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CLINICAL RESEARCH

Peripheral Determinants of Oxygen Utilization in Heart Failure With Preserved Ejection Fraction

Central Role of Adiposity

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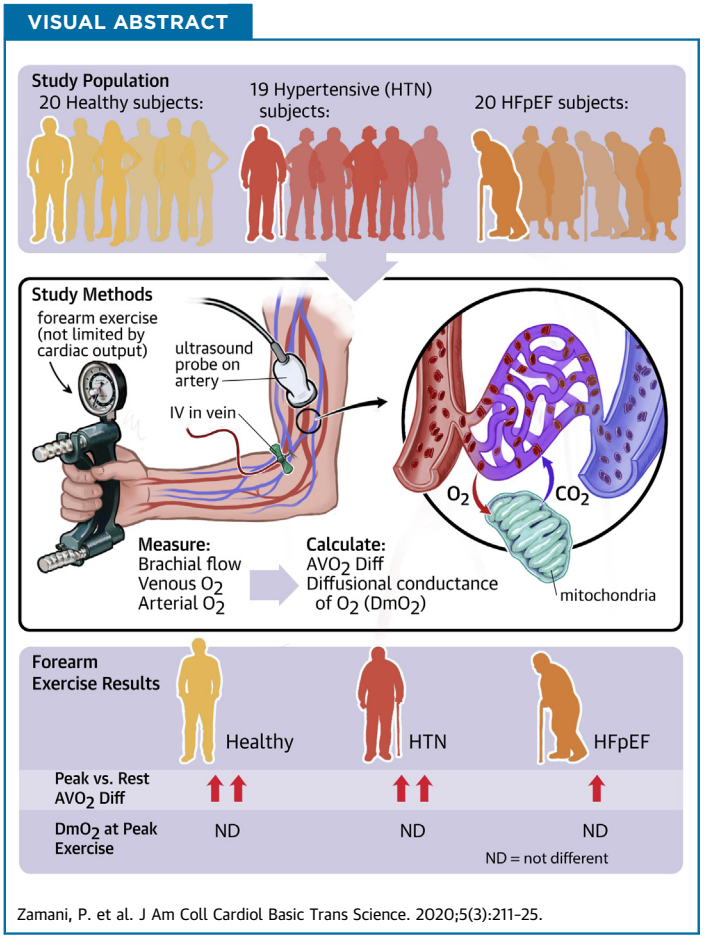
VISUAL ABSTRACT



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ABBREVIATIONS AND ACRONYMS

CO = cardiac output

ΔAV_{O_2} = arteriovenous oxygen content difference

DEXA = dual-energy x-ray absorptiometry

DmO_2 = skeletal muscle diffusional conductance for oxygen

FIo_2 = fraction of inspired oxygen

HFpEF = heart failure with preserved ejection fraction

MVC = maximal voluntary contraction force

NT-proBNP = N-terminal pro-brain natriuretic peptide

Po_2 = partial pressure of oxygen

Vo_2 = oxygen consumption

HIGHLIGHTS

- **ΔAV_{O_2} during exercise is a complex metric that incorporates into its calculation skeletal muscle blood flow and DmO_2 across the skeletal muscle capillary membrane.**
- **Although ΔAV_{O_2} was reduced in patients with HFpEF during both systemic and local (forearm) exercise, there was no difference in forearm DmO_2 among subjects with HFpEF, those with hypertension, and healthy control subjects; therefore, abnormalities in forearm DmO_2 cannot explain the reduced forearm ΔAV_{O_2} seen in subjects with HFpEF.**
- **Local forearm exercise performance predicted about one-third of the variability in systemic aerobic capacity, demonstrating that peripheral factors are important in determining whole-body exercise tolerance.**
- **Degree of adiposity strongly correlated with ΔAV_{O_2} during both local and whole-body exercise, suggesting that adipose tissue may play an active role in limiting exercise capacity in subjects with HFpEF.**

SUMMARY

The aim of this study was to determine the arteriovenous oxygen content difference (ΔAV_{O_2}) in adult subjects with and without heart failure with preserved ejection fraction (HFpEF) during systemic and forearm exercise. Subjects with HFpEF had reduced ΔAV_{O_2}. Forearm diffusional conductance for oxygen, a lumped conductance parameter that incorporates all impediments to the movement of oxygen from red blood cells in skeletal muscle capillaries into the mitochondria within myocytes, was estimated. Forearm diffusional conductance for oxygen was not different among adults with HFpEF, those with hypertension, and healthy control subjects; therefore, diffusional conductance cannot explain the reduced forearm ΔAV_{O_2}. Instead, adiposity was strongly associated with ΔAV_{O_2}, suggesting an active role for adipose tissue in reducing exercise capacity in patients with HFpEF. (J Am Coll Cardiol Basic Trans Science 2020;5:211–25)

