 cm²/m², women >11.5 cm²/m²), FAC <35%, TAPSE <17 mm, RV' <9.5 cm/s, RVFWS <20% and increased estimated RAP [20].

**Classification according to HFA-PEFF diagnostic algorithm**
The HFA-PEFF score was calculated as recommended [12].

**Stress echocardiography**
Since supine bicycle exercise test is cumbersome in the elderly; the patients were instructed and encouraged to actively and repeatedly perform leg raise in the supine position until exhaustion or at until a ≥15% increase in heart rate, and then turn to the lateral position and continue the exercise by repeated right arm lift during imaging. Acquisition (measurement) in apical views included pulsed-wave Doppler of E and the LV outflow tract (velocity time integral, VTI), tissue Doppler of the medial mitral annulus (medial e’ and medial systolic velocity, s’), and TR velocity. The cardiac index was calculated using pulsed-wave Doppler in the LV outflow tract.

**Reproducibility**
Reproducibility was tested in 10 randomly selected patients and estimated using intra-class correlation coefficients for the key parameters. Intra-observer (inter-observer) variability was as follows: LVMI, 0.94 (0.82); LASr, 0.92 (0.84); LASct, 0.94 (0.85); medial, e’ 0.96 (0.98); E/e’ mean, 0.98 (0.92); a’, 0.99 (0.98); LAVI, 0.96 (0.93); LAVI/a’, 0.99 (0.99); and RVIVRT, 0.97 (0.85).

**Statistics**
Distribution was tested for normality using the Shapiro–Wilk test and visual analysis. Continuous variables were presented as the mean ± standard deviation (SD) or as the median (inter-quartile range). Categorical variables were presented as numbers and percentages. Continuous variables were compared using Student’s t-test or the Mann–Whitney U-test as appropriate. Categorical variables were compared using Fisher’s exact test. Receiver operating characteristic curves were used to assess the area under the curve (AUC) of different echocardiographic parameters, and two different cut-off limits were chosen. One with a sensitivity >90% that may be used in order to rule out disease, and one with a specificity >90% in order to rule in disease.

The purpose was to better display the performance in these specific groups and to determine the proportion of patients with intermediate values that can be considered non-diagnostic and requiring the use of other signs. As a single parameter is insufficient for diagnosis, the use of two cut-off limits reduces the number of conflicting values and makes the diagnostic workup more efficient. Bivariate correlations of LASr were analysed using Spearman’s rank correlation. p-value >.05 was considered statistically significant. IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for the analysis.

**Compliance with ethical standards**
The protocol was approved by the regional ethics review board in Gothenburg (812-13) and conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants included in the study.

**Results**

**Baseline clinical and echocardiographic characteristics**
There was no significant difference between the groups in terms of hypertension, age, or sex (Table 1). Six HFrEF patients had a history of atrial fibrillation and were at the time of echocardiography in sinus rhythm since at least 4 months. The echocardiographic parameters had a high feasibility of 97–100%, except for RVSP, which was available in 61% of cases. Parameters reflecting LA size and function, including strain and a’, showed significant differences (Table 2). The e’ was significantly lower for the medial side, while the difference for the lateral side was statistically non-significant. The RVIVRT showed 100% feasibility with highly significant differences, reflecting a higher RVSP in patients with HFrEF. The RVIVRT correlated to TR velocity (r = 0.67, p = .001). The epicardial adipose tissue thickness was not significantly different between groups.

RV function was similar without significant differences between groups, except for a larger RVADI in patients with

| Table 1. Study population characteristics. |
|------------------------------------------|
| **Controls (n=16)** | **HFrEF (n=17)** | **p** |
|---------------------|-----------------|-------|
| Male n (%) | 5 (31) | 7 (41) | .55 |
| Age (year) | 77.3 ± 3.8 | 79.3 ± 6.4 | .29 |
| Heart rate (n/min) | 69.0 ± 6.7 | 62.5 ± 10.5 | .04 |
| SBP (mmHg) | 145 (132–155) | 149 (136–171) | .32 |
| DBP (mmHg) | 76 ± 10 | 72 ± 9 | .22 |
| Pulse pressure (mmHg) | 68 (60–81) | 110 (70–88) | .029 |
| NYHA I/II/III n (%) | 16 (100%) /0/0 | 0 /4 (24) /13 (76) |
| BMI (kg/m²) | 25.3 ± 3.4 | 27.6 ± 2.9 | .04 |
| Obesity, n (%) | 1 (6) | 4 (24) | .34 |
| Hypertension, n (%) | 16 (100) | 17 (100) | .75 |
| Diabetes, n (%) | 1 (7) | 6 (35) | .09 |
| History of CAD, n (%) | 0 | 7 (41) | .007 |
| GFR (ml/min/1.73 m²) | 74 ± 16 | 51 ± 22 | .001 |
| Six-MWT (m) | 477 ± 60 | 275 ± 92 | <.0001 |
| NT-proBNP (ng/l) | 79 (17–111) | 1530 (1110–1905) | <.0001 |
| Beta-blocker, n (%) | 3 (19) | 14 (82) | .001 |
| ACEI or ARB, n (%) | 9 (56) | 10 (59) | .76 |
| Diuretic, n (%) | 1 (6) | 11 (65) | <.0001 |
| Calcium blocker, n (%) | 7 (44) | 4 (24) | .15 |

