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Identification of Patients with Preclinical Heart Failure with preserved Ejection Fraction Using the H_2FPEF Score

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a common disorder with few effective treatments. There is currently no evidence-based method to identify preclinical HFpEF. The H_2FPEF score is a validated instrument to identify patients with overt HFpEF. Here we show the H_2FPEF score can identify individuals with preclinical HFpEF. Among individuals where heart failure was excluded (n=160), increasing H_2FPEF score was shown to be associated with greater left atrial dilation, left ventricular hypertrophy, and more severe diastolic dysfunction. Patients with increasing H_2FPEF score displayed higher pulmonary artery pressures, higher left heart filling pressures, lower cardiac index, and more severely impaired aerobic capacity during exercise. In summary, we show that among adults without heart failure, higher H_2FPEF score is associated with subclinical abnormalities that resemble those observed in HFpEF. These findings broaden the external validity of the H_2FPEF score and suggest that this instrument may help identify patients positioned to benefit from preventive interventions.

Keywords

hemodynamics; heart failure; HFpEF; exercise; diastolic function; prevention

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is the most common form of HF among older adults.[1–3] Few effective treatments have been identified,

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Author Contributions

Study Conception and Design: KEK and BAB: Project Supervision: BAB, Data acquisition: KEK, YNVR, MO, HS, FHV, CCJ, ACE, MMR, TPO, BAB: Data analysis: KEK, YNVR, and BAB, Manuscript Drafting: KEK, YNVR, and BAB, Manuscript critical revision: KEK, YNVR, MO, HS, FHV, CCJ, ACE, MMR, TPO, and BAB.

Competing Interests

The authors declare no competing interests.

emphasizing the importance of prevention. HFpEF develops gradually over years, with a prolonged risk factor exposure preceding symptom manifestation, and no single cause is typically identified. While there is evidence that interventions targeting risk factors such as hypertension,[4–8] obesity,[9–13] and physical inactivity[14–16] may reduce HF risk, no prospective trial has yet tested whether HFpEF can in fact be prevented.

One barrier to preventive intervention is the lack of accurate, easy-to-apply methods to identify patients with preclinical disease. Patients with overt HFpEF display typical impairments in cardiac function that lead to abnormal hemodynamics and reduced exercise capacity.[17–19] It therefore follows that patients with preclinical HFpEF could be defined as those with similar, though less severe cardiac, hemodynamic and functional abnormalities.

Recently, the H_2FPEF score, which is based on a combination of clinical characteristics and echocardiographic findings, was demonstrated to accurately estimate the probability that HFpEF is present among patients with unexplained dyspnea.[20] The present study tested the hypothesis that application of the H_2FPEF score would allow for identification of patients with subclinical hemodynamic and functional impairments, even when the diagnosis of HFpEF had been carefully excluded.

Results

Clinical Characteristics

A total of 160 individuals free of HF were included in the final analysis: 136 who had undergone invasive hemodynamic exercise testing and 24 asymptomatic individuals free of dyspnea undergoing noninvasive exercise and echocardiography testing. Patients in the invasive cohort had slightly lower BMI and slightly higher creatinine and prevalence of coronary disease compared to the non-invasive cohort, but other baseline characteristics were similar in these groups (Supplementary Table 1).

Participants were middle to older aged, overweight to obese, with a low prevalence of diabetes (11%), atrial fibrillation (3%) and coronary disease (22%, Table 1). Around half of the patients had hypertension (49%). Relative to Groups 1 and 2, individuals in Group 3 demonstrated the highest rate of comorbid diseases and were accordingly more likely to be treated with cardiovascular medications. Plasma NT-proBNP levels and HFA-PEFF score both increased with increasing H2FPEF score (Table 1).

Patients in Group 1 were more likely to be categorized as ACC/AHA Stage 0 or A, whereas patients in Group 3 were more likely to be ACC/AHA Stage A or B. However, there was substantial overlap in ACC/AHA stages in the different H_2FPEF probability groups (Table 1). For example, 46% of patients in the high probability H_2FPEF Group were categorized as only ACC/AHA Stage A.

Cardiac Structure and Function

Despite the absence of clinically overt HFpEF, Group 3 participants displayed more adverse cardiac structural remodeling, with higher left ventricular (LV) mass, greater LV end diastolic dimension, and increased left atrial (LA) volume (Table 2). As expected, due to

the incorporation of E/e' and estimated right ventricular systolic pressure (RVSP) in the H_2FPEF score probability, these metrics worsened with increasing probability.

Exercise Capacity Decreases with Higher H_2FPEF Score

A total of 95 of the 160 participants underwent maximal-effort, upright exercise testing at a separate visit, distinct from the assessment at cardiac catheterization (71/136 in the invasive cohort and 24/24 in the noninvasive cohort). Participants in Group 3 displayed the greatest impairment in peak VO_2 (Table 2), which decreased in a linear fashion with increasing H_2FPEF probability score (Figure 2). Conversely, there was no relationship between peak VO_2 and ACC/AHA HF stage (p=0.16) or HFA-PEFF score (p=0.17).

