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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

The Oxygen Cascade According to HFpEF Likelihood

A Focus on Sex Differences

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ABSTRACT

BACKGROUND Women are at greater risk for heart failure with preserved ejection fraction (HFpEF).

OBJECTIVES The aim of the study was to compare sex differences in the pathophysiology of exertional breathlessness in patients with high vs low HFpEF likelihood.

METHODS This cohort study evaluated consecutive patients (n = 1,936) with unexplained dyspnea using cardiopulmonary exercise testing and simultaneous echocardiography and quantified peak oxygen uptake (peak VO_2) and its determinants. HFpEF was considered likely when the H_2FPEF or HFA-PEFF score was ≥6 or ≥5, respectively. Sex differences were evaluated with the Student's *t*-test or Mann-Whitney *U* test and determinants of exercise capacity with a multivariable linear regression.

RESULTS The cohort included 1,963 patients (49% women and 28% [n = 555] with a high HFpEF likelihood). HFpEF likelihood did not impact the magnitude of sex differences in peak VO_2 and its determinants. Overall, women had lower peak VO_2 (mean difference −4.4 mL/kg/min [95% CI: −3.7 to −5.1 mL/kg/min]) secondary to a reduced O_2 delivery (−0.5 L/min [95% CI: −0.4 to −0.6 L/min]) and less oxygen extraction (−2.9 mL/dL [95% CI: −2.5 to −3.2 mL/dL]). Reduced O_2 delivery was due to lower hemoglobin (−1.2 g/dL [95% CI: −0.9 to −1.5 g/dL]) and smaller stroke volume (−15 mL [95% CI: −14 to −17 mL]). Women demonstrated increased mean pulmonary artery pressure/cardiac output slope (+0.5 mm Hg/L/min [95% CI: 0.3-0.7 mm Hg/L/min]) and left ventricular ejection fraction (+1% [95% CI: 1%-2%]), while they had smaller left ventricular end-diastolic volumes (−9 mL/m^2 [95% CI: −8 to −11 mL/m^2]) and mass (−12 g/m^2 [95% CI: −9 to −14 g/m^2]) and more often iron deficiency (55% vs 33%; $P < 0.001$).

CONCLUSIONS Women with unexplained dyspnea had significantly lower peak VO_2, regardless of HFpEF likelihood, attributed to both lower peak exercise O_2 delivery and extraction. This suggests that physiologic sex differences, and not HFpEF likelihood, are an important factor contributing to functional limitations in females with exertional breathlessness. (JACC Adv 2024;3:101039) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

a-vO_2diff = arteriovenous O_2 extraction

CaO_2 = arterial oxygen content

CO = cardiac output

DMO_2 = muscle oxygen diffusive conductance

FEV_1 = forced expiratory volume per second

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

mPAP = mean pulmonary artery pressure

SV = stroke volume

VO_2 = oxygen uptake

Reducing the burden of heart failure with preserved ejection fraction (HFpEF) poses a major health care challenge. The majority of patients affected by HFpEF are women.[1] Diagnosing HFpEF is complex, often arising from unexplained dyspnea requiring a complex series of evaluations to determine its underlying cause.[2-4] Despite improvements in diagnostic algorithms, many patients with exertional breathlessness remain uncategorized, especially in female cohorts.[2-4] By the time HFpEF is diagnosed, women experience lower exercise tolerance (peak oxygen uptake [VO_2]) than men, greater limitation of daily activities, and increased rates of frailty, leading to reduced quality of life.[5-7] Sex-specific differences in pathophysiology (eg, increased sensitivity to afterload) and response to therapies highlight the need to understand sex disparities, which have been underappreciated due to the underrepresentation of women in key trials.[8-10] Prior studies indicate that women with HFpEF have smaller ventricles, exaggerated increases in mean pulmonary artery pressures/cardiac output (mPAPs/CO), higher left ventricular (LV) afterload, and decreased peak exercise stroke volume (SV), CO, and skeletal muscle oxygen extraction.[8,9,11] However, the use of invasive hemodynamics measures limited these studies to small, selected cohorts, leaving uncertainty regarding sex disparities in larger, more diverse patient populations with symptoms suggestive of HFpEF. Moreover, similar sex-related differences in peak VO_2, cardiac structure, and cardiac function are also seen in healthy individuals,[1] making it unclear whether sex differences in exercise intolerance in individuals with or at risk for HFpEF reflect female physiology or sex-related differences in pathophysiology. Consequently, the mechanisms underpinning women's lower exercise tolerance across the continuum from unexplained dyspnea to HFpEF remain unclear.[1] To address this gap, our study aimed to comprehensively and noninvasively investigate sex differences in peak VO_2 and its Fick principle-derived determinants in patients with unexplained dyspnea according to differing HFpEF probabilities. We hypothesized that regardless of their diagnostic HFpEF scores, women would have reduced peak VO_2 due to impairments at multiple steps along the O_2 cascade, including decreased O_2 delivery and extraction.[12]

METHODS

STUDY DESIGN. This was a secondary analysis of an ongoing patient cohort study designed to investigate the clinical and physiological characteristics of patients referred to a multidisciplinary dyspnea clinic. The detailed study design and methodology, and primary outcomes discussing the utility of this clinic for evaluation of HFpEF and unexplained dyspnea have been published previously.[13,14] The study obtained approval from the local ethics committee (JESSA ethische toetsingcommissie, 2022/014).

STUDY SAMPLE. We analyzed consecutive patients referred to a dedicated dyspnea clinic (Jessa Ziekenhuis, Hasselt, Belgium) between January 2016 and December 2022 who presented with exertional dyspnea or fatigue (Supplemental Figure 1). Patients with a LV ejection fraction <50% or HFpEF mimickers (pericardial disease, congenital heart disease, high-output heart failure, and infiltrative, restrictive, or hypertrophic cardiomyopathy) were excluded.[4,14] Additionally, patients with more than mild established pulmonary disease or significant valve lesions (including any mitral stenosis, more than mild primary mitral regurgitation, more than mild aortic regurgitation, more than moderate aortic stenosis and severe tricuspid and functional mitral regurgitation) were excluded.

DYSPNEA CLINIC PROTOCOL. The dyspnea clinic utilized a standardized work-up as previously described, including clinical evaluation and chart review, laboratory testing, spirometry test, transthoracic echocardiography, 12-lead electrocardiogram at rest, and cardiopulmonary exercise test combined with exercise echocardiography (CPET*echo*).[14] The spirometry yielded the forced expiratory volume per second (FEV_1) over forced vital capacity. Maximal voluntary ventilation was calculated as the FEV_1 multiplied by 40. Breathing reserve was calculated by measuring the ratio of peak ventilation to estimated maximal voluntary ventilation. Iron deficiency was defined as ferritin <100 μg/L and transferrin saturation <20% with ferritin 100 to 300 μg/L.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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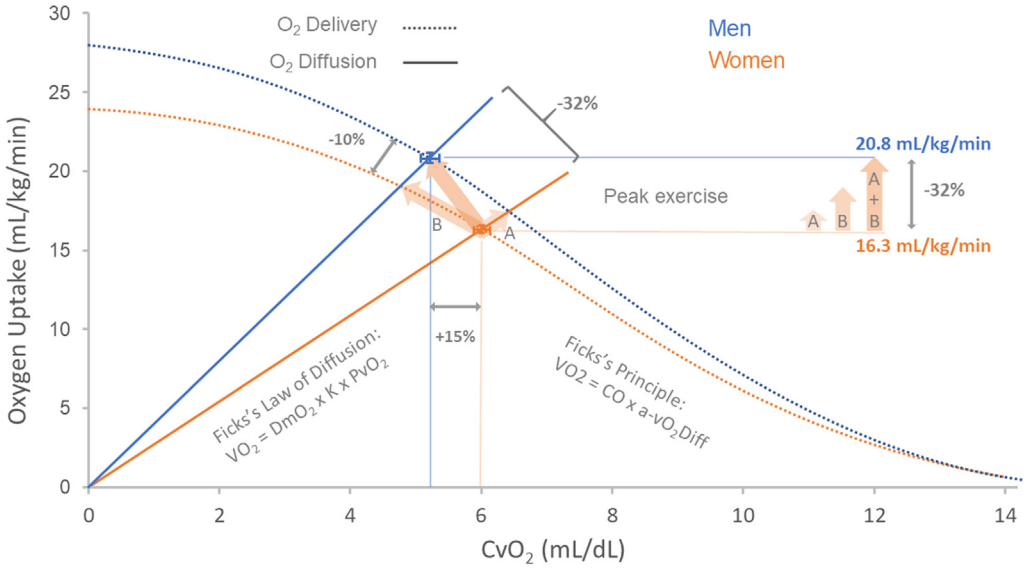
FIGURE 1 Noninvasive Wagner Diagram