Continuous variables are presented as the mean ± SD or as the median (inter-quartile range). Categorical variables are presented as n (%). HFrEF, heart failure with preserved ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; BMI, body mass index; CAD, coronary artery disease; GFR, estimated glomerular filtration rate; Six-MWT, 6-minute walk test; NT-proBNP, N-terminal pro-brain natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Table 2. Echocardiographic data.

|                      | Controls (n = 16) | HFP EF (n = 17) | p       |
|----------------------|------------------|----------------|---------|
| EF (%)               | 63 ± 4.7         | 64 ± 5.7       | .87     |
| LVMi (g/m²) (1,0) a  | 80 ± 14          | 115 ± 25       | <.0001 b|
| GLS (%) (1,0) a      | 21.5 ± 3.0       | 18.3 ± 2.5     | <.0001 b|
| E/e’ mean (0.2) a    | 10.9 (10.4–14.3)| 17.1 (14.9–24.6)|<.0001 b|
| Lateral e’ (cm/s) (0.2) a | 6.0 ± 1.3 | 5.7 ± 1.3 | .61     |
| Medi a’ (cm/s)       | 5.3 ± 1.1        | 4.2 ± 1.1      | .009    |
| a’ (cm/s)            | 8.4 ± 1.4        | 5.1 ± 1.5      | <.0001 b|
| E/A                  | 0.85 (0.5–1.2)   | 1.2 (0.6–3.5)  | <.001 b |
| DT (ms) (0.1) a      | 178 ± 35         | 160 ± 39       | .19     |
| E/DT (m/s) (0.1) b   | 4.0 ± 1.3        | 6.4 ± 2.2      | <.001   |
| S/D (0.1) b          | 1.5 (0.9–3.2)    | 1.0 (0.5–1.8)  | <.0001   |
| LAVI (ml/m²)         | 28.6 (25–32)     | 44.0 (38–49)   | <.0001   |
| LAVI/a’ (ml/m²/cm/s) | 3.5 ± 0.8        | 10.0 ± 4.7     | <.0001   |
| LASr (%) (1,0) b     | 23 (22–32)       | 16 (13–20)     | <.0001   |
| LASct (%) (1,0) b    | 16 ± 4.4         | 7.7 ± 3.9      | <.0001   |
| LASr/E’ (1,2) b      | 2.9 ± 0.8        | 0.9 ± 0.3      | <.0001   |
| EAT (mm)             | 3.3 ± 0.8        | 3.8 ± 0.8      | .08     |
| Right ventricle      |                  |                |         |
| RVADI (cm²/m²) (1,0) a | 8.2 ± 1.1   | 9.8 ± 2.0      | .01     |
| FAC (%) (2,0) b      | 43 ± 4.4         | 40 ± 5.0       | .15     |
| RV-s’ (cm/s)         | 12.7 ± 2.3       | 11.4 ± 2.1     | .09     |
| TAPSE (mm)           | 25 ± 5.0         | 24 ± 5.4       | .31     |
| RVFS (%) (2,2) b     | 26 ± 5.6         | 24 ± 6.6       | .42     |
| RVIRVT (ms)          | 60 ± 20          | 95 ± 14        | <.0001 b|
| RVSP (mmHg) (6,7) b  | 25.7 ± 3.7       | 38.5 ± 10.0    | <.0001   |
| TAPSE/RVSP mm/mmHg (6,7) b | 0.92 ± 0.15 | 0.59 ± 0.15 | <.0001 b|
| RV dysfunction, n (%)| 0                | 3 (18)         | .23     |
| Stress echocardiography |             |                |         |
| Exercise time (min)  | 3.3 ± 0.45       | 3.6 ± 0.45     | .09     |
| HR peak (beats/min)  | 93 ± 8.6         | 77 ± 8.7       | <.0001 b|
| CI (l/min/m²) (0.1) a | 4.3 ± 0.70   | 3.4 ± 0.45     | .002 b  |
| s’-medial (cm/s) (1,0) b | 7.3 ± 1.2 | 5.4 ± 0.7 | <.0001 b|
| E/e’ mean (1,0) b    | 14.1 ± 4.3       | 25.0 ± 7.4     | <.0001 b|
| TR velocity (m/s) (6,6) b | 2.7 ± 0.29 | 3.5 ± 0.35 | <.0001 b|

Data are presented as the mean ± SD or as the median (inter-quartile range).

aStatistically significant after Bonferroni-Holmes correction for multiple testing.