Invasive Hemodynamics Worsen with Higher H_2FPEF Score

A total of 136 participants underwent maximal-effort supine exercise testing with simultaneous right heart catheterization. By study design, central hemodynamics at rest and during exercise fell within the normal range in all individuals (Table 3). However, even when restricted to this normal range, individuals in Group 3 displayed the highest resting pulmonary artery pressures, along with the highest resting PCWP and right atrial pressures. Cardiac index at rest was lower in Groups 2 and 3, along with higher pulmonary vascular resistance. Consistent with a lower cardiac index, there was a higher resting C_{aO2}-C_{vO2} in Groups 2 and 3 (Table 3).

With exercise, both HR and cardiac index were lower in Groups 2 and 3 compared to Group 1 (Table 3, Figure 3). Group 3 patients also developed more profound systolic hypertension during exercise, which was associated with impaired systemic vasodilation (higher systemic vascular resistance and effective arterial elastance). Compared to Groups 1 and 2, individuals in Group 3 demonstrated more abnormal pulmonary vascular hemodynamics during exercise, including significantly higher PCWP, PASP and mPAP (Figure 3, Table 3). Relative to Group 1, Groups 2 and 3 also displayed a higher PVR and lower cardiac index.

A higher H_2FPEF score-based probability was associated with a higher rest and exercise mean PA pressure, RAP, and PCWP in simple linear regression analysis (Supplementary Table 2). Cardiac index was inversely associated with a greater probability both at rest and with exercise.

Sensitivity Analyses

Significant correlations were also observed between hemodynamics and the categorical H_2FPEF score in sensitivity analyses in place of the continuous score (Supplementary Tables 3 and 4). Among individual components of the H2FPEF score, exercise PCWP were more markedly abnormal in participants with history of prior AF and among those with older age (Supplementary Table 5). Hemodynamic abnormalities at rest and with exercise were greater in patients with higher HFA-PEFF scores, similar to H_2FPEF score terciles (Supplementary Table 6). In contrast to differences by H_2FPEF score-based stratification, there were no differences in PCWP at rest or with exercise when comparing patients with or without isolated comorbidities associated with HFpEF, including hypertension, obesity, diabetes, and coronary disease (Supplementary Table 7). In a sensitivity analysis restricted to the healthy

volunteers with no dyspnea, higher H_2FPEF probability score again remained strongly and inversely correlated with peak VO_2 (r= −0.51, p=0.01).

Discussion

Patients with clinically overt HFpEF display pathognomonic elevations in ventricular filling pressure during activity and impairments in aerobic capacity.[1, 2] The H_2FPEF score was developed to estimate the probability that a patient with unexplained dyspnea has HFpEF defined according to this reference standard.[20] The present study shows that even when applied to individuals where the diagnosis of HFpEF has been excluded, the presence of a higher H_2FPEF score identifies traits that are typical of, but less severe than, overt HFpEF, including LV diastolic dysfunction, concentric remodeling, left atrial dilatation, elevated filling pressures, exercise-induced pulmonary hypertension, abnormal systemic arterial vasodilation, and reductions in exercise capacity. These findings broaden the external validity of the H_2FPEF score to a larger population of patients, indicating that even when the clinical diagnosis of HFpEF has been excluded, patients with elevated score are more apt to display preclinical disease that may respond to preventive interventions.

Some physiologic or pathologic states are discrete and binary; they are either present or absent. Examples include pneumococcal pneumonia, pregnancy, or death. In contrast, other disorders such as HF exist along a continuum, a fact emphasized by the staging system first proposed by the ACC/AHA HF guideline committee in 2005,[21] and evaluated in community based cohorts in more recent years.[22] In this scheme, stage A refers to asymptomatic patients with HF risk factors; stage B includes asymptomatic patients with cardiac structural or functional abnormalities; stage C refers to symptomatic HF; and stage D refers to end-stage HF. Implicit in this scheme is the notion that each stage is preceded by another where some abnormalities are present but not others, and that interventions applied during the earlier stages may delay or prevent transition to the next stage.[21]

There is currently no consensus for how preclinical HFpEF should be defined. To justify consideration for any scheme as a means to characterize preclinical HFpEF, one might argue that it should satisfy 2 critical requirements: (1) patients should display functional and hemodynamic abnormalities that resemble (but are less severe than) individuals with clinically overt disease, and (2) patients should display increased risk for progression to overt disease during long-term follow up. Selvaraj and colleagues have recently demonstrated the latter to be true in a large community-based study.[23] In that study, individuals with dyspnea and increased H_2FPEF score but no established clinical diagnosis of HF displayed a significantly increased risk of being diagnosed with HFpEF over 5 years, with a hazard ratio of 3.26 (95% CI, 2.12–5.02) for scores of 3–4 and 3.37 (95% CI, 2.14–5.31) for scores ≥5.[23] However, as pointed out in the accompanying editorial,[24] the association between higher score and worse outcomes does not provide insight into causality.

Rather than showing an increased risk for clinical events in the future, as in the prior study,[23] the present study directly shows for the first time that entity of preclinical HFpEF is associated with elevation in H_2FPEF score. For this study, we define preclinical HFpEF

as sub-pathologic abnormalities in hemodynamics and mild impairments in exercise capacity and cardiac structure/function. As hypothesized, individuals without HFpEF but with higher H_2FPEF score displayed abnormalities that are typical of (but less severe than) symptomatic HFpEF, including lower peak VO_2, higher PCWP and PA pressures during exercise, and poorer cardiac output reserve. These provide strong evidence to support the hypothesis that patients with higher H_2FPEF score display preclinical HFpEF.