An increasing number of patients have heart failure with preserved ejection fraction (HFpEF) (1), leading to hospitalizations and decreased quality of life (2). The heterogeneity of the condition, in addition to its incompletely understood pathophysiologic mechanisms, has led to a dearth of effective therapeutic options for these patients (3). In addition to myocardial abnormalities (4), increasing evidence suggests that abnormalities outside the heart exist, giving rise to the possibility of "peripheral" contributors to exercise intolerance in patients with HFpEF. Several studies have focused on the arteriovenous oxygen content difference (ΔAV_{O_2}), noting its reduction at peak exercise in subjects with HFpEF (5–7) and suggesting that this reflects impairments within the skeletal muscle itself. However, ΔAV_{O_2} is a complex metric, as the movement of oxygen out of skeletal muscle capillaries and into mitochondria is governed both by its delivery to the skeletal muscle capillary network ("convective transport") and by factors that drive oxygen out of red blood cells and ultimately into skeletal muscle

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mitochondria ("diffusive transport") (8). Because slower blood flow through the capillary can lead to greater oxygen extraction because of longer capillary transit time, ΔAV_{O_2} is not dependent solely on skeletal muscle properties (7). In contrast, skeletal muscle diffusional conductance for oxygen (DmO_2) is a lumped parameter that summarizes all impediments to the transfer of oxygen from red blood cells into mitochondria, accounting for differences in blood flow. Thus, DmO_2 is a purer reflection of skeletal muscle properties than ΔAV_{O_2}, incorporating features such as capillarity, fiber size, and fiber composition into its determination. An assessment of DmO_2 is essential to help resolve the mechanistic basis for the deficits in ΔAV_{O_2} seen in patients with HFpEF.

We determined forearm DmO_2 in adults with HFpEF and control subjects using an exercise paradigm that engages the small muscle mass of the forearm and therefore is not constrained by limitations in cardiac output (CO) (9). We hypothesized that subjects with HFpEF would exhibit lower DmO_2, explaining their ΔAV_{O_2} abnormalities. Contrary to our hypothesis, we did not find reductions in forearm DmO_2 in subjects with HFpEF. Instead, we found the degree of adiposity to be a key correlate of ΔAV_{O_2}, supporting a deleterious role of body fat per se in patients with HFpEF and suggesting a novel mechanistic link between obesity and the limitations in aerobic capacity in patients with HFpEF.

METHODS

PARTICIPANTS. This was a cross-sectional analysis of subjects with HFpEF, patients with hypertension without heart failure symptoms, and healthy control subjects. Inclusion criteria for subjects with HFpEF included symptomatic heart failure (New York Heart Association functional class II or III) in the context of a preserved ejection fraction (≥50%) and stable medical management for at least 1 month. Subjects were required to have evidence of elevated filling pressure, which included at least 1 of the following: 1) prior admission for heart failure requiring intravenous diuretic agents; 2) history of elevated invasively determined filling pressures (pulmonary capillary wedge pressure >15 mm Hg or left ventricular end-diastolic pressure >16 mm Hg); 3) mitral E/septal e′ ratio >15; or 4) mitral E/e′ ratio >8 in addition to 1 of the following: elevated N-terminal pro-brain natriuretic peptide (NT-proBNP), left atrial volume index >34 ml/m^2, or chronic use of loop diuretic agents for control of heart failure symptoms. Given the near ubiquitous presence of hypertension in patients with HFpEF, we enrolled a group of patients with hypertension without heart failure symptoms as an additional control group. Patients with hypertension included those who were treated with antihypertensive medications, had been on stable medical therapy for at least 1 month, and had no histories or symptoms consistent with heart failure. Healthy control subjects were those who did not have histories of hypertension or heart failure. Although other cardiovascular conditions were exclusionary, treated hypercholesterolemia was allowed in the healthy group to allow representation of elderly subjects within the healthy control group. Exclusion criteria were as follows: current atrial fibrillation; inability to exercise; moderate or greater aortic or mitral valve disease; hemoglobin <10 g/dl; known hypertrophic, inflammatory, or infiltrative cardiomyopathy; pericardial disease; current angina due to clinically significant obstructive epicardial coronary disease; acute coronary syndrome within the past 2 months; primary pulmonary arterial hypertension; clinically significant lung disease (e.g., current use of supplemental oxygen aside from nocturnal oxygen as part of treatment for obstructive sleep apnea, use of steroids or antibiotics within the past 6 months for an acute exacerbation of obstructive pulmonary disease, most proximal pulmonary function testing with a forced expiratory volume in 1 s <50% predicted, and most proximal 6-min walk test with arterial oxygen desaturation); ischemia on stress testing without subsequent revascularization or demonstration of nonobstructive coronary disease on coronary angiography; significant liver disease affecting synthetic function or volume control; uncontrolled hypertension (blood pressure >180/110 mm Hg at baseline), estimated glomerular filtration rate <30 ml/min/m^2 or creatinine >2.5 mg/dl; alcohol dependence; and chronic narcotic use that could not be interrupted. The University of Pennsylvania Institutional Review Board approved the study. All subjects provided written informed consent prior to entry.