HFpEF, heart failure with preserved ejection fraction; LVMi, left ventricular mass index; GLS, global longitudinal strain; E/e’ mean, ratio of early diastolic mitral inflow velocity to early diastolic tissue velocity as mean of lateral and medial mitral annulus; e’, tissue Doppler early velocity during diastolic contraction; E/A, ratio of early to late diastolic mitral inflow velocity; DT, deceleration time of early mitral inflow; S/D, ratio of systolic to diastolic pulmonary vein inflow velocity; LAVI, left atrial volume index; LA, left atrium; TAPSE, tricuspid annulus peak systolic excursion; RVFS, right ventricular free wall strain; RVIRVT, right ventricular isovolumic relaxation time; TRVSP, right ventricular systolic pressure; HR, heart rate; SV, stroke volume; CI, cardiac index; s’, medial, systolic tissue velocity at medial mitral annulus; TR, tricuspid regurgitation.

HFpEF. Stress echocardiography was performed in all participants with multiple differences between the groups. During stress, patients with HFpEF showed lower HR, cardiac index, and medial a’, and higher E/e’ and TR gradients.

Diagnostic performance of echocardiography

As shown in Table 3, several resting echocardiographic parameters performed very well in identifying patients with HFpEF with an AUC ≥ 0.9. Parameters reflecting LA size and function, such as LAVI, LA Sr, LASct, and a’, showed high diagnostic accuracy. In addition, LAVI/a’ ratio > 5.0 ml/m²/cm/s showed both sensitivity and specificity of 94%, and there was a close relation between estimated filling pressure and LAVI/a’, as shown in Figure 3A. The TAPSE/RVSP showed an AUC > 0.9, but was available in only 61% of the patients, due to missing RVSP. The TAPSE showed an AUC of only 0.6.

The correlation between LASr and 6 MWT is shown in Figure 3B. LASr was correlated also with LAVI (r = 0.57, p = .001), LA Sr (r = 0.91, p < .0001), GLS (r = 0.57, p = .001), E/e’ (r = 0.58, p = .001), S/D (r = 0.45, p = .0012), RVIRVT (r = 0.56, p = .1), TAPSE/RVSP (0.63, p = .004), stress TR velocity (r = 0.66, p = .001), stress E/e’ (r = 0.55 p = .001), and NT-proBNP (r = 0.64, p = .001). a’ was correlated also with LAsct (r = 0.79, p < .0001).

Parameters with moderate diagnostic accuracy were only reliable diagnostic markers when their values were close to the end range. A short DT < 150 ms had 94% specificity but a low sensitivity of 50%.

Validation of the echocardiographic algorithms

The validation of the 2016 ASE/EACVI echocardiographic algorithms for diastolic function and for filling pressure are shown in Figure 4A and B, respectively. Regarding the 2016 classification for filling pressure, 18% of patients were classified as indeterminate. When the additional step with PV-A and MV-A duration was applied in the indeterminate situation, the filling pressure was classified as high in 94% of all patients with HFpEF and as normal in all controls, leaving no patient indeterminate. Using LASr < 18% as a sign of increased filling pressure in this indeterminate situation (according to EACVI 2021) [10] showed normal filling pressure in all controls and increased filling pressure in 94% of patients with HFpEF, leaving no patient as indeterminate (Figure 4C).

Validation of the HFA-PEFF diagnostic algorithm

All HFpEF patients received a high probability score of 6 and the controls received a median of 2.5 points (range 1–5). The majority of controls received an intermediate score (Figure 4D), and the sources for points were E/e’ > 9, low e’, LAVI > 29 ml/m², and high NT-pro-BNP, which were found in 94%, 75%, 50%, and 31% of controls, respectively. After stress echocardiography was added, 74% of the controls received an intermediate score, and 20% received a high score (5 points). Patients with HFpEF had higher scores (8–9 points, Table 4).

