Am J Physiol Heart Circ Physiol 329: H1126–H1136, 2025.
First published September 30, 2025; doi:10.1152/ajpheart.00587.2025

american physiological society

AMERICAN JOURNAL OF PHYSIOLOGY
HEART AND CIRCULATORY PHYSIOLOGY

RESEARCH ARTICLE

Integrative Cardiovascular Physiology and Pathophysiology

Mechanisms of exercise limitation in heart failure with preserved ejection fraction and obesity: a case of engine-chassis mismatch

Stephen J. Foulkes,[1,2]* Sara Moura-Ferreira,[3,4]* Mauricio Milani,[3,5] Youri Bekhuis,[3,4,6,7] Maarten Falter,[2,3,4] Boris Delpire,[3,4,6,7] Rik Pauwels,[3,4,6,7] Sarah Stroobants,[3] Siddharth Jogani,[3] Simon Vanhentenrijk,[3,8] Sibel Altintas,[3] Ruta Jasaityte,[3] Jan Stassen,[3] Lieven Herbots,[3,4] Guido Claessen,[3,4] Mark J. Haykowsky,[1]* and Jan Verwerft[3,4]*

[1]*Integrated Cardiovascular Exercise Physiology and Rehabilitation (iCARE) Lab, College of Health Sciences, University of Alberta, Edmonton, Alberta, Canada;* [2]*Heart, Exercise and Research Trials (HEART) Lab, St Vincent's Institute of Medical Research, Fitzroy, Melbourne, Australia;* [3]*Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium;* [4]*Faculty of Medicine and Life Sciences, University of Hasselt, Hasselt, Belgium;* [5]*Faculty of Rehabilitation Sciences, University of Hasselt, Hasselt, Belgium;* [6]*Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium;* [7]*Department of Cardiology, University Hospitals Leuven, Leuven, Belgium; and* [8]*Kaufman Center for Heart Failure Treatment and Recovery, Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, United States*

Abstract

Obesity is a major risk factor for heart failure with preserved ejection fraction (HFpEF), but its impact on limitations in peak oxygen uptake ($\dot{V}O_{2peak}$) and its Fick determinants remains unclear. We assessed these factors in patients with obesity and patients without obesity with HFpEF, and non-HFpEF controls. Patients with HFpEF were subgrouped by body mass index [body mass index (BMI) $\geq$ 30 or $<$ 30 kg/m^2] into HFpEF with ($HFpEF_{Obese}$, $n = 139$) or without obesity ($HFpEF_{Nonobese}$, $n = 317$), and non-HFpEF controls (CON, $n = 270$). Cardiopulmonary exercise testing with simultaneous echocardiography assessed $\dot{V}O_{2peak}$, cardiac output (CO), stroke volume (SV), heart rate (HR), mean pulmonary artery pressure (mPAP) dynamics, and arterio-venous oxygen difference (a-vO_2diff). $HFpEF_{Obese}$ tended to have higher absolute $\dot{V}O_{2peak}$ (+7%, $P = 0.069$), and significantly higher peak exercise CO and SV, with no differences in HR or a-vO_2diff. Resting and exercise mPAP and mPAP/CO slopes did not differ between HFpEF obesity phenotypes. In contrast, bodyweight-indexed $\dot{V}O_{2peak}$ was markedly lower in $HFpEF_{Obese}$ (−23%) despite comparable indexed peak CO and SV. Regardless of HFpEF subgroup, $\dot{V}O_{2peak}$, central (CO, HR, mPAP) and peripheral factors (a-vO_2diff) were markedly impaired in HFpEF versus CON ($P < 0.05$ for all). Therefore, although patients with $HFpEF_{Obese}$ have preserved absolute $\dot{V}O_{2peak}$ and cardiac reserve, bodyweight-indexing reveals that these adaptations are insufficient for the heightened metabolic and functional demands induced by obesity. Alternatively, several physiological HFpEF features are not exacerbated by obesity. This highlights the importance of incorporating weight loss alongside multicomponent therapeutic strategies to address exercise intolerance in HFpEF.

NEW & NOTEWORTHY Patients with obesity with heart failure with preserved ejection fraction (HFpEF) have larger hearts and preserved cardiac reserve, but this was insufficient to maintain bodyweight-indexed $\dot{V}O_{2peak}$ at comparable levels to patients without obesity. Obesity did not exacerbate other HFpEF impairments, such as decreased oxygen extraction or elevated pulmonary pressures. This suggests weight loss may help to improve exercise intolerance in obese patients with HFpEF, but should be combined with other treatments to target all of the features that contribute to exercise intolerance in HFpEF.

cardiac reserve; exercise echocardiography; HFpEF; obesity; oxygen uptake

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a multifaceted syndrome characterized by a complex interplay of cardiac and noncardiac impairments, reduced exercise tolerance, and increased risk of cardiovascular and all-cause mortality (1, 2). The burden of comorbidities in HFpEF directly contributes to and worsens the inherent exercise limitations experienced by these individuals (1–3). The high prevalence of obesity among individuals with HFpEF (~50%

*S. J. Foulkes and S. Moura-Ferreira contributed equally to this work. M. J. Haykowsky and J. Verwerft contributed equally to this work.
Correspondence: S. J. Foulkes (foulkes@ualberta.ca).
Submitted 1 August 2025 / Revised 3 September 2025 / Accepted 23 September 2025

0363-6135/25 Copyright © 2025 The Authors. Licensed under Creative Commons Attribution CC-BY 4.0.
Published by the American Physiological Society.

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

with class I obesity or higher) underscores its significance as both a major risk factor and a common comorbidity (3, 4), associated with decreased quality of life, decreased functional performance, and increased disability (4–7). However, studies investigating the impact of obesity on exercise tolerance (as objectively measured by peak oxygen uptake, $\dot{V}O_{2peak}$) and the underlying HFpEF pathophysiology report conflicting results (7–10), likely due to the relatively small sample sizes in studies performed to date, varied use of weight (un)adjusted values, and body position during exercise assessments (i.e., upright vs. supine). Understanding the impact of obesity on $\dot{V}O_{2peak}$ and the oxygen cascade in HFpEF will be critical for individualized treatment of obese individuals with HFpEF. This is particularly relevant with the emerging evidence from (non)pharmacologic weight-loss targeted therapies in obese patients with HFpEF such as caloric restriction (11), bariatric surgery, glucagon-like peptide-1 (GLP-1) (12) agonists, and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (13, 14) that show promising effects on clinical outcomes such as mortality and physical function. Yet their impact on impairments in $\dot{V}O_{2peak}$ and its determinants [a major driver of symptom burden in HFpEF (6)] remains unclear.

The aim of this study was to determine the impact of obesity [defined as body mass index (BMI) $\geq$30 kg/m^2] on $\dot{V}O_{2peak}$ and its Fick determinants [i.e., cardiac output, CO, and arteriovenous oxygen content difference (a-vO_{2diff})] in adults with HFpEF using comprehensive oxygen cascade analysis derived from combined cardiopulmonary exercise testing and echocardiography (CPETecho) assessment. We hypothesized that HFpEF plus obesity ($HFpEF_{Obese}$) would be associated with superior absolute $\dot{V}O_{2peak}$ and hemodynamic values but these same measures would be significantly lower than in nonobese individuals with HFpEF ($HFpEF_{Nonobese}$) when indexed to body mass or body surface area (BSA). We also hypothesize that regardless of obesity status, patients with HFpEF will have significant deficits in $\dot{V}O_{2peak}$ and its Fick determinants relative to non-HFpEF controls (CON).

METHODS

Study Design and Population

This is a secondary analysis from an ongoing patient cohort study investigating the physiologic and clinical determinants and outcomes of patients referred to a multidisciplinary dyspnea clinic from October 2015 to April 2023 (Jessa Hospital, Hasselt, Belgium) (15). The detailed dyspnea clinic diagnostic evaluation protocol has been described previously (15, 16). In brief, patients underwent clinical evaluation, chart review, spirometry, blood-based laboratory testing, resting transthoracic echocardiography, 12-lead electrocardiogram, and CPETecho assessments.

A diagnosis of HFpEF was made if patients had a resting left-ventricular ejection fraction >50%, and met predefined cutoff scores suggestive of HFpEF using either the Heart Failure Association Pretest probability, Echocardiography, Functional testing, and Final diagnosis (HFA-PEFF) score (17) or the H2FPEF score (18) (Heavy; Hypertensive; Atrial Fibrillation; Pulmonary hypertension; Elder; Filling pressure). A score of $\geq$5 on the HFA-PEFF scale or $\geq$6 on the H2FPEF scale indicated a diagnosis of HFpEF, in the absence of HFpEF mimickers such as pericardial disease, congenital heart disease, high-output heart failure or idiopathic, restrictive or hypertrophic cardiomyopathy. Patients with more than mild primary valve disease and more than mild pulmonary disease were also excluded. Patients were then subgrouped according to BMI into obese HFpEF ($HFpEF_{Obese}$; HFpEF + BMI $\geq$ 30 kg/m^2) or nonobese ($HFpEF_{Nonobese}$; HFpEF + BMI $<$ 30 kg/m^2). We also included an additional comparator group of control participants from the clinic database without HFpEF (CON). Inclusion criteria for CON were *1*) aged >50 yr (the minimum age of the HFpEF cohort), *2*) HFA-PEFF score $\leq$1 and/or H2FPEF score $\leq$3, and *3*) no history of atrial fibrillation, or significant cardiac, valvular or pulmonary disease.

Clinical Assessment

A detailed clinical examination and chart review was performed by a certified cardiologist and pulmonologist to derive participant demographic information and document medical history, comorbidities, and medications. A peripheral venous blood sample was drawn for the assessment of N-terminal of pro-hormone B-type natriuretic peptide (NT-proBNP), total blood counts (including hemoglobin concentration), iron, transferrin saturation, ferritin, serum creatinine, and glycated hemoglobin (HbA1c).

