The H_2FPEF and HFA-PEFF Algorithms for Predicting Exercise Intolerance and Abnormal Hemodynamics in Heart Failure with Preserved Ejection Fraction

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Research Article

Keywords: diagnostic algorithm, exercise intolerance, exercise testing, heart failure

Posted Date: September 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-919359/v1

Version of Record: A version of this preprint was published at Scientific Reports on January 7th, 2022.
See the published version at https://doi.org/10.1038/s41598-021-03974-6.

Abstract

Exercise intolerance is a primary manifestation of patients with heart failure with preserved ejection fraction (HFpEF) and is associated with abnormal hemodynamics and poor quality of life. Two multiparametric scoring systems have been proposed to diagnose HFpEF. This study sought to determine the performance of the H_2FPEF and HFA-PEFF scores for predicting exercise capacity and echocardiographic measures of intracardiac pressures during exercise. Patients with HFpEF (n = 83) and control subjects without HF (n = 104) underwent bicycle exercise echocardiography. In a subset, simultaneous expired gas analysis was performed to measure peak oxygen consumption (VO_2). The H_2FPEF score was obtainable in all patients while the HFA-PEFF score could not be calculated in 23 patients (feasibility 88%). Both H_2FPEF and HFA-PEFF scores were correlated with higher E/e' ratio (r = 0.49 and r = 0.46), lower systolic tricuspid annular velocity (r=-0.44 and =-0.24), and lower cardiac output (r=-0.28 and r=-0.24) during peak exercise. Peak VO_2 and exercise duration decreased with increasing the H_2FPEF score (r=-0.40 and r=-0.32), and the H_2FPEF score predicted reduced aerobic capacity (AUC 0.71, p = 0.0005), but the HFA-PEFF score did not (p = 0.07). These data provide new insights into the role of the H_2FPEF and HFA-PEFF scores for predicting exercise intolerance and abnormal hemodynamics in patients HFpEF.

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for more than half of cases of all HF. The prevalence is increasing worldwide with limited proven treatment, making it one of the most important healthcare problems in modern cardiology.[1] Exercise intolerance is a primary manifestation of patients with HFpEF and is associated with symptoms of dyspnea, abnormal central hemodynamics, and poor quality of life.[2–4] Thus, identification of reduced aerobic capacity may have potentially important therapeutic implications in people with HFpEF.

Recent studies have proposed two multiparametric scoring systems to help diagnose HFpEF among patients with dyspnea. The H_2FPEF score is based on four clinical (body mass index [BMI], two or more antihypertensive medicines, atrial fibrillation [AF], and age) and two echocardiographic variables (E/e' ratio and pulmonary artery [PA] systolic pressure [PASP]).[5] The HFA-PEFF score employs a more complex approach in scoring natriuretic peptide levels and echocardiographic measures of cardiac function and structure.[6] In addition to the diagnostic value, recent studies have demonstrated the association between the two algorithms and clinical outcomes in patients with HFpEF.[7–10] However, few data are available regarding whether these diagnostic schemes could predict aerobic capacity in HFpEF.

Accordingly, we examined the performance of the two algorithms for predicting exercise capacity and echocardiographic estimates of intracardiac pressures during ergometry exercise echocardiography.

Material And Methods

Study Population

This was a retrospective cross-sectional study to determine the performance of the HFpEF scores for predicting exercise capacity and echocardiographic measures of hemodynamics during exercise. Consecutive patients who were referred to the echocardiographic laboratory of the Gunma University Hospital for exercise stress echocardiography for exertional dyspnea between September 2019 and July 2021 were enrolled in this study. HFpEF was defined by typical clinical symptoms (dyspnea and fatigue), normal left ventricular (LV) EF (> 50%), and objective evidence of elevated left heart filling pressures at rest and/or with exercise: (1) the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI)-recommended echocardiographic diastolic dysfunction; (2) the ratio of transmitral E to mitral annular e' velocities at septal annulus (E/e') during exercise > 15; or (3) invasively-measured pulmonary capillary wedge pressure [PCWP] at rest > 15mmHg and/or with supine ergometry exercise ≧ 25mmHg.[5,11,12]

Control subjects who were also referred to exercise echocardiography because of clinical indication of exertional dyspnea were also included as a comparator group (controls). The control subjects were required to have no evidence of HF (criteria above). Patients with EF < 50%, significant left-sided valvular heart disease (> moderate regurgitation, >mild stenosis), infiltrative, restrictive, or hypertrophic cardiomyopathy, and non-Group II pulmonary artery hypertension (PAH) or exercise-induced pulmonary hypertension without elevation in E/e'. The study was approved by our Institutional Review Board with the waiver of consent because of its retrospective design (Gunma University Hospital, Clinical Research Review Board), and was performed in accordance with the Declaration of Helsinki. All authors have read and agreed to the manuscript as written.