STUDY PROCEDURES. Subjects presented to the Center for Human Phenomic Science at the University of Pennsylvania in a fasting state. Blood was obtained for basic chemistry, complete blood count, and NT-proBNP measurement (Cobas e411 Analyzer, Roche Diagnostics, Indianapolis, Indiana). One heart failure cardiologist (P.Z.) reviewed the medical history of each subject, and anthropomorphic data were collected.

DUAL ENERGY X-RAY ABSORPTIOMETRY (DEXA). Whole-body DEXA was performed for body composition on a Hologic Horizon scanner (analysis version 13.5.3.1, Hologic, Bedford, Massachusetts). Whole-body (fat mass, lean mass [including lean mass plus

bone mineral content], total mass, and percentage fat) and limb-specific composition data were obtained.

ECHOCARDIOGRAPHY AND HEMODYNAMIC MEASUREMENTS. Subjects underwent resting and exercise echocardiography using a GE Vivid E9 machine (GE Healthcare, Fairfield, Connecticut). The left ventricular outflow tract Doppler velocity-time integral was obtained from the 5-chamber view at rest and during exercise. Stroke volume was calculated as the product of the left ventricular outflow tract velocity-time integral and its cross-sectional area; CO was calculated as stroke volume × heart rate (10,11).

EXERCISE PROTOCOL. As described previously, subjects underwent a maximal-effort supine exercise test using cycle ergometry with gas exchange measurements (Parvo Medics, Sandy, Utah) (10,11). Work rate began at 15 W for 3 min, increasing to 25 W for 3 min, then increasing by 25 W every 3 min thereafter. A metronome was used to maintain a cadence of 60 rpm. The exercise test was terminated either at the time of volitional fatigue or when the cadence could not be maintained above 50 rpm, despite strong verbal encouragement. In a prior study using an identical protocol, our subjects with HFpEF were able to exercise for approximately 15 min (10). After completion of the 125-W stage (18 min), the duration of each stage for patients with hypertension and healthy subjects was reduced to 2 min to speed completion of the protocol.