The interplay between O_2 delivery (dotted line) and O_2 diffusion (solid lines) in females and males with unexplained dyspnea. Fick Principle and law of diffusion determinants of peak VO_2 for males vs females (Peak VO_2: 20.8 in males vs 16.3 mL/kg/min in females; 32% lower in females) are represented by a modified the Wagner diagram. The average non-invasive estimation of CvO_2 on the x-axis was 15% higher in females (6.0 vs 5.2 mL/dL), while O_2 delivery (peak CaO_2 x peak CO) corrected for body weight was 10% lower in females (23.9 vs 26.5 mL/kg/min). The Fick's diffusion law slope (estimated muscle diffusive oxygen conductance, $DmO_2 = VO_2 \div CvO_2$) line is 32% lower in females. Estimated DmO_2 reflected O_2 diffusion and utilization more accurately than CvO_2 or a-vO_2Diff since DmO_2 corrects for the shorter capillary transit time associated with the higher cardiac output in males. Arrow A shows the hypothetical effect of increasing female O_2 delivery to the male level with a constant O_2 diffusion (DmO_2 slope). CvO_2 would increase (and avO_2Diff decrease) because of a shorter capillary transit time, and VO_2 would increase marginally. Only a combined optimization of O_2 delivery and DmO_2 (arrow A + B) up to the level of males would allow females to reach equivalent male values for peak VO_2. CvO_2 = peak mixed venous O_2 content ($CaVO_2$ - a-vO_2Diff); CaO_2 =peak arterial O_2 content (hemoglobin × 1.34 × peak SpO_2); a-vO_2Diff = peak arterio-venous difference in O_2 content (peak $VO_2 \div$ peak cardiac output); DmO_2 = estimated O_2 diffusion from capillary to mitochondria ($VO_2 \div CvO_2$); O_2 delivery = cardiac output x SpO_2 × hemoglobin × 1.34.

Cardiopulmonary exercise test with exercise echocardiography. All patients underwent a maximal, symptom-limited, semi-supine bicycle test with simultaneous continuous respiratory gas analysis and echocardiography (ie, CPET*echo*) using a ramp protocol (5-20 W/min) designed for the patient to achieve an exercise duration of 8 to 10 min.[14-17] The protocol was personalized to the patient's age, weight, and functional class by dividing the maximal load during a previous upright exercise test by 10 (rounded down). Breath-by-breath VO_2, carbon dioxide production, tidal volume, and respiratory rate were continuously recorded. Patients were monitored with a 12-lead electrocardiogram, pulse oximetry for peripheral capillary O_2 saturation, and cuff blood pressure throughout exercise and recovery. Echocardiographic views and Doppler samples were obtained at rest, intermediate and peak exercise, as previously described.[18] Briefly, the load was kept constant when passing the first ventilatory threshold but always with a heart rate <100 beats/min until the intermediate exercise set of echocardiographic measures were obtained (for 2-3 minutes). Then, the ramp protocol was continued until exhaustion. Shortly before reaching peak exercise (onset of severe symptoms, aiming for a respiratory exchange ratio >1.10), the load was kept constant (for a shorter time; 0-1 minutes) for the second time to obtain the peak exercise data set. The mPAP/CO slope was calculated as previously described and validated by invasive exercise hemodynamics.[18]

HFA-PEFF and H_2FPEF scores to determine HFpEF likelihood. A positive HFpEF score was defined as a total HFA-PEFF score ≥5 or a H_2FPEF ≥6. A positive diastolic stress test added 3 or 2 points to the total HFA-PEFF score, whether or not the tricuspid regurgitation velocity during exercise was >3.4 m/s. Agitated colloid (1-3 mL) was routinely injected intravenously, as described previously, to improve feasibility and accuracy of the tricuspid regurgitant velocity measurement (Supplemental Figure 2).[18]

FICK PRINCIPLE DETERMINANTS OF PEAK VO_2. The Fick components comprised CO and arteriovenous O_2 extraction (a-vO_2diff). SV was estimated by the time velocity integral of the flow at the left ventricular outflow tract multiplied by the surface area or 0.785 × aortic annulus diameter.[2] CO was calculated as: SV × heart rate. Oxygen delivery was calculated as: CO × arterial O_2 content (CaO_2) (calculated as hemoglobin × arterial O_2 saturation × 1.34). Peak a-vO_2diff was determined as peak exercise VO_2 divided by CO. Arteriovenous O_2 extraction values are reported unadjusted and adjusted for hemoglobin concentration, while muscle O_2 diffusive conductance (DmO_2) was estimated noninvasively as previously described and illustrated in **Figure 1**.[19-21] In brief, mixed venous O_2 content was calculated as CaO_2-a-vO_2diff. Estimated DmO_2 was then calculated as peak VO_2-venous O_2 content. Resting arterial elastance was calculated as 0.9 × systolic blood pressure x SV, while LV stiffness was calculated as: E/e′ ÷ LVEDV (LV end-diastolic volume).[22]

STATISTICAL ANALYSIS. Females and males were compared in the: 1) total cohort; and 2) according to HFpEF likelihood (positive or negative HFpEF score). Continuous variables were expressed as the mean ± SD for normally distributed data or median (IQR) for non-normally distributed data. Categorical data were expressed as numbers and percentages and compared with the Pearson chi-square test or Fisher's exact test when appropriate. Continuous variables in 2 groups were compared with the Student's *t*-test or Mann-Whitney *U* test, while ANOVA with post hoc testing (Tukey test) was used for more than 2 groups (males vs females across HFpEF likelihood groups). Mean differences were reported with 95% CIs. Univariable and multivariable linear regression was employed to identify the association between age, sex and Fick determinants (hemoglobin, peak exercise SV, heart rate, arterial O_2 saturation, and a-vO_2diff) with cycling power-to-weight ratio (as an alternative to peak VO_2, as a-vO_2diff values are directly calculated from peak VO_2 and therefore violate the assumption of independence) and peak VO_2. Multicollinearity was tested with the variance inflation factor. Statistical significance was defined as at a 2-tailed probability level of <0.05. All statistics were performed using Jamovi (version 2.3).