Spirometry Assessment

A seated spirometry assessment was completed to measure forced vital capacity, forced expiratory volume in one second, and their ratio and to rule out participants with overt pulmonary disease as a source of their unexplained dyspnea. Maximal voluntary ventilation was calculated as the forced expiratory volume in one second $\times$ 40.

Resting Transthoracic Echocardiography and 12-Lead ECG

A comprehensive resting echocardiographic assessment was performed in a semirecumbent position (on the semirecumbent cycle prior to the CPETecho) by experienced sonographers using a Vivid E9 or E95 ultrasound machine (General Electric Healthcare, Chicago, IL). All analyses were performed offline on EchoPAC (v.203, General Electric Healthcare, Chicago, IL) using two-dimensional (2-D), Doppler, and tissue Doppler datasets in accordance with current guidelines (19, 20).

Combined Cardiopulmonary Exercise Testing and Exercise Echocardiography

Participants underwent a maximal cardiopulmonary exercise test to volitional fatigue on an electromagnetically braked semisupine cycle ergometer at a 45° tilt with concurrent metabolic gas analysis and transthoracic echocardiography. Breath-by-breath values for oxygen uptake, carbon dioxide, minute ventilation, tidal volume, and respiratory frequency were recorded throughout the test, with continuous monitoring of heart rate (HR) and rhythm from 12-lead electrocardiography and arterial oxygen saturation from pulse oximetry. Echocardiographic datasets were obtained

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

at rest (outlined earlier), intermediate exercise, defined by first ventilatory threshold, and peak exercise.

Following acquisition of the full resting dataset, participants cycled continuously (>60 revolutions per minute) against increasing resistance using an incremental ramp protocol (5–20 W/min) individualized to their clinical and demographic characteristics with the aim of reaching peak effort within 8–15 min. Once participants reached their first ventilatory threshold (or a heart rate of ~90–100 beats/min) the resistance was kept constant for ~2–3 min to acquire the intermediate exercise echocardiographic data set. The ramp protocol was then continued until participants were near exhaustion (peak respiratory exchange ratio of ~1.10 and/or onset of severe symptoms) where the load was again held constant for a short time (~1 min) to obtain the peak exercise echocardiographic dataset. Participants then continued cycling (if possible) to volitional fatigue.

The Fick determinants of $\dot{V}O_{2peak}$ included cardiac output (CO) and the arteriovenous oxygen content difference (a-vO_{2diff}). Cardiac output was also compartmentalized into its components [i.e., stroke volume (SV) and HR]. Stroke volume was quantified using Doppler echocardiography from the time velocity integral from flow measurement at the left ventricular outflow tract, multiplied by 0.785 × aortic diameter^2. The a-vO_{2diff} was then calculated in accordance with the Fick equation as $\dot{V}O_{2peak} \div CO$, and is reported unadjusted, and adjusted for hemoglobin concentration. Oxygen delivery was calculated as peak CO multiplied by arterial oxygen content (1.34 × hemoglobin concentration × arterial oxygen saturation). Mean pulmonary arterial pressure (mPAP) was derived from the maximal pressure gradient of the tricuspid regurgitant velocity (or the right ventricular-to-right atrial gradient) using the Chemla formula (0.61 × tricuspid regurgitant gradient + 2) without incorporating a right atrial pressure estimate (21). Agitated colloid (1–3 mL) was administered intravenously at rest, intermediate, and peak exercise stages to enhance the accuracy and feasibility of exercise tricuspid regurgitant gradient (22, 23). The exercise gradient envelope with the clearest and most defined profile was selected for analysis. In addition, gradient profiles were carefully reviewed for artifacts, such as linear noise signals caused by transit-time effects, which were excluded from analysis. We have previously validated the accuracy of this contrast-enhanced approach against CO and mPAP derived from invasive hemodynamics and real-time magnetic resonance imaging (22). We have also documented excellent inter- and intrarater agreement for deriving peak exercise CO (intraclass correlation coefficient, ICC: 0.917 and 0.937) and mPAP (ICC: 0.878 and 0.948) using this approach (24).

Individual linear regression using the resting, intermediate, and peak exercise mPAP and CO datapoints was used to derive the mPAP/CO slope. Cardiac volumes and $\dot{V}O_{2peak}$ were reported unadjusted and adjusted for BSA or bodyweight, respectively.

Statistical Analysis

Statistics were performed using Jamovi v2.4.1.1—an R-based platform retrieved from https://www.jamovi.org. Normally distributed variables are reported as means ± SD or mean [95% confidence interval (95% CI)], with nonnormally distributed variables reported as median (25th and 75th percentile), and categorical variables reported as frequencies (%). Group characteristics were compared using one-way ANOVA with Tukey's post hoc correction (normally distributed continuous variables), Kruskal–Wallis test (nonnormally distributed continuous or ordinal variables) or χ^2 test (categorical variables). Subsequent analyses of $\dot{V}O_{2peak}$ and its determinants, as well as other phenotypic HFpEF variables, were performed using analysis of covariance (ANCOVA) with adjustment for age, sex, hypertension, and diabetes, and additional post hoc analyses were performed with Tukey correction. Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Overall, 456 consecutive patients with HFpEF and 270 CON who underwent CPETecho assessment were included in this analysis. A comprehensive summary of these demographic and clinical characteristics is provided in Table 1. Within the HFpEF group, 317 (70%) patients with normal or overweight BMI were classified as nonobese ($HFpEF_{Nonobese}$, BMI: 25.0 ± 2.9 kg/m^2) and 139 (30%) as obese ($HFpEF_{Obese}$, BMI: 34.1 ± 3.5 kg/m^2). There was a similar proportion of females in $HFpEF_{Obese}$ and $HFpEF_{Nonobese}$ groups. The $HFpEF_{Obese}$ group was slightly younger, had lower NT-proBNP, and marginally lower resting left-ventricular ejection fraction (60 ± 8% vs. 63 ± 9%, $P = 0.012$), with higher rates of hypertension and diabetes. Both groups had comparable rates of iron deficiency, transferrin saturation, and prevalence of atrial fibrillation. In contrast, compared with both HFpEF groups, the CON group ($n = 270$) was younger and had fewer females, lower rates of hypertension and iron deficiency, better kidney and lung function, and lower NT-proBNP. BMI, HbA1c, and prevalence of diabetes were similar in CON and $HFpEF_{Nonobese}$ groups.

$\dot{V}O_{2peak}$ and Its Fick Determinants in HFpEF according to Obesity Status

Peak exercise responses and Fick determinants are reported in Table 2 and Fig. 1, *A–H*, respectively. All groups showed comparable peak exercise effort during CPETecho (peak respiratory exchange ratio; $HFpEF_{Nonobese}$: 1.09 ± 0.12 vs. $HFpEF_{Obese}$: 1.09 ± 0.10, CON: 1.10 ± 0.09, $P = 0.70$). $HFpEF_{Obese}$ had a trend to higher absolute $\dot{V}O_{2peak}$ values than $HFpEF_{Nonobese}$ (+7%, $P = 0.069$; Fig. 1*A*) secondary to higher peak CO (+7%, $P = 0.013$; Fig. 1*B*), SV (+8%, $P < 0.001$; Fig. 1*C*), and, subsequently, oxygen delivery (+9%, $P = 0.009$; Table 2), as values for peak exercise HR (Fig. 1*D*, $P = 0.45$) and a-vO_{2diff} (Fig. 1*E*, $P = 0.74$) were comparable between the two groups. In contrast, indexing values to body mass or BSA either reversed or negated the absolute differences between obese and nonobese HFpEF groups. Specifically, $\dot{V}O_{2peak}$ indexed to bodyweight was significantly lower in $HFpEF_{Obese}$ than $HFpEF_{Nonobese}$ (−23%, $P < 0.001$; Fig. 1*F*), with a trend for lower cardiac index (CI; −6%, $P = 0.057$; Fig. 1*G*) and SV index (SVi; −6%, $P = 0.084$; Fig. 1*H*). Despite their tendency for higher absolute $\dot{V}O_{2peak}$, $HFpEF_{Obese}$ had comparable peak power output to $HFpEF_{Nonobese}$ (70 ± 32 W vs. 68 ± 31 W, $P = 0.46$).

Overall, compared with CON, patients with HFpEF had markedly reduced $\dot{V}O_{2peak}$ (absolute and indexed; 24%–38%

