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ORIGINAL ARTICLE

Haemodynamic validation of the three-step HFA-PEFF algorithm to diagnose heart failure with preserved ejection fraction

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Abstract

Aims The HFA-PEFF algorithm (Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology) is a three-step algorithm to diagnose heart failure with preserved ejection fraction (HFpEF). It provides a three-level likelihood of HFpEF: low (score < 2), intermediate (score 2–4), or high (score > 4). HFpEF may be confirmed in individuals with a score > 4 (rule-in approach). The second step of the algorithm is based on echocardiographic features and natriuretic peptide levels. The third step implements diastolic stress echocardiography (DSE) for controversial diagnostic cases. We sought to validate the three-step HFA-PEFF algorithm against a haemodynamic diagnosis of HFpEF based on rest and exercise right heart catheterization (RHC).

Methods and results Seventy-three individuals with exertional dyspnoea underwent a full diagnostic work-up following the HFA-PEFF algorithm, including DSE and rest/exercise RHC. The association between the HFA-PEFF score and a haemodynamic diagnosis of HFpEF, as well as the diagnostic performance of the HFA-PEFF algorithm vs. RHC, was assessed. The diagnostic performance of left atrial (LA) strain $< 24.5\%$ and LA strain/E/E′ $< 3\%$ was also assessed. The probability of HFpEF was low/intermediate/high in 8%/52%/40% of individuals at the second step of the HFA-PEFF algorithm and 8%/49%/43% at the third step. After RHC, 89% of patients were diagnosed as HFpEF and 11% as non-cardiac dyspnoea. The HFA-PEFF score resulted associated with the invasive haemodynamic diagnosis of HFpEF ($P < 0.001$). Sensitivity and specificity of the HFA-PEFF score for the invasive haemodynamic diagnosis of HFpEF were 45% and 100% for the second step of the algorithm and 46% and 88% for the third step of the algorithm. Neither age, sex, body mass index, obesity, chronic obstructive pulmonary disease, or paroxysmal atrial fibrillation influenced the performance of the HFA-PEFF algorithm, as these characteristics were similarly distributed over the true positive, true negative, false positive, and false negative cases. Sensitivity of the second step of the HFA-PEFF score was non-significantly improved to 60% ($P = 0.08$) by lowering the rule-in threshold to >3. LA strain alone had a sensitivity and specificity of 39% and 14% for haemodynamic HFpEF, increasing to 55% and 22% when corrected for E/E′.

Conclusions As compared with rest/exercise RHC, the HFA-PEFF score lacks sensitivity: Half of the patients were wrongly classified as non-cardiac dyspnoea after non-invasive tests, with a minimal impact of DSE in modifying HFpEF likelihood.

Keywords HFpEF; Haemodynamics; Echocardiography; Exercise; HFA-PEFF algorithm

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Background

Diagnosing non-secondary heart failure (HF) with preserved ejection fraction (HFpEF) can be a challenge, especially in normovolaemic patients without a prior hospitalization for HF.[1–4] Accordingly, algorithms and scores have been proposed in recent years, to help clinicians evaluating patients with exertional dyspnoea.[5,6] In particular, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) proposed the HFA-PEFF algorithm (where the PEFF acronym stands for 'Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology') based on expert consensus.[5] Key echocardiographic parameters and natriuretic peptides' dosage compose the second step of the algorithm, whose performance has been validated against the advice of experienced HF physicians and/or previous hospitalization for HF,[7] as well as against invasive haemodynamics.[8] However, the second step of the HFA-PEFF algorithm may have a lower sensitivity than the simpler H_2FPEF score.[8] Indeed, many individuals may fall in the intermediate-risk category, requiring to move on with the third step of the algorithm, that is, the use of additional (functional) tests to confirm or exclude the diagnosis of HFpEF. In particular, a diastolic stress echocardiography might be used as an additional non-invasive tool before considering rest/exercise right heart catheterization (RHC).[2,3] However, the third (non-invasive) step of the HFA-PEFF score has not been validated against RHC. Thus, the aim of this study was to provide a validation of the three-step HFA-PEFF score vs. invasive resting and exercise haemodynamics, in a consecutive cohort of individuals referred for exertional dyspnoea who underwent a structured assessment comprehensive of all the items required by the HFA-PEFF algorithm.