RESULTS

COHORT CHARACTERISTICS. The final cohort included 1,963 patients with unexplained dyspnea (mean age: 64 ± 15 years; n = 951, 49% women; mean BMI: 27 ± 5 kg/m^2, 22% obese) (**Tables 1 and 2**). Average peak VO_2 was 18.6 ± 8.6 mL/kg/min (77% ± 23% predicted), hemoglobin of 13.8 ± 1.5 g/dL, and a median N-terminal prohormone B-type natriuretic peptide of 130 (52-300) ng/L. Mean FEV_1 over forced vital capacity was 0.80 ± 0.13, and their FEV_1 was 83% ± 22% of the predicted. FEV_1 was similar between sexes (P = 0.13), but women had a higher ratio of forced FEV_1/forced vital capacity (Tiffenau index, P < 0.001) and were less likely to be active or former smokers than men (P = 0.003 for both). Both the median (IQR) HFA-PEFF score (including the points attributed by exercise echocardiography) and H_2FPEF score were 2 (1-4). HFpEF was likely in 29% of patients (n = 555) based on a positive HFA-PEFF or H_2FPEF score, with a significantly higher proportion of females (34%, n = 321) compared to males (24%, n = 234) from the total cohort classified with a positive HFpEF score (P = 0.001). The use of negative inotropic drugs was comparable in males and females.

SEX DIFFERENCES IN PEAK VO_2 AND ITS DETERMINANTS IN THE TOTAL COHORT PRESENTING WITH UNEXPLAINED DYSPNEA. Women with unexplained dyspnea had a lower peak VO_2 and cycling power-to-weight ratio than men with unexplained dyspnea (16.3 ± 7.1 mL/kg/min vs 20.8 ± 9.3 mL/kg/min; 1.2 ± 0.7 W/kg vs 1.6 ± 0.9 W/kg, P < 0.001 for both) (**Central Illustration**, **Tables 1 and 2**, Supplemental Figure 3). The lower peak VO_2 was associated with reduced O_2 delivery (1.7 ± 0.6 L/min vs 2.2 ± 0.8 L/min, P < 0.001) and a-vO_2diff (11.5 ± 3.0 mL/dL vs 14.3 ± 4.0 mL/dL, P < 0.001). Regarding O_2 delivery, women had lower hemoglobin (13.2 ± 1.2 g/dL vs 14.4 ± 1.6 g/dL, P < 0.001) and peak exercise CO (9.8 ± 2.9 L/min vs 11.8 ± 3.6 L/min, P < 0.001). Furthermore, their lower peak exercise CO was due to a smaller SV (78 ± 17 mL/beat vs 93 ± 21 mL/beat, P < 0.001) as peak heart rate was similar between groups (126 ± 25 beats/min vs 127 ± 23 beats/min, P = 0.52). Women had a smaller peak SV even when indexed for body size (44 ± 9 mL/m2 vs 47 ± 11 mL/m^2, P < 0.001). Finally, in addition to a lower hemoglobin concentration, the reduced a-vO2diff in women in the total cohort was mediated by a lower DmO_2 (**Figure 1**). Results were similar when excluding patients in atrial fibrillation at the time of testing (n = 56; 3% of the total cohort), as well as those with a history of atrial fibrillation (n = 315, 16% of the total cohort).

SEX DIFFERENCES IN INDIVIDUALS WITH A POSITIVE HFpEF SCORE. Similar sex differences were observed in patients with both low and high HFpEF scores as in the total cohort (**Central Illustration**, **Figure 2**, **Table 3**). In 28% of the total cohort (n = 555), HFpEF was considered likely, with a higher proportion (58%)

TABLE 1 Total Unexplained Dyspnea Group: Sex Differences in Demographics

	N	Total (N = 1,936, 100%)	Females (n = 951, 49%)	Males (n = 985, 51%)	Mean Difference (95% CI)	*P* Value
Age, y	1,936	64 ± 15	65 ± 14	63 ± 15	2 (1-3)	0.003
Height, cm	1,936	170 ± 10	163 ± 7	175 ± 8	−13 (−12 to −14)	<0.001
Weight, kg	1,936	77 ± 15	71 ± 14	83 ± 14	−12 (−13 to −11)	<0.001
Body surface area, m^2	1,936	1.9 ± 0.2	1.8 ± 0.2	2.0 ± 0.2	−0.2 (−0.2 to −0.3)	<0.001
Body mass index, kg/m	1,936	27 ± 5	27 ± 5	27 ± 4	-	0.731
Obesity (BMI >30 kg/m^2)	1,936	430 (22)	240 (25)	190 (19)	-	0.002
Atrial fibrillation	1,936	329 (17)	146 (15)	178 (18)	-	0.109
Diabetes mellitus	1,932	247 (13)	109 (11)	138 (14)	-	0.093
Hypertension	1,936	856 (44)	428 (45)	428 (43)	-	0.491
Negative chronotropic drug	1,652	444 (47)	403 (48)	374 (46)	-	0.370
Respiratory characteristics						
Smoking active	676	65 (10)	30 (8)	35 (13)	-	0.003
Smoking former	676	135 (20)	69 (17)	66 (24)	-	0.003
FEV_1/FVC	1,782	0.80 ± 0.13	0.82 ± 12	0.78 ± 14	0.04 (0.02-0.05)	<0.001
FEV_1, %	1,787	83 ± 22	84 ± 21	82 ± 22	2 (4-0)	0.129
HFpEF scores						
H_2FPEF score	1,936	2 (1-4)	3 (1-4)	2 (1-4)	-	0.075
Logistic H_2FPEF score	1,936	42 (24-70)	44 (26-74)	39 (22-67)	-	0.001
HFA-PEFF score	1,936	2 (1-4)	2 (1-5)	2 (1-4)	-	<0.001
Positive HFpEF score[a]	1,936	555 (29)	321 (34)	234 (24)	-	0.001
Positive HFA-PEFF score	1,936	468 (24)	278 (29)	190 (19)	-	<0.001
Positive H_2FPEF score	1,936	219 (11)	120 (13)	99 (10)	-	0.07
Laboratory results						
NT-proBNP, ng/L	1,118	130 (52-300)	150 (68-310)	100 (50-258)		<0.001
eGFR CKD-EPI, mL/min/1.73 m^2	1,517	78 ± 23	76 ± 22	80 ± 23	−4 (−2 to −6)	<0.001
HBA1c, %	1,034	5.8 ± 0.7	5.7 ± 0.7	5.8 ± 0.8	−0.1 (0 to −0.2)	0.035

Values are mean ± SD, n (%), or median (IQR). *P* values for post hoc group comparison female vs male. [a]A positive HFpEF score was defined as a total HFA-PEFF score ≥5 or a H_2FPEF ≥6. A negative HFpEF score was defined as a total HFA-PEFF score <5 or a H_2FPEF <6.

BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; GFR = estimated glomerular filtration rate calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; H2FPEF = (Heavy; Hypertensive; atrial Fibrillation; Pulmonary hypertension; Elder; Filling pressure) score; HbA1c = glycated hemoglobin; HFA-PEHFA-PEFF = Heart Failure Association Pretest probability Echocardiography, Functional testing, Final diagnosis; NT-proBNP = N-terminal prohormone B-type natriuretic peptide.

with a positive HFpEF score being women. Patients with a positive HFpEF score (H_2FPEF score ≥6 or HFA-PEFF score ≥5 points) had lower peak VO_2 and its determining Fick principle components than those with a negative HFpEF score (Figure 2). Compared to men with a positive HFpEF score, women with a positive HFpEF score had lower peak exercise a-vO_2diff, CO, SV, and hemoglobin. Peak heart rate and O_2 saturation showed no significant differences. Like in the total cohort, women with a positive HFpEF score had worse exercise tolerance (peak VO_2 13.1 ± 4.1 mL/kg/min vs 15.9 ± 5.5 mL/kg/min, $P < 0.001$) and significant limitations in both central (CO: −1.5 ± 0.5 L/min, $P < 0.001$; SV: −13 ± 3 mL, $P < 0.001$; mPAP/CO slope: +0.4 ± 0.4 mm Hg/L/min, $P = 0.016$) and peripheral Fick components (a-VO_2diff: −1.9 ± 0.6 mL/dL, $P < 0.001$, hemoglobin: −0.8 ± 0.3 g/dL, $P < 0.001$) compared to men with a positive HFpEF score. Oxygen delivery remained significantly lower in females with a positive HFpEF score even when indexed for body size (cardiac index −0.3 ± 0.2 L/min/m^2, $P = 0.009$, and indexed SV −3 ± 2 mL/m^2, $P = 0.002$). Despite having similar if not higher LV ejection fraction at rest and peak exercise, females with a positive HFpEF score had a smaller LVEDV and mass, even when corrected for body size, and a higher ratio of left atrial to LV volume than males with a positive HFpEF score. The elevated mPAP/CO slope was unlikely to be due to a difference in pulmonary vascular resistance, as this did not coincide with meaningful differences in O_2 saturation or ventilatory efficiency. Notably, women with a positive HFpEF score had the lowest values for peak VO_2, CO, and O_2 delivery from all groups (compared to females with a negative HFpEF score, and males with a positive or negative HFpEf score).