Assessment of Cardiac Structure and Function

Two-dimensional and Doppler echocardiography was performed by experienced sonographers using a commercially available ultrasound system (Vivid E95, GE Healthcare, Horten, Norway). EF and the systolic mitral annular tissue velocity at the septal and lateral annulus (mitral s') were measured to assess LV systolic function. LV deformation analyses were also performed offline with the commercially available software (EchoPAC, GE, Milwaukee, Wisconsin) to measure LV longitudinal strain. Apical four-chamber view was used to calculate the LV longitudinal strain. Early diastolic mitral inflow velocity (E), early diastolic mitral annular tissue velocity at the septal and lateral annulus (e'), and the average E/e' ratio were used to assess LV diastolic function.[11] Stroke volume (SV) was determined from the LV outflow dimension and pulse Doppler profile, and cardiac output (CO) was then calculated from the product of heart rate and SV. Pulmonary artery systolic pressure (PASP) was calculated as 4 × (peak tricuspid regurgitation [TR] velocity)^2 + estimated RA pressure (RAP). Right ventricular (RV) systolic function was assessed using systolic tissue velocities at the lateral tricuspid annulus (TV s').

All subjects underwent supine cycle ergometry echocardiography, starting at 20 W for 5 minutes, increasing 20W increments in 3-minute stages to subject-reported exhaustion as previously described.[13]

Echocardiographic images were obtained at baseline and during all stages of exercise. During exercise, mitral annular tissue velocities were measured at the septal annulus. All Doppler measures represent the mean of ≥ 3 beats. All studies were interpreted offline and in a blinded fashion by a single investigator (M.O.). In a subset of participants, expired gas analysis was performed simultaneously with echocardiography at rest and throughout the exercise to measure breath-by-breath oxygen consumption (VO_2).

Calculation of the H_2FPEF and HFA-PEFF Scores

The H_2FPEF score is based on four clinical parameters (BMI > 30 kg/m^2 [2 points], treatment with two or more antihypertensive medicines [1 point], AF [3 points], and age > 60 years [1 point]) and two echocardiographic variables (E/e' ratio > 9 [1 point] and PASP > 35 mmHg [1 point]).[5] This results in a categorical H_2FPEF score ranging from 0 to 9.[5] The H_2FPEF scores of 0–1 are associated with a low probability of HFpEF (< 25%) and a score of 6–9 is associated with a high probability of HFpEF (> 90%).

Assessment of the HFA-PEFF score was limited to step 2 of the algorithm, as all participants had exertional dyspnea (step 1), and this study aimed to examine the performance of HFpEF scores to predict exercise capacity.[6] The score is calculated as the sum of echocardiographic functional (age-specific cut-offs for e' velocity, E/e' ratio, TR velocity, and longitudinal strain: maximum 2 points) and morphological domains (rhythm-specific LA volume, relative wall thickness, and sex-specific measures of LV mass: maximum 2 points) and natriuretic peptide domains (maximum 2 points). Patients with a total score of 0 to 1 are considered to have a low probability of HFpEF, 2 to 4 as intermediate, and 5 to 6 as high probability. The HFA-PEFF score was calculated if all three domains were available.

Statistical Analysis

Data are reported as mean (SD), median (IQR), or number (%) unless otherwise specified. Between-group differences were compared by unpaired t-test, Wilcoxon rank-sum test, or chi-square test, as appropriate. Pearson's (normally distributed data) or Spearman's correlation coefficients (non-normally distributed data) were used to assess relationships between two variables of interest, as appropriate. Receiver operating curves (ROC) were constructed to evaluate the performance of HFpEF diagnostic schemes for predicting reduce exercise capacity (peak VO_2 < 14 mL/min/kg).[14] All tests were 2-sided, with a value of $P < 0.05$ considered significant. All statistical analyses were performed with JMP 14.0.0 (SAS Institute, Cary, NC, USA).

Results

Subject Characteristics

Of 187 participants, 83 patients were found to have HFpEF, and 104 had non-cardiac dyspnea (controls). Clinical characteristics between HFpEF patients and controls are shown in Table 1. As compared to control subjects, patients with HFpEF were older and had higher prevalence of systemic hypertension,

diabetes, coronary artery disease, AF, and elevated natriuretic peptide levels. Sex, BMI, and vital signs were similar between groups. Compared to controls, patients with HFpEF were treated with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, beta-blockers, and loop diuretics more frequently.

Table 1
Baseline Characteristics

	Controls (n = 104)	HFpEF (n = 83)	P value
Age (years)	63 ± 13	74 ± 8	< 0.0001
Female, n (%)	68 (65%)	50 (60%)	0.47
Body mass index (kg/m^2)	23.1 ± 5.0	24.4 ± 4.2	0.06
Comorbidities			
Coronary disease, n (%)	5 (5)	12 (15)	0.02
Diabetes mellitus, n (%)	12 (12)	20 (24)	0.03
Hypertension, n (%)	69 (66)	67 (81)	0.03
Atrial fibrillation, n (%)	10 (10)	31 (37)	< 0.0001
Medications			
ACEI or ARB, n (%)	30 (29)	38 (46)	0.02
Beta-blocker, n (%)	9 (9)	31 (37)	< 0.0001
Loop diuretics, n (%)	15 (14)	28 (34)	0.002
Laboratories			
BNP (pg/mL), n = 128	34 (17, 60)	98 (39,158)	< 0.0001
NT-proBNP (pg/mL), n = 83	99 (66, 153)	558 (152, 1378)	< 0.0001
Vital signs			
Heart rate (bpm)	76 ± 14	73 ± 15	0.12
Systolic BP (mmHg)	130 ± 23	130 ± 20	0.81
Saturation (%)	97 ± 2	97 ± 1	0.52
LV and LA structures			
LV diastolic dimension (mm)	43 ± 5	44 ± 6	0.08
LV mass index (g/m^2)	79 ± 19	93 ± 23	< 0.0001

Data are mean ± SD, median (interquartile range), or n (%). Abbreviations; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BNP, B-type natriuretic peptide; HFpEF, BP, blood pressure; E/e' ratio, the ratio of early diastolic mitral inflow to mitral annular tissue velocities; heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and TV, tricuspid valvular.