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

Table 1. *Demographic and clinical characteristics of included participants*

Characteristic	Controls	$HFpEF_{Nonobese}$	$HFpEF_{Obese}$	*P* Value
Number of patients	270	317	139	
Female, *n* (%)	136 (51%)	193 (61%)†	90 (65%)†	0.006
Age, yr	65 ± 7	74 ± 8†	72 ± 9†*	<0.001
Height, cm	170 ± 10	166 ± 9†	164 ± 9†	<0.001
Weight, kg	77.9 ± 14.8	69.3 ± 10.8†	92.0 ± 12.2†*	<0.001
Body surface area, m^2	1.90 ± 0.21	1.78 ± 0.18†	2.04 ± 0.18†*	<0.001
Body mass index, kg/m^2	26.9 ± 4.4	25.0 ± 2.9†	34.1 ± 3.5†*	<0.001
Coronary artery disease, *n* (%)	21 (8%)	65 (21%)†	29 (21%)†	<0.001
Atrial fibrillation, *n* (%)	0 (0%)	145 (46%)†	77 (55%)†	<0.001
Diabetes mellitus, *n* (%)	38 (14%)	36 (11%)	34 (25%)†*	<0.001
Hypertension, *n* (%)	105 (39%)	215 (68%)†	111 (80%)†*	<0.001
Systolic blood pressure, mmHg	140 ± 19	145 ± 22†	146 ± 24†	0.015
Diastolic blood pressure, mmHg	82 ± 11	78 ± 14†	80 ± 16	0.002
Medications				
Beta-blocker, *n* (%)	63 (23%)	164 (52%)†	83 (60%)†	<0.001
ACE-I or ARB, *n* (%)	85 (31%)	126 (40%)†	70 (50%)†*	<0.001
MRA, *n* (%)	16 (6%)	86 (27%)†	36 (26%)†	<0.001
Calcium channel blocker, *n* (%)	38 (14%)	56 (19%)	27 (19%)	0.32
Loop diuretic, *n* (%)	16 (6%)	65 (21%)†	35 (25%)†	<0.001
Thiazide diuretic, *n* (%)	28 (10%)	48 (15%)	36 (26%)†*	<0.001
Statin, *n* (%)	110 (41%)	161 (51%)†	77 (55%)†	0.008
Ezetimibe, *n* (%)	19 (7%)	10 (3%)†	15 (11%)*	0.005
GLP1-RA, *n* (%)	0 (0%)	0 (0%)	2 (1%)	0.09
SGLT-2i	6 (2%)	2 (1%)	6 (4%)*	0.024
Metformin, *n* (%)	20 (7%)	16 (5%)	25 (18%)†*	<0.001
FEV_1/FVC	0.84 ± 0.06	0.79 ± 0.12†	0.82 ± 0.14	<0.001
FEV_1, % predicted	95 ± 14	81 ± 22†	80 ± 19†	<0.001
H_2FPEF score	2 [1, 3]	4 [3, 6]†	7 [5, 8]†*	<0.001
Logistic H_2FPEF score, %	30 [21, 43]	78 [56, 89]†	92 [81, 95]†*	<0.001
HFA-PEFF score	1 [0, 1]	5 [5, 7]†	5 [3, 6]†	<0.001
NT-proBNP, ng/L	64 [43, 97]	370 [233, 782]†	290 [139, 470]†*	<0.001
GFR CKD-EPI, mL/min/1.73 m^2	84.6 ± 15.5	64.8 ± 22.1†	63.4 ± 21.2†	<0.001
Hemoglobin, g/dL	14.2 ± 1.3	13.2 ± 1.6†	13.4 ± 1.6†	<0.001
Transferrin saturation, %	29.0 ± 11.0	25.9 ± 11.1†	23.9 ± 8.0†	<0.001
Ferritin, ng/mL	170 [92, 230]	120 [68, 226]	150 [68, 266]	0.051
Iron deficiency, *n* (%)	74 (37%)	131 (52%)†	53 (50%)†	0.005
HbA1c, %	5.7 ± 0.5	5.8 ± 0.6	6.1 ± 0.8†*	0.001

Date are means ± SD, median (25th and 75th percentile) or *n* (%). ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GFR CKD-EPI, glomerular filtration rate assessed by Chronic Kidney Disease Epidemiology Collaboration equation; GLP1-RA, glucagon-like peptide peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; SGLT-2i, sodium glucose cotransporter-2 inhibitor. †$P < 0.05$ vs. CON; *$P < 0.05$ vs. $HFpEF_{Nonobese}$.

lower, $P < 0.001$ for all), CO (19%–25% lower, $P < 0.001$ for all), CI (21%–25% lower, $P < 0.001$ for all), SVi (3%–8% lower, $P < 0.05$ for all), HR (18%–19% lower, $P < 0.001$ for all), and a-vO_{2diff} (13%–14% lower, $P < 0.001$ for all), regardless of obesity status (i.e., $HFpEF_{Obese}$ or $HFpEF_{Nonobese}$). Although SV was similar in $HFpEF_{Obese}$ compared with controls (2% lower, $P = 0.95$). Excluding participants taking beta-blocker medication resulted in a modest attenuation of differences between CON and both HFpEF groups for $\dot{V}O_{2peak}$ (absolute and indexed; 19%–33% lower, $P < 0.001$ for all), CO (13%–20% lower, $P < 0.001$ for all), CI (17%–21% lower, $P < 0.001$ for all), and HR (14%–15% lower, $P < 0.001$). There were also no statistically significant age-by-obesity or sex-by-obesity interactions. Additional adjustment for a history of coronary artery disease, or excluding the minority of participants with inducible ischemia ($n = 14$), did not significantly impact any of the primary and secondary analyses.

Obesity and Additional Components of HFpEF Physiology

The $HFpEF_{Obese}$ group showed significantly higher values for left-ventricular end-diastolic volume and right ventricular end-diastolic area, with similar left-atrial volume to $HFpEF_{Nonobese}$ (Table 3). However, when indexed to BSA, left-ventricular end-diastolic volume index and left-atrial volume index were lower in $HFpEF_{Obese}$, and left-ventricular mass index was not significantly different. Although resting left-ventricular ejection fraction was slightly lower in $HFpEF_{Obese}$ versus $HFpEF_{Nonobese}$, peak exercise left-ventricular ejection fraction was similar between HFpEF groups. In contrast, E/e' was significantly lower at rest and during intermediate exercise in $HFpEF_{Obese}$ versus $HFpEF_{Nonobese}$. Compared with CON, both HFpEF groups showed a number of differences typical for HFpEF (regardless of obesity status) including significantly higher left-atrial volumes, and left-ventricular mass, higher E/e', increased left-ventricular stiffness, and lower peak exercise left-ventricular ejection fraction (Table 3).

Resting and exercise mPAP values and the corresponding mPAP/CO slopes for both HFpEF groups and controls are shown in Fig. 2, *A* and *B*. Both HFpEF groups showed comparable mPAP at rest ($HFpEF_{Obese}$ 17.4 ± 4.2 mmHg vs. $HFpEF_{Nonobese}$ 17.6 ± 3.6 mmHg, $P = 0.84$) and peak exercise

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

Table 2. *Cardiopulmonary exercise test variables in controls and patients with HFpEF with or without obesity*

Characteristic	Control	$HFpEF_{Nonobese}$	$HFpEF_{Obese}$	*P* Value	*P* Value Adjusted
Number	270	317	139		
$\dot{V}O_{2peak}$, % predicted	79 ± 21	68 ± 21†	61 ± 16†*	<0.001	<0.001
Peak PO, W	112 ± 45	68 ± 31†	70 ± 32†	<0.001	<0.001
Peak PO, W/kg	1.45 ± 0.55	0.98 ± 0.42†	0.77 ± 0.33†*	<0.001	<0.001
RER	1.10 ± 0.09	1.09 ± 0.12	1.09 ± 0.10	0.13	0.70
O_2 pulse, mL/beat	8.9 ± 4.6	6.5 ± 3.9†	8.1 ± 3.7*	<0.001	<0.001
Oxygen delivery, L/min	2.12 ± 0.60	1.47 ± 0.50†	1.60 ± 0.53†*	<0.001	<0.001
Cardiac output/$\dot{V}O_2$ slope	5.3 ± 1.7	5.6 ± 2.5	5.3 ± 2.1	0.35	0.33
a-vO_{2diff}/Hb	0.93 ± 0.25	0.93 ± 0.28	0.92 ± 0.26	0.97	0.14
Mixed venous O_2 saturation, %	31 [22, 43]	33 [22, 44]	32 [21, 44]	0.61	0.48
$\dot{V}E/\dot{V}CO_2$ slope	29.9 ± 5.5	32.8 ± 7.2	31.7 ± 5.7	<0.001	0.056
$\dot{V}E_{peak}$, L/min	59.6 ± 18.7	42.2 ± 13.8†	43.3 ± 14.2†	<0.001	<0.001
$\dot{V}E_{peak}$/MVV, %	58 ± 13	57 ± 19	61 ± 17†*	0.011	0.009
Sp_{O_2} at peak, %	98 [97, 99]	97 [96, 99]†	97 [95, 99]†	<0.001	<0.001

Data are means ± SD or median (25th, 75th percentile). Groups compared by ANOVA (unadjusted) and ANCOVA (adjusted) with adjustment for age, sex, hypertension, and diabetes and Tukey-corrected post hoc assessment. ANCOVA, analysis of covariance; a-vO_{2diff}/Hb, arterio-venous oxygen content difference corrected for hemoglobin concentration; HFpEF, heart failure with preserved ejection fraction; PO, power output; $\dot{V}E_{peak}$, peak minute ventilation; $\dot{V}E_{peak}$/MVV, ratio of peak minute ventilation to estimated maximal voluntary ventilation; $\dot{V}E/\dot{V}CO_2$ slope, minute ventilation to volume of carbon dioxide slope; $\dot{V}O_{2peak}$, peak oxygen uptake; Sp_{O_2}, peripheral capillary oxygen saturation. Post hoc: †$P < 0.05$ vs. CON; *$P < 0.05$ vs. $HFpEF_{Nonobese}$.

(33.5 ± 6.1 mmHg vs. 32.7 ± 6.1 mmHg, $P = 0.39$), with no difference in mPAP/CO slope (4.2 ± 2.1 mmHg/L/min vs. 4.3 ± 2.5 mmHg/L/min, $P = 0.91$). In contrast, CON had significantly lower ($P < 0.001$ for both HFpEF groups and all outcomes) resting (13.7 ± 3.4 mmHg) and peak exercise mPAP (27.9 ± 7.3 mmHg) and mPAP/CO slope (2.5 ± 1.1 mmHg/L/min).