SEX DIFFERENCES IN INDIVIDUALS WITH NEGATIVE HFpEF SCORES. Patients with negative HFpEF scores were younger and, more frequently, men (Table 3). However, women with a negative HFpEF score

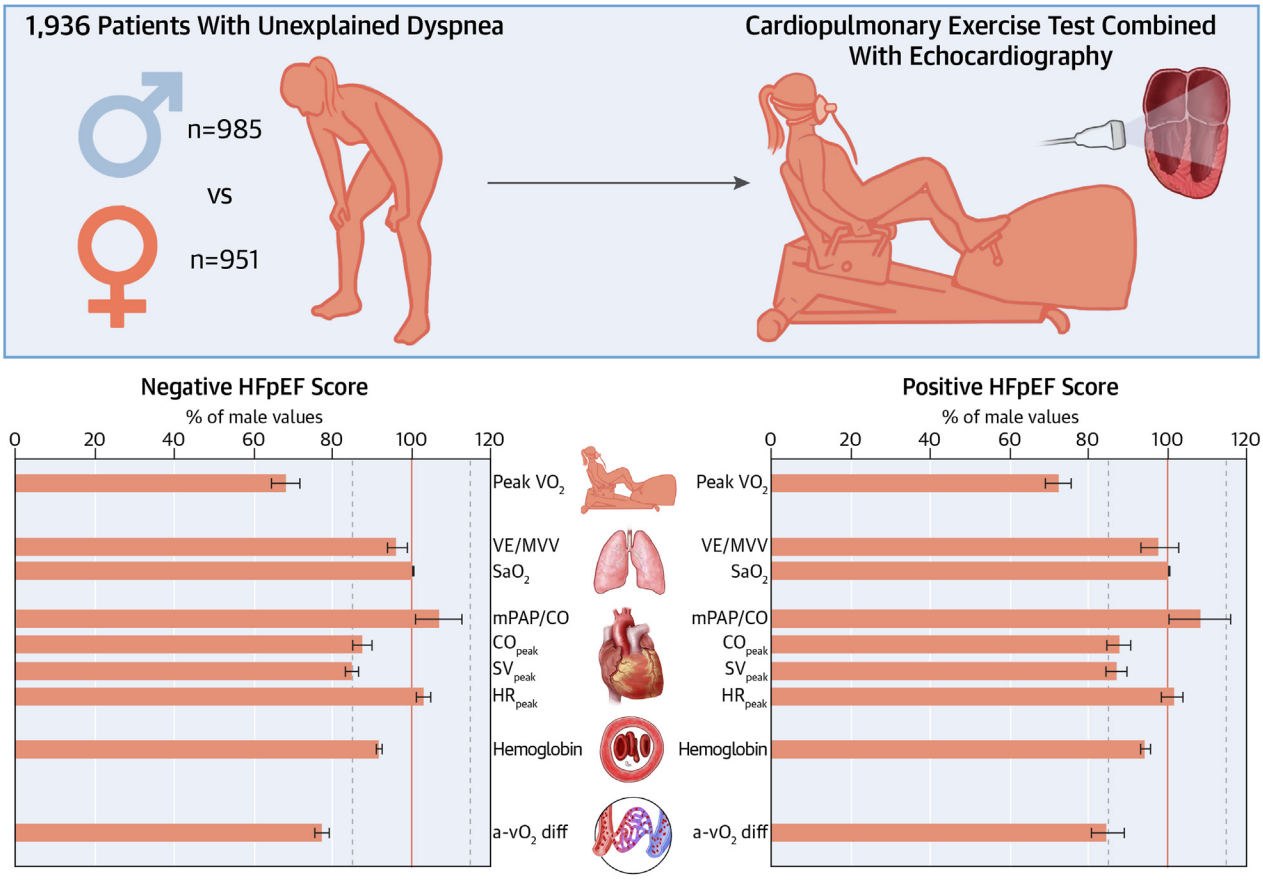
TABLE 2 Total Unexplained Dyspnea Group: Sex Differences in Rest and Peak Exercise Values