Methods

This study was approved by the Ethics Committees of the Istituto Auxologico Italiano (Protocol No. 2020_04_21_03), Milan, Italy, and the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Ref ID 195/2017), Milan, Italy. We included consecutive patients with exertional dyspnoea referred for a structured work-up at the two dyspnoea units of the above-mentioned hospitals, which have adopted a similar methodology, in agreement with the HFA-PEFF algorithm. After an initial clinical assessment, outpatients complaining exertional breathlessness underwent rest and diastolic stress echocardiography on the same day, along with dosage of natriuretic peptides. After an outpatient re-evaluation, indication to proceed with RHC was considered and shared with the patient.

We included in the present analysis all the consecutive patients who, after a pre-test assessment, underwent the exams suggested by the HFA-PEFF algorithm, with a time lag in between the initial evaluation and echocardiography, as well as in between echocardiography and RHC, of no more than 6 weeks. Additionally, no changes in patients' conditions or background treatment had to intervene in between the first clinical assessment and RHC.

We excluded patients with left ventricular (LV) ejection fraction $< 50\%$, secondary forms of HFpEF (restrictive, hypertrophic, or infiltrative cardiomyopathy), congenital heart disease, constrictive pericarditis, inducible myocardial ischaemia, pre-capillary pulmonary hypertension at rest [defined by a mean pulmonary artery pressure (PAP) $>$ 20 mmHg with pulmonary vascular resistance $>$ 3 WU and pulmonary artery wedge pressure (PAWP) $<$ 15 mmHg[9]], more than mild primary valvular regurgitation, any valvular stenosis, more than moderate respiratory disorders, and clinically unstable patients.

A final diagnosis of HFpEF was eventually established when, at the time of RHC, end-expiratory PAWP was ≥15 mmHg at rest and/or ≥25 mmHg at peak exercise and/or if the slope of the relationship between PAWP and cardiac output (CO) from rest to peak exercise was $>$2 mmHg/L/min.[2,3,10,11]

Non-invasive assessment

Clinical data were extracted from the clinical charts. Echocardiography was performed with a Vivid E9/E95 scanners (GE Vingmed, Horten, Norway) in both recruiting centres by experienced cardiologists following current recommendations.[12] LV and left atrial (LA) strain analyses[13] were performed using vendor-licensed software (EchoPAC 204, GE Vingmed). Exercise echocardiography was performed with a step-incremental protocol on a semi-recumbent cycle ergometer up to exhaustion, with echocardiographic acquisition focused on pulsed wave Doppler of mitral inflow, medial and lateral tissue Doppler of the mitral annulus, and tricuspid regurgitation (TR) velocity, to collect the items required by the third step of the HFA-PEFF algorithm.[5] The presence of dynamic mitral regurgitation was checked in all patients. Images were stored in digital format for quantitative analysis, which were performed offline by trained personnel, blinded to clinical and haemodynamic data.

HFA-PEFF score calculation

The HFA-PEFF score (two-step) was calculated integrating morphological and functional data coming from echocardiography at rest with natriuretic peptides, as recommended.[5] An HFA-PEFF score $<$ 2 classifies a low probability of HFpEF (HFpEF unlikely); score values between 2 and 4 classify an intermediate probability of HFpEF (HFpEF possible); and a score $>$ 4 classifies a high probability of HFpEF (HFpEF likely).

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Diastolic stress echocardiography was considered positive when E/E′ was ≥15, conferring 2 points to be added to the score obtained at the second step of the algorithm. When E/E′ ≥ 15 is associated with a TR velocity > 3.4 m/s, 3 points can be added to the second-step HFA-PEFF score.[5] As measurement of E/E′ might not be possible at high heart rate due to fusion of the waves of the mitral inflow pattern, we reported both the maximal workload reached during diastolic stress echocardiography and the workload at which echocardiographic measures were taken.