DISCUSSION

The major new findings of our study evaluating the Fick components in patients with HFpEF with and without obesity are as follows: *1*) obese patients with HFpEF demonstrated a tendency for higher absolute values for $\dot{V}O_{2peak}$ and increased peak CO, through a higher SV compared with nonobese patients with HFpEF—inferring increased aerobic power and cardiac reserve; *2*) when adjusted for body mass, however, individuals with $HFpEF_{Obese}$ had lower $\dot{V}O_{2peak}$ despite similar if not lower hemodynamic output, suggesting that the cardiac adaptations associated with obesity are insufficient to fully compensate for the mechanical inefficiency imposed by excess weight; and *3*) obesity was not associated with an accentuation of other key features of HFpEF during the semisupine CPETecho evaluation, such as exaggerated increases in pulmonary pressures or impaired oxygen extraction. Taken together, in $HFpEF_{Obese}$, excess weight may contribute to functional limitations, similar to an oversized chassis straining an underpowered engine. Therefore, weight loss strategies can be particularly beneficial for offloading the overburdened engine and improving functional performance in these patients. However, HFpEF imposes additional limitations beyond obesity, such as increased pulmonary pressures and reduced a-vO_{2diff}, that results in a lower $\dot{V}O_{2peak}$ compared with CON. These factors also contribute to exercise intolerance, impaired physical function and diminished quality of life, and adverse cardiovascular health outcomes (25, 26). Consequently, comprehensive management of HFpEF should include (non)pharmacologic weight loss strategies combined with therapies (such as exercise) targeting these contributing factors (i.e., loss of muscle, vascular dysfunction, and myosteatosis) to optimize patient outcomes.

There is significant debate regarding the impact of obesity on $\dot{V}O_{2peak}$ in patients with HFpEF, with some studies concluding that $\dot{V}O_{2peak}$ is higher (8) and others concluding that it is lower (9, 10, 18). Our findings clarify both viewpoints, as we found that absolute (L/min) $\dot{V}O_{2peak}$ tended to be higher in $HFpEF_{Obese}$ versus $HFpEF_{Nonobese}$, but the reverse was seen when $\dot{V}O_{2peak}$ was indexed to body mass. In fact, this is consistent with the values reported by the majority of these previous studies—where absolute $\dot{V}O_{2peak}$ was 17%–32% higher in $HFpEF_{Obese}$ (7, 8, 10), whereas bodyweight indexed $\dot{V}O_{2peak}$ was 12%–15% lower (7, 9, 10). The most profound differences are seen at the extreme end of obesity, with Sarma et al. (8) demonstrating higher absolute and comparable bodyweight-indexed $\dot{V}O_{2peak}$ in morbidly obese (BMI 39.3 ± 2.4 kg/m^2) versus overweight-obese (BMI: 30.8 ± 3.3 kg/m^2) patients with HFpEF. Our findings highlight the importance of reporting both absolute and indexed values for $\dot{V}O_{2peak}$, as they may provide complimentary information yet differing conclusions depending on which approach is used to evaluate the impact of obesity on the exercise physiology of HFpEF. Absolute $\dot{V}O_{2peak}$ represents a direct representation of a patient's physiologic reserve capacity (dictated by the absolute capacity and function of the pulmonary, cardiovascular, and skeletal muscle systems). The implications of the higher absolute $\dot{V}O_{2peak}$ in $HFpEF_{Obese}$ have not been definitively established, but may provide an explanation—at least in part—for the obesity paradox in heart failure (27). Bodyweight-indexed $\dot{V}O_2$ provides a more wholistic representation of how sufficient a patient's physiologic reserve capacity is relative to their body size—which is particularly important for physical tasks that have a substantial requirement to overcome gravity (e.g., climbing stairs, walking uphill), and can be impacted by extra body tissue (such as adipose tissue) that does not contribute to locomotion. Indeed, Shah et al. (28) showed that among predominantly obese patients with HFpEF, there is a substantial metabolic cost associated with limb movement during unloaded cycling (~27% of $\dot{V}O_{2peak}$) that is partly explained by

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

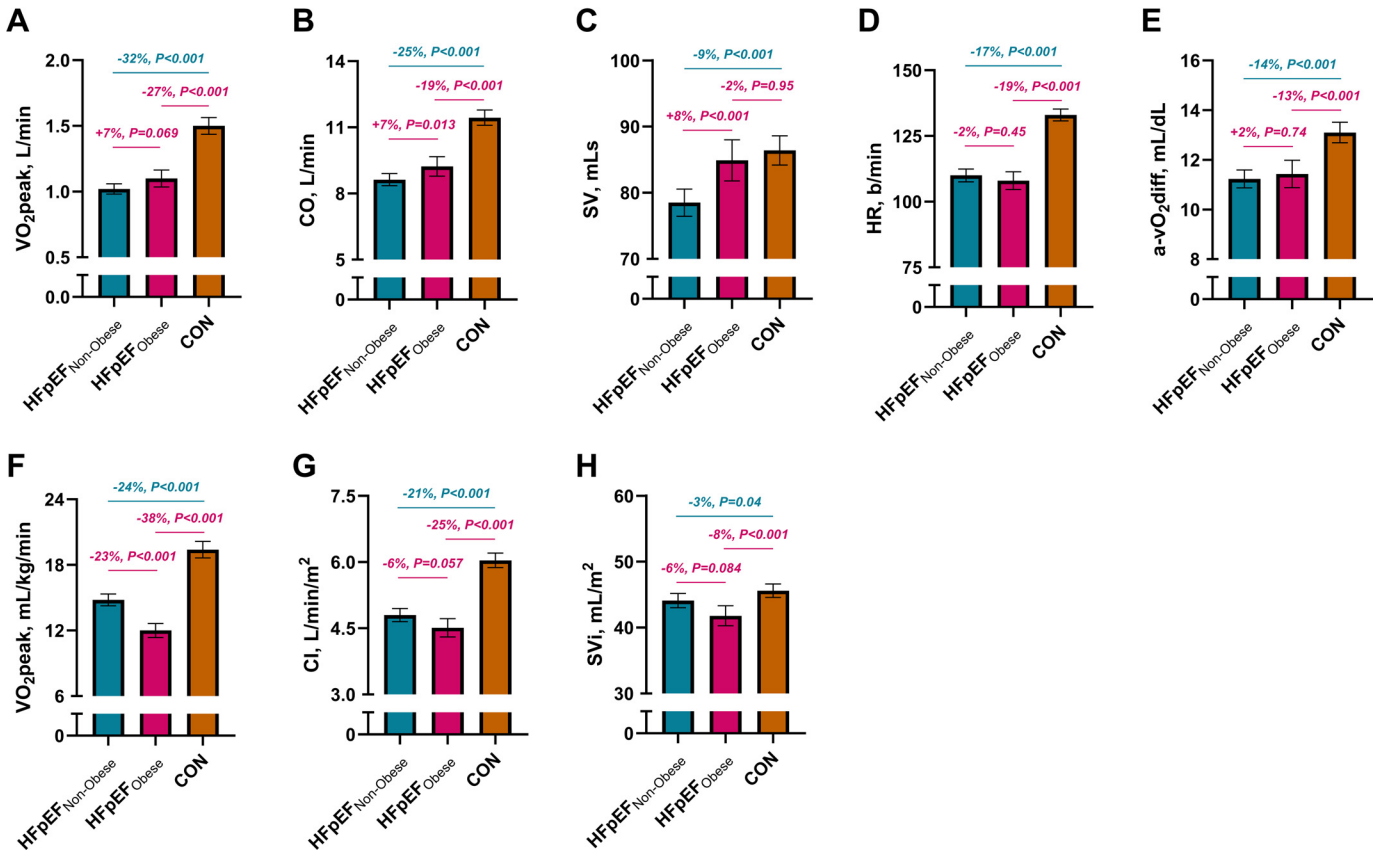

Figure 1. Impact of heart failure with preserved ejection fraction (HFpEF) with or without obesity on peak oxygen uptake ($\dot{V}O_{2peak}$) and its Fick determinants. Mean [95% confidence interval (CI)] values for absolute $\dot{V}O_{2peak}$ (L/min) (*A*), and its determinants including peak exercise cardiac output (CO, L/min) (*B*), stroke volume (SV, mL) (*C*), heart rate (HR, beats/min) (*D*), and arteriovenous oxygen content difference (a-vO_{2diff}, mL/dL) (*E*), as well as body weight-indexed $\dot{V}O_{2peak}$ (mL/kg/min) (*F*), cardiac index (CI, L/min/m^2) (*G*), and stroke volume index (SVi, mL/m^2) (*H*) in nonobese and obese patients with heart failure with preserved ejection fraction ($HFpEF_{Nonobese}$, $N = 317$; $HFpEF_{Obese}$, $N = 139$, respectively) and non-HFpEF controls (CON, $N = 270$). Compared with HFpEFNonobese, $HFpEF_{Obese}$ show a tendency for increased absolute $\dot{V}O_{2peak}$ due to increased CO and SV, yet this is insufficient for their increased body mass, highlighted by lower indexed $\dot{V}O_{2peak}$, CI, and SVi. Importantly, the impact of HFpEF (i.e., HFpEF vs. CON) is much larger than the impact of obesity for $\dot{V}O_{2peak}$ and its Fick determinants—CO and a-vO_{2diff}. Groups compared using analysis of covariance (ANCOVA) adjusted for age, sex, hypertension, and diabetes with Tukey-correction for multiple comparisons.

the increased cost of moving the leg against gravity. Our finding that absolute $\dot{V}O_{2peak}$ was higher despite similar peak CO and peak power output also supports the notion of added mechanical inefficiency associated with $HFpEF_{Obese}$. Taken together, this highlights that $HFpEF_{Obese}$ have increased physiologic capacity of their aerobic system, but this capacity is insufficient for the added demands of movement with their increased body size. Put simply, the $HFpEF_{Obese}$ engine is bigger, but is mismatched to the size of its chassis.