	N	Total (N = 1,936, 100%)	Females (n = 951, 49%)	Males (n = 985, 51%)	Mean Difference (95% CI)	*P* Value
Exercise capacity						
Respiratory exchange ratio (RER)	1,807	1.11 ± 0.11	1.10 ± 0.11	1.11 ± 0.11	−0.02 (−0.01 to −0.03)	<0.001
Load/weight, W/kg	1,869	1.4 ± 0.8	1.2 ± 0.7	1.6 ± 0.9	−0.4 (−0.3 to −0.5)	<0.001
Peak VO_2, mL/kg/min	1,837	18.6 ± 8.6	16.3 ± 7.1	20.8 ± 9.3	−4.4 (−3.7 to −5.1)	<0.001
Peak VO_2 (Wasserman), % pred	1,837	72 ± 23	75 ± 22	71 ± 23	+4 (2-6)	<0.001
Peak VO_2 peak (Gläser), % pred	1,829	77 ± 23	77 ± 23	77 ± 23	-	0.70
Cardiac morphology						
LA volume index, mL/m^2	1,739	25 ± 11	25 ± 12	24 ± 11	+1 (2-0)	0.20
End-systolic LA/LV volume, %	1,421	149 ± 100	178 ± 104	131 ± 93	+37 (−27 to 47)	<0.001
LV end-diastolic volume index rest, mL/m	1,478	51 ± 16	46 ± 13	55 ± 16	−9 (−8 to −10)	<0.001
LV mass index, g/m^2	1,728	83 ± 26	78 ± 31	90 ± 37	−12 (−9 to −14)	<0.001
Relative wall thickness	1,739	0.43 (0.37-0.51)	0.43 (0.36-0.51)	0.43 (0.38-0.51)		0.07
Diastolic LV internal diameter, mm	1,743	45 ± 7	43 ± 6	47 ± 7	−4 (−3 to −4)	<0.001
RV end-diastolic area, cm^2	1,504	18 ± 5	16 ± 5	20 ± 5	−4 (−4 to −5)	<0.001
Rest and exercise cardiac function						
LA booster function by LACI (mL/s/m/cm)	1,128	3.4 (2.2-5.1)	3.5 (2.3-5.3)	3.2 (2.2-5.0)		0.08
MAPSE rest, mm	797	10 ± 3	9 ± 3	10 ± 3	−1 (−1 to −2)	<0.001
MAPSE peak, mm	780	13 ± 3	12 ± 3	14 ± 3	−2 (−2 to −3)	<0.001
Arterial elastance rest (Ea), mm Hg/mL	1,845	2.0 ± 0.5	2.1 ± 0.6	1.8 ± 0.5	0.2 (0.2-0.3)	<0.001
E/e' rest	1,912	11 ± 5	12 ± 5	10 ± 4	+2 (1-2)	<0.001
E/e' intermediate exercise	1,902	11 ± 5	12 ± 5	11 ± 4	+1. (1-2)	<0.001
LV stiffness (E/e'/LVEDV), mL^{-1}	1,864	0.13 ± 0.08	0.16 ± 0.09	0.10 ± 0.06	+0.06 (0.05-0.07)	<0.001
mPAP/CO slope, mm Hg/L/min	1,936	3.0 ± 2.0	3.2 ± 2.1	2.8 ± 1.7	+0.5 (0.3-0.7)	<0.001
exTRV, m/s	1,934	3.4 ± 0.4	3.4 ± 0.3	3.4 ± 0.4	−0 (0 to −0.1)	0.003
RVFAC, %	1,002	48 ± 11	50 ± 11	47 ± 11	3 (2-4)	<0.001
TAPSE, mm	973	17.0 ± 5.5	16.8 ± 5.4	17.9 ± 5.2	−1.1 (−1.8 to 0.5)	<0.001
TAPSE/sPAP, mm/mm Hg	973	0.83 ± 0.68	0.82 ± 0.63	0.92 ± 0.82	−0.10 (−0.20 to −0.01)	0.024
RVESPAR, mm Hg/cm^2	1,004	2.9 ± 1.4	3.3 ± 1.5	2.4 ± 1.1	0.9 (0.8-1.1)	<0.001
LV end-diastolic volume index peak, mL/m^2	1,846	51 ± 15	46 ± 13	56 ± 16	−9 (−8 to −11)	<0.001
LV ejection fraction rest, %[2]	1,883	62 ± 8	63 ± 8	62 ± 8	+1 (1-2)	<0.001
LV ejection fraction peak, %	1,423	69 ± 10	69 ± 10	68 ± 10	+1 (2 to −0)	0.20
Stroke volume index rest, mL/m^2	1,935	37 ± 9	37 ± 9	38 ± 10	−1 (0 to −2)	0.10
Stroke volume index peak, mL/m^2	1,936	45 ± 10	44 ± 9	47 ± 11	−3 (−2 to −4)	<0.001
Stroke volume peak, mL	1,936	86 ± 21	78 ± 17	93 ± 21	−15 (−14 to −17)	<0.001
Heart rate peak, beats/min	1,936	127 ± 25	126 ± 25	127 ± 23	−1 (2 to −3)	0.518
Heart rate reserve, %	1,936	65 ± 24	65 ± 25	66 ± 23	-	0.50
Cardiac output peak, L/min	1,936	10.9 ± 3.4	9.8 ± 2.9	11.8 ± 3.6	−2.0 (−1.7 to −2.3)	<0.001
Oxygen delivery, L/min	1,495	1.9 ± 0.7	1.7 ± 0.6	2.2 ± 0.8	−0.5 (−0.4 to −0.6)	<0.001
Cardiac index peak, L/min/m^2	1,827	5.8 ± 1.8	5.6 ± 1.7	5.9 ± 1.9	−0.4 (−0.2 to −0.5)	<0.001
Noncardiac factors						
a-vO2Diff, mL/dL	1,822	12.9 ± 3.8	11.5 ± 3.0	14.3 ± 4.0	−2.9 (−2.5 to −3.2)	<0.001
a-vO2Diff/Hb	1,542	0.93 ± 0.27	0.87 ± 0.23	1.01 ± 0.28	−0.14 (−0.11 to −0.17)	<0.001
Cardiac output/VO_2 slope	1,835	5.6 ± 2.1	6.1 ± 2.2	5.2 ± 2.0	+0.9 (0.8-1.1)	<0.001
Mixed venous saturation, %	1,484	27 ± 20	32 ± 17	22 ± 20	+11 (9-13)	<0.001
Hemoglobin, g/dL	1,574	13.8 ± 1.5	13.2 ± 1.2	14.4 ± 1.6	−1.2 (−1.0 to −1.3)	<0.001
Transferrin saturation, %	1,201	27 ± 12	26 ± 12	29 ± 13	−4 (−3 to −5)	<0.001
Iron deficiency	1,219	541 (44)	349 (55)	192 (33)		<0.001
Ve/MVV	1,793	0.60	0.60 ± 0.18	0.60 ± 0.20	-	0.30
SpO_2	1,777	98 (96-99)	98 (96-99)	97 (96-98)	+0 (0-1)	0.001

Values are mean ± SD, median (IQR), or n (%). *P* values for post hoc group comparison female vs male.

CO/VO2a-vO_2Diff/Hb = peak arteriovenous difference in oxygen content corrected for hemoglobin; Ea = arterial elastance (0.9. systolic blood pressure ÷ stroke volume); E/e' = ratio of early diastolic blood flow (E) over septal annular velocity (e'); exTRV = maximal tricuspid regurgitation velocity during exercise; LA = left atrium; LACI = left atrial volumetric/mechanical coupling index = indexed max left atrial volume ÷ late diastolic mitral annular velocity', (mL/s/m/cm); LV = left ventricle; MAPSE = mitral annular plane systolic excursion; mPAP/CO slope = mean pulmonary artery pressure over cardiac output slope; RVESPAR = right ventricular end-systolic pressure area ratio; RVFAC = right ventricular fractional area change; sPAP = systolic pulmonary artery pressure; SpO_2 = exercise saturation by pulse oximetry; TAPSE = tricuspid annular plane systolic excursion; Ve/MVV = peak ventilation over maximal voluntary ventilation; VO_2 = oxygen uptake.

CENTRAL ILLUSTRATION **Sex Differences Across the Oxygen Cascade in Patients With Unexplained Dyspnea: Negative vs Positive HFpEF Scores**

