Diagnostic value of echocardiographic markers for diastolic dysfunction and heart failure with preserved ejection fraction

Elisa Dal Canto 1,2 & Sharon Remmelzwaal 1 & Adriana Johanne van Ballegooijen 1,3 & M. Louis Handoko 4 & Stephane Heymans 5,6,7 & Vanessa van Empel 5 & Walter J. Paulus 8 & Giel Nijpels 2 & Petra Elders 2 & Joline WJ Beulens 1,9

Published online: 2 June 2020
© The Author(s) 2020

Abstract
This study aimed to evaluate the diagnostic performance of echocardiographic markers of heart failure with preserved ejection fraction (HFpEF) and left ventricular diastolic dysfunction (LVDD) in comparison with the gold standard of cardiac catheterization. Diagnosing HFpEF is challenging, as symptoms are non-specific and often absent at rest. A clear need exists for sensitive echocardiographic markers to diagnose HFpEF. We systematically searched for studies testing the diagnostic value of novel echocardiographic markers for HFpEF and LVDD. Two investigators independently reviewed the studies and assessed the risk of bias. Results were meta-analysed when four or more studies reported a similar diagnostic measure. Of 353 studies, 20 fulfilled the eligibility criteria. The risk of bias was high especially in the patients’ selection domain. The highest diagnostic performance was demonstrated by a multivariable model combining echocardiographic, clinical and arterial function markers with an area under the curve of 0.95 (95% CI, 0.89–0.98). A meta-analysis of four studies indicated a reasonable diagnostic performance for left atrial strain with an AUC of 0.83 (0.70–0.95), a specificity of 93% (95% CI, 90–97%) and a sensitivity of 77% (95% CI, 59–96%). Moreover, the addition of exercise E/e′ improved the sensitivity of HFpEF diagnostic algorithms up to 90%, compared with 60 and 34% of guidelines alone. Despite the heterogeneity of the included studies, this review supported the current multivariable-based approach for the diagnosis of HFpEF and LVDD and showed a potential diagnostic role for exercise echocardiography and left atrial strain. Larger well-designed studies are needed to evaluate the incremental value of novel diagnostic tools to current diagnostic algorithms.

Keywords Heart failure with preserved ejection fraction · Diastolic dysfunction · Echocardiography · Systematic review · Meta-analysis

List of abbreviations
HFpEF Heart failure with preserved ejection fraction
LVEF Left ventricular ejection fraction
NPs Natriuretic peptides

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10741-020-09985-1) contains supplementary material, which is available to authorized users.

Joline WJ Beulens
j.beulens@amsterdamumc.nl

1 Department of Epidemiology and Biostatistics, Amsterdam University Medical Center, Amsterdam, The Netherlands
2 Department of General Practice and Elderly Care Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands
3 Department of Nephrology, Amsterdam University Medical Center, Amsterdam, The Netherlands
4 Department of Cardiology, Amsterdam University Medical Center, Amsterdam, The Netherlands
5 Department of Cardiology, CARIM School for Cardiovascular Diseases, Maastricht University Medical Centre, Maastricht, The Netherlands
6 Department of Cardiovascular Sciences, Centre for Molecular and Vascular Biology, Leuven, KU, Belgium
7 The Netherlands Heart Institute (NL-HI), Utrecht, The Netherlands
8 Department of Physiology, Amsterdam University Medical Center, Amsterdam, The Netherlands
9 Julius Center for Health Sciences and Primary Care, Utrecht University Medical Center, Utrecht, The Netherlands
Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome associated with high morbidity and mortality, which now accounts for 56% of the subjects with HF, and its prevalence is increasing [1]. HFpEF is defined by the presence of symptoms and/or signs of HF, a preserved left ventricular (LV) ejection fraction (LVEF, > 50%), elevated levels of natriuretic peptides (NPs) and the evidence of cardiac functional and structural alterations underlying HF [2]. Structural alterations include an increased left atrial volume index (LAVI) or left ventricular mass index (LVMI), whereas functional alterations mostly include left ventricular diastolic dysfunction (LVDD). LVDD is defined as the presence of impaired LV relaxation and increased LV chamber stiffness, which increases LV filling pressures (LVFP) [3]. Evidence of LVDD can be obtained invasively through rest or exercise right-sided heart catheterization or non-invasively through echocardiography [2]. There is no single echocardiographic measure that provides evidence of LVDD, but rather a combination of several abnormal indices is recommended to evaluate LV diastolic function: tissue Doppler indices (E/e’ ratio and e’ velocities), LAVI and tricuspid regurgitation velocity are the currently recommended variables [3]. However, only a relatively small number of studies validated the use of these echocardiographic indices, showing only a modest correlation with invasive hemodynamic parameters and limited discriminative power [4]. Additionally, the echocardiographic indices proposed by guidelines are normal in 40–75% of subjects with invasively proven HFpEF [4, 5] and showed lower accuracy in individuals at an early stage of the disease. In fact, these subjects often show a normal or indeterminate diastolic function at resting echocardiography because LVFP are not elevated, or because they vary over time, depending on volume status [6]. Recently, a new stepwise diagnostic approach that includes clinical, laboratory and imaging tests—the HFA-PEFF score—was proposed by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) with the purpose of integrating novel information into a comprehensive algorithm, in order to better identify subjects with HFpEF at different stages [7]. These recommendations include some of the new techniques that are currently being evaluated as potential diagnostic tools to improve diagnosis and staging of subjects with HFpEF, such as measures of LV deformation by 2D speckle tracking echocardiography (STE) and diastolic stress test (DST)-derived parameters [7]. In addition to these, left atrial (LA) functional parameters such as LA strain recently demonstrated significant correlation with both clinical status and invasive measures of LVFP in subjects with HFpEF and thus could improve HFpEF diagnosis [8]. With this review, we aim to systematically evaluate the diagnostic value of novel echocardiographic indices and multivariable models on accuracy and incremental utility to identify LVDD and HFpEF.