Results were largely similar using the HFA-PEFF score, which increased with increasing H2FPEF score. Patients in the higher tercile of HFA-PEFF score generally displayed more abnormal hemodynamics compared to lower scores as well. In contrast, the presence of isolated comorbidities associated with HFpEF such as hypertension, obesity, coronary disease, or diabetes was not associated with elevation in PCWP. This suggests that the combination of risk factors and echocardiographic findings in the H_2FPEF score is of greater value than individual risk factors considered in isolation.

Clinical trials in HFpEF published to date have largely been neutral, making prevention an even greater priority.[1–3] The H_2FPEF score combines both cardiac functional indices (E/e' and RVSP) with key risk factors that are related to the amount of excess body fat, hypertension, age, and atrial fibrillation (a biomarker reflective of underlying left atrial myopathy[25]). While it may be expected that patients with this collection of risk factors and echocardiographic findings may be more apt to display preclinical HFpEF, the ability to detect this probability using a simple scoring instrument has great potential clinical significance as it may be used to stratify risk and apply different preventive strategies based upon that risk. This score can be easily calculated based upon widely available clinical criteria, both at the bedside and automatically as part of electronic health records. The latter may in particular facilitate identification of patients for preventive intervention.[20]

An advantage of the H_2FPEF score is that many of the individual components of the score also present actionable therapeutic targets. Obesity has emerged as a major driver of HFpEF in the modern era.[26] Weight loss induced by bariatric surgery decreases the risk of incident HF,[9, 12] possibly related to favorable changes in central hemodynamics.[11] Weight loss also reduces the burden of atrial fibrillation,[13] which is important for HFpEF prevention since atrial fibrillation is one of the strongest risk factors for HFpEF.[27] Treatment of hypertension is well-known to reduce risk for HF events, many of which are likely related to HFpEF,[4–7] especially diuretic-based antihypertensive therapies, which may also reduce PCWP.[8]

The H_2FPEF categorical or continuous score could be readily calculated automatically a provided as part of the patient's electronic health record, providing caregivers with an instant readout for the probability that preclinical or even overt HFpEF is present. This information could be used to help educate and motivate patients about the importance of medication adherence and lifestyle interventions to deter progression HFpEF, or as a reminder to consider the diagnosis of HFpEF if the patient complains of dyspnea. While the H_2FPEF score is here shown to predict probability of preclinical HFpEF, clinical judgement is still required when interpreting the data. For example, a patient at higher risk by high age alone, with few other risk factors, might be considered to be low risk for preclinical HFpEF,

particularly if alternative causes for abnormalities are present, such as chronic lung disease which may cause elevated PA pressure.

Finally, an increased H_2FPEF score can be used to identify patients with preclinical HFpEF for prevention trials. While many preventive measures are already broadly indicated (such as recommendation of regular exercise, weight loss, or control of blood pressure), others may be more optimally applied to patients at greater risk due to cost, risk, or patient burden. Examples include high intensity exercise training, pharmacologic or surgical weight loss interventions, catheter ablation for atrial fibrillation, or drug therapies, each of which could potentially reduce risk for new-onset HFpEF based upon preliminary studies,[11, 28–30] but would ideally be applied only to high risk patients. Such strategies will require testing in future preventive trials, but the present data show that the H2FPEF score can be used to stratify risk to identify patients to enroll in such trials.

There is selection bias in that patients in the invasive cohort were referred for assessment due to unexplained dyspnea. However, the invasive CPET is necessary to verify that HFpEF was not present and provided the ability to quantify the hemodynamic abnormalities suggesting preclinical HFpEF, which would have otherwise not been possible. To address selection bias in the invasive cohort, a separate cohort of healthy volunteers without dyspnea and no prior cardiovascular disease was recruited to undergo noninvasive CPET, and sensitivity analyses restricted to this subgroup showed similar results. Use of an unadjusted linear model might reduce the reproducibility of the findings. Aerobic capacity and exercise hemodynamics worsen with aging and increasing adiposity, two factors that are both incorporated in the H_2FPEF score. However, the purpose of this study was not to demonstrate that the H_2FPEF score identifies preclinical HFpEF independent of these risk factors, but rather to show that the score, which relies in part upon the presence of these risk factors, can identify patients with preclinical HFpEF.

HFpEF is a chronic disorder that may be amenable to preventive or disease modifying therapies if applied early in the disease course, but to date there have not been evidence-based methods to identify patients with preclinical disease. The present study shows that higher H_2FPEF score identifies early-stage abnormalities in cardiac structure, function, and hemodynamics that contribute to the functional limitations that eventually develop in patients with overt HFpEF. This expands the external validity of the H_2FPEF score to include a broader population of patients at risk, reinforces the importance of systemic comorbidities and in the pathogenesis of HFpEF, and suggests that the H_2FPEF instrument may be helpful to identify patients with preclinical HFpEF who may stand to benefit from preventive interventions.

Methods

The studies were approved by the Mayo Clinic Institutional Review Board (registration numbers 15–003310 and 18–000830). Written informed consent was obtained by all participants before participation in study-related procedures.

Study population

The present study examined subjects with normal EF (≥50%) and no evidence of HF derived from two sources: (1) patients with non-cardiac dyspnea undergoing invasive cardiopulmonary exercise testing (CPET), and (2) healthy volunteers without dyspnea participating in a prospective study including CPET and exercise echocardiography.