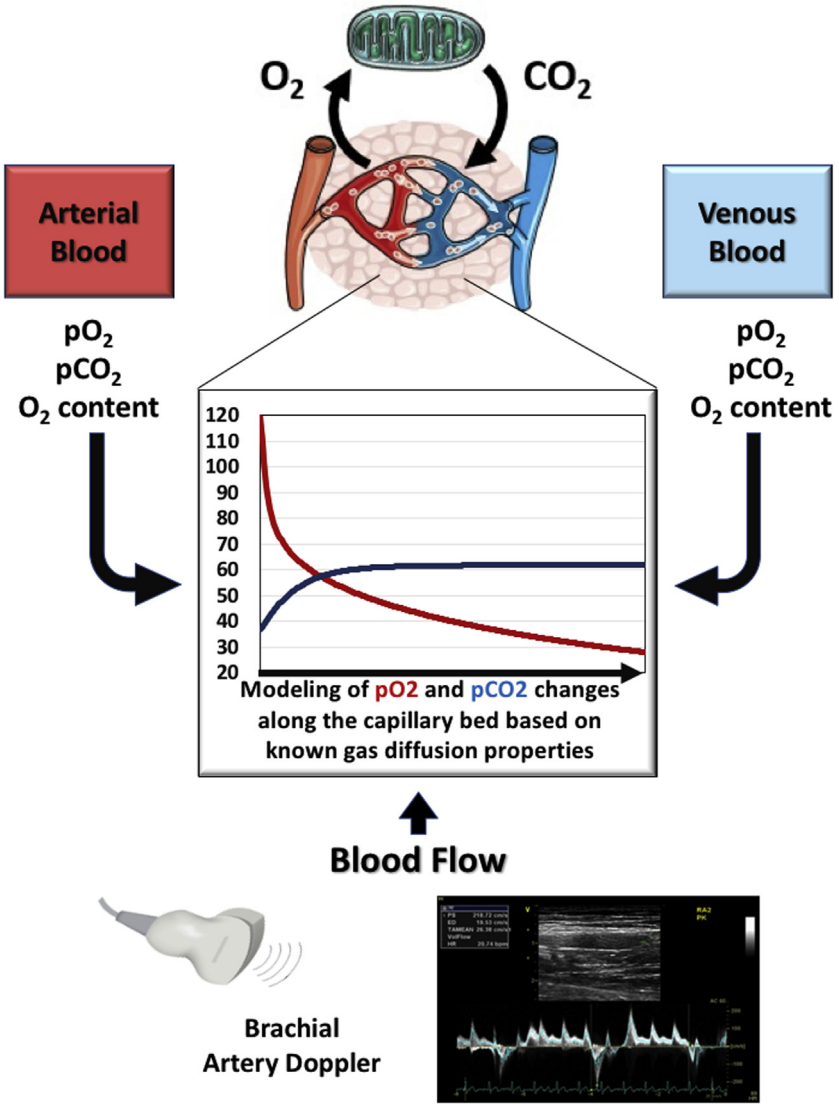
Custom-designed software was programmed in MATLAB version R2016b (The MathWorks, Natick, Massachusetts) for processing and quantification of cardiopulmonary exercise testing data. Breath-by-breath measurements were passed through a low-pass frequency filter to remove random noise in the measurements. Baseline measurements were obtained from the minute prior to the initiation of exercise. Peak oxygen consumption (V_{O_2}) and other gas-exchange measurements were defined as the average values obtained during the last 30 s of exercise. Peak predicted V_{O_2} was calculated using the Wasserman/Hansen equations (12). Respiratory exchange ratio was calculated as the ratio of carbon dioxide production to V_{O_2} at peak exercise. Heart rate was monitored throughout exercise using a 12-lead electrocardiographic system (XScribe 5, Mortara Instruments, Milwaukee, Wisconsin). Systemic ΔAV_{O_2} was determined as the ratio of V_{O_2} to CO. A venous blood gas sample was obtained from a standard indwelling antecubital catheter at the end of the cycle ergometric exercise protocol. An arterial blood gas sample was obtained from the radial artery at peak exertion, immediately after the cessation of cycle exercise (generally within 10 s of exercise cessation). Blood gas samples throughout the protocol were analyzed using a GEM Premier 4000 automated analyzer (Instrumentation Laboratory, Bedford, Massachusetts). Values were measured at 37°C. Blood pressure was measured throughout exercise using a validated oscillometric device (Tango M2 blood pressure monitor, SunTech Medical Instruments, Morrisville, North Carolina) (13). Peripheral vascular resistance was computed as mean arterial pressure/CO and expressed in Wood units. Pulmonary vascular resistance was also indexed to body surface area to account for differences in body size (14).

FOREARM EXERCISE PROTOCOL. Following cycle ergometric exercise, subjects were provided with a standardized meal. Approximately 1 h later, a 20-gauge, 1-inch venous catheter (BD Insyte Autoguard BC shielded intravenous catheter, Becton Dickinson Infusion Therapy Systems, Sandy, Utah) was inserted into a deep antecubital vein of the dominant arm, ensuring that the vein selected did not take a superficial course but rather went deep into the muscle, by visual inspection (15).

A grip-force transducer (linear range: 0–800 N; accurate to within 5%) was connected to a PowerLab data acquisition module (ADInstruments, Colorado Springs, Colorado) running LabChart Pro on a Macintosh personal computer. Subjects performed 3 maximal-effort 1-s isometric handgrip contractions, with the peak force output (newtons) averaged to determine maximal voluntary contraction force (MVC). Subjects then began a graded forearm exercise protocol during which they performed handgrip exercise at 40% MVC for 1 min, increasing immediately thereafter to exercise at 50% MVC for 1 min, and then maximal effort for 1 min. Contractions were sustained at a given force for 1 s followed by 2 s of rest (0.33 Hz). A combination of visual and auditory cues was used to maintain cadence and grip strength. During the final 15 s of each stage, deep venous blood was drawn into a heparinized blood gas syringe, placed on ice, and immediately run on the blood gas analyzer. Forearm handgrip data (average %MVC and total work performed) was automatically abstracted by the LabChart software for the final 20 s of each exercise increment.