Discussion

This case–control study in elderly patients with hypertension with or without HFpEF demonstrated that resting echocardiography is a powerful tool for accurate HFpEF diagnosis. Furthermore, the HFA-PEFF score is clinically helpful for estimating the probability of HFpEF, as it incorporates clinical signs, echocardiographic findings, and NT-proBNP levels. Despite its small sample size, this case–control cohort was not only typical for HFpEF with a high mean age of 78 years and multiple comorbidities but was...
Our results are when the transition occurs from hypertension with diastolic dysfunction to heart failure (HFpEF). Furthermore, it is clinically difficult to determine the underlying mechanism in most patients with HFpEF. Each blue dot represents a control and each red dot a HFpEF patient. Figure 3 shows a moderate correlation between LASr and the result of 6 MWT. EACVI, European association of cardiovascular imaging. Other abbreviations as in Table 1.

A: LAVI/a’ in relation to the 2021 EACVI filling pressure algorithm

B: Correlation between LASr and six-MWT

Figure 3. Each blue dot represents a control and each red dot a HFpEF patient. (A) LAVI/a’ in relation to EACVI 2021 filling pressure. Normal, classified with normal filling pressure according to the 2021 EACVI algorithm; Elevated, classified with elevated filling pressure according to the 2021 EACVI algorithm. The ratio LAVI/a’ > 5.0 ml/m^2/cm/s showed both sensitivity and specificity of 94%, for HFpEF diagnosis and there was a close relation between estimated filling pressure and LAVI/a’, as shown in the Figure. EACVI, European association of cardiovascular imaging. Other abbreviations as in Table 1. (B) Correlation between LASr and 6 MWT. The figure shows a moderate correlation between LASr and the result of 6 MWT.

Table 3. Diagnostic performance of single echocardiographic parameters to rule in or rule out HFpEF.

| Parameter                                      | AUC (CI)       | Rule in cut-off | Sens (%) | Spec (%) | Rule out cut-off | Sens (%) | Spec (%) |
|------------------------------------------------|----------------|-----------------|----------|----------|-----------------|----------|----------|
| LVMI (g/m²)                                    | 0.91 (0.81–1.0) | > 98            | 77       | 93       | < 82            | 92       | 40       |
| E/e’ mean                                      | 0.91 (0.81–1.0) | > 16.0          | 73       | 94       | < 12.0          | 93       | 69       |
| LAVI (ml²/m³)                                  | 0.98 (0.95–1.0) | > 37.0          | 88       | 94       | < 34.0          | 100      | 81       |
| a’ (cm/s)                                      | 0.94 (0.87–1.0) | < 6.1           | 65       | 94       | > 7.6           | 94       | 69       |
| LASr (%)                                       | 0.93 (0.84–1.0) | < 21.0          | 88       | 93       | > 23.0          | 94       | 53       |
| LASr/E/e’ (%)                                  | 0.98 (0.94–1.0) | < 1.3           | 93       | 93       | > 1.3           | 93       | 93       |
| LASct (%)                                      | 0.93 (0.84–1.0) | < 11            | 82       | 94       | > 16            | 94       | 47       |
| RVSP (mmHg)                                    | 0.90 (0.71–0.95) | > 30             | 90       | 90       | < 30            | 90       | 90       |
| RVIVRT (ms)                                    | 0.92 (0.82–1.0) | > 95            | 41       | 94       | < 70            | 94       | 75       |
| TAPSE/RVSP (mm/mmHg)                           | 0.93 (0.82–1.0) | < 0.70          | 60       | 90       | > 0.79          | 90       | 70       |
| Medial e’ (cm/s)                               | 0.78 (0.62–0.94) | < 4.0           | 47       | 94       | > 5.0           | 88       | 50       |
| Lateral e’ (cm/s)                              | 0.63 (0.43–0.83) | < 5.0           | 29       | 94       | > 7.0           | 88       | 20       |
| GLS (%)                                        | 0.79 (0.65–0.96) | < 16.5          | 38       | 94       | > 22            | 94       | 60       |
| E/A                                           | 0.83 (0.69–0.98) | > 1.1           | 65       | 94       | < 0.6           | 94       | 13       |
| DT (ms)                                        | 0.66 (0.46–0.86) | < 150          | 35       | 94       | > 210          | 94       | 6        |
| E/DT (m²/s)                                    | 0.86 (0.72–1.0) | > 6.4           | 50       | 94       | < 4.4           | 94       | 69       |
| S/D                                           | 0.88 (0.76–1.00) | < 1.1           | 56       | 94       | > 1.4           | 94       | 62       |
| Stress TR velocity (m/s)                       | 0.96 (0.89–1.0) | > 3.1           | 82       | 90       | < 2.9           | 100      | 80       |
| Stress E/e’ medial                            | 0.94 (0.84–1.0) | > 18.5          | 88       | 93       | < 17.0          | 94       | 73       |