In the invasive cohort (n=136), HFpEF was excluded based upon normal rest and exercise hemodynamics (resting and exercise pulmonary capillary wedge pressures (PCWP) of <15 mmHg and <25 mmHg, respectively) in accordance with current diagnostic guidelines.[31] For the noninvasive cohort (n=24), patients were required to have no symptoms of dyspnea, with no major or minor echocardiographic morphologic or functional indicators of HFpEF according to the same guidelines.[31]

Individuals with cardiomyopathies, rest or exercise-induced pulmonary hypertension, unstable coronary disease, history of low EF (<50%), constrictive pericarditis, high-output HF, significant valvular heart disease, pulmonary embolism and right ventricular myopathies were excluded.

Assessment of Cardiac Structure and Function

Comprehensive 2-dimensional, M-mode, Doppler and tissue Doppler echocardiography was performed by experienced sonographers by imaging the heart from the apical and short axis views at rest.[32] Echocardiography data were obtained retrospectively from echocardiograms performed within 1 year for subjects undergoing invasive CPET and simultaneously with the CPET in the non-invasive cohort.

Cardiopulmonary Exercise Testing

Two separate cardiopulmonary exercise tests were performed in this study, one of which was invasive and performed in the supine position (n=136), while the other was non-invasive and performed in the upright position (n=95). Every participant completed one or the other, and 71 completed both exercise tests. The upright exercise study was included because patients achieve higher VO_2 with upright exercise as compared to supine ergometry,[19] and because most exercise in daily life is performed in the upright position.

All exercise studies were performed using expired gas analysis (MedGraphics, St. Paul, MN) to measure breath-by-breath oxygen consumption (VO_2) and CO_2 production (VCO_2). Respiratory exchange ratio (RER= VCO_2/VO_2), and ventilatory efficiency (minute ventilation [V_E]/VCO_2 nadir) were calculated. Peak exercise VO_2 and RER were taken as the average of the final 30 seconds of exercise as previously described.[17–19]

Invasive hemodynamic exercise testing

Right heart catheterization was performed via the right internal jugular vein in the fasted state and supine position to measure rest and exercise hemodynamics.[17, 33] Pressures in the right atrium (RA), pulmonary artery (PA), and pulmonary capillary wedge pressure (PCWP) were measured at end-expiration using high fidelity micromanometers. Hemodynamics were assessed at rest and during supine cycle ergometry exercise, starting at a 20 Watt

(W) workload, increasing in 20W increments until patient-reported volitional exhaustion. Arterial-venous O_2 content difference (C_aO_2-C_vO_2) was calculated from the difference between systemic and mixed venous (PA) O_2 contents from direct blood sampling (=saturation*hemoglobin*1.34). Oxygen consumption (VO_2) was determined using the same methods as the noninvasive CPET (above). Cardiac output (CO) was calculated using the direct Fick method at rest and exercise. Systemic vascular resistance and effective arterial elastance were calculated using standard formulas.[34]

Application of H_2FPEF Score

The H_2FPEF score estimates the probability that HFpEF is present based upon widely-available clinical characteristics and echocardiographic data, including body mass index, number of hypertensive medications, presence of atrial fibrillation, age, and estimation of pulmonary artery systolic pressure and filling pressures based upon the septal E/e' ratio.[20] The components of the H_2FPEF score are summed to estimate HFpEF probability using either a categorical score ranging from 0–9 points (Figure 1A) or continuous scale ranging from 0–100% (Figure 1B). The continuous H_2FPEF score model was used for the primary analysis given its greater precision.

Alternative Risk Stratification Methods

To contrast H_2FPEF score-based identification to other staging schemes, patients were also categorized according to the HFA-PEFF score,[31] and the ACC/AHA HF staging system.[21, 22] According to the latter scheme, patients with risk factors for HF including hypertension, obesity, coronary artery disease, diabetes, or chronic kidney disease, but no significant cardiac structural disease or functional abnormalities on echocardiogram were categorized as stage A HFpEF, as previously applied.[22] Patients with echocardiographic abnormalities including elevated E/e' ratio (>13), elevated LV mass index (>109 g/m^2 in women and >132 g/m^2 in men), or greater than mild aortic or mitral valve disease were categorized as Stage B HFpEF.[21, 22] Subjects not meeting either of these criteria were categorized as Stage 0.

Statistical Analysis

Data are reported as mean ± standard deviation (SD) or median (interquartile range). Normality was assessed through visual inspection of all data distributions. For the primary analysis, participants were divided into terciles of continuous H_2FPEF score probability [Group 1 (low, 0–29%), Group 2 (intermediate, 30–60%) and Group 3 (high, >60%)]. A sensitivity analyses was performed comparing groups using the categorical H_2FPEF score. One-way Analysis of Variance (ANOVA) or the Wilcoxon Rank Sum test was used to examine the differences among the 3 groups for continuous variables with Normal and skewed distributions, respectively. Chi square or Fisher's Exact test were used for categorical variables. For comparisons where the ANOVA or Wilcoxon p was significant, pairwise comparisons among the 3 groups were made using Tukey's HSD test (or the Steel-Dwass test for skewed distributions) in order to control the family error rate for multiple comparisons among the terciles. To control for Type I error in the number of hypotheses tested, Holm's test was applied to each family of comparisons, with families defined thematically as those based upon echocardiographic evaluation, resting hemodynamics, or

exercise hemodynamics. Simple linear regression was used to evaluate relationships between exercise measures of interest (VO_2, PCWP, dependent variable) and the continuous and categorical H_2FPEF scores (independent variable). All tests were 2-sided and a p value of <0.05 was considered significant. Analyses were performed using JMP 14.2.0 (SAS Institute, Cary, North Carolina).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

Deidentified participant data will be made available on reasonable request. Requests should be directed to the corresponding author (BAB). Requestors will be required to sign a data access agreement to ensure the appropriate use of the study data.