To our knowledge, our study provides one of the largest characterizations of the determinants of $\dot{V}O_{2peak}$ in patients with HFpEF with or without obesity. We found that $HFpEF_{Obese}$ had significantly increased peak exercise CO and SV relative to $HFpEF_{Nonobese}$, with a comparable a-vO_{2diff}. This is consistent with studies assessing peak exercise hemodynamics (nonindexed) in individuals with HFpEF during upright CPET with acetylene rebreathing (8), and supine exercise during invasive CPET (5). The increased CO and SV in $HFpEF_{Obese}$ may be the consequence of increased cardiac remodeling seen with obesity (9, 29). Indeed, we saw $HFpEF_{Obese}$ had significantly higher resting right-ventricular area and a tendency for higher left-ventricular end-diastolic volumes. The more modest cardiac remodeling seen in our study compared with others may reflect the lesser difference in BMI between our $HFpEF_{Obese}$ and $HFpEF_{Nonobese}$ compared with previous studies (7, 10). The increased cardiac volumes seen with obesity (including $HFpEF_{Obesity}$) are attributed to increases in total blood volume (13, 25), which may facilitate increased ventricular filling at rest and during exercise, but may also stimulate chronic cardiac remodeling. However, there may also be a role for the increased lean body mass and added hemodynamic and metabolic demands associated with performing physical daily activities among individuals with obesity (25). Notably, indexing CO and SV to BSA equalized peak exercise CI and SVi between $HFpEF_{Obese}$ and $HFpEF_{Nonobese}$, which is in agreement with invasive CPET studies (9, 10). Combining this with the fact that a-vO_{2diff} was no different between obesity groups highlights that the predominant reason body-weight-indexed $\dot{V}O_{2peak}$ is lower in $HFpEF_{Obese}$ is excess adiposity (rather than an insufficient CO or a-vO_{2diff}). Ultimately, this suggests that the "engine-chassis mismatch" in $HFpEF_{Obese}$ is primarily driven by an excessively large chassis, whereas the under-powered or poorly-functioning

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

Table 3. *Cardiac morphology and function assessed from resting and exercise echocardiography in controls and patients with HFpEF with or without obesity*

Characteristic	Control	$HFpEF_{Nonobese}$	$HFpEF_{Obese}$	*P* Value	*P* Value Adjusted
Number, %	270	317	139		
Cardiac morphology					
LA volume, mL	39 ± 13	60 ± 26†	59 ± 25†	<0.001	<0.001
LA Volume index, mL/m^2	21.7 ± 7.5	34.3 ± 13.7†	30.5 ± 13.2†*	<0.001	<0.001
LV end-diastolic volume, mL	97 ± 29	88 ± 29†	93 ± 31*	0.001	0.03
LV end-diastolic volume index, mL/m^2	50.0 ± 12.3	49.8 ± 15.8	45.0 ± 15.3†*	0.013	0.008
LV mass index, g/m^2	72.6 ± 17.1	91.8 ± 28.7†	89.2 ± 26.1†	<0.001	<0.001
Relative wall thickness	0.40 ± 0.08	0.47 ± 0.17†	0.48 ± 0.12†	<0.001	0.028
RV end-diastolic area, cm^2	17.9 ± 5.2	16.9 ± 5.0	18.3 ± 6.0*	0.033	0.02
RV end-diastolic area index, cm^2/m^2	9.5 ± 2.4	8.9 ± 2.6	9.4 ± 2.5	0.12	0.17
Rest and exercise cardiac function					
Ea rest, mmHg/mL	1.89 ± 0.49	2.09 ± 0.62†	1.96 ± 0.54	<0.001	0.013
E/*e*′ rest	8.7 ± 2.3	15.8 ± 5.9†	14.6 ± 5.6†*	<0.001	<0.001
E/*e*′ intermediate exercise	9.1 ± 2.2	16.8 ± 6.6†	15.0 ± 5.7†*	<0.001	<0.001
LV stiffness (*E*/*e*′/LVEDV)	0.10 ± 0.04	0.20 ± 0.11†	0.18 ± 0.09†*	<0.001	<0.001
RVFAC rest, %	48 ± 11	48 ± 10	45 ± 12*	0.056	0.034
RVFAC peak, %	55 ± 11	51 ± 12	50 ± 11†	0.014	0.032
LV ejection fraction rest, %	62 ± 8	63 ± 9	60 ± 8†*	0.009	0.01
LV ejection fraction peak, %	71 ± 10	67 ± 10†	67 ± 10†	0.013	0.03

Data are means ± SD. Groups compared by ANOVA (unadjusted) and ANCOVA (adjusted) with adjustment for age, sex, hypertension, and diabetes and Tukey-corrected post hoc assessment. ANCOVA, analysis of covariance; Ea, arterial elastance; *E*/*e*′, ratio of early mitral inflow to annular tissue velocity; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left-ventricular; LVEDV, left ventricular end-diastolic volume; RV, right-ventricular; RVFAC, right-ventricular fractional area change. Post hoc: †$P < 0.05$ vs. CON; *$P < 0.05$ vs. $HFpEF_{Nonobese}$.

engine is a feature of HFpEF irrespective of obesity. What should also be highlighted is that other factors—such as chronotropic incompetence and altered peripheral oxygen extraction and/or utilization—are also important components of exercise intolerance in HFpEF regardless of obesity. The lower peak HR was partly due to increased use of beta-blocker medication. However, peak exercise $\dot{V}O_2$, CO, and HR remained markedly lower after excluding participants taking beta-blocker medications, consistent with previous observations that chronotropic incompetence/reluctance (30) and/or premature exercise termination due peripheral muscle or pulmonary constraints (30–32) may also contribute to decreased $\dot{V}O_{2peak}$ in HFpEF. In addition, the lower avO_{2diff} is consistent with clinical studies (33–35) and preclinical models of HFpEF (36, 37) showing decreased skeletal muscle capillarity, oxidative capacity, and mitochondrial content. Ultimately, this reiterates the complex nature of HFpEF pathophysiology extends well beyond obesity.

A noteworthy finding from our study was the lack of difference in estimated pulmonary pressures at rest and during exercise in $HFpEF_{Obese}$ versus $HFpEF_{Nonobese}$. Previous studies performing invasive CPET and/or right-heart catheterization have shown $HFpEF_{Obese}$ individuals have exaggerated pulmonary capillary wedge pressures at rest and during exercise compared with $HFpEF_{Nonobese}$ (5, 9, 10). This has led to the viewpoint that obesity worsens LV stiffness (a major feature of HFpEF), and has been proposed as a major cause of functional limitations in the obese HFpEF phenotype (13). We failed to confirm this with our study, where we saw similar resting and peak exercise mPAP values and mPAP/CO slopes between HFpEF obesity groups (which in both cases were significantly higher than CON). Although this could

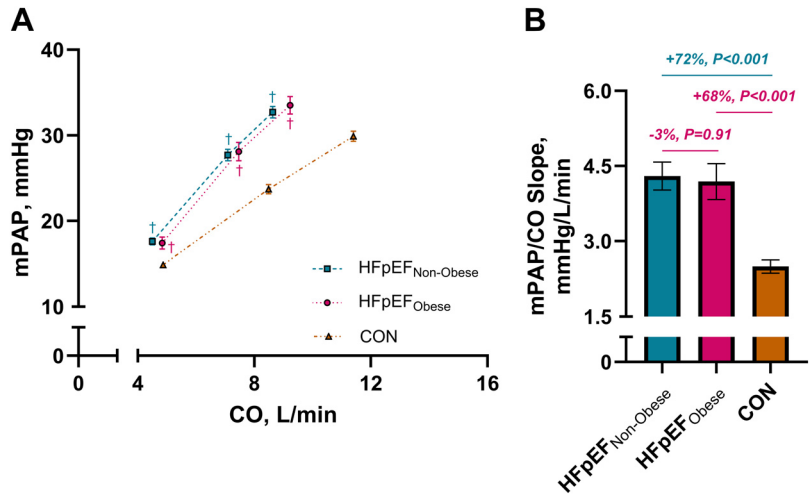

Figure 2. Impact of heart failure with preserved ejection fraction (HFpEF) with or without obesity on mean pulmonary artery pressures indexed to cardiac output at rest and during exercise. Mean [95% confidence interval (CI)] values for mean pulmonary artery pressure (mPAP) plotted against cardiac output (CO) at rest, intermediate, and peak exercise (*A*); and mPAP/CO slope in nonobese and obese patients with heart failure with preserved ejection fraction ($HFpEF_{Nonobese}$, $N = 317$; $HFpEF_{Obese}$, $N = 139$, respectively) and non-HFpEF controls (CON, $N = 270$) (*B*). There were no differences between $HFpEF_{Nonobese}$ and $HFpEF_{Obese}$ in mPAP at rest or during exercise, with a similar mPAP/CO slope, all of which were substantially higher than CON. Groups compared using a linear mixed model adjusted for age, sex, hypertension and diabetes with Tukey-correction for multiple comparisons. Post hoc: †$P <$ 0.05 for $HFpEF_{Nonobese}$ (blue symbols) or $HFpEF_{Obese}$ (pink symbols) vs. CON (orange symbols).

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

partly be attributed to the noninvasive estimation of mPAP using echocardiography, our approach has been previously validated with excellent agreement to invasive measurements during exercise (22). Postural differences between our study and previous studies provide a more likely explanation for these discrepant findings (38). Indeed, all the previous studies (5, 9, 10) performed invasive exercise testing in the supine posture, which can be particularly prone to error and exacerbation of pulmonary pressures and exercise limitations in individuals with obesity (38). Notably, pulmonary capillary wedge pressure is influenced by both LV stiffness/relaxation properties, but also intrathoracic pressures as well as total and stressed blood volume. The compressive forces from increased thoracic tissue mass in individuals with obesity have been shown to dramatically increase intrathoracic pressures and subsequently, pulmonary pressures in the supine versus upright position (39, 40)—which significantly confounds the interpretation of pulmonary and left-ventricular pressures in individuals with obesity. In contrast, semi-supine exercise (which was used in our study) has been shown to more closely approximate the physiology of upright exercise (41). This highlights the importance of considering exercising posture in the diagnosis and assessment of exercise limitations in individuals with overt or suspected HFpEF, and raises the question of whether exaggerated increases in pulmonary and left-ventricular pressures are a cause of exercise limitations in individuals with HFpEF during upright exercise. We should note, however, that mPAP and mPAP/CO slope is a noninvasive echocardiographic measure that incorporates left-ventricular properties alongside upstream measures of pulmonary vascular resistance, so our results do not provide conclusive determination of the impact of obesity on left-ventricular pressures during exercise, but the combined effect of both of these components. Regardless, comparison of our findings with existing literature highlights the importance of considering posture when evaluating hemodynamics in individuals with obesity. In particular, our conflicting findings emphasize the need for additional studies to better understand how obesity does (or does not) modulate intrathoracic, left-ventricular, and pulmonary pressures in HFpEF during upright exercise—which better reflects the physiology and demands of many instrumental activities of daily living.