AUC, area under the curve; CI, confidence interval; sens, sensitivity; spec, specificity. HFpEF, heart failure with preserved ejection fraction; LVMI, left ventricular mass index; GLS, global longitudinal strain; E/e’ mean, ratio of early diastolic mitral flow velocity to early diastolic tissue velocity as mean of lateral and medial mitral annulus; e’, tissue Doppler early diastolic velocity; a’, medial mitral anulus tissue Doppler velocity during atrial contraction; E/A, ratio of early to late diastolic mitral inflow velocity; DT, deceleration time of early mitral inflow; S/D, ratio of systolic to diastolic pulmonary vein inflow velocity; LAVI, left atrial volume index; LASr, LA reservoir strain; LASct, LA contraction strain; TAPSE, tricuspid anulus peak systolic excursion; RVIVRT, right ventricular isovolumic relaxation time; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

also highly selective by only including participants with hypertension. This is pertinent, as hypertension is a part of the underlying mechanism in most patients with HFpEF. Furthermore, it is clinically difficult to determine when the transition occurs from hypertension with diastolic dysfunction to heart failure [11,27]. Our results are clinically relevant, as there is a widespread consensus that the diagnostic approach for HFpEF remains challenging. Although there are recommended diagnostic algorithms available for diagnosing HFpEF, they are still inadequately validated, and there is a need for improved echocardiographic diagnostics.

Our study showed the following findings from six different aspects. First, the parameters of LA size and function were highly diagnostic of HFpEF. LAVI, LASr, and the simple measure of tissue Doppler a’ showed an AUC >0.9. The ratio LAVI/a’ had an AUC of 0.99 (confidence interval, 0.95–1.0). Second, the E/e’ had an AUC of 0.91 but was non-diagnostic due to mitral calcifications or intermediate values in 33% of participants. Third, the differences regarding RV were less pronounced, except for RVIVRT, which was available in all participants and prolonged in HFpEF, reflecting higher RVSP. Fourth, according to the ASE/EACVI algorithm, a reduced diastolic function showed a high sensitivity of 94%, while a normal diastolic function was present in only 62% of controls. Fifth, the recent 2021 EACVI filling pressure algorithm [10] showed high accuracy. Classification as high filling pressure had a sensitivity of 94%, while a normal diastolic function was present in only 62% of controls. Sixth, the HFA-PEFF diagnostic algorithm showed a sensitivity of 100% for HFpEF. However, the ability to exclude HFpEF was low, with most
controls classified as having an intermediate probability for HFpEF.

The high diagnostic performance of LA function parameters is in line with previous studies in younger patients [8,24,28,29] and supports the notion that reduced LA function resulting in ‘atrial myopathy’ is an essential mechanism in the transition from hypertension to HFpEF in the elderly. Normal, compliant LA with high LASr modulates LV filling, allowing blood flow into the LA during ventricular systole without excessive LA pressure, thereby protecting the lungs from congestion. LASr at rest is correlated with PCWP at rest and even stronger with PCWP during exercise and is a specific marker of invasively confirmed HFpEF [8,16,24]. Even though the optimal cut-off levels have varied between studies the levels are concordant when applying the same software to a population of similar age. The study by Lundberg et al.
found LASr 21% to have a sensitivity of 88% and specificity of 92% for HFpEF diagnosis [16].

LASr is also feasible when E/e’ cannot be used, such as valvular calcifications, left bundle branch block, or aortic prosthesis [9,23]. LASr correlated with 6 MWT, which was in line with previous results [30]. Recently, reduced LASr was found to correlate with peak VO2 [31] and with leg muscle endurance, suggesting a pathophysiological link between central and peripheral factors in explaining reduced exercise capacity [32].

The high diagnostic performance and the levels of a’ are in line with two previous studies in a similar diagnostic context [33,34]. Reduced a’, below 7.25 cm/s, was recently showed to be a sign of increased filling pressure [33]. In a healthy population, a’ increases up to 80 years of age, and LA contraction may be a factor compensating for reduced LV relaxation that ceases when it can no longer contribute to LV filling due to increased LV end-diastolic stiffness and reduced LA contractility [22,35]. Reduced a’ conveys a worse prognosis in HFpEF with sinus rhythm [36], comparable with patients with HFpEF and atrial fibrillation, implying the importance of LA dysfunction in sinus rhythm [10,37]. A’ correlated closely with LASct, an accurate diagnostic parameter of HFpEF [8]. Furthermore, LA contraction is related to LA reservoir function, as the decrease in LA pressure after contraction contributes to LA filling during early ventricular systole [10]. To our knowledge, the diagnostic value of the LAVI/a’ ratio seems to be a novel finding. However, the ratio has been studied in other contexts; that is, in suspected HFpEF, an increased ratio was associated with more advanced diastolic function and worse prognosis [22], and in hypertensive patients, an increased ratio was associated with a higher risk for paroxysmal atrial fibrillation [38]. The current HFpEF patients displayed elevated pulse pressure and LVMi, indicating higher stiffness of the aorta and LV. A hypothesis is that this may raise LV end-diastolic pressure, a measure of LA afterload, and over time mediate lower a’ due to atrial contraction failure [10,22,36].