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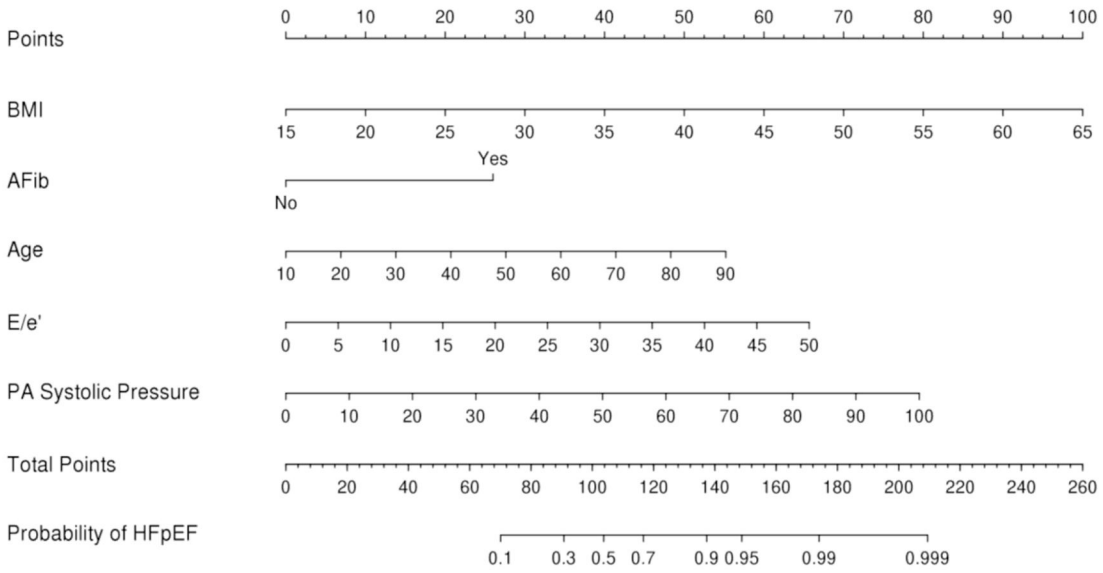
A



B

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

Figure 1: H_2FPEF Score Calculation.

[A] The continuous H_2FPEF score is calculated from age, body mass index, atrial fibrillation history, E/e' ratio, and estimated pulmonary artery (PA) systolic pressure by echocardiography. This score is then transformed into a probability score ranging from 0–100% according to the nomogram. Note that even as some patients have higher pre-test probabilities suggestive of possible HFpEF, all were demonstrated not to have HFpEF (invasively) or did not have any dyspnea or echocardiographic abnormalities to suggest HFpEF (outpatient cohort). [B] The categorical H_2FPEF score ranges from 0–9 and is based upon 6 binary measures including obesity (BMI>30, 2 points), treatment with 2 or more

anti-hypertensives (1 point), history of any atrial fibrillation (3 points), elevated pulmonary artery pressure by echocardiography (1 point), age above 60 years (1 point), and elevation in left ventricular filling pressures by echocardiography (E/e' ratio>9, 1 point). Figures modified with permission from Reddy et al.[20]