Finally, among echocardiographic parameters measured at rest but not included in the HFA-PEFF algorithm, we also evaluated LA reservoir strain and the ratio between LA strain and E/E′, given their diagnostic potential in patients with exertional breathlessness.[14,15] They were considered abnormal and, thus, potentially indicative of HFpEF when <24.5% and at <3%, respectively.[15]

Right heart catheterization

Patients were studied on chronic medications, in the non-fasting state, without sedation, in supine position. A 7 F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein or an antecubital vein under fluoroscopic guidance. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace and by an oxygen saturation > 94% sampled at the tip of the catheter. A 4 F catheter was placed in the radial artery under local anaesthesia using the Seldinger technique. The transducers were zeroed at the midthoracic line using a laser calliper. Haemodynamic measurements were performed at rest, after 1 min of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited exercise test, as previously described.[10] The increment in workload was personalized in order to obtain at least three steps of exercise before exhaustion.[10] Two millilitres of blood was sampled at the same time from the tip of the Swan-Ganz catheter and from the radial artery, in order to calculate CO by the direct Fick method. Pressures were measured at end-expiration, and haemodynamic data reflect the agreement of two expert independent readers blinded to patients' data, who visually reviewed all pressure traces offline. As described above, a haemodynamic diagnosis of HFpEF was defined by either an end-expiratory PAWP ≥ 15 mmHg at rest and/or ≥25 mmHg at peak exercise or a PAWP/CO slope > 2 mmHg/L/min.[2,3,10,11]

Statistical analysis

Continuous variables are reported as mean ± standard deviation normal when normally distributed (*P*-value of Shapiro's test > 0.05) and as median together with [25th and 75th percentiles] otherwise. Categorical data are showed as frequencies and proportions.

Independency or dependency between variables was assessed creating contingency tables and performing the Fisher exact test with R, where *P*-values were computed through Monte Carlo simulation as required for tables larger than 2 × 2. A significant association between variables (rows and column of the table) was assessed by a *P*-value < 0.05.

Results

Between June 2016 and June 2021, 73 consecutive patients with dyspnoea and suspicion of HFpEF were evaluated (58 at Istituto Auxologico Italiano and 15 at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan). All of them had all items required by the second and third steps of the HFA-PEFF algorithm, including echocardiography at rest, natriuretic peptides' values, diastolic stress echocardiography, and RHC at rest and during exercise.

General characteristics

General characteristics of our cohort are summarized in *Table 1*. Median age was 71 years, 67% were females, and mean body mass index was 26 kg/m^2. The majority of patients had exertional dyspnoea (New York Heart Association II). Arterial hypertension was the most represented cardiovascular risk factors (67%), followed by dyslipidaemia (44%) and obesity (16%). All individuals were in sinus rhythm, with 15% of patients who experienced paroxysmal atrial fibrillation. Twenty-two per cent of patients had mild chronic obstructive pulmonary disease.

Table 1 General characteristics of the study cohort

Anthropometrics and demographics	
Age, years	71 [65, 75]
Female sex, *n* (%)	49 (67%)
Body mass index, kg/m^2	26 ± 5
Symptoms	
NYHA class II, *n* (%)	50 (69%)
NYHA class III, *n* (%)	23 (31%)
Comorbidities	
Obesity, *n* (%)	12 (16%)
Arterial hypertension, *n* (%)	49 (67%)
Diabetes mellitus, *n* (%)	4 (5%)
Dyslipidaemia, *n* (%)	32 (44%)
Coronary artery disease, *n* (%)	11 (15%)
Paroxysmal atrial fibrillation, *n* (%)	11 (15%)
Chronic obstructive pulmonary disease, *n* (%)	16 (22%)
Blood tests	
Creatinine, mg/dL	0.9 [0.76, 1.01]
eGFR, mL/min/1.73 m^2	71 [50, 86]

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

HFA-PEFF score, second step: echocardiography at rest and natriuretic peptides

Echocardiographic and natriuretic peptide data are reported in *Table 2*. Echocardiography at rest showed a normal median LA size (32 mL/m^2), with a mean LA reservoir strain of 27%, and a mean E/E′ of 9. TR was present and measurable in 93% of the cohort, with a median TR velocity of 2.6 m/s and an estimated median systolic PAP of 31 mmHg. Median N-terminal pro-brain natriuretic peptide was 193 ng/L.