To our knowledge, the high diagnostic performance of RVIVRT seems to be a novel finding. Prolonged RVIVRT is associated with an increased TR gradient, due to delayed RV relaxation with increased RV afterload. Or alternatively because of RV failure—common in HFpEF—which may, besides increased TR gradient, have contributed to the high accuracy. Other reasons for prolongation are right bundle branch block or pacemaker rhythm, while elevated RAP and tachycardia shortens RVIVRT [25,39]. In our study, the TR gradient was missing in ~1/3 of the patients, for which RVIVRT may be a feasible surrogate.

Regarding RV failure, others have found a higher prevalence, which may be due to higher body weight and the inclusion of patients with AF [40]. These factors may cause higher PCWP and RVSP due to pericardial restraint and eventually RV failure [41].

The ASE/EACVI diastolic function algorithm was invasively validated by Obokata et al., and they found low sensitivity (34%), and rather high specificity (80%) in a population with different characteristics [42] compared with the current cohort which was older, probably more affected, with no age difference between groups. As e’ declines with age, the E/e’ ratio tends to increase. The ratio is also higher during sinus rhythm than during atrial fibrillation [9], and all participants had sinus rhythm during echocardiography. The body mass index was lower, making the indexing of LA volume for BSA less pronounced.

The performance of the HFA-PEFF diagnostic algorithm has recently been validated in a European cohort with 69% of the HFpEF classified as high probability; all patients with HFpEF in the current study were classified with high probability, which may reflect more severe disease. Similar to the current study, a majority (74%) of controls was classified as intermediate probability, implicating cardiovascular risk factor-mediated subclinical aberrations in this relatively healthy but aged group. The cut-off limits in the HFA-PEFF algorithm for e’, E/e’, and LAVI are within normal limits for healthy Europeans aged > 60 years [9,10].

**Clinical implications**

In a scenario of clinical suspicion of HFpEF in an elderly patient with sinus rhythm, a high HFA-PEFF score (≥ 5 points) provides strong supporting evidence for diagnosis, while intermediate scores are inconclusive. As a first step, we recommend the additional application of the 2021 filling pressure algorithm, including the use of LA strain and, in case of sustained uncertainty, LAVI/a’ and RVIVRT to reach a diagnosis on an individual basis.

**Study limitations**

The current study had several limitations, such as its small size and lack of diagnosis-confirming invasive filling pressure data. Even though the echocardiographic filling pressure algorithms were highly accurate for HFpEF diagnosis, the resting filling pressure may not be correctly classified in all patients, as the algorithm in patients with preserved EF is not perfect [10]. The short stress test is not a validated methodology, but haemodynamic alterations are known to occur already at a low level of exercise [42]. The case-control design with two contrasting groups rather than a continuum of disease progression might have enhanced the diagnostic performance of the studied parameters. A recent
study with younger and more obese patients found a substantial proportion of invasively diagnosed HFpEF patients to have normal levels of NT-proBNP and more subtle echocardiographic abnormalities compared with HFpEF with elevated NT-proBNP [4]. The current HFpEF patients all had elevated NT-proBNP. Patients were included in the Optimize study based on 2012 guideline recommendations [17], requiring signs of reduced diastolic function which might have increased sensitivity. Indeed, we did consider that the accuracy may be inflated because of the selection of patients through a HFpEF study (OPTIMIZE-HF) in which echocardiographic parameters were a part of inclusion criteria. Meanwhile, a correct diagnosis of HFpEF is vital, which often requires an overall assessment of different diagnostic performances including biomarker and echocardiographic measurements. This is because none of diagnostic performances for HFpEF are specific. For instance, one echocardiographic finding often considered a sufficient criteria of reduced diastolic function in our daily clinical practice was reduced e', (medial e' medial <8 cm/s or e' lateral <10 cm/s). In the current cohort, this was however found in both all patents and in all controls. The current control group was asymptomatic, so the first step of the HFA-PEF algorithm (i.e. assessing symptoms and signs) was ignored when calculating the scores. However, as non-cardiac dyspnoea is common in the elderly, there is a need for specific diagnostic methods, irrespective of symptoms [6,12]. The presented cut-off limits have not been evaluated in a separate test group, and the levels may be different in younger patients or other groups of the diverse HFpEF syndrome. The study included only patients with a sinus rhythm. However, in symptomatic patients with atrial fibrillation, hypertension, or diabetes, the probability of heart failure has been reported to be >90% [43].