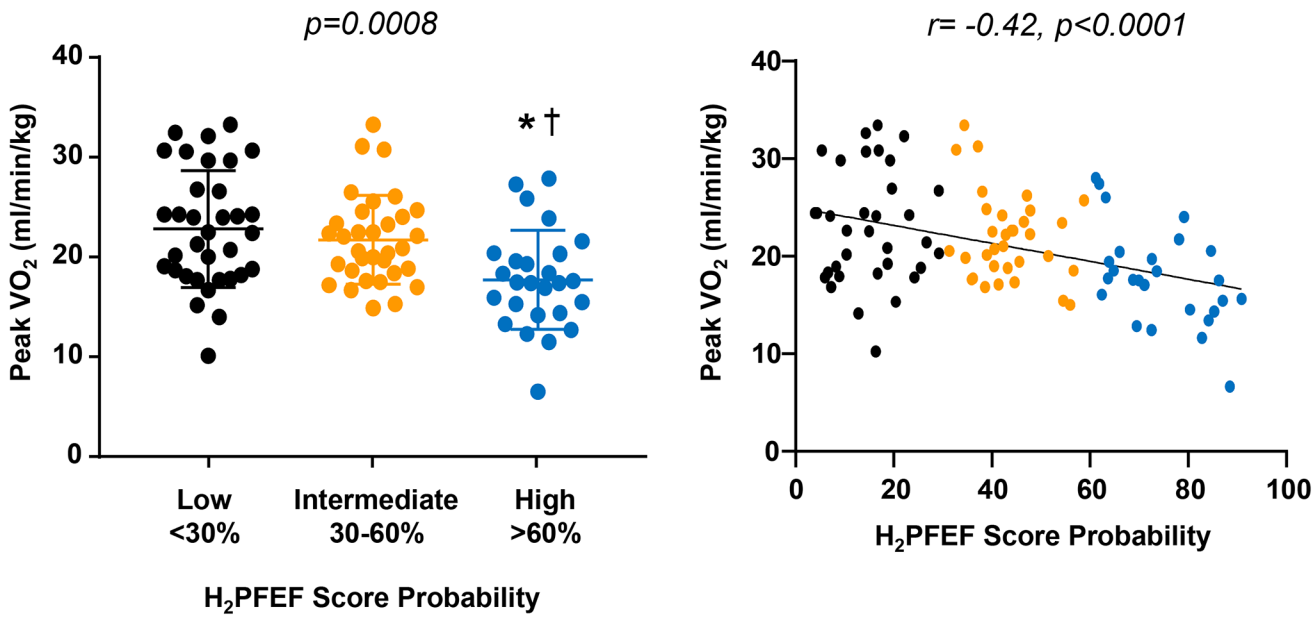


Figure 2: Exercise Capacity and the H_2FPEF Score.

Relationships between aerobic capacity assessed by peak oxygen consumption (VO_2) and probability of HFpEF estimated by the continuous H_2FPEF score model. Center lines depict group means and whiskers indicate standard deviations from n=93 independent observations across 3 groups. *p=0.0007 compared to Group 1, †p=0.01 compared to Group 2 by Tukey HSD test.

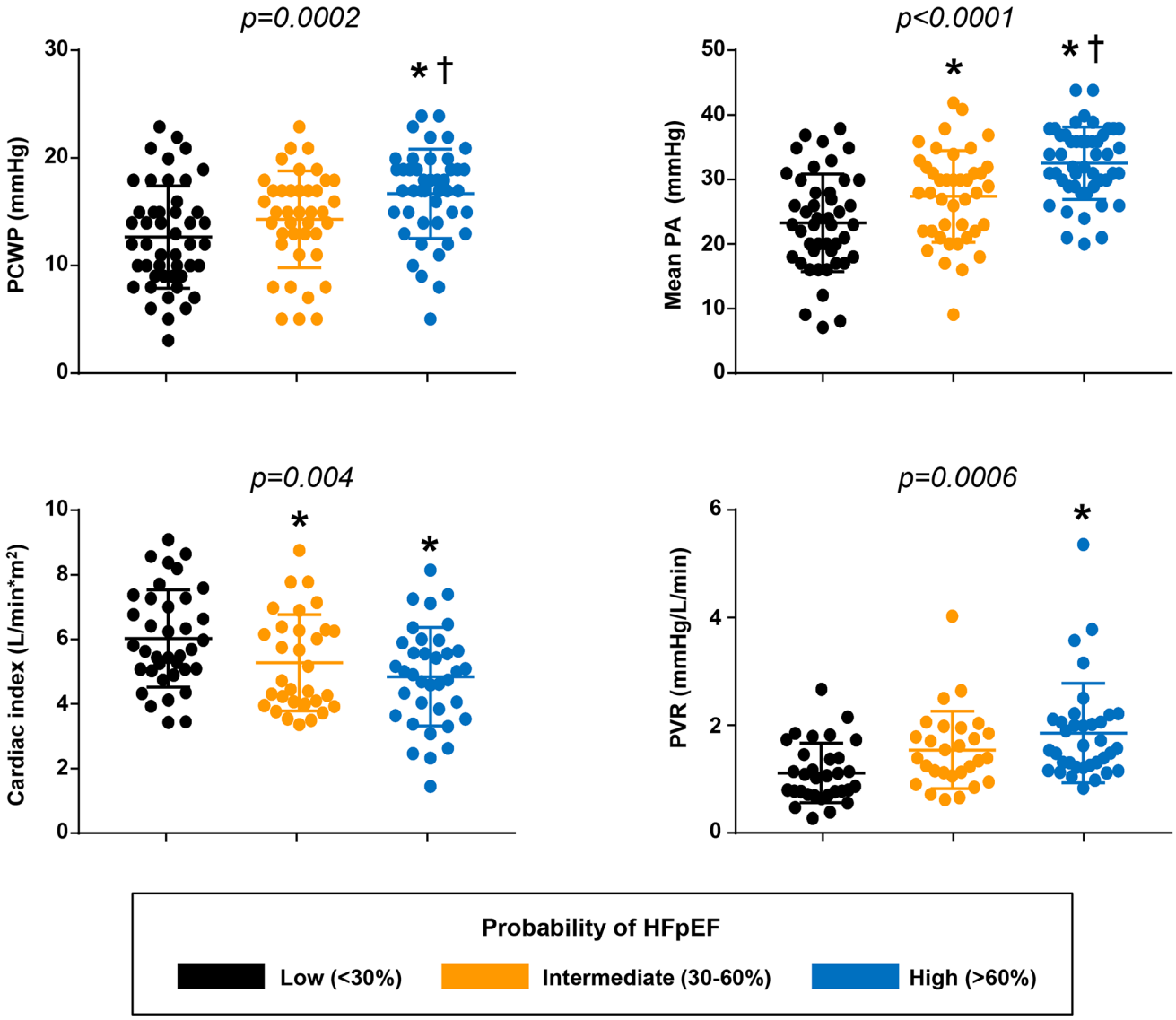


Figure 3: Exercise Hemodynamics and the H_2FPEF Score.