Median HFA-PEFF score (second step) was 4. Eight per cent of individuals had a low probability of HFpEF (HFA-PEFF score < 2), 52% an intermediate probability (score 2–4), and 40% a high probability (score > 4).

HFA-PEFF score, third step: diastolic stress echocardiography

Diastolic stress echocardiography results are reported in *Table 3*. During exercise, median E/E′ increased to 9.3. TR was present and measurable in 80% of the cohort, with a mean exercise TR velocity of 3.4 m/s. Eight patients displayed a positive diastolic stress echocardiography (E/E′ $\geq$ 15), five of whom had also a TR velocity $>$ 3.4 m/s. Six out of these eight patients with a positive diastolic stress echocardiography already had an HFA-PEFF score $>$ 4 at the second step of the algorithm. Thus, only 6 of the 29 individuals at high risk of HFpEF after the second step of the HFA-PEFF algorithm (21%) had a positive diastolic stress echocardiography. Two patients with an HFA-PEFF score = 3, belonging to the intermediate HFpEF risk category (4% of this latter cohort), shifted to the high-risk category after the diastolic stress echocardiography. No patient with a low risk of HFpEF based on the second step of the HFA-PEFF score had a positive diastolic stress echocardiography.

Accordingly, the distribution of HFpEF risk based on the HFA-PEFF score marginally changed from the second step to the third step of the algorithm (two intermediate-risk individuals shifted to the high-risk category).

Table 2 Second step of the HFA-PEFF algorithm

Natriuretic peptides	
NT-proBNP, ng/L	193 [101; 311]
Echocardiography	
Interventricular septum thickness, mm	10 [9; 11]
Posterior wall thickness, mm	9 [8; 10]
Relative wall thickness	0.41 [0.37; 0.45]
Left ventricular end-diastolic diameter, mm	44 ± 6
Left ventricular mass index, g/m^2	80 ± 20
Left ventricular end-diastolic volume, mL	80 [67; 103]
Left ventricular ejection fraction, %	62 ± 5
Left ventricular global longitudinal strain, %	−18.7 ± 2.2
Left atrial volume index, mL/m^2	32 [26; 38]
Left atrial reservoir longitudinal strain, %	27 ± 9
E/E′	9.0 [7.3; 10.8]
Tricuspid regurgitation velocity, m/s (n = 68)	2.55 [2.40; 2.90]
Pulmonary artery systolic pressure, mmHg	31 [29; 40]
HFA-PEFF score, 2 steps	
Median value	4 [3; 5]
Low probability, n (%)	6 (8)
Intermediate probability, n (%)	38 (52)
High probability, n (%)	29 (40)

HFA-PEFF, Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3 Third step of the HFA-PEFF algorithm and invasive haemodynamics

Diastolic stress echocardiography	
Workload, W	65 [50; 95]
Workload @ echocardiographic measurements, W	55 [35; 70]
Averaged E/E′	9.3 [7.5; 12.0]
Tricuspid regurgitation velocity, m/s (n = 58)	3.40 ± 0.56
HFA-PEFF score, 3 steps	
Median value	4 [3; 5]
Low probability, n (%)	6 (8)
Intermediate probability, n (%)	36 (49)
High probability, n (%)	31 (43)
Invasive haemodynamics	
Workload, W	50 [40; 75]
PAWP at rest, mmHg	11 [9; 13]
PAWP at peak, mmHg	29 ± 10
PAWP/CO slope, mmHg/L/min	3.50 [2.08; 4.45]
PAWP peak ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min, n (%)	65 (89)

CO, cardiac output; HFA-PEFF, Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology; PAWP, pulmonary artery wedge pressure.