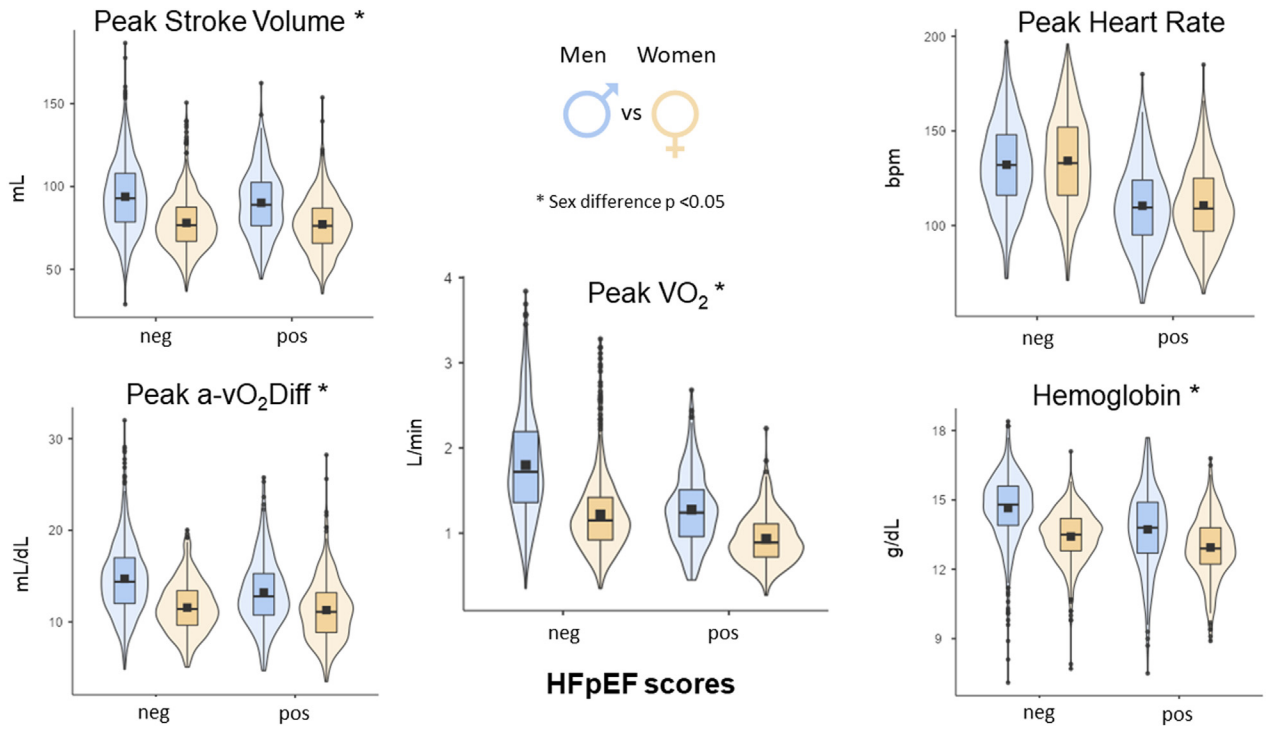


Verwerft J, et al. JACC Adv. 2024;3(7):101039.

HFpEF = heart failure with preserved ejection fraction.

exhibited lower peak VO_2 (−4.3 ± 0.9 mL/kg/min, $P < 0.001$) (Figure 2), peak exercise CO (−1.9 ± 0.4 L/min, $P < 0.001$), SV (−16 ± 2 mL, $P < 0.001$), hemoglobin (−1.3 ± 0.2 g/dL, $P < 0.001$), and a-vO_2diff (−3.1 ± 0.4 mL/dL, $P < 0.001$), compared to men with negative HFpEF scores (Figure 2). The sex difference in mean peak VO_2, whether absolute or bodyweight-indexed, was even larger at a lower HFpEF probability (according to the logistic H_2FPEF score described in the Supplemental Methods and Supplemental Figure 4) ($P < 0.001$ for interaction). Like those with a positive HFpEF score, women with negative HFpEF scores had smaller hearts (indexed lower LVEDV and LV mass) and higher resting LV stiffness, arterial elastance and mPAP/CO slope than men with a negative HFpEF score (Table 3) ($P < 0.05$ for all). Women with a negative HFpEF score also had significantly lower transferrin saturation and were more likely iron deficient (53% vs 31%, $P < 0.001$). Notably, despite being, on average, 12 years younger, women with negative HFpEF scores had a lower peak exercise SV (−12 ± 3 mL, $P < 0.001$), hemoglobin (−0.3 ± 0.25 g/dL, $P = 0.003$), and a-vO_2diff (−1.6 ± 0.5 mL/dL, $P < 0.001$) than men with a positive HFpEF score (Figure 2). However, their peak heart rate was higher (+24 ± 3 beats, $P < 0.001$), resulting in a comparable O_2 delivery and peak VO_2 to men with a positive HFpEF score. Women with negative HFpEF scores had indexed SV (−1.6 ± 1.5 mL/m^2) as low as men with a positive HFpEF score. However, when corrected for their 12 ± 2 kg lower body weight, their peak VO_2 was 2.2 ± 1.0 mL/kg/min higher than men with a positive HFpEF score ($P < 0.001$).

FIGURE 2 Violin Plots With Sex Differences in VO_2 and its Determinants in 555 Patients With a Positive (H_2FPEF ≥6 or HFA-PEFF ≥5) vs 1,381 With a Negative HFpEF Score



Oxygen uptake (VO_2) (central), and the Fick components determining VO_2: peak stroke volume (upper left), peak heart rate (upper right), hemoglobin (lower right), and peak oxygen extraction (a-vO_2difference) (lower left) Females without HFpEF (according to the HFpEF scores) have a lower average peak VO_2, stroke volume, oxygen extraction and hemoglobin than males with HFpEF, while their heart rate is higher. HFpEF = heart failure with preserved ejection fraction.

WHICH FICK COMPONENTS EXPLAIN THE SEX DIFFERENCE IN EXERCISE CAPACITY? Age, sex, and all Fick variables were significant univariable predictors of exercise capacity (power-to-weight ratio). In a multivariable linear regression analysis predicting cycling power-to-weight ratio (W/kg), age and the following Fick components emerged as independent predictors of power-to-weight ratio (in descending order of importance): peak heart rate, a-vO_2diff, and SV (standardized estimates: −0.211 [age] and 0.462; 0.382; 0.324). In contrast, arterial O_2 saturation and, importantly, sex were not independent predictors of the power-to-weight ratio in this multivariable model (**Table 4**, Supplemental Figure 5). Furthermore, hemoglobin was weakly and even negatively correlated with power-to-weight ratio in this model (standardized estimate −0.037). As male and female HR were similar, a-vO2diff and SV are the modifiable Fick components accounting for the sex difference in cycling power-to-weight ratio. Peak SV and a-vO2diff remained independent predictors of power-to-weight ratio even when correcting for HFpEF probability (either as a binary outcome or when considered as the logistic H_2FPEF score described in the Supplemental Methods). Similar results were obtained when replacing SV by indexed SV as the independent variable, or by replacing power-to-weight ratio with peak VO_2 as the dependent variable: SV and a-vO_2diff consistently explained the sex difference in exercise capacity. HFpEF score (positive or negative) was not a significant, independent predictor of peak VO_2 or power-to-weight ratio in the multivariable model (standardized estimate: 0.04, $P = 0.22$). Collinearity between SV with a-vO_2diff was acceptable (variance inflation factor: 1.53 and 1.54) both in the model predicting VO_2 and power-to-weight ratio.

DISCUSSION

To our knowledge, this is the largest cohort study investigating sex differences in peak VO_2 and its Fick principle determinants among patients with unexplained dyspnea undergoing evaluation for HFpEF. The study found that women exhibited lower peak

TABLE 3 Sex Differences: Negative vs Positive HFpEF Scores[a]