With increasing H_2FPEF score probability there was a graded increase in exercise pulmonary capillary wedge pressure (PCWP, n=131 across the 3 groups), mean pulmonary artery (PA, n=134) pressure, and pulmonary vascular resistance (PVR n=95), and a graded reduction in exercise cardiac index (n=104). Center lines depict group means and whiskers indicate standard deviations. *p<0.05 compared to Group 1, †p<0.05 compared to Group 2 by Tukey HSD test.

Table 1:

Baseline Characteristics

	Overall Cohort	Group 1	Group 2	Group 3	
		Low H_2FPEF Probability <30	Intermediate H_2FPEF Probability 30–60	High H_2FPEF Probability >60	*p value*
	n= 160	n=54	n=52	n=54	
Demographics					
Age, years	59 ± 14	46 ± 12	65 ± 10 *	67 ± 9 *	<0.0001
Female, n (%)	98 (62)	41 (76)	25 (48) *	32 (59)	0.01
BMI, kg/m^2	28.6 ± 5.5	25.2 ± 3.7	28.5 ± 3.9 *	32.3 ± 5.9 *†	<0.0001
Comorbidities					
Diabetes, n (%)	17 (11)	2 (4)	3 (6)	12 (22) *†	0.004
Hypertension, n (%)	79 (49)	14 (26)	27 (52) *	38 (70) *	<0.0001
Atrial fibrillation, n (%)	5 (3)	0 (0)	0 (0)	5 (9) *†	0.01
CAD, n (%)	32 (22)	3 (6)	9 (20) *	20 (40) *†	0.0002
Obesity, n (%)	64 (40)	5 (9)	21 (40) *	38 (70) *†	<0.0001
Laboratories					
Hemoglobin, g/dL	13.6 ± 1.3	13.3 ± 1.4	13.7 ± 1.4	13.8 ± 1.2	0.22
eGFR, ml/min	90 ± 33	95 ± 27	87 ± 41	85 ± 33	0.33
NT-proBNP (ng/dL)	88 (45,204)	50 (25,113)	105 (71,184) *	125 (58,503) *	0.0006
Medications					
ACEI/ARB, n (%)	38 (24)	6 (11)	7 (13)	25 (46) *†	<0.0001
Beta-blocker, n (%)	40 (25)	5 (9)	16 (31) *	19 (35) *	0.004
Diuretic, n (%)	38 (24)	9 (17)	8 (15)	21 (39) *†	0.007
ACC/AHA Staging					
Stage 0, n (%)	38 (24)	31 (57)	4 (8)	3 (6)	
Stage A, n (%)	77 (48)	17 (32)	35 (67)	25 (46)	<0.0001
Stage B, n (%)	45 (28)	6 (11)	13 (25)	24 (48)	
H_2FPEF Score					
Probability, %	45 (19, 65)	16 (10, 20)	45 (39, 51)	73 (65, 79)	-
Categorical Score	2 (1, 4)	1 (0, 1)	2 (1, 3)	4 (3, 5)	-
HFA-PEFF Score	3 (1, 4)	1 (0, 3)	3 (1, 4) *	4 (2, 5) *†	<0.0001

Data presented as mean (standard deviation), median (interquartile range) or number (percentage). BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

* p<0.05 compared to Group 1 by Tukey or Steel-Dwass test,

† p<0.05 compared to Group 2 by Tukey or Steel-Dwass test

Table 2:

Cardiac Structure, and Function Upright Exercise Capacity

	Overall Cohort	Group 1	Group 2	Group 3	
		Low H_2FPEF Probability <30	Intermediate H_2FPEF Probability 30–60	High H_2FPEF Probability >60	*p value*
Echocardiography	*n= 160*	*n=54*	*n=52*	*n=54*	
LVEDD, mm	47 ± 7	45 ± 6	47 ± 7	49 ± 5 *	0.02 **
LVMI, g/m^2	82 ± 21	75 ± 20	80 ± 15	88 ± 21 *	0.001 **
LVEF, %	62 ± 5	62 ± 5	63 ± 6	64 ± 4	0.19
LAVI, ml/m^2	29 ± 12	25 ± 11	29 ± 10	32 ± 14 *	0.01 **
E/e' ratio	11 ± 5	8 ± 4	11 ± 4 *	13 ± 7 *	<0.0001 **
LV e' (cm/s)	8.4 ± 2.4	10.0 ± 2.4	8.2 ± 1.9 *	7.0 ± 1.78 *	<0.0001 **
Est RVSP, mmHg	28 ± 7	25 ± 6	27 ± 6 *	33 ± 8 *	<0.0001 **
Noninvasive CPET	*n=95*	*n=34*	*n=34*	*n=27*	
Peak VO_2,, ml/min/kg	21.1 ± 6.0	23.0 ± 6.0	21.9 ± 4.4	17.9 ± 5.0 *†	0.0008 **
Peak RER	1.14 ± 0.10	1.17 ± 0.09	1.15 ± 0.09	1.10 ± 0.09 *	0.02 **
V_E/VCO_2 Slope	32 ± 5	31 ± 5	33 ± 5	32 ± 4	0.29

Data presented as mean (standard deviation), median (interquartile range) or number (percentage).