Performance of the HFA-PEFF algorithm against invasive haemodynamics

At RHC, 65 out of 73 individuals (89%) presented a PAWP at peak exercise $\geq$ 25 mmHg and/or a PAWP/CO slope $>$ 2 mmHg/L/min. Invasive haemodynamic data of our cohort are reported in *Table 3*.

The HFA-PEFF score (either two steps or three steps), subdivided in low, intermediate, and high probability of HFpEF, resulted significantly associated with the haemodynamic diagnosis of HFpEF based on exercise RHC ($P < 0.001$).

Among the eight individuals in whom HFpEF was not confirmed by RHC, four were in the low-risk and four in the intermediate-risk two-step HFA-PEFF strata. Among the 65 individuals in whom HFpEF was confirmed by RHC, 2 belonged to the low-risk category, 34 to the intermediate-risk category, and 29 to the high-risk category of the two-step HFA-PEFF score. *Figure 1* represents the proportion of patients classified as HFpEF or non-HFpEF after RHC, stratified according to the pre-RHC probability, based on both the two-step and three-step HFA-PEFF scores.

Figure 1 Proportion of patients classified as heart failure with preserved ejection fraction (HFpEF), or non-HFpEF, based on invasive haemodynamics ($HFpEF_{haemo}$), stratified according to the pre-test probability provided by the two-step and three-step HFA-PEFF (Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology) scores.

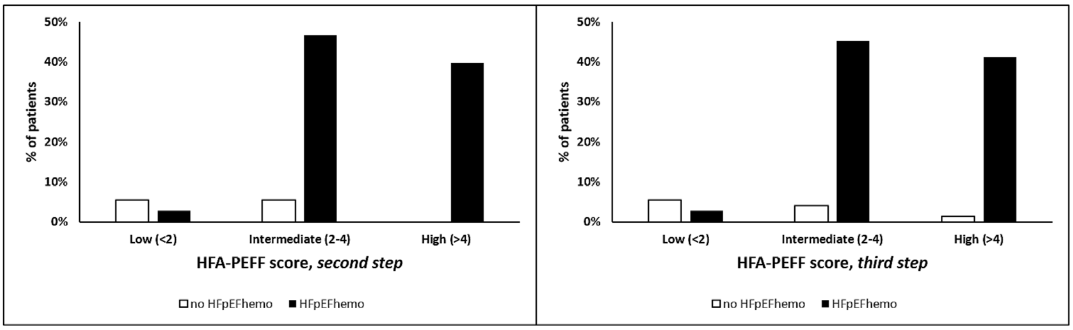

Figure 2 Proportion of correctly [true positive (TP) and true negative (TN)] and incorrectly [false negative (FN) and false positive (FP)] diagnosed patients, based on the two-step and three-step HFA-PEFF (Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology) scores, using invasive haemodynamics as gold-standard diagnostic reference.

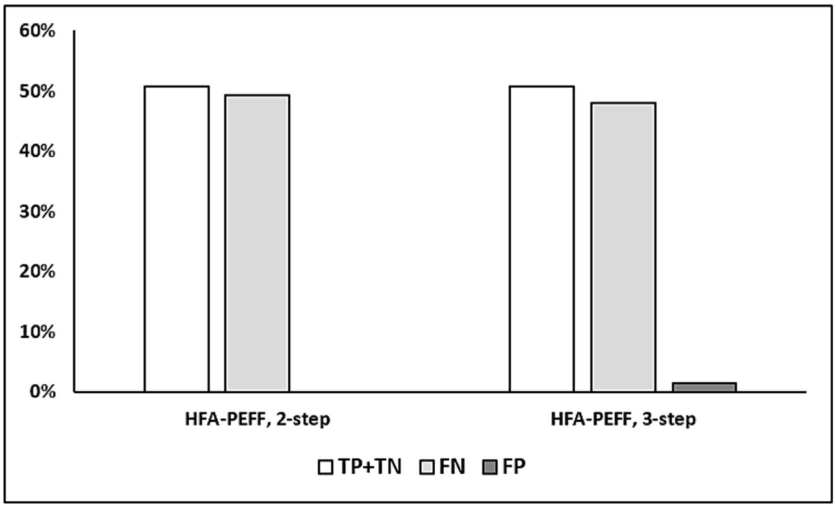

Table 4 Performance of the two-step and three-step 'rule-in' HFA-PEFF algorithm, both with the usual diagnostic threshold (>4) and with a lower diagnostic threshold (>3) to diagnose HFpEF, as compared with invasive haemodynamics