	Negative HFpEF Score		Positive HFpEF Score	
	Females (n = 630, 46%)	Males (n = 751, 54%)	Females (n = 321, 58%)	Males (n = 234, 42%)
Age, y	61 ± 15	60 ± 15	73 ± 8	73 ± 9
Height, cm	164 ± 7	177 ± 8[b]	161 ± 6	173 ± 7[b]
Weight, kg	70 ± 14	84 ± 14[b]	72 ± 14	82 ± 14[b]
Body surface area, m^2	1.8 ± 0.2	2.0 ± 0.2[b]	1.8 ± 0.2	2.0 ± 0.2[b]
Body mass index, kg/m	26 ± 5	27 ± 4[b]	28 ± 6	27 ± 4
Fat mass index (fat mass/body weight)	0.35 ± 0.08	0.27 ± 0.06[b]	0.38 ± 0.08	0.28 ± 0.06[b]
Atrial fibrillation	23 (3)	68 (9)[b]	123 (38)	110 (47)
Diabetes mellitus	65 (10)	99 (13)	44 (14)	39 (17)
Hypertension	213 (34)	263 (35)	215 (67)	165 (70)
NT-proBNP, ng/L	130 (50-170)	90 (25-130)[b]	310 (190-520)	350 (150-480)
Exercise capacity				
Respiratory exchange ratio (RER)	1.10 ± 0.11	1.11 ± 0.11	1.08 ± 0.11	1.11 ± 0.10[b]
Load/weight, W/kg	1.3 ± 0.7	1.7 ± 0.9[b]	0.8 ± 0.4	1.1 ± 0.5[b]
Peak VO_2, mL/kg/min	18.1 ± 7.8	22.2 ± 9.7[b]	13.1 ± 4.1	15.9 ± 5.5[b]
Peak VO_2, (Wasserman), % pred	78 ± 23	73 ± 23[b]	68 ± 20	63 ± 20[b]
Peak VO_2 (Gläser), % pred	81 ± 24	80 ± 23	69 ± 18	71 ± 21[b]
Cardiac morphology				
LA volume index, mL/m^2	21 ± 8	21 ± 9	32 ± 14	33 ± 12
End-systolic LA/LV volume, %	143 ± 82	113 ± 64[b]	212 ± 122	183 ± 134[b]
LV end-diastolic volume index rest, mL/m^2	47 ± 13	56 ± 16[b]	45 ± 13	55 ± 15[b]
LV mass index, g/m^2	72 ± 20	85 ± 24[b]	87 ± 28	101 ± 28[b]
Relative wall thickness	0.41 (0.35-0.48)	0.43 (0.37-0.50)	0.46 (0.40-0.56)	0.46 (0.39-0.56)
Diastolic LV internal diameter, mm	43 ± 6	47 ± 7[b]	43 ± 6	47 ± 7[b]
RV end-diastolic area, cm^2	16 ± 5	20 ± 6	16 ± 4	20 ± 5
Rest and exercise cardiac function				
LA booster function by LACI (mL/s/m/cm)	3.0 (2.1-4.1)	3.0 (2.0-4.3)	3.5 (2.3-5.3)	3.2 (2.2-5.0)
MAPSE rest, mm	9 ± 3	10 ± 3[b]	8 ± 3	9 ± 3[b]
MAPSE peak, mm	13 ± 3	15 ± 3[b]	11 ± 3	12 ± 3[b]
Arterial elastance rest (Ea), mm Hg/mL	2.0 ± 0.6	1.8 ± 0.5[b]	2.1 ± 0.6	1.8 ± 0.5[b]
E/e' rest	10 ± 3	9 ± 3[b]	16 ± 7	14 ± 6[b]
LV stiffness (E/e'/LVEDV), mL^{-1}	0.13 ± 0.06	0.09 ± 0.04[b]	0.21 ± 0.12	0.15 ± 0.07[b]
E/e' intermediate exercise	10 ± 3	9 ± 2[b]	16 ± 6	15 ± 5
mPAP/CO slope, mm Hg/L/min	2.7 ± 1.7	2.5 ± 1.5[b]	4.3 ± 2.1	3.9 ± 1.7[b]
exTRV, m/s	3.3 ± 0.3	3.4 ± 0.4[b]	3.5 ± 0.3	3.6 ± 0.4
LV end-diastolic volume index peak	47 ± 13	56 ± 16[b]	46 ± 12	56 ± 17[b]
LV ejection fraction rest, %	63 ± 8	62 ± 8[b]	63 ± 8	62 ± 8[b]
LV ejection fraction peak, %	69 ± 10	69 ± 10	69 ± 11	67 ± 10[b]
Stroke volume index rest, mL/m^2	37 ± 8	37 ± 10	37 ± 9	39 ± 11[b]
Stroke volume index peak, mL/m^2	44 ± 9	47 ± 11[b]	43 ± 11	46 ± 11[b]
Stroke volume peak, mL	78 ± 17	94 ± 22[b]	77 ± 17	90 ± 20[b]
Heart rate peak, beats/min	134 ± 24	132 ± 23	111 ± 21	110 ± 22
Cardiac output peak, L/min	10.5 ± 3.0	12.4 ± 3.6[b]	8.5 ± 2.2	10.0 ± 2.9[b]
Cardiac index peak, $L/min/m^2$	6.0 ± 1.7	6.2 ± 1.9[b]	4.8 ± 1.2	5.1 ± 1.5[b]
Heart rate reserve, %	71 ± 23	69 ± 22	54 ± 24	55 ± 25
Oxygen delivery, L/min	1.9 ± 0.6	2.4 ± 0.7[b]	1.4 ± 0.4	1.8 ± 0.6[b]

Continued on the next page

VO_2 due to both reduced O_2 delivery and extraction than men. Women displayed these oxygen cascade differences regardless whether their HFpEF scores were positive or negative. Women had lower peak exercise O_2 delivery primarily due to a blunted peak exercise SV, which was associated with smaller, stiffer hearts, and greater afterload. This highlights an important contribution of female physiology to the greater functional limitations in women with unexplained dyspnea undergoing evaluation for HFpEF.

Few studies have examined sex differences in peak VO_2 and its determinants in individuals with unexplained dyspnea with or without HFpEF.[8,9,11,12,17,21,23] We confirmed previous findings, demonstrating that females with a positive HFpEF score have smaller stiffer hearts, higher afterload, and lower peak VO_2,

TABLE 3 Continued

	Negative HFpEF Score		Positive HFpEF Score	
	Females (n = 630, 46%)	Males (n = 751, 54%)	Females (n = 321, 58%)	Males (n = 234, 42%)
Noncardiac factors				
a-vO$_2$Diff, mL/dL	11.6 ± 2.8	14.7 ± 4.0[b]	11.3 ± 3.6	13.2 ± 3.5[b]
a-vO$_2$Diff/Hb	0.86 ± 0.21	1.02 ± 0.27[b]	0.88 ± 0.26	0.97 ± 0.30[b]
CO/VO$_2$ slope	6.2 ± 2.1	5.2 ± 1.9[b]	5.9 ± 2.4	5.3 ± 2.3[b]
Mixed venous saturation, %	33 ± 16	21 ± 20[b]	31 ± 17	24 ± 16[b]
Hemoglobin, g/dL	13.4 ± 1.1	14.7 ± 1.5[b]	12.9 ± 1.4	13.7 ± 1.7[b]
Transferrin saturation, %	26 ± 9	30 ± 12[b]	24 ± 10	26 ± 11
Iron deficiency	202 (53)	130 (31)[b]	147 (58)	62 (37)[b]
Ve/MVV	0.60 ± 17	0.60 ± 0.21	0.59 ± 0.21	0.61 ± 0.16
SpO$_2$, %	98 (96-99)	97 (96-98)[b]	97 (96-98)	98 (95-98)

Values are mean ± SD, n (%), or median (IQR). [a]A positive HFpEF score was defined as a total HFA-PEFF score ≥5 or a H$_2$FPEF ≥6. A negative HFpEF score was defined as a total HFA-PEFF score <5 or a H$_2$FPEF <6. [b]*P* values <0.05 for post hoc group comparison female vs male.

a-vO2Diff/Hb = arteriovenous difference in oxygen content corrected for hemoglobin; CO/VO$_2$ slope = cardiac output/oxygen uptake slope; Ea = arterial elastance (0.9. systolic blood pressure ÷ stroke volume); E/e' = ratio of early diastolic blood flow (E) over septal annular velocity (e'); exTRV = maximal tricuspid regurgitation velocity during exercise; LA = left atrium; LACI = left atrial volumetric/mechanical coupling index = indexed max left atrial volume ÷ late diastolic mitral annular velocity', (mL/s/m/cm); LV = left ventricle; LVEDV = LV end-diastolic volume; MAPSE = mitral annular plane systolic excursion; mPAP/CO slope = mean pulmonary artery pressure over cardiac output slope; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; SpO2 = exercise saturation by pulse oximetry; VO$_2$ = oxygen uptake.