	Controls (n = 104)	HFpEF (n = 83)	P value
Relative wall thickness	0.43 ± 0.08	0.46 ± 0.11	0.02
LA volume index (mL/m^2)	24 (19, 31)	39 (30, 50)	< 0.0001
LV and RV function			
LV ejection fraction (%)	64 ± 7	63 ± 7	0.21
LV longitudinal strain (%), n = 172	17.7 ± 3.1	15.4 ± 3.7	< 0.0001
E-wave (cm/sec)	66 ± 18	85 ± 27	< 0.0001
Mitral septal e' (cm/sec)	7.0 ± 2.5	5.4 ± 2.3	< 0.0001
Mitral septal s' (cm/sec)	7.6 ± 1.5	6.5 ± 1.7	< 0.0001
Mitral lateral e' (cm/sec)	9.4 ± 3.2	7.2 ± 2.9	< 0.0001
Mitral lateral s' (cm/sec)	9.2 ± 2.5	7.6 ± 2.1	< 0.0001
E/e' ratio (average)	8.6 ± 2.6	14.2 ± 7.9	< 0.0001
Cardiac output (L/min)	4.2 ± 1.3	4.0 ± 1.0	0.30
TV s' (cm/sec)	12.6 ± 3.0	11.6 ± 3.3	0.04
PASP (mmHg)	20 ± 6	24 ± 9	< 0.0001
RAP (mmHg)	3 ± 1	5 ± 3	0.0004
HFpEF Scores			
H_2FPEF score, n = 187	1.8 ± 1.3	3.6 ± 1.7	< 0.0001
HFA-PEFF score, n = 164	3.1 ± 1.3	4.8 ± 1.3	< 0.0001
H_2FPEF score, low/intermediate/high (%)	46%/54%/0%	4%/79%/17%	< 0.0001
HFA-PEFF score, low/intermediate/high (%)	11%/76%/13%	0%/34%/66%	< 0.0001

Data are mean ± SD, median (interquartile range), or n (%). Abbreviations; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BNP, B-type natriuretic peptide; HFpEF, BP, blood pressure; E/e' ratio, the ratio of early diastolic mitral inflow to mitral annular tissue velocities; heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and TV, tricuspid valvular.

On resting echocardiography, HFpEF patients had larger LV mass index, relative wall thickness, and LA volume index and poorer LV shortening evidenced by lower longitudinal strain and mitral s' tissue velocities than control subjects (Table 1). As compared to controls, LV diastolic function was more

abnormal in patients with HFpEF, with lower mitral e' velocities and higher E/e' ratio. Patients with HFpEF displayed higher estimated PASP and RAP and lower TV s' than controls.

The H_2FPEF and HFA-PEFF Scores

The H_2FPEF score was obtainable in all patients while the HFA-PEFF score could not be calculated in 23 patients (feasibility 88%) because of missing natriuretic peptide data. Among the entire cohort, subjects were more likely to be classified as low or intermediate probabilities on the H_2FPEF score and as high probability on the HFA-PEFF score (Fig. 1). As expected, both H_2FPEF and HFA-PEFF scores were higher in HFpEF patients than controls (Table 1). The H_2FPEF score was more likely to classify control subjects as low or intermediate probabilities (46% and 54%) while the HFA-PEFF score categorized HFpEF patients into intermediate or high HFpEF probabilities (34% and 66%). This indicates that the H_2FPEF score was highly specific while the HFA-PEFF algorithm was sensitive to identify HFpEF.

Exercise Capacity and Echocardiographic Measures during Peak Exercise

As compared to controls, peak exercise workload was lower, exercise duration was shorter, and peak VO_2 was lower in HFpEF patients (Table 2). During peak exercise, heart rate was lower in patients with HFpEF than in controls while systolic blood pressure and oxygen saturation were similar between groups. Differences in mitral e' and s' tissue velocities and E/e' ratio between groups increased further during peak exercise. Compared to control subjects, HFpEF patients displayed lower CO and TV s' and higher PASP during peak exercise. The severities of e' and s' velocities, E/e' ratio, CO, and TV s' were consistently associated with poorer exercise capacity (Fig. 2 and Table 3).