Overall, the finding that $HFpEF_{Obese}$ have decreased mechanical efficiency but preserved cardiac reserve suggests $HFpEF_{Obese}$ could benefit significantly from weight loss therapies that target this "engine-chassis" mismatch. This is supported by results from the SECRET1 trial (11) in which caloric restriction resulted in a 1.3 mL/kg/min (9%) improvement in bodyweight indexed $\dot{V}O_{2peak}$ (but no significant change in absolute $\dot{V}O_{2peak}$). Moreover, the STEP-HFpEF (12) and SUMMIT trials (14) showed improvements in 6-min walk distance (+22 m and +18 m or +7% and +6%, respectively) among obese patients with HFpEF taking Semaglutide (GLP1-RA) or Tirzepatide (combined GIP and GLP1-RA), respectively. However, the improvements in exercise performance (either $\dot{V}O_{2peak}$ or walk distance) with sole weight loss interventions have been relatively modest, and this may be due to the fact that obesity is only one factor underlying exercise limitations in HFpEF (1, 2, 25). Indeed, although the mechanical inefficiency from obesity may exacerbate exercise limitations in HFpEF, we showed that regardless of obesity status, individuals with HFpEF (vs. CON) had marked impairment in other physiologic features—increased mPAP, mPAP/CO slope, lower CO, chronotropic incompetence, and decreased a-vO_{2diff}. This is important, because weight loss therapies (e.g., GIP and GLP1-RAs) are unlikely to adequately address these additional HFpEF impairments, thereby emphasizing the need for a broad, multimodal approach to HFpEF treatment.

In fact, extreme weight loss could worsen some of the "engine" limitations imposed by HFpEF by decreasing the output and absolute capacity of several body systems. For example, a meta-analysis quantifying the effects of diet or surgically induced weight loss in individuals without HFpEF showed that weight loss comes at the cost of significant reductions in absolute $\dot{V}O_{2peak}$ (−0.23 L/min), CO (−1.45 L/min), and a-vO_{2diff} (−0.78 mL/dL). This is likely the result of cardiac and skeletal muscle atrophy secondary to the loss in total body mass and/or energy deficiency (42, 43). Patients may not initially notice these effects if the loss in body mass is sufficient to result in a net improvement in bodyweight indexed $\dot{V}O_{2peak}$, but this could become the perfect storm for worsened exercise tolerance and increased risk of disability in the long-term among individuals who regain weight—which has been shown to be predominantly fat mass (44). Therefore, a better approach is likely to be combining weight loss (to address the "chassis") with other therapeutic approaches for the HFpEF-related "engine" limitations. Exercise training, that incorporates aerobic exercise—to provide a hemodynamic volume load to prevent cardiac atrophy—alongside resistance exercise (combined with protein supplementation) to provide a strength and nutritional stimulus to the musculoskeletal system when body mass decreases may be particularly useful for this purpose. This is supported by results from the SECRET1 (11) and SECRET2 (45) trials, in which combined aerobic training + caloric restriction (+2.5 mL/kg/min or +17%), or combined aerobic + resistance training + caloric restriction (+2.4 mL/kg/min or +16%) resulted in approximately twice the magnitude of improvements in $\dot{V}O_{2peak}$ than that seen with caloric restriction alone.

Limitations

A key limitation is the noninvasive hemodynamic evaluation, although this was mitigated by a larger sample size and complementary noninvasive assessments, providing valuable insights that invasive methods alone might not capture. In addition, the oxygen cascade and exercise hemodynamics were assessed in a semi-supine rather than a fully upright position. However, this provides a close approximation in exercise responses to upright exercise (41) while addressing many of the respiratory and hemodynamic limitations imposed by fully supine exercise in individuals with obesity (38). Indeed, the use of semi-supine (instead of supine) exercise assessments in our study has generated novel findings that challenge the current view of how obesity modulates left-ventricular and/or pulmonary pressures in HFpEF established using supine exercise testing. We also used BMI as the sole means of characterizing obesity. This is a pragmatic approach and reflects the criteria used to select patients for therapy and/or clinical trials. However, there is growing

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

awareness that the pathophysiologic impact of obesity in HFpEF may be more closely linked to specific fat depots such as visceral, epicardial, and/or inter/intramuscular adipose tissue that we were unable to characterize (9, 46–48). Furthermore, the lack of lean body mass assessment limits our ability to use more precise indexing, particularly for peripheral measurements, where lean mass may provide a more accurate reflection of metabolic and functional capacity. Indeed, lean mass abnormalities such as reduced lean mass and number of oxidative (Type I) fibers, increased muscle fat infiltration (myosteatosis), decreased capillarity, and mitochondrial dysfunction have all been implicated in reduced $\dot{V}O_{2peak}$ in patients with HFpEF (26, 48–50). Therefore, the degree to which obesity impacts on these other mechanistic drivers of reduced $\dot{V}O_{2peak}$ in HFpEF remains an important direction for future research. Finally, the observational cross-sectional design, and the lack of physical activity and body composition assessments prevent us from determining the factors mediating the physiologic differences between $HFpEF_{Obese}$ and $HFpEF_{Nonobese}$. Further longitudinal studies are needed to understand the clinical implications of our observed engine-chassis mismatch in $HFpEF_{Obese}$, and how this physiology adapts to weight loss therapy.

Conclusions

Although obese patients with HFpEF demonstrated preserved absolute $\dot{V}O_{2peak}$ and CO responses, these adaptations were insufficient when indexed to body size, revealing significant inefficiencies in oxygen transport and utilization. The identical power output between patients with obesity and without obesity, despite greater absolute oxygen consumption in the former, underscores the added metabolic cost of moving excess body mass. Our findings suggest weight loss may have utility in addressing engine-chassis matching and improving mechanical efficiency (i.e., metabolic demands of locomotion) in obese patients with HFpEF. However, the observation that obesity did not accentuate many other HFpEF features emphasizes the importance of complimenting weight loss with other strategies such as exercise training to address other components of exercise intolerance in HFpEF not directly related to obesity, some of which (muscle atrophy, cardiac deconditioning) could be exacerbated by weight loss.

DATA AVAILABILITY

The data will be made available upon reasonable request to the authors.

ACKNOWLEDGMENTS

The authors thank the cardiology fellows who have contributed to performing the exams in the dyspnea clinic of Jessa Hospital (Hasselt, Belgium) over the years. In addition, the authors are grateful to the nurses for their vital paramedic support in the dyspnea clinic.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

L.H., G.C., and J.V. conceived and designed research; S.M.-F., Y.B., M.F., B.D., R.P., S.S., S.J., S.V., S.A., R.J., J.S., L.H., G.C., and J.V. performed experiments; S.J.F., S.M.-F., Y.B., M.F., S.V., R.J., G.C., and J.V. analyzed data; S.J.F., S.M.-F., M.M., Y.B., M.F., S.V., R.J., L.H., G.C., M.J.H., and J.V. interpreted results of experiments; S.J.F., M.J.H., and J.V. prepared figures; S.J.F., M.J.H., and J.V. drafted manuscript; S.J.F., S.M.-F., M.M., Y.B., M.F., B.D., R.P., S.S., S.J., S.V., S.A., R.J., J.S., L.H., G.C., M.J.H., and J.V. edited and revised manuscript; S.J.F., S.M.-F., M.M., Y.B., M.F., B.D., R.P., S.S., S.J., S.V., S.A., R.J., J.S., L.H., G.C., M.J.H., and J.V. approved final version of manuscript.