	Rule-in approach, HFA-PEFF score > 3				Rule-in approach, HFA-PEFF score > 4			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
HFA-PEFF, 2 steps	60%	100%	100%	24%	45%	100%	100%	18%
HFA-PEFF, 3 steps	62%	88%	98%	22%	46%	88%	97%	17%

HFA-PEFF, Heart Failure Association-Pre-test assessment, Echocardiography and natriuretic peptide score, Functional testing in cases of uncertainty, Final aetiology; HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

The 'rule-in approach', which arbitrarily dichotomizes the score in >4 (HFpEF) and ≤4 (no HFpEF), correctly classified 37 (51%) patients as either HFpEF or non-HFpEF, both at the second step and at the third step, respectively (*Figure 2*). However, 36 (49%) and 35 (48%) patients resulted false negative both with two-step and with three-step HFA-PEFF algorithm. Only the three-step algorithm provided one false positive case. Accordingly, specificity and positive predictive value of the HFA-PEFF were high, but sensitivity and negative predictive value were low (*Table 4*). Neither age, sex, body mass index, obesity, chronic obstructive pulmonary disease, or paroxysmal atrial

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fibrillation influenced the performance of the HFA-PEFF algorithm, as these characteristics were similarly distributed over the true positive, true negative, false positive, and false negative cases. Lowering the threshold of the two-step HFA-PEFF score to >3 vs. >4 resulted in non-significantly higher sensitivity (60% vs. 45%, P = 0.08) and accuracy (64% vs. 51%, P = 0.09), without losing specificity (100% vs. 100%).

Performance of other echocardiographic parameters proposed to diagnose heart failure with preserved ejection fraction

LA reservoir strain, with a cut-off < 24.5% to diagnose HFpEF, was significantly interrelated both with the three-step HFA-PEFF score (P = 0.024) and with the haemodynamic diagnosis of HFpEF (P = 0.023). Sensitivity, specificity, and accuracy of this parameter were 39%, 14%, and 50%, respectively.

The ratio between LA reservoir strain and E/E′, with a cut-off < 3% to diagnose HFpEF, was significantly associated both with the two-step and three-step HFA-PEFF scores (P < 0.001) and with the haemodynamic diagnosis of HFpEF (P = 0.037). Sensitivity, specificity, and accuracy of this parameter were 52%, 22%, and 36%, respectively.

Discussion

This is the first study reporting the performance of the three-step HFA-PEFF score against rest and exercise RHC in consecutive patients with unexplained dyspnoea. Our results show that, compared with invasive rest and exercise haemodynamics, the HFA-PEFF score is characterized by good specificity but suboptimal sensitivity. Moreover, the implementation of the diastolic stress echocardiography did not seem to add significantly to the diagnostic performance of the score. Conversely, lowering the diagnostic threshold of the second step of the HFA-PEFF score to >3 vs. >4 slightly improved its diagnostic performance. Other echocardiographic parameters suggested to help in the diagnosis of HFpEF (such as LA reservoir strain and the ratio between LA strain and E/E′) taken in isolation did not perform better than the HFA-PEFF algorithm.