Table 2
Exercise Capacity and Echocardiographic Measures during Peak Exercise

	Controls (n = 104)	HFpEF (n = 83)	P value
Exercise capacity			
Peak watts (W)	63 ± 24	50 ± 23	0.0003
Exercise time (min)	10.2 ± 3.3	8.6 ± 3.2	0.001
Peak VO_2 (mL/min/kg), n = 107	13.3 ± 4.3	11.6 ± 3.3	0.03
Vital signs			
Heart rate (bpm)	118 ± 21	111 ± 24	0.04
Systolic BP (mmHg)	167 ± 32	161 ± 33	0.20
Saturation (%)	94 ± 4	95 ± 4	0.68
Echocardiographic measures			
LV ejection fraction (%)	72 ± 8	69 ± 9	0.03
E-wave (cm/sec)	106 ± 24	129 ± 30	< 0.0001
Mitral e' (cm/sec)	10.0 ± 2.5	7.4 ± 2.0	< 0.0001
Mitral s' (cm/sec)	9.3 ± 2.3	7.3 ± 2.2	< 0.0001
E/e' ratio (septal)	11.0 ± 2.6	18.4 ± 6.3	< 0.0001
Cardiac output (L/min)	7.8 ± 2.2	6.6 ± 2.1	0.0003
TV s' (cm/sec)	15.2 ± 3.0	12.8 ± 3.6	< 0.0001
PASP (mmHg)	37 ± 11	45 ± 12	< 0.0001

Data are mean ± SD or median (interquartile range). VO_2, oxygen consumption, and other abbreviations as in Table 2.

Table 3
Correlations between Echocardiographic Measures of Hemodynamics and Exercise Capacity

	Exercise duration		Peak VO_2	
	r coefficient	P value	r coefficient	P value
Mitral e' (cm/sec)	0.47	< 0.0001	0.47	< 0.0001
Mitral s' (cm/sec)	0.44	< 0.0001	0.29	0.0009
E/e' ratio	-0.32	< 0.0001	-0.22	0.01
Cardiac output (L/min)	0.48	< 0.0001	0.50	< 0.0001
TV s' (cm/sec)	0.41	< 0.0001	0.35	< 0.0001
PASP (mmHg)	-0.01	0.90	0.15	0.15
Abbreviations as in Tables 1 and 2.				

Correlations of the HFpEF Scores with Echocardiographic Measures during Peak Exercise and Exercise Capacity

The H_2FPEF score was correlated with echocardiographic measures during peak ergometry exercise (Table 4). Particularly, greater H_2FPEF score was associated with lower LV systolic function (s' velocity, r=-0.46, p < 0.0001), higher E/e' ratio (r = 0.49, p < 0.0001), and lower RV systolic function (TV s', r=-0.44, p < 0.0001) during peak exercise. There were similar correlations between the HFA-PEFF score and these echocardiographic measures.

Table 4
Correlations of the Two HFpEF Scores with Exercise Capacity and Echocardiographic Measures during Peak Exercise

	H_2FPEF score		HFA-PEFF score	
	r coefficient	P value	r coefficient	P value
Echocardiographic measures during peak exercise				
Mitral e' (cm/sec)	-0.35	< 0.0001	-0.47	< 0.0001
Mitral s' (cm/sec)	-0.46	< 0.0001	-0.47	< 0.0001
E/e' ratio	0.49	< 0.0001	0.46	< 0.0001
Cardiac output (L/min)	-0.28	< 0.0001	-0.24	0.002
TV s' (cm/sec)	-0.44	< 0.0001	-0.24	0.002
PASP (mmHg)	0.18	0.01	0.20	0.01
*Comparisons of r coefficients between the two scores. Abbreviations as in Tables 1 and 2.				

Peak VO_2 and exercise duration decreased with increasing the H_2FPEF score (Fig. 3, r=-0.40 and − 0.32, both $p < 0.0001$). As expected, both peak VO_2 and exercise duration were related to age (r=-0.27, $p = 0.005$ and r=-0.41, $p < 0.0001$), and the H_2FPEF score remained significantly associated with peak VO_2 and exercise time even after adjusting for age ($p = 0.002$ and $p = 0.036$). The H_2FPEF score demonstrated a good discriminatory ability for identifying reduced aerobic capacity (peak VO_2 < 14 mL/min/kg) (AUC 0.71, $p = 0.0005$). Among components of the H_2FPEF score, age, BMI, E/e' ratio, and treatment with 2 or more antihypertensives were related to peak VO_2 but each relationship was modest (Table 5). The HFA-PEFF score was correlated with exercise duration (r=-0.26, $p = 0.0008$), but not with peak VO_2 (r=-0.19, $p = 0.07$). The natriuretic peptide domain was the only component of the HFA-PEFF score associates with peak VO_2 (Fig. 4). The HFA-PEFF score did not predict reduced aerobic capacity (AUC 0.61, $p = 0.10$).

Table 5
Correlations of the Components of H_2FPEF and HFA-PEFF Scores with Exercise Capacity

	Peak VO_2		Exercise time	
	r	P value	r	P value
Components of the H_2FPEF Score				
Age (years)	-0.27	0.005	-0.41	< 0.0001
Body mass index (kg/m^2)	-0.25	0.009	0.14	0.06
E/e' ratio	-0.23	0.02	-0.30	< 0.0001
PASP (mmHg)	-0.12	0.21	-0.19	0.01
AF or SR	-	0.10*	-	0.06*
Hypertensive	-	0.01*	-	0.03*
Components of the HFA-PEFF Score				
e' (cm/sec)	0.16	0.10	0.32	< 0.0001
LS (%)	0.21	0.03	0.15	0.05
LA volume index (mL/m^2)	-0.16	0.11	-0.18	0.01
LV mass index (g/m^2)	-0.01	0.91	-0.13	0.07
Ln BNP (n = 65)	-0.26	0.04	-0.30	0.0006
Ln NT-proBNP (n = 30)	-0.25	0.18	-0.36	0.001
Abbreviations as in Tables 1 and 2. *Determined by paired t-tests.				