REFERENCES

1. **Hamo CE**, **DeJong C**, **Hartshorne-Evans N**, **Lund LH**, **Shah SJ**, **Solomon S**, **Lam CSP.** Heart failure with preserved ejection fraction. *Nat Rev Dis Primers* 10: 55, 2024. doi:10.1038/s41572-024-00540-y.
2. **Redfield MM**, **Borlaug BA.** Heart failure with preserved ejection fraction: a review. *JAMA* 329: 827–838, 2023. doi:10.1001/jama.2023.2020.
3. **Mentz RJ**, **Kelly JP**, **Von Lueder TG**, **Voors AA**, **Lam CSP**, **Cowie MR**, **Kjeldsen K**, **Jankowska EA**, **Atar D**, **Butler J**, **Fiuzat M**, **Zannad F**, **Pitt B**, **O'Connor CM.** Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 64: 2281–2293, 2014. doi:10.1016/j.jacc.2014.08.036.
4. **Yang M**, **Kondo T**, **Adamson C**, **Butt JH**, **Abraham WT**, **Desai AS**, **Jering KS**, **Køber L**, **Kosiborod MN**, **Packer M**, **Rouleau JL**, **Solomon SD**, **Vaduganathan M**, **Zile MR**, **Jhund PS**, **McMurray JJV.** Impact of comorbidities on health status measured using the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with reduced and preserved ejection fraction. *Eur J Heart Fail* 25: 1606–1618, 2023. doi:10.1002/ejhf.2962.
5. **Litwin SE**, **Komtebedde J**, **Seidler T**, **Borlaug BA**, **Winkler S**, **Solomon SD**, **Eicher J**, **Mazimba S**, **Khawash R**, **Sverdlov AL**, **Hummel SL**, **Bugger H**, **Boenner F**, **Hoendermis E**, **Cikes M**, **Demers C**, **Silva G**, **Van Empel V**, **Starling RC**, **Penicka M**, **Cutlip DE**, **Leon MB**, **Kitzman DW**, **Van Veldhuisen DJ**, **Shah SJ**; **REDUCE LAP-HF Investigators and Research Staff.** Obesity in heart failure with preserved ejection fraction: Insights from the REDUCE LAP-HF II trial. *Eur J Heart Fail* 26: 177–189, 2024. doi:10.1002/ejhf.3092.
6. **Reddy YNV**, **Rikhi A**, **Obokata M**, **Shah SJ**, **Lewis GD**, **AbouEzzedine OF**, **Dunlay S**, **McNulty S**, **Chakraborty H**, **Stevenson LW**, **Redfield MM**, **Borlaug BA.** Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail* 22: 1009–1018, 2020. doi:10.1002/ejhf.1788.
7. **Reddy YNV**, **Lewis GD**, **Shah SJ**, **Obokata M**, **Abou-Ezzedine OF**, **Fudim M**, **Sun J-L**, **Chakraborty H**, **McNulty S**, **LeWinter MM**, **Mann DL**, **Stevenson LW**, **Redfield MM**, **Borlaug BA.** Characterization of the obese phenotype of heart failure with preserved ejection fraction: a RELAX Trial Ancillary Study. *Mayo Clin Proc* 94: 1199–1209, 2019. doi:10.1016/j.mayocp.2018.11.037.
8. **Sarma S**, **MacNamara J**, **Livingston S**, **Samels M**, **Haykowsky MJ**, **Berry J**, **Levine BD.** Impact of severe obesity on exercise performance in heart failure with preserved ejection fraction. *Physiol Rep* 8: e14634, 2020. doi:10.14814/phy2.14634.
9. **Sorimachi H**, **Omote K**, **Omar M**, **Popovic D**, **Verbrugge FH**, **Reddy YNV**, **Lin G**, **Obokata M**, **Miles JM**, **Jensen MD**, **Borlaug BA.** Sex and central obesity in heart failure with preserved ejection fraction. *Eur J Heart Fail* 24: 1359–1370, 2022. doi:10.1002/ejhf.2563.
10. **Obokata M**, **Reddy YNV**, **Pislaru SV**, **Melenovsky V**, **Borlaug BA.** Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 136: 6–19, 2017. doi:10.1161/CIRCULATIONAHA.116.026807.
11. **Kitzman DW**, **Brubaker P**, **Morgan T**, **Haykowsky M**, **Hundley G**, **Kraus WE**, **Eggebeen J**, **Nicklas BJ.** Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 315: 36–46, 2016. doi:10.1001/jama.2015.17346.

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

12. **Kosiborod MN**, **Abildstrøm SZ**, **Borlaug BA**, **Butler J**, **Rasmussen S**, **Davies M**, **Hovingh GK**, **Kitzman DW**, **Lindegaard ML**, **Møller DV**, **Shah SJ**, **Treppendahl MB**, **Verma S**, **Abhayaratna W**, **Ahmed FZ**, **Chopra V**, **Ezekowitz J**, **Fu M**, **Ito H**, **Lelonek M**, **Melenovsky V**, **Merkely B**, **Núñez J**, **Perna E**, **Schou M**, **Senni M**, **Sharma K**, **Van der Meer P**, **von Lewinski D**, **Wolf D**, **Petrie MC**; **STEP-HFpEF Trial Committees and Investigators.** Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med* 389: 1069–1084, 2023. doi:10.1056/NEJMoa2306963.
13. **Borlaug BA**, **Jensen MD**, **Kitzman DW**, **Lam CSP**, **Obokata M**, **Rider OJ.** Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. *Cardiovasc Res* 118: 3434–3450, 2023. doi:10.1093/cvr/cvac120.
14. **Packer M**, **Zile MR**, **Kramer CM**, **Baum SJ**, **Litwin SE**, **Menon V**, **Ge J**, **Weerakkody GJ**, **Ou Y**, **Bunck MC**, **Hurt KC**, **Murakami M**, **Borlaug BA**; **SUMMIT Trial Study Group.** Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med* 392: 427–437, 2025. doi:10.1056/NEJMoa2410027.
15. **Verwerft J**, **Bertrand PB**, **Claessen G**, **Herbots L**, **Verbrugge FH.** Cardiopulmonary exercise testing with simultaneous echocardiography: blueprints of a dyspnoea clinic for suspected HFpEF. *JACC Heart Fail* 11: 243–249, 2023. doi:10.1016/j.jchf.2022.11.004.
16. **Verwerft J**, **Soens L**, **Wynants J**, **Meysman M**, **Jogani S**, **Plein D**, **Stroobants S**, **Herbots L**, **Verbrugge FH.** Heart failure with preserved ejection fraction: relevance of a dedicated dyspnoea clinic. *Eur Heart J* 44: 1544–1556, 2023. doi:10.1093/eurheartj/ehad141.
17. **Pieske B**, **Tschöpe C**, **De Boer RA**, **Fraser AG**, **Anker SD**, **Donal E**, **Edelmann F**, **Fu M**, **Guazzi M**, **Lam CSP**, **Lancellotti P**, **Melenovsky V**, **Morris DA**, **Nagel E**, **Pieske-Kraigher E**, **Ponikowski P**, **Solomon SD**, **Vasan RS**, **Rutten FH**, **Voors AA**, **Ruschitzka F**, **Paulus WJ**, **Seferovic P**, **Filippatos G.** How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 40: 3297–3317, 2019 [Erratum in *Eur Heart J* 42: 1274, 2021]. doi:10.1093/eurheartj/ehz641.
18. **Reddy YNV**, **Carter RE**, **Obokata M**, **Redfield MM**, **Borlaug BA.** A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 138: 861–870, 2018. doi:10.1161/CIRCULATIONAHA.118.034646.
19. **Nagueh SF**, **Smiseth OA**, **Appleton CP**, **Byrd BF 3rd**, **Dokainish H**, **Edvardsen T**, **Flachskampf FA**, **Gillebert TC**, **Klein AL**, **Lancellotti P**, **Marino P**, **Oh JK**, **Alexandru Popescu B**, **Waggoner AD**, **Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri.** Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 17: 1321–1360, 2016. doi:10.1093/ehjci/jew082.
20. **Lang RM**, **Badano LP**, **Mor-Avi V**, **Afilalo J**, **Armstrong A**, **Ernande L**, **Flachskampf FA**, **Foster E**, **Goldstein SA**, **Kuznetsova T**, **Lancellotti P**, **Muraru D**, **Picard MH**, **Rietzschel ER**, **Rudski L**, **Spencer KT**, **Tsang W**, **Voigt J-U.** Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 16: 233–270, 2015 [Erratum in *Eur Heart J Cardiovasc Imaging* 17: 412, 2016]. doi:10.1093/ehjci/jev014.
21. **Chemla D**, **Castelain V**, **Humbert M**, **Hébert J-L**, **Simonneau G**, **Lecarpentier Y**, **Hervé P.** New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest* 126: 1313–1317, 2004. doi:10.1378/chest.126.4.1313.
22. **Claessen G**, **La Gerche A**, **Voigt J-U**, **Dymarkowski S**, **Schnell F**, **Petit T**, **Willems R**, **Claus P**, **Delcroix M**, **Heidbuchel H.** Accuracy of echocardiography to evaluate pulmonary vascular and RV function during exercise. *JACC Cardiovasc Imaging* 9: 532–543, 2016. doi:10.1016/j.jcmg.2015.06.018.
23. **Verwerft J**, **Stassen J**, **Falter M**, **Bekhuis Y**, **Hoedemakers S**, **Gojevic T**, **Ferreira SM**, **Vanhentenrijk S**, **Stroobants S**, **Jogani S**, **Hansen D**, **Jasaityte R**, **Cosyns B**, **Van De Bruaene A**, **Bertrand PB**, **De Boer RA**, **Gevaert AB**, **Verbrugge FH**, **Herbots L**, **Claessen G.** Clinical significance of exercise pulmonary hypertension with a negative diastolic stress test for suspected heart failure with preserved ejection fraction. *J Am Heart Assoc* 13: e032228, 2024. doi:10.1161/JAHA.123.032228.
24. **Falter M**, **Bekhuis Y**, **L'Hoyes W**, **Milani M**, **Hoedemakers S**, **Soens L**, **Moura-Ferreira S**, **Dhont S**, **Pauwels RIK**, **Jacobs A**, **De Schutter S**, **Delpire B**, **Verbeeck J**, **Stassen JAN**, **Gevaert AB**, **Debonnaire P**, **Van De Bruaene A**, **Bertrand PB**, **Herbots L**, **Jasaityte R**, **Verbrugge FH**, **Claessen G**, **Verwerft JAN.** Exercise Echocardiography for Risk Stratification in Unexplained Dyspnea: The Incremental Value of the Mean Pulmonary Artery Pressure/Slope. *J Am Soc Echocardiogr* 38: 875–889, 2025. doi:10.1016/j.echo.2025.06.007.
25. **Pandey A**, **Patel KV**, **Vaduganathan M**, **Sarma S**, **Haykowsky MJ**, **Berry JD**, **Lavie CJ.** Physical activity, fitness, and obesity in heart failure with preserved ejection fraction. *JACC Heart Fail* 6: 975–982, 2018. doi:10.1016/j.jchf.2018.09.006.
26. **Haykowsky MJ**, **Tomczak CR**, **Scott JM**, **Paterson DI**, **Kitzman DW.** Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. *J Appl Physiol (1985)* 119: 739–744, 2015. doi:10.1152/japplphysiol.00049.2015.
27. **Alebna PL**, **Mehta A**, **Yehya A**, **daSilva-deAbreu A**, **Lavie CJ**, **Carbone S.** Update on obesity, the obesity paradox, and obesity management in heart failure. *Prog Cardiovasc Dis* 82: 34–42, 2024. doi:10.1016/j.pcad.2024.01.003.
28. **Shah RV**, **Schoenike MW**, **Armengol De La Hoz MÁ**, **Cunningham TF**, **Blodgett JB**, **Tanguay M**, **Sbarbaro JA**, **Nayor M**, **Rouvina J**, **Kowal A**, **Houstis N**, **Baggish AL**, **Ho JE**, **Hardin C**, **Malhotra R**, **Larson MG**, **Vasan RS**, **Lewis GD.** Metabolic cost of exercise initiation in patients with heart failure with preserved ejection fraction vs community-dwelling adults. *JAMA Cardiol* 6: 653–660, 2021. doi:10.1001/jamacardio.2021.0292.
29. **Turkbey EB**, **McClelland RL**, **Kronmal RA**, **Burke GL**, **Bild DE**, **Tracy RP**, **Arai AE**, **Lima JAC**, **Bluemke DA.** The impact of obesity on the left ventricle. *JACC Cardiovasc Imaging* 3: 266–274, 2010. doi:10.1016/j.jcmg.2009.10.012.
30. **Sarma S**, **Stoller D**, **Hendrix J**, **Howden E**, **Lawley J**, **Livingston S**, **Adams-Huet B**, **Holmes C**, **Goldstein DS**, **Levine BD.** Mechanisms of chronotropic incompetence in heart failure with preserved ejection fraction. *Circ Heart Fail* 13: e006331, 2020. doi:10.1161/CIRCHEARTFAILURE.119.006331.
31. **Leahy MG**, **Wakeham DJ**, **MacNamara JP**, **Brazile T**, **Abulimiti A**, **Hearon CM**, **Samels M**, **Tomlinson AR**, **Balmain BN**, **Babb TG**, **Levine BD**, **Sarma S.** Heart-lung interactions in HFpEF. *JACC Heart Fail* 13: 102523, 2025. doi:10.1016/j.jchf.2025.102523.
32. **Houstis NE**, **Eisman AS**, **Pappagianopoulos PP**, **Wooster L**, **Bailey CS**, **Wagner PD**, **Lewis GD.** Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O_2 pathway analysis. *Circulation* 137: 148–161, 2018. doi:10.1161/CIRCULATIONAHA.117.029058.
33. **Lewsey SC**, **Samuel TJ**, **Schär M**, **Sourdon J**, **Goldenberg JR**, **Yanek LR**, **Lai S**, **Steinberg AM**, **Bottomley PA**, **Gerstenblith G**, **Weiss RG.** Skeletal muscle quantity versus quality in heart failure: exercise intolerance and outcomes in older patients with HFpEF are related to abnormal skeletal muscle metabolism rather than age-related skeletal muscle loss. *Circ Heart Fail* 18: e012512, 2025. doi:10.1161/CIRCHEARTFAILURE.124.012512.
34. **Weiss K**, **Schär M**, **Panjrath GS**, **Zhang Y**, **Sharma K**, **Bottomley PA**, **Golozar A**, **Steinberg A**, **Gerstenblith G**, **Russell SD**, **Weiss RG.** Fatigability, exercise intolerance, and abnormal skeletal muscle energetics in heart failure. *Circ Heart Fail* 10: e004129, 2017. doi:10.1161/CIRCHEARTFAILURE.117.004129.
35. **Molina AJA**, **Bharadwaj MS**, **Van Horn C**, **Nicklas BJ**, **Lyles MF**, **Eggebeen J**, **Haykowsky MJ**, **Brubaker PH**, **Kitzman DW.** Skeletal muscle mitochondrial content, oxidative capacity, and mfn2 expression are reduced in older patients with heart failure and preserved ejection fraction and are related to exercise intolerance. *JACC Heart Fail* 4: 636–645, 2016. doi:10.1016/j.jchf.2016.03.011.
36. **Bowen TS**, **Herz C**, **Rolim NPL**, **Berre A-MO**, **Halle M**, **Kricke A**, **Linke A**, **Da Silva GJ**, **Wisloff U**, **Adams V.** Effects of endurance training on detrimental structural, cellular, and functional alterations in skeletal muscles of heart failure with preserved ejection fraction. *J Card Fail* 24: 603–613, 2018. doi:10.1016/j.cardfail.2018.08.009.
37. **Bowen TS**, **Rolim NPL**, **Fischer T**, **Baekkerud FH**, **Medeiros A**, **Werner S**, **Brønstad E**, **Rognmo O**, **Mangner N**, **Linke A**, **Schuler G**, **Silva GJJ**, **Wisløff U**, **Adams V**; **Optimex Study Group.** Heart failure