Conclusions

Echocardiographic parameters, such as LASr, E/e', a', and LAVI/a', were highly accurate for the diagnosis of HFpEF in elderly patients with hypertension. The optimal cut-off limits for the parameters were presented. The 2021 EACVI filling pressure algorithm showed a high sensitivity and specificity. The diastolic function algorithm and the HFA-PEFF diagnostic algorithm were highly sensitive but with low capability to exclude HFpEF.

Acknowledgments

The authors thank biomedical scientists Valentina Dram-Sondberg and Anna Komarovska for their excellent work with echocardiographic exams and measurements, and Anders Thurin for compiling the data.

Disclosure statement

M.C.J. and A.R. have no interest to declare. M.F. received personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Vifor-Fresenius, unrelated to the present work.

Funding

This study was supported by The Healthcare Board; Region of Västra Götaland (Hälsos och Sjukvårdstjänsterna), Sweden [VGFouREG 929862, VGFouREG – 558801, VGFouREG – 733691], and the Swedish Research Council [2018-02527].

References

[1] Shah AM, Claggott B, Loehr LR, et al. Heart failure stages among older adults in the community: the atherosclerosis risk in communities study. Circulation 2017;135(3):224–240.
[2] Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation 2021;143(8):e254–e743.
[3] Farazdaghi GR, Wohlfart B. Reference values for the physical work capacity on a bicycle ergometer for women between 20 and 80 years of age. Clin Physiol. 2001;21(6):682–687.
[4] Verbrugge FH, Omote K, Reddy YNV, et al. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. Eur Heart J. 2022;43(20):1941–1951.
[5] Lee KK, Doudes D, Anwar M, et al. Development and validation of a decision support tool for the diagnosis of acute heart failure: systematic review, Meta-analysis, and modelling study. BMJ 2022;377:e068424.
[6] Selvaraj S, Myhre PL, Vaduganathan M, et al. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. JACC Heart Fail. 2020;8(8):640–653.
[7] Barandiarián Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, et al. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. Eur J Heart Fail. 2020;22(3):413–421.
[8] Telles F, Nanayakkara S, Evans S, et al. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. Eur J Heart Fail. 2019;21(4):495–505.
[9] Naghueh SF, Smiseth OA, Appleton CP, Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur J Heart Cardiovasc Imaging. 2016;17(12):1321–1360.
[10] Smiseth OA, Morris DA, Cardim N, Reviewers: This document was reviewed by members of the 2018–2020 EACVI Scientific Documents Committee, et al. Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Society of Cardiovascular Imaging. Eur J Heart Cardiovasc Imaging. 2022;23(2):e34–e61.
[11] Pugliese NR, Mazzola M, Fabiani I, et al. Haemodynamic and metabolic phenotyping of hypertensive patients with and without heart failure by combining cardiopulmonary and echocardiographic stress test. Eur J Heart Fail. 2020;22(3):458–468.
[12] Pieske B, Tschöpe C, de Boer RA, et al. 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). Eur J Heart Fail. 2020;22(3):391–412.
[13] Nikorowitsch J, Bei der Kellen R, Kirchhof P, et al. Applying the ESC 2016, H2PEFF, and HFA-PEFF diagnostic algorithms for heart failure with preserved ejection fraction to the general population. ESC Heart Fail. 2021;8(5):3603–3612.
[14] Churchill TW, Li SX, Curreri L, et al. Evaluation of 2 existing diagnostic scores for heart failure with preserved ejection fraction against a comprehensively phenotyped cohort. Circulation 2021;143(3):289–291.

[15] Parcha V, Malla G, Kalra R, et al. Diagnostic and prognostic implications of heart failure with preserved ejection fraction scoring systems. ESC Heart Fail. 2021;8(3):2089–2102.

[16] Lundberg A, Johnson J, Hage C, et al. Left atrial strain improves estimation of filling pressures in heart failure: a simultaneous echocardiographic and invasive haemodynamic study. Clin Res Cardiol. 2019;108(6):703–715.

[17] Fu M, Zhou J, Thunstrom E, et al. Optimizing the management of heart failure with preserved ejection fraction in the elderly by targeting comorbidities (OPTIMIZE-HFPEF). J Card Fail. 2016;22(7):539–544.

[18] Mehlig K, Berg C, Björck L, et al. Cohort profile of the INTERGENE study. Int J Epidemiol. 2017;46(6):1742–1743h.

[19] Mapelli M, Salvioni E, Paneroni M, et al. Brisk walking can be a maximal effort in heart failure patients: a comparison of cardiopulmonary exercise and 6 min walking test cardiorespiratory data. ESC Heart Fail. 2022;9(2):812–21.

[20] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233–270.