Discussion

In this study, we examined the performance of the H_2FPEF and HFA-PEFF scores for predicting exercise capacity and echocardiographic measures during exercise stress echocardiography. We observed that the HFA-PEFF score displayed relatively low feasibility because of the requirement of natriuretic peptide levels while the H_2FPEF score displayed perfect feasibility. We further demonstrated that both H_2FPEF and HFA-PEFF algorithms predicted lower LV systolic and diastolic function, higher estimated LV filling pressure, lower CO, and reduced RV systolic function during peak ergometry exercise. Despite the requirement of fewer input variables, the H_2FPEF score provided a good discriminatory ability for identifying poor exercise capacity among patients with dyspnea while the HFA-PEFF score did not. These data provide new insights into the role of the H_2FPEF and HFA-PEFF scores for predicting exercise intolerance and hemodynamics correlates in patients presenting with exertional dyspnea.

Abnormal Exercise Hemodynamics and Exercise Intolerance in HFpEF.

Exercise intolerance is a hallmark of patients with HFpEF and studies to date have uniformly reported that peak VO_2 is depressed in HFpEF.[2,3,15–18] Reduced exercise capacity is associated with symptoms of dyspnea and poor quality of life, making it an important therapeutic target in this syndrome.[3,19] While multiple mechanisms can contribute to exercise intolerance in HFpEF, including abnormalities in the heart, lungs, and the periphery, pathologic increases in cardiac filling pressures developed during exercise stress may play an important role in limiting exercise performance in HFpEF.[2,3,20–22] As expected, the current study demonstrated that exercise capacity was reduced in patients with HFpEF compared to control subjects as evidenced by lower peak exercise workload, shorter exercise duration, and depressed peak oxygen consumption. Compared to controls, patients with HFpEF displayed lower mitral e' and s' tissue velocities, higher E/e' ratio, reduced CO, and lower TV s' during peak exercise and the severities of these abnormalities were consistently associated with depressed exercise capacity. These data confirm that abnormal exercise hemodynamics and reduced CO reserve contribute to exercise intolerance in patients with HFpEF.

The H_2FPEF and HFA-PEFF Scores

Two multiparametric scoring systems have been proposed to help diagnose HFpEF among patients with dyspnea. The H_2FPEF score is developed among patients with unexplained dyspnea using the currently-recommended gold standard test (i.e., invasive exercise hemodynamic testing), and combines clinical characteristics and echocardiographic measures.[5] The HFA-PEFF score is a consensus-based approach that employs more complex scoring systems based on echocardiographic indices and natriuretic peptide levels.[6] As expected, the H_2FPEF score was obtainable in all patients while the HFA-PEFF score could not be calculated in 12% of patients due to the lack of natriuretic peptide data. Although evaluation of natriuretic peptides is the key in the diagnostic approach in HFpEF, they may not be measured in all patients with dyspnea.[6] On the other hand, echocardiography is performed in essentially all patients in whom there is clinical suspicion for HFpEF.[23] The current study also demonstrated that the HFA-PEFF scores categorized more patients into high HFpEF probability compared to the H_2FPEF score. Further studies are required to directly compare the diagnostic value between two scores using the gold standard of invasive exercise hemodynamic testing.

The H_2FPEF and HFA-PEFF Scores and Exercise Capacity

In addition to the diagnostic value, recent studies have shown the association between the two algorithms and clinical outcomes in patients with HFpEF.[7–10] However, few data are available regarding whether these diagnostic schemes could predict aerobic capacity in HFpEF. In this study, we found that the H_2FPEF score was associated with reduced exercise capacity as assessed by both peak VO_2 and exercise duration, which is consistent with a previous study.[24] In contrast, while the HFA-PEFF score was modestly correlated with exercise duration (r=-0.26), it was unrelated to peak VO_2. We further

demonstrated that the H_2FPEF score identified reduced peak VO_2, but the HFA-PEFF algorithm did not. The plausible reason for this may be related to the inclusion of both clinical and echocardiographic variables in the H_2FPEF score, but not in the HFA-PEFF score. It is clear that HFpEF is associated with comorbidities, including obesity, hypertension, diabetes, and AF.[16–19] Previous studies have demonstrated that higher BMI and AF are related to decreased exercise capacity in patients with HFpEF.[16,18,25,26] Indeed, the present study showed that individual component of H_2FPEF score was associated with peak VO_2. In contrast, only LV longitudinal strain and BNP were correlated with peak oxygen consumption among the components of the HFA-PEFF score. It is also worth pointing out that the weighted H_2FPEF score is more predictive of peak VO_2 than the individual components. This suggests the usefulness of the H_2FPEF score not only for diagnosing HFpEF but also for predicting exercise capacity.

The association between the H_2FPEF score and peak VO_2 may raise the question of whether therapies targeting the components of the score could improve aerobic capacity in patients with HFpEF. Obesity may be a promising target given its high prevalence and pathophysiologic significance.[18] Kitzman and colleagues demonstrated that weight loss induced by caloric restriction or aerobic exercise training improved peak VO_2, reduced LV mass and inflammatory markers, and enhanced quality of life in patients with obese HFpEF.[27] Bariatric surgery has been demonstrated to improve functional capacity in obese patients with HF with reduced EF.[28] Obesity and increased adiposity may better response to sodium-glucose co-transporter 2 inhibitors by reducing plasma volume and visceral and epicardial fat. A substantial proportion of patients with HFpEF develop AF, and they suffer from more biatrial dysfunction, worse functional capacity, RV dysfunction, and increased risk of death.[16,29,30] Catheter ablation may be effective to reverse or at least prevent the adverse consequences of AF,[31,32] but this should be tested in prospective trials. Intensive treatment of isolated hypertension was shown to be effective for the prevention of the development of HF.[33] Further studies are required to test whether it will prevent or mitigate the progression of HFpEF.