LVEDD, left ventricular end diastolic dimension; LVMI, left ventricular mass index; LVEF= left ventricular ejection fraction; LAVI= left atrial volume index; RVSP= right ventricular systolic pressure; CPET, cardiopulmonary exercise testing; VO_2, volume of oxygen consumed; RER, respiratory exchange ratio; V_E/VCO_2, ventilation/volume carbon dioxide produced

* p<0.05 compared to Group 1,

† p<0.05 compared to Group 2 by Tukey or Steel-Dwass test,

** comparison significant after adjusting for the number of comparisons in each Family of tests (echocardiography or CPET) using Holm's test.

Table 3:

Invasive Hemodynamics

	Overall Cohort	Group 1	Group 2	Group 3	
		Low H_2FPEF Probability <30	Intermediate H_2FPEF Probability 30–60	High H_2FPEF Probability >60	*p value*
	n=136	n=47	n=41	n=48	
Resting Vital Signs					
HR, bpm	67 ± 13	73 ± 13	62 ± 12 *	62 ± 13 *	<0.0001 **
SBP, mmHg	143 ± 25	127 ± 20	144 ± 28	152 ± 24 *†	0.001 **
DBP, mmHg	72 ± 11	69 ± 11	71 ± 10	72 ± 10	0.47
Resting Central Pressures					
RAP, mmHg	5 ± 3	5 ± 3	4 ± 2	6 ± 3 *†	0.001 **
PCWP, mmHg	9 ± 3	8 ± 3	8 ± 3	10 ± 3 *†	0.01 **
PASP, mmHg	28 ± 7	26 ± 7	28 ± 7	31 ± 6 *	0.0004 **
mPAP, mmHg	17 ± 4	15 ± 5	16 ± 4	19 ± 4 *†	<0.0001 **
Resting Arterial Afterload					
PVR, WU	1.7 ± 0.8	1.4 (0.8, 1.8)	1.7 (1.2, 2.2)	1.8 (1.3, 2.3) *	0.01 **
SVRI, DSC	2800 ± 760	2380 ± 710	2880 ± 610	3060 ± 810	0.004 **
EaI, mmHg.m^2/ml	3.2 ± 1.0	2.9 ± 0.9	3.2 ± 1.0	3.5 ± 1.1	0.11
Resting O_2 Transport					
Cardiac Index, L/min/m^2	2.8 ± 0.8	3.1 ± 0.9	2.7 ± 0.5 *	2.6 ± 0.9 *	0.009 **
C_{aO2}-C_{vO2}, mL/dL	4.1 ± 1.0	3.8 ± 0.90	4.3 ± 0.5 *	4.5 ± 0.9 *	0.001 **
Exercise Vital Signs					
HR, bpm	112 ± 26	124 ± 29	105 ± 23 *	105 ± 22 *	0.0002 **
SBP, mmHg	175 ± 39	156 ± 35	176 ± 38	189 ± 38 *	0.01 **
DBP, mmHg	76 ± 14	73 ± 14	76 ± 13	79 ± 14	0.24
Exercise Central Pressures					
RAP, mmHg	8 ± 5	7 ± 5	8 ± 5	9 ± 4	0.08
PCWP, mmHg	15 ± 5	13 ± 5	14 ± 5	17 ± 4 *†	0.0002 **
PASP, mmHg	43 ± 13	37 ± 12	44 ± 13	51 ± 9 *†	<0.0001 **
mPAP, mmHg	28 ± 8	23 ± 8	27 ± 7 *	33 ± 6 *†	<0.0001 **
Exercise Arterial Afterload					
PVR, WU	1.3 (0.9, 1.8)	0.9 (0.7, 1.4)	1.4 (0.9, 1.9)	1.6 * (1.2, 2.1)	<0.0001 **
SVRI, DSC	1717 ± 735	1300 ± 380	1790 ± 530	2120 ± 900 *	0.005 **
EaI, mmHg.m^2/ml	3.8 ± 1.4	3.0 ± 1.0	3.7 ± 1.6	4.4 ± 1.1 *	0.007 **
Exercise O_2 Transport					
Cardiac Index, L/min/m^2	5.4 ± 1.6	6.1 ± 1.5	5.3 ± 1.5 *	4.9 ± 1.5 *	0.004 **

	Overall Cohort	Group 1	Group 2	Group 3	
		Low H_2FPEF Probability <30	Intermediate H_2FPEF Probability 30–60	High H_2FPEF Probability >60	*p value*
	n=136	n=47	n=41	n=48	
C_{aO2}-C_{vO2}, mL/dL	9.4 ± 1.9	9.1 ± 1.6	10.3 ± 2.1 *	10.0 ± 2.1	0.03

Data presented as mean (standard deviation), median (interquartile range) or number (percentage).

RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; PASP, pulmonary arterial systolic pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; WU, Wood units; SVRI, systemic vascular resistance index; DSC, dyne*sec*m^2/cm^5; EaI, arterial elastance index; C_{aO2}-C_{vO2}, arteriovenous oxygen content difference.

* p<0.05 compared to Group 1,

† p<0.05 compared to Group 2 by Tukey or Steel-Dwass test,

** comparison significant after adjusting for the number of comparisons in each Family of tests (resting hemodynamics or exercise hemodynamics) using Holm's test.