Methods

Data sources and searchers

We performed a systematic review of PubMed and EMBASE from their inception to (SR and LS) May 13, 2019, according to the PRISMA-DTA Statement [8]. Search terms included indexed terms from MeSH in PubMed and EMBASE, as well as free-text terms. This search was used for a set of three systematic reviews that describe different types of diagnostic markers for LVDD and HFpEF (NPs, echocardiographic markers and biomarkers). Bibliographies of the identified articles were also hand-searched for relevant publications (see Appendix A). The protocol and search strategy was preregistered on PROSPERO (registration number: CRD42018065018).

Study selection

Two reviewers independently screened titles, abstracts and full-text articles. Inconsistencies in study selection were resolved through discussion until consensus was reached and, if needed, through the consultation of a third reviewer (SR, EDC, AJvB or JWJB). The eligibility of studies was assessed according to the inclusion and exclusion criteria listed in Supplementary Table 1.
Quality assessment

Two reviewers (SR and EDC) independently performed the quality assessment for each study using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies) [9]. QUADAS-2 consists of four domains: patient selection, index test, reference standard and flow and timing. Quality is assessed in each domain to estimate risk of bias and concerns regarding applicability. The patient selection domain assessed whether the selection of participants could have introduced bias. The index test and reference standard domains assessed whether the conduct or interpretation of the index test and reference standard, respectively, may have introduced bias. The flow and timing domain addressed the time interval between index test and reference standard (9). Any discrepancies or disagreements between the authors were resolved through discussion until consensus was reached and, if needed, through the consultation of a third reviewer (JWJB).

Diagnostic performance and data extraction

Two authors (SR and EDC) extracted data independently, according to a standard protocol that included first author, year of publication, country, journal, study design, markers (echocardiographic ± clinical/laboratory parameters), outcome measures, population description, reference diagnosis and measures of diagnostic performance.

Data synthesis

Study characteristics of the studies were described in a systematic manner according to the diagnostic markers. Studies were meta-analysed using a random-effects model when three or more studies investigated the same diagnostic measure for the same echocardiographic marker in a similar study population and with a similar control population. In addition, the studies had to provide confidence intervals (95% CI) of this diagnostic performance measure or sufficient information (2 × 2 table) to compute these confidence intervals. Forest plots of random-effects meta-analyses were fitted for AUCs, sensitivities and specificities. Heterogeneity was tested using \( I^2 \), where an \( I^2 > 75\% \) is considered as substantial heterogeneity. All analyses and plots were performed in RStudio version 3.4.2 using the metafor package [10].

Results

Search results

We screened 11,727 titles, which yielded 353 potentially relevant studies. In total, 20 studies met the inclusion criteria.

The remainder was excluded according to the criteria listed in the PRISMA flowchart (see Supplementary Fig. 1).

Quality assessment

The QUADAS-2 domain with the highest proportion of high risk of bias was patient selection (Supplementary Fig. 2) with 13 studies (65%) demonstrating a high risk of bias mostly due to case-control design or to a non-consecutive or non-random inclusion of subjects. In the other three of the four QUADAS-2 domains (index test, reference test and flow and timing), eight (40%), three (15%) and eight (40%) studies, respectively, demonstrated a high risk of bias. In the QUADAS-2 domain reference standard, 12 studies (60%) showed an unclear risk of bias. On the other hand, most of the studies showed low concerns regarding applicability with the highest proportion of high concerns for the reference standard domain (six studies, 30%). None of the studies was excluded based on the quality assessment.

Study characteristics

Of the 20 included studies, ten were performed in the USA, seven in Europe, two in Japan and one in Australia (Table 1). Eighteen studies (90%) were published in the past 10 years (2009–2019). Sixteen were cross-sectional and four were case-control studies performed in subjects referred for right- and/or left-sided heart catheterization. As clinical outcome, 13 studies used HFpEF [5, 11–22], two used HFpEF with associated pulmonary hypertension (PH) [23, 24], one used “early” HFpEF [25], and four used LVDD [26–29]. The reference diagnosis always included the echocardiographic evidence of a normal LVEF and one or more invasive measures of elevated LVFP (LV end-diastolic pressure or pulmonary capillary wedge pressure), impaired LV relaxation (isovolumetric relaxation time or constant \( \tau \)) and increased LV stiffness (LV stiffness constant \( b \)). Conventional transthoracic rest echocardiography was the most commonly used index measure \((n = 10)\) followed by STE \((n = 8)\) and by DST \((n = 2)\). As echocardiographic predictor, seven studies used a combination of echocardiographic markers or multivariable models that included also demographics, medications, biochemical and arterial function parameters; eight studies used LV and LA strain parameters; and two studies used DST data and three of them used single standard echocardiographic parameters.

Measures of diagnostic performance: HFpEF

Multivariable models

In general, multivariable predictors showed good diagnostic performance (Table 2). The highest diagnostic performance was demonstrated by a combination of echocardiography
Table 1  Baseline characteristics of the 20 included studies