As already mentioned, the diagnosis of HFpEF poses a unique challenge, especially in those patients with lifestyle-limiting symptoms but no evidence of hypervolaemia. A combination of several items, as those included in the HFA-PEFF score,[5] has been suggested to help in this complex diagnostic process. In such a perspective, our work confirms and expands the evidences coming from previous reports,[8,14] highlighting the relationship between the score and RHC results, and demonstrating the good specificity of the 'rule-in' approach, based on a score > 4 at the second step of the algorithm, compared with rest and exercise RHC. Similar results concerning the validation of the HFA-PEFF algorithm have been shown in a larger two-centre study where, however, diagnosis of HFpEF was not confirmed by invasive haemodynamics but codified either based on the judgement of an expert HF specialist or based on a history of previous HF hospitalization.[7] Using exercise haemodynamics as reference and, in particular, a combination of PAWP at rest > 15 mmHg and/or PAWP at peak ≥ 25 mmHg and/or PAWP/CO slope > 2 mmHg/L/min,[2,3,10,11] our results may suggest that the second step of the HFA-PEFF score might be lowered to >3, slightly improving sensitivity and accuracy, without impacting on specificity (i.e. without collecting false positive diagnosis). Additionally, our data are unique in providing evidence also on the third, non-invasive step of the algorithm. Diastolic stress echocardiography has been advocated to increase the diagnostic yield of resting examination.[5,16,17] However, our data do not seem to confirm such a strong additional value of diastolic stress echocardiography. Indeed, only two patients falling in the intermediate HFpEF risk profile based on the second step of the HFA-PEFF score were reclassified at high likelihood of HFpEF after diastolic stress echocardiography. Unfortunately, one of these two patients had the diagnosis of HFpEF not confirmed by rest and exercise RHC. Accordingly, the diagnostic value of the diastolic stress echocardiography as a third step in the HFA-PEFF algorithm appears questionable based on our results. It is time and resource consuming and does not seem to significantly improve the diagnostic accuracy of the second step of the algorithm. This is at variance from a previous report where diastolic stress echocardiography enhanced the diagnosis of HFpEF if added to the ESC criteria rather than to the comprehensive multiparametric evaluation proposed by the second step of the HFA-PEFF algorithm.[17] This might suggest that diastolic stress echocardiography may hold a place in the differential diagnosis of patients with exertional dyspnoea, when not all the items of the second step of the HFA-PEFF algorithm are available or, as more recently suggested, by lowering the E/E′ decisional threshold.[18] Finally, incorporation of other tests/parameters in a non-invasive algorithm (e.g. cardiopulmonary exercise test data) might provide additional clues on the aetiology of patients presenting with exertional dyspnoea.[19]

Clinical implications

Despite its high specificity, the sensitivity of the HFA-PEFF algorithm is suboptimal, not allowing to diagnose HFpEF in roughly 50% of cases, even when time-consuming and resource-consuming tests such as diastolic stress echocardiography are implemented. Thus, a simpler and more cost-effective approach, for example, based on the H_2FPEF score,[8] might be advisable as a first-line diagnostic evaluation, especially in low-resource settings and/or in primary/secondary health care facilities. A more personalized approach to unexplained dyspnoea, including cardiopulmonary exercise test, potentially combined with advanced rest and exercise stress echocardiography, could be advisable in tertiary referral centres, eventually recurring to exercise RHC in well-selected cases.[19]

Limitations

Several limitations of our work should be acknowledged: first, the relatively small sample size, which might limit generalizability of our results. Additionally, the great majority of our patients were eventually diagnosed with HFpEF after exercise RHC, limiting the information on the negative predictive value of the HFA-PEFF algorithm. However, our cohort was a real-world consecutive population of patients with exertional dyspnoea to whom a standard diagnostic approach was applied and who eventually accepted to undergo RHC, with clinical and haemodynamic characteristics in line with other reports in literature, and that should not be relevantly different to a general outpatient population screened for unexplained dyspnoea.

Conclusions

The HFA-PEFF score is associated with invasive haemodynamics at rest and during exercise, albeit its diagnostic performance is poor, due to low sensitivity (in spite of high specificity). Additionally, diastolic stress echocardiography did not improve the diagnostic yield of the second step of the HFA-PEFF algorithm in our cohort. Conversely, lowering the threshold of the second step of the HFA-PEFF score to >3 might marginally improve sensitivity and accuracy, maintaining high specificity. HFpEF remains a diagnostic challenge, in search for a widely available gold-standard test.

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Conflict of interest

None declared.

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