Brachial artery blood flow was assessed using a vascular probe at rest and during the last 15 s of each exercise transient. Doppler velocity profiles of contraction-relaxation cycles, each lasting 3 s in duration, were obtained at each stage of exercise. Time-averaged mean velocities for each contraction-relaxation cycle were automatically traced using the

FIGURE 1 DmO_2 Method



A forward integration is performed during which the changes in oxygen and carbon dioxide content are simultaneously calculated along each step of the capillary. Skeletal muscle diffusional conductance for oxygen (DmO_2) is iteratively varied until the end-capillary contents match the measured venous blood gas contents for oxygen and carbon dioxide. pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen.

Vivid E9 ultrasound system. Vessel diameter was measured at end-diastole at the same vessel location at which Doppler velocities were obtained. Brachial artery blood flow was determined as the product of the average mean velocity and the vessel cross-sectional area (Figure 1).

After 30 min of rest, the forearm exercise protocol was repeated. To demonstrate that peak forearm exercise performance was limited by oxygen delivery and not by mitochondrial oxidative capacity, additional studies were performed while breathing 100% oxygen ($FIo_2 = 1.00$) to increase arterial oxygen content (9,16). Following 30 min of rest after the room-air transients ($FIo_2 = 0.21$), 2 additional identical exercise transients were then performed while the subject breathed 100% oxygen. Two room-air forearm exercise bouts were always performed first, followed by 2 exercise bouts while breathing 100% oxygen. Within a given FIo_2 (0.21 or 1.00), there was no significant difference in work performed, brachial

flow, or forearm V_{O_2} at maximal exertion; therefore, results from the 2 transients at each FI_{O_2} were averaged together to minimize variation.

A resting arterial blood gas sample was obtained once at each FI_{O_2}. Given the minimal demand of forearm exercise on whole-body exercise capacity, the arterial content was assumed to be constant throughout each forearm exercise transient (17). Venous blood sampling from a deep vein has previously been shown to reflect forearm muscle metabolic activity during handgrip exercise, as evidenced by a commensurate rise in V_{O_2} with exercise (17–19). Arterial and venous oxygen contents were determined as: 1.34 × hemoglobin (g/dl) × oxygen saturation/100 + 0.003 × partial pressure of oxygen (P_{O_2}) (mm Hg). Forearm V_{O_2} was determined as ΔAV_{O_2} multiplied by brachial artery blood flow.

DETERMINATION OF FOREARM DmO_2. In brief, a numeric integration procedure was performed such that, starting with arterial oxygen and carbon dioxide contents, the contents of both gases in capillary blood are incrementally changed as oxygen and carbon dioxide are exchanged across the capillary membrane in small time steps. For any given blood flow, the rate of movement across the membrane is governed by the diffusional conductance for the specific gas, where the diffusional conductance for carbon dioxide is assumed to be 20 times DmO_2. The procedure is repeated iteratively, using different estimates for DmO_2, until the calculated oxygen and carbon dioxide contents at the end of the skeletal muscle capillary match the directly measured venous blood gas contents (**Figure 1**) (see the Supplemental Appendix for additional details on methodology) (9,20,21).

STATISTICAL ANALYSIS. Demographic data are presented as count (percentage), mean ± SD, or median (interquartile range). The Shapiro-Wilk test was used to assess normality. Variables with skewed distributions were compared using the Kruskal-Wallis test, and normally distributed variables were compared using analysis of variance. Post hoc comparisons for between-group differences were performed with Bonferroni correction. Average values from the overall cohort were recorded for both room-air (FI_{O_2} = 0.21) and FI_{O_2} = 1.00 oxygen transients. When a significant difference between FI_{O_2} = 0.21 and FI_{O_2} = 1.00 was detected for a given outcome variable, intergroup differences in the change were compared to assess for differences in the group response to oxygen. Linear mixed-effect models with random intercepts were created using all available data points (FI_{O_2} = 0.21 and FI_{O_2} = 1.00) from the forearm exercise studies to examine relationships between the determinants of V_{O_2} using the Fick principle. The mixed package from STATA/SE version 13.1 (StataCorp., College Station, Texas) was used, assuming an independent covariance structure.