[21] Pugliese NR, Paneni F, Mazzola M, et al. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure. Eur J Heart Fail. 2021;23(11):1858–1871.

[22] Park HJ, Jung HO, Min J, et al. Left atrial volume index over late diastolic mitral annulus velocity (LAVi’A) is a useful echo index to identify advanced diastolic dysfunction and predict clinical outcomes. Clin Cardiol. 2011;34(2):124–130.

[23] Badano LP, Kolas TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/industry task force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018;19(6):591–600.

[24] Reddy YNV, Obokata M, Egbe A, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. Eur J Heart Fail. 2019;21(7):891–900.

[25] Zimbarra Cabrita I, Ruisanchez C, Grapsa J, et al. Validation of the isovolumetric relaxation time for the estimation of pulmonary systolic arterial blood pressure in chronic pulmonary hypertension. Eur J Heart J Cardiovasc Imaging. 2013;14(1):51–55.

[26] Pugliese NR, De Biase N, Conte L, et al. Cardiac reserve and exercise capacity: insights from combined cardiopulmonary and exercise echocardiography stress testing. J Am Soc Echocardiogr. 2021;34(1):38–50.

[27] Pugliese NR, De Biase N, Gargani L, et al. Predicting the transition to and progression of heart failure with preserved ejection fraction: a weighted risk score using bio-humoral, cardiopulmonary, and echocardiographic stress testing. Eur J Prev Cardiol. 2021;28(15):1650–1661.

[28] Ma CS, Liao YP, Fan JL, et al. The novel left atrial strain parameters in diagnosing of heart failure with preserved ejection fraction. Echocardiography 2022;39(3):416

[29] Tomlinson S, Scala GM, Appadurai V, et al. Left atrial reservoir strain provides incremental value to left atrial volume index for evaluation of left ventricular filling pressure. Echocardiography 2021;38(9):1503–1513.

[30] Patel RB, Freed BH, Beussink-Nelson L, et al. Associations of cardiac mechanics with exercise capacity: the multi-ethnic study of atherosclerosis. J Am Coll Cardiol. 2021;78(3):245–257.

[31] Maffèis C, Morris DA, Belyavskiy E, et al. Left atrial function and maximal exercise capacity in heart failure with preserved and mid-range ejection fraction. ESC Heart Fail. 2021;8(1):116–128.

[32] Bekfani T, Hamadanchi A, Ijuin S, et al. Relation of left atrial function with exercise capacity and muscle endurance in patients with heart failure. ESC Heart Fail. 2021;8(6):4528–4538.

[33] Johansson B, Fensrud E, Lundin F, et al. The A’ velocity by tissue-Doppler echocardiography correlates to invasive mean left atrial pressure in patients with normal ejection fraction. Scand Cardiovasc J. 2022;56(1):6–12.

[34] Obokata M, Negishi K, Kurosawa K, et al. Incremental diagnostic value of la strain with leg lifts in heart failure with preserved ejection fraction. JACC Cardiovasc Imaging. 2013;6(7):749–758.

[35] Okura H, Takada Y, Yamabe A, et al. Age- and gender-specific changes in the left ventricular relaxation: a Doppler echocardiographic study in healthy individuals. Circ Cardiovasc Imaging. 2009;2(1):41–46.

[36] Okura H, Kataoka T, Yoshida K. Comparison of left ventricular relaxation and left atrial function in patients with heart failure and preserved ejection fraction versus patients with systemic hypertension and healthy subjects. Am J Cardiol. 2016;118(7):1019–1023.

[37] Oike F, Yamamoto E, Sueta D, et al. Clinical significance of diastolic late mitral annular velocity in heart failure with preserved ejection fraction. Int J Cardiol. 2020;316:145–151.

[38] Toh N, Kanzaki H, Nakatani S, et al. Left atrial volume combined with atrial pump function identifies hypertensive patients with a history of paroxysmal atrial fibrillation. Hypertension 2010;55(5):1150–1156.

[39] Brechot N, Gambotti L, Lafitte S, et al. Usefulness of right ventricular isovolumic relaxation time in predicting systolic pulmonary artery pressure. Eur J Echocardiogr. 2008;9(4):547–554.

[40] 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.

[41] Borlaug BA, Reddy YNV. The role of the pericardium in heart failure: implications for pathophysiology and treatment. JACC Heart Fail. 2019;7(7):574–585.

[42] Obokata M, Kane GC, Reddy YN, et al. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. Circulation 2017;135(9):825–838.

[43] Reddy YNV, Obokata M, Gersh BJ, et al. High prevalence of occult heart failure with preserved ejection fraction among patients with atrial fibrillation and dyspnea. Circulation 2018;137(5):534–535.