| Study          | Study design                  | Predictors                                      | Outcome                  | Study population                                                                 |
|----------------|-------------------------------|-------------------------------------------------|--------------------------|-----------------------------------------------------------------------------------|
| **HFpEF studies** |                               |                                                 |                          |                                                                                   |
| Thenappan USA  | Cross-sectional               | Age, clinical data, echo, haemodynamics         | PH-HFpEF                 | PH registry                                                                       |
| Weber EU [11]  | Cross-sectional               | E/e' + other echo, arterial function, clinical data | HFpEF                    | Subjects referred to RHC for suspected CAD                                        |
| Cameron USA [24] | Cross-sectional               | 2009 ASE/AHA guidelines + multivariable models   | PH-HFpEF                 | Subjects enrolled in the PH program for the assessment of PH                      |
| Dokainish USA [17] | Cross-sectional               | Echocardiographic equations                     | HFpEF                    | Subjects referred to LHC for clinical reasons                                      |
| Dini EU [16]   | Cross-sectional               | Echocardiographic equations                     | HFpEF                    | HF subjects                                                                       |
| Reddy USA [18] | Cross-sectional               | H2FPEF score                                    | HFpEF                    | Subjects undergoing RHC for the evaluation of dyspnoea                            |
| **Left ventricular strain and strain rate** |                               |                                                 |                          |                                                                                   |
| Kasner EU [12] | Case-control                  | Global strain rates and their ratios with early transmural flow | HFpEF                    |                                                                                   |
| Wang USA [14]  | Case-control                  | Global longitudinal strain                      | HFpEF                    |                                                                                   |
| **Left atrial strain** |                               |                                                 |                          |                                                                                   |
| Kurt USA [13]  | Case-control                  | E/LA systolic strain (LA non-invasive stiffness) | HFpEF (DHF)              |                                                                                   |
| Lundberg EU [20] | Cross-sectional               | LA global strain (LA-GS), TR Vmax, LAVi and E/e' | HFpEF                    | Subjects referred to RHF for suspected HF                                         |
| Reddy USA [19] | Cross-sectional               | LA reservoir, conduit and booster strain, LA reservoir strain/E', LA reservoir strain/LAVI | HFpEF                    | Subjects undergoing RHC for dyspnoea                                              |
| Singh USA [21] | Cross-sectional               | Peak LA strain                                  | HFpEF                    | Subjects referred to LHC for various reasons (chest pain, ACS, etc.)               |
| Telles AU [22] | Cross-sectional               | LA global reservoir and LA pump strain          | HFpEF                    | Subjects referred to RHC for exertional dyspnoea                                  |
| **Diastolic stress test markers** |                               |                                                 |                          |                                                                                   |
| Hammoudi EU [25] | Cross-sectional               | Lateral and septal E/E' at low-level exercise (25 and 50 W) | Early HFpEF              | Subjects at high risk for HFpEF                                                   |
| Obokata USA [5] | Cross-sectional               | ESC algorithm + exercise average E/E'           | HFpEF                    | Subjects referred to RHC for exertional dyspnoea                                  |
| **Single conventional echocardiography markers** |                               |                                                 |                          |                                                                                   |
| Nagash USA [15] | Cross-sectional               | Echo estimated RAP > 8 mmHg                     | HFpEF                    | Subjects with exertional dyspnoea enrolled in a multicentre study                 |
| **Left ventricular diastolic dysfunction studies** |                               |                                                 |                          |                                                                                   |
| Goto Jap [27]  | Case-control                  | BNP > 2.2 pg/mL + E velocity < 7.4 cm/s         | LVDD                     | Subjects referred to LHC for the evaluation of CAD                                |
| Weber EU [29]  | Case-control                  | LVETI, E/A, E' and E/E'                         | LVDD                     | Subjects with suspected CAD                                                       |
| Bruch EU [26]  | Cross-sectional               | Tei index                                       | LVDD                     | Subjects referred to LHC or known/suspected CAD                                   |
| Hayashi Jap [28] | Cross-sectional               | Ratios of E wave to peak longitudinal strain (E/LS), E/A and E/E' | LVDD                     | Subjects who underwent LHC for clinical diagnosis of cardiac diseases             |

| Study          | Index group (n); sex (% female); age | Reference group (n); Reference diagnosis                                                                 |
|----------------|--------------------------------------|----------------------------------------------------------------------------------------------------------|
| **HFpEF studies** |                                       |                                                                                                        |
| Thenappan USA  | PH-HFpEF (100); 82%; 64 ± 13          | PAH (522); HF symptoms + LVEF > 50% + PWCP > 15 mmHg/LVEDP > 15 mmHg/PVR > 2.5 wood units              |
| Weber EU [11]  | HFpEF (71); 33.8%; 67.7 ± 8.6         | Non-HFpEF (65); LVEF > 50% + LVEDP > 16 mmHg + NT-proBNP > 220 pg/mL.                                  |
| Cameron USA [24] | PH + LVEDP > 15 mmHg (81); 67%; 62 (56–70) | PH + LVEDP ≤ 15 mmHg (80); PASP > 25 mmHg + LVEDP > 15 mmHg                                             |
| Dokainish USA [17] | LVEF > 50% + LVEDP > 20 mmHg (69); 58%; 55.1 ± 8.5 | LVEF > 50% + LVEDP < 20 mmHg (53); LVEF > 50% + LVEDP > 20 mmHg                                        |
| Dini EU [16]   | HFpEF (55); 35%; 67 ± 12              |HFpEF (123); LVEF > 50% + PCWP > 15 mmHg                                                              |
| Reddy USA [18] | HFpEF (267); 61%; 68 ± 11             | NCD (147); 59%; 56 ± 15; LVEF > 50%, dyspnoea + PCWP at rest ≥ 15 mmHg or during exercise ≥ 25 mmHg  |
| **Left ventricular strain and strain rate** |                                       |                                                                                                        |
| Kasner EU [12] | HFpEF (21); 52%; 43–60               | Subjects with chest pain (12); Healthy subjects (17)                                                  |
| Wang USA [14]  | DHF (20); 35%; 63 ± 11               |                                                                                                        |
| **Left atrial strain** |                                       |                                                                                                        |
| Kurt USA [13]  | DHF (20); 30%; 58 ± 16               | LVH + normal LVEF (19); Clinical criteria + PCWP (ESC 2007 guidelines)                                |
| Table 1 (continued) | Lundberg EU | EF ≥50% (63) + abnormal LAP | Normal LAP (29) | Pulmonary artery wedge pressure (PAWPM) >15 mmHg at rest or ≥23 mmHg during peak exercise |
|---------------------|--|-----------------|-----------------|---------------------------------|
| Reddy USA           | HFpEF (238), 62%, 68 ± 10 | NCD (125), 56%, 58 ± 14 | Clinical symptoms of HF + LVEF ≥50% + PCWP with rest ≥ 15 mmHg and/or exercise ≥ 25 mmHg |
| Singh USA           | HFpEF (7) | LVDP <15 mmHg (25) | Pre-A-wave LVDP > 15 mmHg |
| Telles AU           | HFpEF (49), 71.4%, 69.4 ± 8.0 | NCD (22), 77.3%, 67.0 ± 9.9 | LVEF > 50%, dyspnoea + PCWP ≥ 15 mmHg at rest and/or ≥ 25 mmHg at maximal exertion |