Limitations

The current study has several limitations. All participants were referred for exercise stress echocardiography. This might introduce selection bias. The sample size was relatively small, which could bias overall results. The control group was not truly normal as they were referred for exercise stress echocardiography in the evaluation of exertional dyspnea and had multiple comorbidities, which could also bias the results. LV longitudinal strain was determined using apical four-chamber views.

Conclusions

Both H_2FPEF and HFA-PEFF scores are associated with lower LV systolic and diastolic function, higher estimated LV filling pressure, lower CO, and reduced RV systolic function during peak ergometry exercise. Despite the requirement of fewer input variables, the H_2FPEF score provided a good discriminatory ability

for identifying poor exercise capacity among patients with dyspnea, but the HFA-PEFF score did not. These data provide new insights into the role of the H_2FPEF and HFA-PEFF scores for predicting exercise intolerance and abnormal hemodynamics in patients presenting with exertional dyspnea.

Declarations

Acknowledgments

Dr. Obokata received research grants from the Fukuda Foundation for Medical Technology, the Mochida Memorial Foundation for Medical and Pharmaceutical Research, Nippon Shinyaku, Takeda Science Foundation, the Japanese Circulation Society, and the Japanese College of Cardiology.

Author contributions

SA and TH: Data curation, formal analysis, writing an original draft; KK: data curation; MO: concept and design; and all authors: review and revising a manuscript.

Competing interests

The authors declare no competing interests.

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Figures

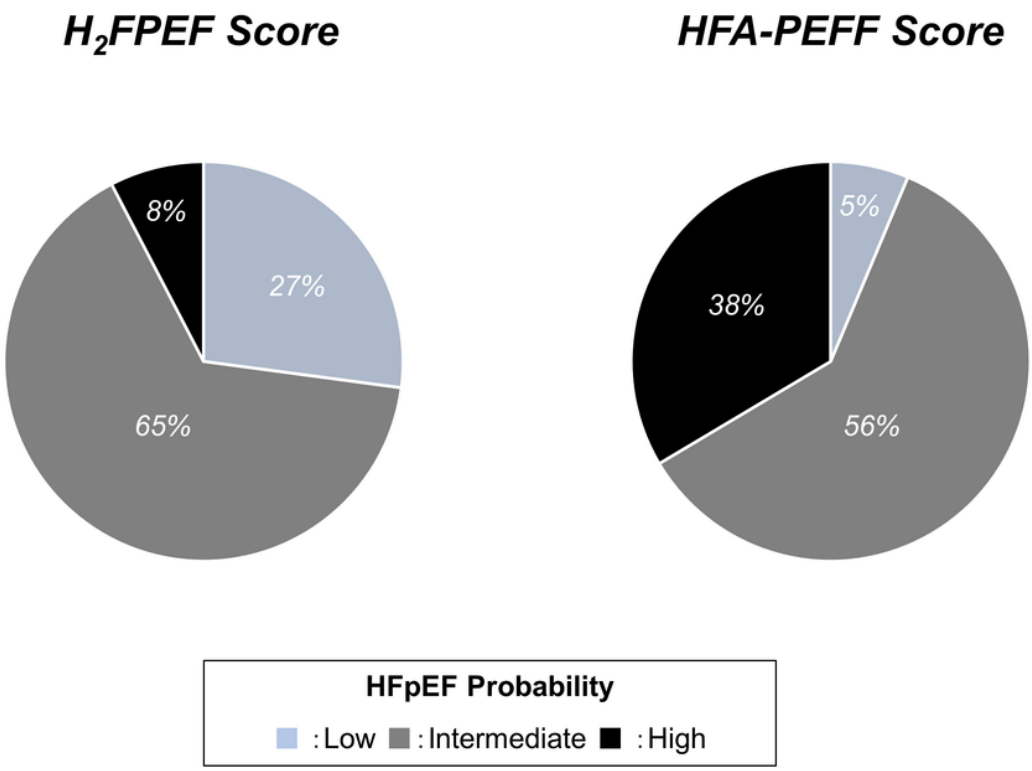

Figure 1

Distribution of H2FPEF and HFA-PEFF scores among all participants. The H2FPEF score was more likely to classify subjects into low or intermediate probabilities while the HFA-PEFF score categorized them as high probability.