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.

with preserved ejection fraction induces molecular, mitochondrial, histological, and functional alterations in rat respiratory and limb skeletal muscle. *Eur J Heart Fail* 17: 263–272, 2015. doi:10.1002/ejhf.239.

38. **Sarma S.** Exercise hemodynamics in heart failure with preserved ejection fraction. *Heart Fail Clin* 21: 27–34, 2025. doi:10.1016/j.hfc.2024.08.003.
39. **Jawad A**, **Tonelli AR**, **Chatburn RL**, **Wang X**, **Hatipoğlu U.** Impact of intrathoracic pressure in the assessment of pulmonary hypertension in overweight patients. *Ann Am Thorac Soc* 14: 1861–1863, 2017. doi:10.1513/AnnalsATS.201704-331RL.
40. **Khirfan G**, **Melillo CA**, **Al Abdi S**, **Lane JE**, **Dweik RA**, **Chatburn RL**, **Hatipoğlu U**, **Tonelli AR.** Impact of esophageal pressure measurement on pulmonary hypertension diagnosis in patients with obesity. *Chest* 162: 684–692, 2022. doi:10.1016/j.chest.2022.04.002.
41. **Dillon HT**, **Dausin C**, **Claessen G**, **Lindqvist A**, **Mitchell A**, **Wright L**, **Willems R**, **La Gerche A**, **Howden EJ.** The effect of posture on maximal oxygen uptake in active healthy individuals. *Eur J Appl Physiol* 121: 1487–1498, 2021. doi:10.1007/s00421-021-04630-7.
42. **Sargsyan N**, **Chen JY**, **Aggarwal R**, **Fadel MG**, **Fehervari M**, **Ashrafian H.** The effects of bariatric surgery on cardiac function: a systematic review and meta-analysis. *Int J Obes (Lond)* 48: 166–176, 2024. doi:10.1038/s41366-023-01412-3.
43. **Nuijten MA**, **Eijsvogels TM**, **Monpellier VM**, **Janssen IM**, **Hazebroek EJ**, **Hopman MT.** The magnitude and progress of lean body mass, fat-free mass, and skeletal muscle mass loss following bariatric surgery: a systematic review and meta-analysis. *Obes Rev* 23: e13370, 2022. doi:10.1111/obr.13370.
44. **Upadhya B**, **Brubaker PH**, **Nicklas BJ**, **Houston DK**, **Haykowsky MJ**, **Kitzman DW.** Long-term changes in body composition and exercise capacity following calorie restriction and exercise training in older patients with obesity and heart failure with preserved ejection fraction. *J Card Fail* 31: 497–507, 2025. doi:10.1016/j.cardfail.2024.06.007.
45. **Brubaker PH**, **Nicklas BJ**, **Houston DK**, **Hundley WG**, **Chen H**, **Molina AJA**, **Lyles WM**, **Nelson B**, **Upadhya B**, **Newland R**, **Kitzman DW.** A randomized, controlled trial of resistance training added to caloric restriction plus aerobic exercise training in obese heart failure with preserved ejection fraction. *Circ Heart Fail* 16: e010161, 2023. doi:10.1161/CIRCHEARTFAILURE.122.010161.
46. **Zamani SK**, **Sarma S**, **MacNamara JP**, **Hynan LS**, **Haykowsky MJ**, **Hearon CM**, **Wakeham D**, **Brazile T**, **Levine BD**, **Zaha VG**, **Nelson MD.** Excess pericardial fat is related to adverse cardio-mechanical interaction in heart failure with preserved ejection fraction. *Circulation* 148: 1410–1412, 2023. doi:10.1161/CIRCULATIONAHA.123.065909.
47. **Koepp KE**, **Obokata M**, **Reddy YNV**, **Olson TP**, **Borlaug BA.** Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *JACC Heart Fail* 8: 657–666, 2020. doi:10.1016/j.jchf.2020.04.016.
48. **Haykowsky MJ**, **Kouba EJ**, **Brubaker PH**, **Nicklas BJ**, **Eggebeen J**, **Kitzman DW.** Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Cardiol* 113: 1211–1216, 2014. doi:10.1016/j.amjcard.2013.12.031.
49. **Haykowsky MJ**, **Nicklas BJ**, **Brubaker PH**, **Hundley WG**, **Brinkley TE**, **Upadhya B**, **Becton JT**, **Nelson MD**, **Chen H**, **Kitzman DW.** Regional adipose distribution and its relationship to exercise intolerance in older obese patients who have heart failure with preserved ejection fraction. *JACC Heart Fail* 6: 640–649, 2018. doi:10.1016/j.jchf.2018.06.002.
50. **Bekfani T**, **Bekhite Elsaied M**, **Derlien S**, **Nisser J**, **Westermann M**, **Nietzsche S**, **Hamadanchi A**, **Fröb E**, **Westphal J**, **Haase D**, **Kretzschmar T**, **Schlattmann P**, **Smolenski UC**, **Lichtenauer M**, **Wernly B**, **Jirak P**, **Lehmann G**, **Möbius-Winkler S**, **Schulze PC.** Skeletal muscle function, structure, and metabolism in patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. *Circ Heart Fail* 13: e007198, 2020. doi:10.1161/CIRCHEARTFAILURE.120.007198.

Downloaded from journals.physiology.org/journal/ajpheart (2001:06A8:2100:0136:0000:0000:0006:001D) on December 1, 2025.