Diastolic stress test markers

| Hammoudi EU | LVEDP > 16 mmHg during exercise (34);23%, 64.8(55.2–73.4) | LVEDP <16 mmHg (12) |
| Obokata USA | HFpEF (50); 54%; 70 ± 11 | NCD (24) |

Single conventional echocardiography markers

| Nagueh USA | HFpEF (50); 44%; 64 ± 9 | Non-HFpEF (79) |

Left ventricular diastolic dysfunction studies

| Goto Jap [27] | Isolated LVDD (91); 18.7%; 67.4 ± 8.2 | Normal diastolic function (189) |
| Weber EU [29] | LVDD (44), 50%, 65.7 (10.1) | Healthy controls (82), 28.1%, 55.6 (8.9) |
| Bruch EU [26] | HFpEF (29); 24%; 63 ± 9 | Normal echo (11) |
| Hayashi Jap [28] | LVEF >50% (47), of whom 38 with τ ≥ 48 ms and 18 HFpEF (30) | Abnormal LV relaxation = τ ≥48 ms; LVMDP ≥ 12 mmHg |

**EU** Europe, **AU** Australia, **Jap** Japan, **PH** pulmonary hypertension, **HFpEF** heart failure with preserved ejection fraction, **PAH** pulmonary arterial hypertension, **LVEF** left ventricular ejection fraction, **PAWP** pulmonary capillary wedge pressure, **LVDD** left ventricular end-diastolic pressure, **NT-proBNP** N-terminal-pro-brain natriuretic peptide, **CAD** coronary artery disease, **RHC** right heart catheterization, **PASP** pulmonary artery systolic pressure, **LHC** left heart catheterization, **LAP** left atrial pressure, **NCD** non-cardiac dyspnoea, **E′/A′** the ratio of early (E′) and late (A′) tissue Doppler diastolic peak velocities, **IVRT** isovolumic relaxation time, **LA** left atrial, **DHF** diastolic heart failure, **E/E′** the ratio of mitral E peak velocity and averaged E′ tissue Doppler velocity, **LVH** left ventricular hypertrophy, **RAP** right atrial pressure, **LVDP** left ventricular diastolic pressure, **EDTE**-wave deceleration time, **AR dur-A dur** difference in duration of pulmonary vein flow and mitral flow velocity at atrial contraction, **LAVI** LA volume index, **E/Vp** ratio of mitral E-wave and colour M-mode flow propagation velocity, **LVFP** left ventricular filling pressures, **LVETI** LV ejection time index, **IDD** isolated diastolic dysfunction, **LVEDVI** left ventricular end-diastolic volume index, **LVMDP** left ventricular mean diastolic pressure
and pulsatile arterial function data with an AUC = 0.95 (95% CI, 0.89–0.98). The addition of aortic pulse pressure to echocardiographic and clinical markers led to a highly significant net reclassification index of up to 33% and reduced the number of undiagnosed HFpEF subjects from 60 to 24 [11]. The H2FPEF score showed a very good diagnostic performance to estimate the likelihood of HFpEF among subjects with unexplained dyspnoea [18]. The H2FPEF score is based on four clinical characteristics (body mass index, anti-hypertensive medications, atrial fibrillation [AF] and age) and two echocardiographic markers (E/e′ and pulmonary artery systolic pressure) and provided good discrimination of HFpEF from subjects with non-cardiac dyspnoea (NCD) (AUC = 0.84, 0.80–0.88). The performance was maintained in the independent validation cohort with an AUC = 0.87 (0.79–0.94) [18].

Meta-analyses on LA strain

The utilization of LA strain indicated high diagnostic performance without clinical or laboratory data. LA global or reservoir or peak strain was most commonly tested [19–22] with the addition of conduit and booster strain [19, 22] and of indirect measures of LA compliance (LA strain/E/e′) [19] and LA stiffness (E/e'/LA strain) [13, 22]. The best diagnostic ability was demonstrated by LA strain for detecting elevated LVFP both at rest (AUC = 0.87) and during exercise (AUC = 0.93) in subjects with HF symptoms, outperforming conventional echocardiographic markers such as E/e′ (delta AUC + 0.19 during rest and + 0.37 during stress) and LAVI (delta AUC + 0.08 during rest and + 0.27 during stress) [20]. Four studies reported sensitivity and specificity for LA global strain with a mean of 77% (59–96%; $I^2 = 93.7\%$) and 93% (90–97%; $I^2 = 0.22\%$), respectively, and three studies reported AUCs with a mean of 0.83 (0.70–0.95, $I^2 = 88.3\%$) (Fig. 1). The high heterogeneity as shown by the meta-analysis for sensitivity and AUC can be explained by the broad range of values observed among the included studies, which for sensitivity ranged from 56 to 92% and for AUC from 0.72 to 0.93 and by the small sample sizes. On the other hand, all the included studies showed a high ability of LA strain to rule out HFpEF and thus a high specificity with low heterogeneity.

Diastolic stress test

Two studies evaluated the role of DST in the diagnosis of HFpEF. The first one found that E/e′ at low-level exercise was valuable for predicting abnormal LVFP with a sensitivity of 90% but only in subjects with cardiac disease [25]. The second study evaluated the incremental utility of DST to the diagnostic approaches proposed by ESC and American Society of Echocardiography/European Society of Cardiovascular Imaging (ASE/EACVI) to diagnose HFpEF: the addition of exercise E/e′ to the ESC and ASE/EACVI 2016 proposed algorithm indicated a much higher sensitivity compared with either of them alone (90 versus 60 and 34%, respectively) [5].