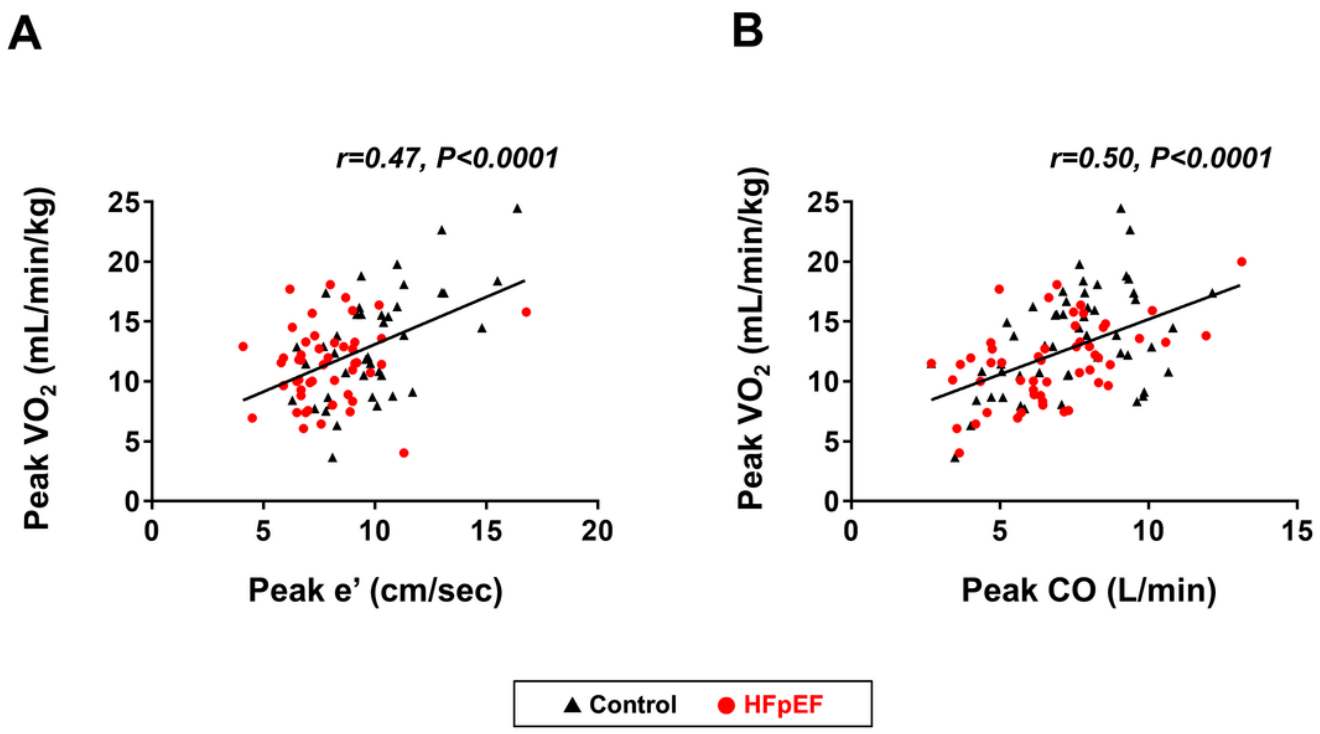

Figure 2

Correlations between echocardiographic measures and exercise capacity. Decreases in mitral annular e' velocity and cardiac output (CO) during exercise were moderately correlated with lower peak oxygen consumption (VO2). HFpEF, heart failure with preserved ejection fraction (HFpEF).