In these models, estimated marginal means of brachial flow indexed to forearm lean muscle were computed to adjust for differences in muscle mass. Analogous models were also created using systemic parameters to assess the change in systemic ΔAV_{O_2} as a function of the change in estimated marginal means of CO, indexed to total leg lean mass. We analyzed the relationships between body composition and local and systemic ΔAV_{O_2} using ordinary least squares linear regression. Additional covariates with biologic plausibility were tested within the model, including age, sex, HFpEF status, forearm DmO_2, and blood flow (brachial artery flow or CO for local and systemic models, respectively). Parsimonious models were created using backward elimination to remove variables that did not significantly contribute to the prediction. Standardized beta values are presented, expressing the change in the dependent variable for each 1-SD change in the independent variable, allowing meaningful comparison of the strength of associations among independent variables in a unitless manner. Ordinary least squares linear regression models were also created to examine the relationship between forearm and cycle ergometric V_{O_2}. Within this regression model, interaction testing was performed to determine if the slope in the relationship between forearm V_{O_2} and cycle ergometry was different between groups. The interaction was not significant and was not included in the final model. The adjusted R^2 values for the multivariate ordinary least squares linear regression models are presented, describing the proportion of variability of the dependent variable that is explained by the covariates. Spearman's rho was used to measure the strength of associations between variables. Analyses were performed in STATA/SE version 13.1, with p values <0.05 considered to indicate statistical significance. One author (P.Z.) had access to all data and takes responsibility for its integrity and data analysis.

RESULTS

STUDY POPULATION. Fifty-nine subjects (20 healthy, 19 with hypertension, 20 with HFpEF) were enrolled in the study and provided exercise data. All subjects with HFpEF were symptomatic. Three subjects with HFpEF were enrolled on the basis of histories of heart failure hospitalization, 11 were enrolled on the basis of elevations in invasively measured intracardiac filling pressures, 3 were enrolled on the

TABLE 1 Subject Characteristics

	Healthy (n = 20)	HTN (n = 19)	HFpEF (n = 20)	p Value
Age, yrs	54 (39–63)	66 (50–71)	67* (62–76)	0.001
Female	6 (30)	7 (37)	13 (65)	0.067
Ethnicity				0.001
White	20 (100)	14 (73.7)	12 (60)	
African American	0 (0)	3 (15.8)	8 (40)	
Asian	0 (0)	2 (10.5)	0 (0)	
Height, cm	171.9 ± 6.8	171.6 ± 9.7	165.3 ± 9.9	0.037
Weight, kg	81.4 (68.7–85.7)	80.4 (73.0–89.0)	99.1* (78.3–113.5)	0.020
BMI, kg/m^2	26.7 (23.6–28.7)	27.7 (24.6–31.5)	32.1*† (28.7–44.4)	<0.001
Total body fat, %	30.8 ± 9.0	34.2 ± 9.4	43.3 ± 7.3*†	<0.001
Total body lean mass, %	69.2 ± 9.0	65.8 ± 9.4	56.7 ± 7.3*†	<0.001
Forearm total mass, kg	1.23 (1.04–1.37)	1.24 (1.13–1.37)	1.24 (1.00–1.49)	0.81
Forearm lean mass, kg	0.89 (0.66–1.03)	0.92 (0.61–1.06)	0.60 (0.53–0.87)	0.10
Forearm fat, %	26.5 (19.9–31.4)	25.2 (21.6–39.2)	43.9*† (33.3–54.6)	<0.001
Hypertension	0 (0)	19 (100)	20 (100)	<0.001
Diabetes	0 (0)	3 (15.8)	11 (55.0)	<0.001
Insulin	0 (0)	0 (0)	4 (20)	0.030
Hyperlipidemia	5 (25)	11 (57.9)	18 (90)	<0.001
Coronary artery disease	0 (0)	0 (0)	4 (20)	0.030
Prior atrial fibrillation/flutter	0 (0)	3 (15.8)	7 (35)	0.008
OSA	1 (5)	4 (21.1)	12 (60)	<0.001
CPAP device	0 (0)	2 (10.5)	7 (35)	0.005
Beta-blocker	0 (0)	6 (31.6)	16 (80)	<0.001
CCB	0 (0)	7 (36.8)	11 (55)	<0.001
ACE inhibitor/ARB	0 (0)	10 (52.6)	14 (70)	<0.001
Loop diuretic	0 (0)	0 (0)	10 (50)	<0.001
Thiazide diuretic	0 (0)	3 (15.8)	4 (20)	0.125
Statin	3 (15)	8 (42.1)	14 (70)	0.002
NYHA functional class II			18 (90)	
eGFR, ml/min	87.3 ± 12.6	79.5 ± 17.8	71.1 ± 19.9*	0.015
Hemoglobin, g/dl	13.9 ± 1.3	14.0 ± 1.0	12.7 ± 1.1*†	<0.001
NT-proBNP, pg/ml	35.0 (17.0–63.5)	65.0 (34.0–127.0)	119.0* (49.0–241.5)	0.002
LV ejection fraction, %	59.6 ± 6.8	59.8 ± 4.5	61.9 ± 5.6	0.388
Tricuspid regurgitant jet velocity, cm/s	199.8 ± 26.8	233.2 ± 40.8‡	265.5 ± 28.8*†	<0.001
Mitral inflow early velocity (E), cm/s	67.4 (54.1–79.4)	75.2 (64.1–84.4)	80.3* (66.5–97.3)	0.035
Septal TD e′ velocity, cm/s	9.6 ± 2.3	8.9 ± 1.9	7.6 ± 2.4*	0.016
Mitral E/septal e′ ratio	6.6 (5.9–8.5)	9.0 (7.0–10.5)	11.9*† (8.4–13.4)	<0.001