Measures of diagnostic performance: diastolic dysfunction

Five studies investigated echocardiographic markers for the detection of LVDD. The best diagnostic performance was demonstrated by the ratio of E wave to peak longitudinal strain (E/LS) to predict elevated LVFP in a population of subjects with suspected cardiac disease (AUC = 0.86 versus 0.74 of E/e′) [28].

Discussion

Since HFpEF is the predominant form of HF [1], the detection of this condition gained considerable interest. Standard resting echocardiography has still a pivotal role in the detection of HFpEF, but it provides only indirect evidence of pressure-volume relationships, and it might leave a significant proportion of subjects undetected. In this systematic review, a large variety of echocardiographic markers were investigated and yielded variable results for the diagnostic performance. The main findings are as follows: (1) multivariable models including clinical, echocardiographic and possibly arterial function variables demonstrated the best diagnostic performance. (2) LA strain may provide good discrimination capacity of HFpEF subjects and enhanced diagnostic accuracy beyond conventional echocardiographic measures. (3) Addition of exercise E/e′ to resting echocardiography findings improves HFpEF diagnosis.

Multivariable models

As expected, multivariable models demonstrated the best diagnostic performance, along the lines of what current guidelines recommend to use in clinical practice for the diagnosis of HFpEF. This can be explained by the complex pathophysiology of HFpEF, which is driven by advanced age and comorbidities, and caused by the interplay of multiple impairments in LV diastolic and systolic function, chronotropic reserve, arterial-ventricular mismatching, vascular and endothelial dysfunction, pulmonary hypertension and impaired systemic vasodilator reserve [30, 31]. Therefore, a multivariable algorithm that provides integrated information on all these aspects is necessary to evaluate diastolic function. Among the included studies, the highest diagnostic accuracy was demonstrated by a multivariable model combining clinical and echocardiographic markers with arterial function measures, thereby demonstrating that measures of pulsatile arterial haemodynamics may complement echocardiography for the diagnosis of...
HFpEF [11, 31]. Another combination of clinical and echocardiographic markers that provided a better discrimination of HFpEF from NCD than currently used diagnostic algorithms is the H2FPEF score, with a delta AUC of +0.17 (0.12–0.22) in the derivation cohort and a delta AUC of +0.21 (0.10–0.31) in the test cohort versus 2016 ESC guidelines [18]. However, external validation, which is a crucial step before introducing a new diagnostic model in clinical practice, was not performed. Overall, none of the included studies performed external validation, and only three performed validation in separate groups of subjects belonging to the same research centre [16, 18, 21]. Recently, the H2FPEF score was validated in the Alberta HEART population, showing a sensitivity of 90% of a score > 2 to detect HFpEF and a specificity of 82% of a score < 6 to rule out HFpEF [32]. Despite these promising results, the H2FPEF score still requires further validation and refinement.

Left atrial strain

The left atrium plays a key role in HFpEF pathophysiology, and indices of LA mechanics have diagnostic and prognostic utility in HFpEF [33]. STE can assess LA function, remodeling and distensibility, and LA strain can impair independently of LA size [33]. Five recent cross-sectional studies demonstrated the ability of LA strain to correctly classify dyspnoeic subjects as HFpEF with superior sensitivity and specificity than standard echocardiographic parameters [13, 19, 22] or to identify elevated LVFP more accurately than guidelines [20, 21]. Specifically, LA reservoir strain enabled to identify HFpEF from NCD with an AUC = 0.72 (0.66–0.77), outperforming other commonly used indices of diastolic function [19, 20]. Similarly, LA global strain managed to detect elevated LVFP both at rest and during exercise (AUCs = 0.87 and 0.93, respectively) and showed a better agreement with invasively determined LVFP than ESC 2016 guidelines (91 versus 81%) [21]. Among the studies that tested novel indices combining LA strain with Doppler measures of LV pressures, LA non-invasive stiffness showed the highest diagnostic performance in distinguishing subjects with HFpEF from those with LVDD, with an AUC = 0.85 (0.72–0.98) [13].

The meta-analysis of four studies indicated a very high specificity (93%) of LA global strain, in combination with a non-significant heterogeneity ($I^2$ of approximately 0%) and a good sensitivity (77%) although with consistent heterogeneity ($I^2 > 90$%), which indicate a high ability of LA strain to rule out HFpEF when normal, and a variable capacity to diagnose HFpEF when abnormal. The meta-analysis of three studies indicated also a good ability of LA strain to predict HFpEF diagnosis with an AUC of 0.83, although with significant heterogeneity ($I^2$ of 88%). Altogether, these results suggest a potential usefulness of LA strain in the non-invasive diagnostic evaluation of HFpEF. However, the studies that evaluated the diagnostic performance of LA strain established different optimal cut-off values for the identification of HFpEF subjects, ranging from −32.3 to −20%, and therefore, further studies are warranted to establish a definitive cut-off for abnormal LA strain. Additionally, it should be noted that STE is not routinely available worldwide and requires post-processing time, which questions its diagnostic utility in clinical practice for non-academic centres.

Diastolic stress test

Another imaging test with a potential diagnostic role in the diagnosis of HFpEF is the DST. Both ESC and ASE/EACVI guidelines already recommended to perform DST when resting echocardiography does not explain the symptoms of HF, especially when dyspnoea is present only with exertion [2, 3]. Recently, the DST has been integrated in the new HFA diagnostic recommendations, as part of the advanced HFpEF workup, to be performed if a subject who already underwent clinical, biomarkers and resting echocardiography assessment has an intermediate HFA-PEF score [7]. The utility of exercise data is clearly evident on top of resting echocardiographic data, as the utilization of exercise E/e’ alone (>14) indeed significantly improved the sensitivity of the diagnostic work-up to 90% compared with 60% of ESC guidelines [5]. Addition of exercise E/e’ also improved classification beyond the resting ESC criteria, with a negative predictive value of 87 versus 83% [5]. Hence, our results confirm the utility of DST not only to identify HFpEF in euvoletic subjects with inconclusive resting echocardiography but also to rule out HFpEF, when unequivocally normal. However, we must point out that the feasibility and the quality of echocardiographic measures decrease during exercise; for instance, tricuspid regurgitation velocity was measurable only in 49% of subjects at peak exercise [5]. Moreover, although a low-level exercise test with stepwise increase of the workload is recommended for the DST, there is no universally adopted protocol at the moment.