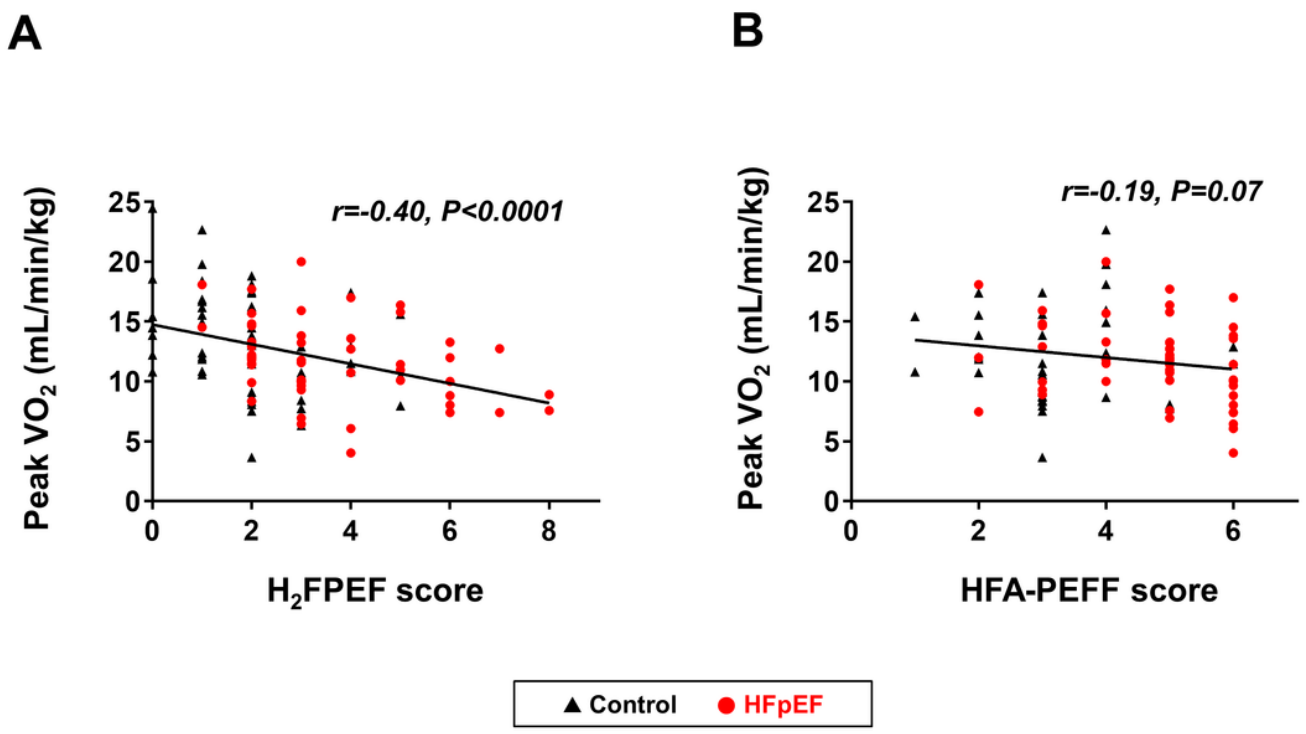

Figure 3

Correlations between HFpEF diagnostic algorithms and exercise capacity. The H2FPEF score was correlated with peak VO2, but the HFA-PEFF score was not. Abbreviations as in Figure 2.

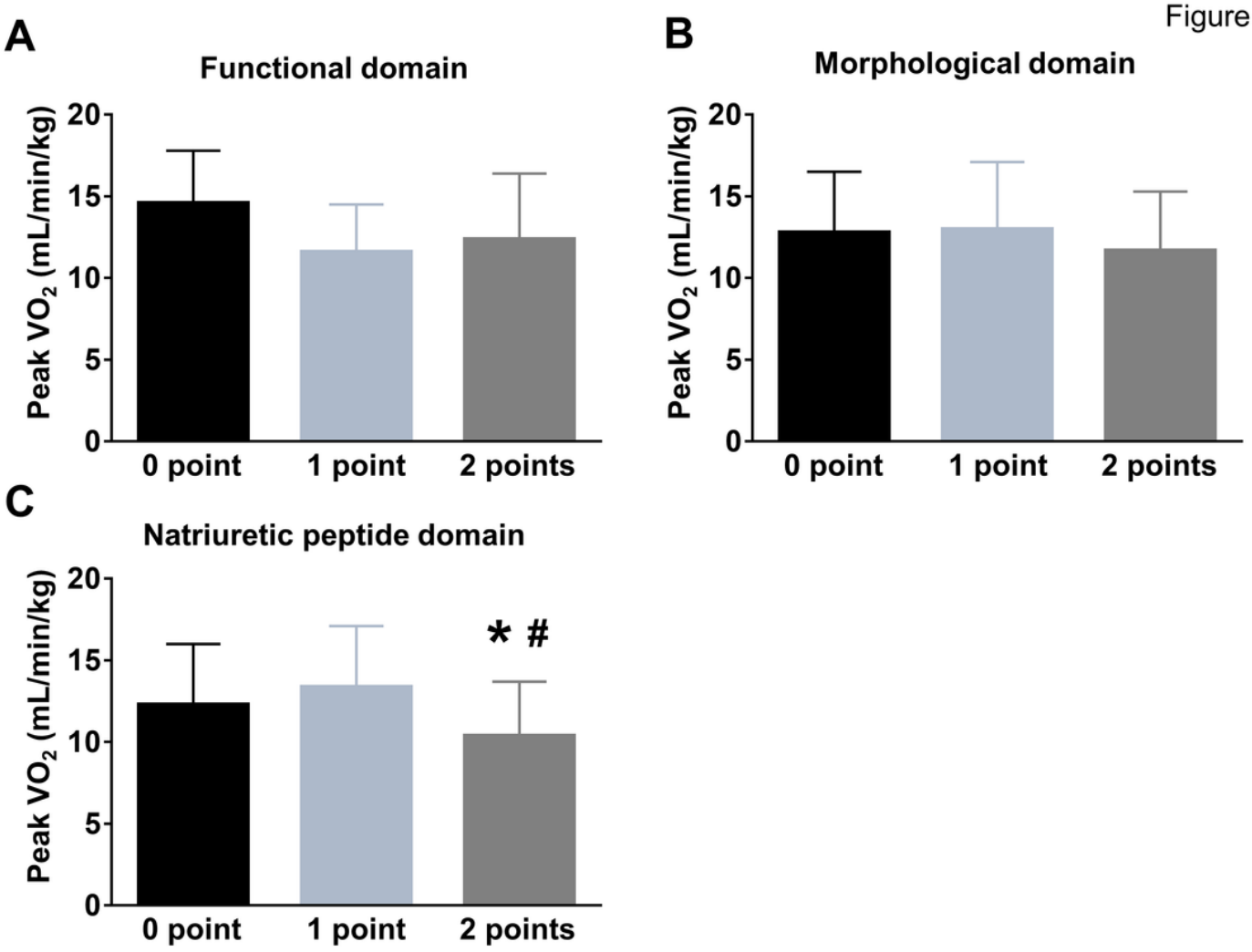

Figure 4

Peak oxygen consumption according to the HFA-PEFF domain scores. (A) Peak VO2 did not differ among the HFA-PEFF functional domain scores. (B) Peak VO2 was similar among the HFA-PEFF morphological domain scores. (C) In contrast, patients with a natriuretic peptide domain of 2 points displayed lower peak VO2 compared to the other groups. *p<0.05 vs. 0 point, #p<0.05 vs. 1 point. Abbreviations as in Figure 2.