Values are median (interquartile range), n (%), or mean ± SD. *HFpEF versus healthy, adjusted $p < 0.05$. †HFpEF versus HTN, adjusted $p < 0.05$. ‡Healthy versus HTN, adjusted $p < 0.05$.

ACEi = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CCB = calcium-channel blocker; CPAP = continuous positive airway pressure; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OSA = obstructive sleep apnea; TD = tissue Doppler.

basis of midrange mitral E/septal e′ ratios of >8 and elevated NT-proBNP, and 3 were enrolled on the basis of midrange E/e′ ratios and chronic loop diuretic agent use.

Demographic and medical history data are presented in Table 1. Subjects with HFpEF were older, were more obese, and had typical comorbidities consistent with the disease, such as hypertension (100%), diabetes (55%), hyperlipidemia (90%), and obstructive sleep apnea (60%). Subjects with HFpEF exhibited higher NT-proBNP and lower hemoglobin concentrations. The tricuspid regurgitant jet velocity was higher in subjects with HFpEF, alongside an increased mitral E/septal e′ ratio. On DEXA, subjects with HFpEF had marked increases in total body and forearm fat (Table 1).

CYCLE ERGOMETRIC EXERCISE DATA. Cycle ergometric exercise data are presented in Table 2. Subjects with HFpEF exercised for a significantly shorter duration than either patients with hypertension or healthy control subjects. Commensurate with this, peak V_{O_2} was reduced in subjects with HFpEF compared with either control group, regardless of how V_{O_2} is presented (unindexed, indexed to body

TABLE 2 Results of Maximal-Effort Cardiopulmonary Exercise Testing

	Healthy (n = 20)	HTN (n = 19)	HFpEF (n = 20)	p Value
Baseline				
Heart rate, beats/min	62.7 ± 10.2	67.2 ± 12.6	69.8 ± 9.7	0.127
MAP, mm Hg	97.0 ± 10.0	99.9 ± 10.6	97.5 ± 14.4	0.724
Stroke volume, ml	73.2 (67.5–88.6)	66.4 (62.5–75.3)	83.4 (71.3–97.6)	0.085
Cardiac output, l/min	4.8 (4.2–5.5)	4.3 (3.6–5.9)	6.0 (5.0–6.5)	0.084
Vo_2, l oxygen/min	0.26 ± 0.04	0.27 ± 0.04	0.27 ± 0.06	0.927
Indexed Vo_2, ml/kg body weight/min	3.4 ± 0.6	3.3 ± 0.8	2.7 ± 0.5*†	0.003
Indexed Vo_2, ml/kg leg lean mass/min	15.2 ± 2.3	15.5 ± 2.6	15.3 ± 2.4	0.915
ΔAVo_2, ml oxygen/dl blood	5.4 (4.8–6.4)	6.1 (4.8–7.1)	4.5*† (4.3–5.3)	0.013
PVR, WU	20.9 ± 5.2	22.3 ± 6.2	17.6 ± 4.9†	0.033
PVR index, WU · m^2	40.3 ± 8.6	45.2 ± 12.5	37.6 ± 9.6	0.090
Peak				
Heart rate, beats/min	148.7 ± 18.4	136.6 ± 26.6	114.6 ± 24.9*†	<0.001
MAP, mm Hg	116.7 ± 12.8	123.8 ± 14.2	122.3 ± 19.7	0.347
Stroke volume, ml	77.5 (65.0–91.4)	67.7 (60.8–79.1)	87.0† (69.8–95.7)	0.027
Cardiac output, l/min	11.5 (10.0–13.8)	9.7 (7.6–11.9)	9.8 (7.5–11.5)	0.079
Arterial oxygen delivery, l oxygen/min	2.1 (1.9–2.6)	1.9 (1.4–2.2)	1.6* (1.2–1.8)	0.016
RER	1.19 ± 0.12	1.17 ± 0.13	1.06 ± 0.13*†	0.004
Arterial lactate, mmol/l	9.4 (7.5–11.8)	7.3 (5.3–9.1)	6.1 (5.1–10.3)	0.066
Venous lactate	7.5 ± 3.2	5.9 ± 2.8	4.4 ± 3.0*	0.014
Borg dyspnea	7.5 (6–9)	7 (5–8)	8 (7.5–9.5)	0.095
Borg fatigue	8 (8–9)	8 (7–9)	8 (6–8)	0.171
Exercise time, min	24.2 (20.1–32.3)	20.0 (13.9–28.5)	5.5*† (3.3–10.8)	<0.001
Work rate, W	208.9 (160.1–312.5)	150.0 (100.0–275.0)	25.0*† (19.8–75.0)	<0.001
Vo_2, l oxygen/min	1.90 (1.31–2.31)	1.49 (1.10–1.68)	0.95*† (0.75–1.34)	<0.001
% predicted Vo_2	89.8 ± 19.7	76.9 ± 15.1	64.0 ± 14.1*	<0.001
Indexed Vo_2, ml/min/kg body weight	23.9 (19.9–31.5)	16.8‡ (12.7–20.7)	10.1*† (7.9–14.7)	<0.001
Indexed Vo_2, ml/min/kg leg lean mass	109.0 ± 23.7	83.2 ± 21.9‡	59.2 ± 16.0*†	<0.001
ΔAVo_2, ml oxygen/dl blood	15.8 (14.3–19.1)	14.9 (11.2–17.5)	11.2*† (8.7–13.0)	<0.001
Oxygen pulse, ml oxygen/beat	12.4 (10.0–15.2)	10.3 (8.1–14.1)	9.0* (6.8–11.5)	0.004
PVR, WU	10.2 (8.3–11.9)	13.4‡ (10.6–17.3)	12.3 (9.9–17.8)	0.037
PVR index, WU · m^2	19.2 (16.4–22.3)	25.8‡ (21.3–34.0)	27.6* (21.0–35.1)	0.004