Strengths and limitations

To our knowledge, this is the first systematic review on novel echocardiographic markers for HFpEF and LVDD including a meta-analysis. Multiple databases were extensively searched, and article selection, data extraction and quality assessment were performed in duplicate according to a standardized protocol. Moreover, no geographical differences were detected, which increases the generalizability of the results. The review findings were limited by the heterogeneity and the quality of the included studies, which applied to the study design (case control versus cross-sectional), the study population (subjects with unexplained dyspnoea versus subjects with suspected coronary artery diseases), the reference standard (different invasive measures with different cut-off values) and the index.
Table 2  Measures of diagnostic performance of the 20 included studies

| Study | Markers | Sensitivity | Specificity | AUC (95% CI) (+p value) | PPV and PNV | Accuracy | LR+ and LR- | NRI and IDI |
|-------|---------|-------------|-------------|------------------------|-------------|----------|-------------|------------|
| HFpEF studies |
| Multivariable models and echocardiographic equations |
| Thenappan USA [23] | Age + WHO functional class, hypertension, obesity, DM, CAD, serum creatinine, diuretic, β-blocker, ACE inhibitors/ARBs + LVPWT, LA and RA enlargement | 90.09% | 0.935; (0.90–0.97) | 90.09% | 0.952 (0.894–0.983 (p = 0.0002) | 90.09% | 0.952 (0.894–0.983) |
| Weber EU [11] | E/e’ + aortic PP + age + ACE-I/ARB + β-blocker + NO-donator | 90.09% | 0.952 (0.894–0.983 (p = 0.0002) | 90.09% | 0.952 (0.894–0.983) |
| Cameron USA [24] | E/A, E/e’, LA diameter (1.5 x LA diameter) + (1.7 x E/e’ septal) | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Dokainish USA [17] | 1) PASP + LAVI/2 > 30 2) (E + LAVI)/2 > 57 | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Dini EU [16] | CART model (EDT < 150 ms + AR duration > 30 ms + E/e’ > 13 + LAVI > 40 mL/m² + E/Vp > 2) | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Reddy USA [18] | HFPEF score: obesity + AF + age > 60 years, treatment with ≥2 antihypertensive drugs + E/e’ > 9 + and PASP > 35 mmHg | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Left ventricular strain and strain rate |
| Kasner EU [12] | SRE, SRV, E’/A’, E/SRE, ESRV and E/e’ lat | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Wang USA [14] | GLS, < −16% | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Kart USA [13] | LA non-invasive stiffness index > 0.99 mmHg | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Lundberg, EU [20] | 1) Rest LA GS (LA-GS, −21%) 2) Stress LA GS | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Reddy, 2019 USA [19] | 1) LA reservoir strain (<−24.5%) 2) LA conduit strain (<−18.4%) 3) LA reservoir strain/E/e’ (<3) 4) LA reservoir strain/LAVI | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Singh USA [21] | Peak LA strain (<−20 mmHg) | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Telles Au [22] | 1) LA global reservoir (<−32.2%) 2) LA pump strain (<−15.5%) (AF subjects excluded) | 90.09% | 0.952 (0.894–0.983) | 90.09% | 0.952 (0.894–0.983) |
| Study | Markers | Sensitivity | Specificity | AUC (95% CI) (+p value) | PPV and | Accuracy | LR + and | NRI and IDI |
|-------|---------|-------------|-------------|-------------------------|---------|----------|----------|-------------|
|       |         |             |             |                         | PNV     | (vs ESC) | LR-       |             |
|       |         |             |             |                         |         |          |          |             |
| Diastolic stress test markers |         |             |             |                         |         |          |          |             |
| Hammoudi | Ex septal E/e at 25 W ≥ 8 | 71% | 83% | 0.79 (0.67–0.92) (p<0.0001) |         |          |          |             |
| Obokata | 1) ESC + Ex E/e’ > 14 | 1) 90% | 1) 71% | 1) 0.80 (0.68–0.89) (p<0.05 vs ESC) | 1) 87% | 1) 3.1 and |          |             |
|         | 2) ESC + 20 W Ex E/E’ > 14 | 2) 80% | 2) 88% | 2) 0.84 (0.73–0.91) (p<0.05 vs ESC) | 2) 93% | 2) 6.7 and |          |             |
| Single conventional echocardiography markers |         |             |             |                         |         |          |          |             |
| Nagueh | RAP > 8 mmHg | 76% | 89% | | 80% | 85% |          |             |
| Diastolic dysfunction studies |         |             |             |                         |         |          |          |             |
| Goto Jap [27] | BNP > 22.4 pg/mL + E velocity < 7.4 cm/s | 44% | 86.8% | | 61.5% | 76.3% | 76% |             |
| Weber EU | LVETI (427.1 ms) | 70% | 82% | 0.81 (0.72–0.89), p<0.0001 |         |          |          |             |
| Bruch EU | Tei index > 0.49 | 37% | 86% | 0.61 ± 0.08 |         |          |          |             |
| Hayashi Jap [28] | E wave/peak longitudinal strain (E/LS) > 680 cm/s | 72% | 88% | 0.80 |         |          |          |             |