CO, SV, hemoglobin, and a-vO$_2$diff compared to males with HFpEF. Our study expands these findings by using a noninvasive, clinically feasible approach with assessments performed in the semi-supine posture (as opposed to supine measures performed in several previous invasive studies).[11,24] Additionally, we observed similar sex differences in the O$_2$ pathway of individuals with unexplained dyspnea not fulfilling noninvasive diagnostic HFpEF criteria. Notably, women also had more often iron deficiency, possibly contributing to their lower a-vO$_2$diff. This provides important context, by highlighting that the greater functional limitation reported in women with HFpEF may be primarily a result of sex-related physiological differences that precede the development of overt HFpEF, that combine in an additive way to the HFpEF specific contributions to reduced peak VO$_2$. Indeed, the relationship between HFpEF probability and peak VO$_2$ is shifted downward and to the left in women (Supplemental Figure 4): Women have a lower exercise capacity for a given HFpEF probability threshold and they cross a given peak VO$_2$ threshold at a lower HFpEF likelihood.

TABLE 4 Multivariable Linear Regression for Predicting Cycling Power-to-Weight Ratio by Fick Components Adjusted for Age and Sex

	Estimate	SE	*P* Value	Stand. Estimate
Age	−0.01140	0.00112	1.79e0-23	−0.2112
O$_2$ saturation	−0.00372	0.00453	0.4117	−0.0129
Hemoglobin (g/dL)	−0.01872	0.00887	0.0351	−0.0367
Heart rate peak	0.01426	6.07e-4	2.17e-103	0.4624
Stroke volume peak	0.01278	7.18e-4	4.33e0-64	0.3236
Oxygen extraction peak	0.07711	0.00385	1.01e0-78	0.3817
Female-male	0.01531	0.03087	0.6199	0.0196

In addition to functional limitations, our results suggest there may be some sex-related factors that also contribute to greater burden of HFpEF-like features in women. A critical observation was that compared to men, women with or without a positive HFpEF score had smaller hearts—measured as lower LVEDV and LV mass, adjusted for body size, with the worst values seen in women with a positive HFpEF score. This finding aligns with a previous study, showing that women consistently exhibit smaller ventricular volumes and mass throughout adulthood.[25] However, there is growing recognition that these differences in LVEDV contribute to decreased exercise tolerance and an increased risk of HFpEF in women.[26,27] Resting and exercise cardiac magnetic resonance imaging studies have shown a strong association between resting LVEDV and peak VO$_2$ in ostensibly healthy middle-aged women, with individuals in the smallest LVEDV quartile exhibiting the smallest resting and peak exercise SV and CO, with limited ability to decrease LV end-systolic volume during exercise.[26] Additionally, in patients with HFpEF, those with smaller resting LVEDV and higher ejection fraction—mostly women—had increased LV diastolic stiffness.[28] Our observations of a higher mPAP/CO slope and decreased peak CO (in the absence of differences in pulmonary vascular resistance) in women regardless of HFpEF scores are consistent with these previous findings, suggesting that the smaller female heart is stiffer and exhibits decreased capacity to augment CO during exercise, contributing to lower O$_2$ transport and peak VO$_2$. Notably, the lower hemoglobin concentration in women was also an important contributor to their decreased O$_2$ delivery. Therefore,

addressing the lower hemoglobin (and related factors such as iron deficiency) may be a more feasible strategy to address much of the sex-related deficit in O_2 delivery and peak VO_2 than trying to improve the function of an aged, stiff cardiovascular system that has lost much of its plasticity.

There is also growing awareness of the importance of noncardiac factors to limitations in peak VO_2 in both individuals with and without HFpEF. Indeed, Lau et al[8] reported noncardiac factors contribute to impaired exercise tolerance in female HFpEF patients, with peak exercise a-vO_2diff being 14% lower in female patients than in males. We confirm and extend this finding by demonstrating that compared to men, women have a significantly lower a-vO_2diff due to the combination of a lower CaO_2 (secondary to lower hemoglobin) and also a lower DmO_2, representing the transport of O_2 from microvasculature to skeletal muscle mitochondria (**Figure 1**). Solely increasing convective O_2 delivery up to the value seen in men would increase peak VO_2 to a lower extent compared to what would occur by increasing DmO_2 without altering O_2 delivery (**Figure 1**). The mechanisms underlying the lower DmO_2 in women remain uncertain; however, they may result from a decreased capillary-to-fiber ratio and mitochondrial oxidative capacity shown by reduced aerobic enzyme activity.[29] Therefore, targeting skeletal muscle microvasculature and mitochondria with therapies such as exercise training may be a crucial therapeutic target to improve peak VO_2 in women at risk for or with HFpEF.[30] Whether emerging HFpEF therapies such as glucagon-like peptide 1 agonists and sodium glucose cotransporter protein 2 inhibitors can also influence these factors is also an intriguing question.[31]

CLINICAL IMPLICATIONS. Exercise deficiency or a blunted response to exercise training in women throughout the lifespan may explain their cardiac and noncardiac impairments, emphasizing the need for exercise programs tailored to and focused on enrolling women with or at risk for HFpEF. Indeed, exercise training is one of the few therapies that has established beneficial effects on the peripheral components of the O_2 cascade in individuals with HFpEF.[32,33] Alternatively, current diagnostic and therapeutic strategies do not adequately address the key variables differentiating men and women either at risk for or with probable HFpEF, highlighting the value of additional phenotypic information provided by diagnostic approaches used in this study. Considering the involvement of central and peripheral steps in the O_2 cascade, future interventions targeting exercise limitation in women should aim to improve both O_2 delivery and utilization.

STUDY LIMITATIONS. Aside from the inherent limitations and biases of an observational single-center study, invasive hemodynamic measures of filling pressures and hemodynamics at rest and exercise were not included. However, our large study cohort represents the patient population and diagnostic work-up encountered in daily clinical practice. Likewise, DmO_2, arterial elastance, and LV stiffness were estimated noninvasively, and therefore simplifications of their invasive counterparts. The assumptions made by the noninvasive methods are, however, less a limitation when evaluating group differences than absolute values. Moreover, all sex differences unveiled noninvasively in the HFpEF group concur with the findings from smaller invasive HFpEF cohorts,[8,9,11] supporting the validity of the differences identified in the group with negative HFpEF scores. Finally, a relatively modest proportion of our cohort met the criteria for a positive HFpEF score (28% of the total cohort). However, due to the total size of our cohort, this still represents one of the largest studies of individuals with HFpEF that includes detailed measurement of the O2 cascade.

CONCLUSIONS

Women with unexplained dyspnea displayed lower exercise tolerance related to central and peripheral deficits in their O_2 cascade, regardless of HFpEF likelihood based on diagnostic scores. Smaller ventricular size, increased LV-arterial stiffness, and compromised peripheral vascular-muscle function together may contribute to the vulnerability of women to develop HFpEF and exercise limitations.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: We noninvasively evaluated the sex differences in Fick-derived determinants of peak VO_2 in a large cohort of patients with exertional dyspnea using combined cardiopulmonary exercise testing and echocardiographic CO estimates.

COMPETENCY IN MEDICAL KNOWLEDGE: Combined exercise echocardiography and respiratory gas analysis, evaluating the entire oxygen cascade, demonstrated sex differences established by invasive cardiopulmonary exercise testing in HFpEF. Sex differences in these parameters were identical in patients with low or high HFpEF scores. Women had smaller and stiffer hearts with increased afterload, resulting in reduced SV and CO reserve. These factors, combined with lower hemoglobin and peripheral oxygen diffusion, contributed to a diminished peak exercise oxygen delivery, extraction, and exercise capacity.

TRANSLATIONAL OUTLOOK: Exercise deficiency or a blunted response to exercise in women may explain cardiac and noncardiac impairments, emphasizing the need for exercise programs tailored to and focused on enrolling women with HFpEF and unexplained dyspnea without a high HFpEF likelihood scores. Future interventions targeting exercise limitation in women should aim to improve both O_2 delivery and utilization.

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APPENDIX For supplemental methods and figures, please see the online version of this paper.