The most significant echo markers and multivariable models including echo parameters were reported. EU Europe, AU Australia, Jap Japan, DM diabetes mellitus, CAD coronary artery disease, ACE inhibitors angiotensin-converting enzyme inhibitors, ARBs angiotensin II receptor blockers, LVPWT left ventricular posterior wall thickness, LA left atrial, RA right atrial, RAP RA pressure, PASP pulmonary artery systolic pressure, CO cardiac output, e’ peak early diastolic tissue velocity, E/e’ peak early filling over early diastolic tissue velocities ratio, PWV pulse wave velocity, PP pulse pressure, NO nitric oxide, AP augmented pressure, Pb amplitude of the backward wave, Pf amplitude of the forward wave, SRpeak global strain rate (SR) during early diastole, SRendo SR during isovolumetric relaxation, E’/A’ the ratio of early (E’) and late (A’) tissue Doppler diastolic peak velocities, GLS global longitudinal strain, EDT E-wave deceleration time, AR dur-A dur the difference in duration of pulmonary vein flow and mitral flow velocity at atrial contraction, LAVI LA volume index, E/Vp ratio of mitral E-wave and colour M-mode flow propagation velocity, BNP brain natriuretic peptide, LVFP left ventricular filling pressures, Ex exercise.
Summary sensitivity of LA strain

| Author, year, pos cases/tot HFpEF cases | Sensitivity [95% CI] |
|-----------------------------------------|----------------------|
| Telles, 2019, 43/49                     | 0.88 [0.79, 0.97]    |
| Singh, 2019, 5/7                        | 0.71 [0.38, 1.00]    |
| Reddy, 2019, 133/238                    | 0.56 [0.50, 0.62]    |
| Lundberg, 2019, 58/63                   | 0.92 [0.85, 0.99]    |

Summary estimate ($I^2 = 93.7\%$)

| Sensitivity |
|-------------|
| 0.77 [0.59, 0.96] |

Summary specificity of LA strain

| Author, year, neg cases/tot NCD cases | Specificity [95% CI] |
|---------------------------------------|----------------------|
| Telles, 2019, 17/22                   | 0.60 [0.42, 0.77]    |
| Singh, 2019, 24/25                    | 0.96 [0.88, 1.00]    |
| Reddy, 2019, 117/125                  | 0.94 [0.89, 0.98]    |
| Lundberg, 2019, 26/29                 | 0.90 [0.79, 1.00]    |

Summary estimate ($I^2 = 91.2\%$)

| Specificity |
|-------------|
| 0.86 [0.72, 1.00] |

Summary AUC of LA strain

| Author, year, pos cases/tot HFpEF cases | AUC [95% CI] |
|----------------------------------------|-------------|
| Telles, 2019, 43/49                    | 0.85 [0.76, 0.94] |
| Reddy, 2019, 133/238                   | 0.72 [0.67, 0.77] |
| Lundberg, 2019, 58/63                  | 0.93 [0.85, 1.00] |

Summary estimate ($I^2 = 88.3\%$)

| AUC |
|-----|
| 0.83 [0.70, 0.95] |
test (different combinations of echocardiographic techniques and clinical markers). In addition, quality assessment showed a large number of studies with high risk of bias across several domains. For example, 15 of 20 studies excluded subjects not in sinus rhythm. It is well known that HFpEF with concurrent arrhythmias and especially with AF is increasingly common [34]. The exclusion of subjects with AF questions the possibility to efficiently and practically use the newly tested echocardiographic markers in individuals with HFpEF and rhythm abnormalities, limiting generalizability. Another aspect that may have affected the results is the interpretation of the index test, since the echocardiographic analysis was often not blinded from the catheterization or not simultaneous, performed by different investigators, and only in three studies, the cut-off value of the echocardiographic marker was specified before the analysis [11, 22, 24, 25]. This could have resulted in an overestimation of performance of the proposed predictor, questioning its validity.

Conclusions

In conclusion, despite the considerable heterogeneity of the included studies which does not allow to draw definite conclusion, this study supports an integrated approach for the diagnosis of HFpEF, which includes multiple clinical and echocardiographic measures. New echocardiographic indices such as LA strain and DST data have potential diagnostic value to enhance the detection of HFpEF and LVDD. However, before their implementation into the diagnostic workup, their added diagnostic utility, beyond the established clinical and echocardiographic HFpEF features, should be proven by larger studies of HFpEF versus NCD subjects.

Funding information The research of SH has received funding from the European Union Commission’s Seventh Framework programme under grant agreement N 305507 (HOMAGE), N 602904 (FIBROTARGETS) and N261409 (MEDIA) and N 278249 (EU MASCARA) and the Marie-Curie Industry Academy Pathways and Partnerships (CARDIOMIR) N 285991, FP7-Health-2013-Innovations-1 N602156 (HECATOS). It was supported by research grants from the Netherlands Organization for Scientific Research (NWO) Vidi 91796338. This research is co-financed as a PPP-allowance Research and Innovation by the Ministry of Economic Affairs within Top Sector Life sciences & Health. We acknowledge the support from the Netherlands Cardiovascular Research Initiative, an initiative with support of the Dutch Heart Foundation, CVON2016-Early HFPEF, 2015-10, and CVON She-PREDICTS, grant 2017-21. Joline WJ Beulens is supported by a ZonMw VIDI grant (91 71 8304).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S et al (2018) Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades. JACC Cardiovasc Imaging 11(1):1–11
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juarréty JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers (2016) 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18(8):891–975
3. Naghhi SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T et al (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 17(12):1321–1360
4. Nauta JF, Hummel YM, van der Meer P, Lam CSP, Voors AA, van Melle JP (2018) Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. Eur J Heart Fail 20(9):1303–1311
5. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA (2017) Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. Circulation 135(9):825–838
6. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A et al (2008) Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the IMPRESERVE trial. Eur J Heart Fail 10(2):149–156
7. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E et al (2020) How to diagnose heart failure with preserved ejection fraction: the HFA-PFEF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail 22(3):391–412
8. Morris DA, Belyavskiy E, Aravind-Kumar R, Kroepf M, Frydias A, Braunauer K, Marquez E, Krisper M, Lindhorst R, Osmanoglu E, Boldt LH, Blaschke F, Haverkamp W, Tschöpe C, Edelmann F, Pieiske B, Pieiske-Kraigher E (2018) Potential usefulness and clinical relevance of adding left atrial strain to left atrial volume index in the detection of left ventricular diastolic dysfunction. JACC Cardiovasc Imaging 11(10):1405–1415

9. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ (2018) Statistical methods for multivariate meta-analysis of diagnostic tests: an overview and tutorial. Stat Methods Med Res 25(4):1596–1619

10. Ma X, Nie L, Cole SR, Chu H (2016) Pulsatile hemodynamics in patients with exertional dyspnea: potentially of value in the diagnostic evaluation of suspected heart failure with preserved ejection fraction. J Am Coll Cardiol 61(18):1874–1883

11. Asnash G, Goub R, Sinning D, Westermann D, Steendijk P, Hoffmann W, Schultheiss HP, Tschöpe C (2010) Global strain rate imaging for the estimation of diastolic function in HFN female patients with overall cardiac and isolated diastolic dysfunction. Ultrasound Med Biol 36(4):597–607

12. Kurt M, Wang J, Torre-Amione G, Naghue SF (2009) Left atrial function in diastolic heart failure. Circ Cardiovasc Imaging 2(1):10–15

13. Wang J, Khoary DS, Yue Y, Torre-Amione G, Naghue SF (2008) Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Circ Heart Fail 1(9):743–751

14. Kurt M, Chandra G, Naghue SF (2007) Mean right atrial pressure for estimation of left ventricular filling pressure in patients with normal left ventricular ejection fraction: invasive and noninvasive validation. J Am Soc Echocardiogr 31(7):799–806

15. Dini FL, Ballo P, Badano L, Barbier P, Chella P, Conti U, de Tommasi SM, Galderisi M, Ghiyo S, Magagnini E, Pieroni A, Ross L, Rascon C, Temporelli PL (2010) Validation of an echocardiographic Doppler model used to predict left ventricular filling pressure in patients with heart failure independently of ejection fraction. J Am Soc Cardiovasc Imaging 11(8):703–710

16. Dokainish H, Nguyen J, Sengupta R, Pillai M, Alam M, Bobek J, Lakos N (2010) New, simple echocardiographic indexes for the estimation of filling pressure in patients with cardiac disease and preserved left ventricular ejection fraction. Echocardiography 27(8):946–953

17. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA (2018) A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation 138(9):861–870

18. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, Carter R, Borlaug BA (2019) Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. Eur J Heart Fail 21(7):891–900

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

20. Singh A, Medvedovsky D, Mediratta A, Balancy B, Kruse E, Ciszek B, Shah AP, Blair JE, Maffessanti F, Addetta K, Mor-Avi V, Lang RM (2019) Peak left atrial strain as a single measure for the non-invasive assessment of left ventricular filling pressures. Int J Cardiovasc Imaging 35(1):23–32

21. Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, William J, Marwick TH, Kaye DM (2019) Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. Eur J Heart Fail 21(4):495–505

22. Thennappan T, Shah SJ, Gomberg-Maitland M, Collander B, Vallakati A, Shroff P, Rich S (2011) Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. Circ Heart Fail 4(3):257–265

23. Cameron DM, McLaughlin VV, Rubenfire M, Visovatti S, Bach DS (2017) Usefulness of echocardiography/Doppler to reliably predict elevated left ventricular end-diastolic pressure in patients with pulmonary hypertension. Am J Cardiol 119(5):790–794

24. Hammodi N, Laveuf F, Helft G, Cozic N, Barthelemy O, Ceccaldi A, Petroni T, Berman E, Komajda M, Michel PL, Mallet A, le Feuvre C, Isnard R (2017) Low level exercise echocardiography helps diagnose early stage heart failure with preserved ejection fraction: a study of echocardiography versus catheterization. Clin Res Cardiol 106(3):192–201

25. Bruch C, Schmermund A, Dages N, Katz M, Bartel T, Erbel R (2002) Tei-index in coronary artery disease—validation in patients with overall cardiac and isolated diastolic dysfunction. Z Kardiol 91(6):472–480

26. Goto T, Ohte N, Wakami K, Asada K, Fukuta H, Mukai S, Tani T, Kimura G (2010) Usefulness of plasma brain natriuretic peptide measurement and tissue Doppler imaging in identifying isolated left ventricular diastolic dysfunction without heart failure. Am J Cardiol 106(1):87–91

27. Hayashi T, Yamada S, Iwano H, Nakabuchi M, Okada K, Murai D, Nishino H, Kusunose K, Watanabe K, Ishizu T, Wakami K, Yamada H, Doi K, Seo Y, Ohte N, Mikami T, Tsutsui H (2016) Left ventricular global strain for estimating relaxation and filling pressure: a multicenter study. Circ J 80(5):1163–1170

28. Weber T, Auer J, O'Rourke MF, Punzengruber C, Kvas E, Eber B (2006) Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. Heart 92(11):1616–1622

29. Borlaug BA, Paulus WJ (2011) Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 32(6):670–679

30. Ikonomidis I, Aboyans V, Blacher J, Brodmann M, Brutsaert DL, Chirinos JA et al (2019) The role of ventricular-arterial coupling in cardiac disease and heart failure: assessment, clinical implications and therapeutic interventions. A consensus document of the European Society of Cardiology Working Group on Aorta & Peripheral Vascular Diseases, European Association of Cardiovascular Imaging, and Heart Failure Association, Eur J Heart Fail 21(4):402–424

31. Sepehrvand N, Alemayehu W, Dyck GJB, Dyck JRB, Anderson T, Howlett J, Paterson I, McAlister FA, Ezekowitz JA, On behalf of the Alberta HEART Investigators (2019) External validation of the H2F-PEF model in diagnosing patients with heart failure and preserved ejection fraction. Circulation 139(20):2377–2379

32. Santos AB, Kraigher-Krainer E, Gupta DK, Claggett B, Zile MR, Fuster V, Wang J, Torre-Amione G, Naghue SF (2006) Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. Heart 92(11):1616–1622

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.