Values are mean ± SD or median (interquartile range). *HFpEF versus healthy, adjusted $p < 0.05$. †HFpEF versus HTN, adjusted $p < 0.05$. ‡Healthy versus HTN, adjusted $p < 0.05$.

ΔAVo_2 = arteriovenous oxygen content difference; MAP = mean arterial pressure; PVR = peripheral vascular resistance; RER = respiratory exchange ratio; Vo_2 = oxygen consumption; WU = Wood units; other abbreviations as in Table 1.

mass, or indexed to leg lean mass). Although the mean respiratory exchange ratio was lower in the HFpEF group, comparably increased blood lactate levels and Borg scores were present in all 3 groups at peak, supportive of exhaustive effort, particularly when one considers the older age of the participants with HFpEF (**Table 2**) (22).

The CO response to exercise was commensurate with the rise in Vo_2 in all groups: for every 1 l of oxygen consumed per minute, CO increased by 4.5 ± 1.5 l/min in healthy subjects, 4.5 ± 1.7 l/min in those with hypertension, and 5.5 ± 2.2 l/min in those with HFpEF ($p = 0.173$). Although the peak arterial oxygen delivery was reduced in subjects with HFpEF primarily because of reduced arterial oxygen content, the change in arterial oxygen delivery versus the change in Vo_2 from baseline to peak exercise was no different between groups ($p = 0.718$) (see the Supplemental Data in the Supplemental Appendix).

Systemic ΔAVo_2, calculated as the ratio of Vo_2 to CO according to the Fick principle, was significantly lower at peak exercise in patients with HFpEF. Similarly, the oxygen pulse, which is derived from directly measured variables (oxygen pulse = Vo_2/heart rate), was also reduced in patients with HFpEF (**Table 2**).

FOREARM EXERCISE AND DmO_2. Forearm exercise data are presented in **Table 3**. Exhaustive effort was achieved in all groups, as evidenced by similar relative effort at peak exertion (%MVC) and similar total work performed during the final 20 s. Peak forearm Vo_2 was not different among groups.

Supplemental oxygen ($FIo_2 = 1.00$) increased forearm maximal Vo_2, compared with $FIo_2 = 0.21$, confirming that maximal forearm Vo_2 was limited by

TABLE 3 Forearm Exercise Parameters During Maximal Effort

	Room Air Transients				100% Oxygen Transients						
	Healthy (n = 20)	HTN (n = 17)	HFpEF (n = 18)	p Value	Healthy (n = 20)	HTN (n = 17)	HFpEF (n = 18)	p Value	RA Transients	100% Transients	p Value
Exercise parameters at peak effort											
% MVC	71.7 (62.2–79.4)	70.4 (58.4–76.3)	72.6 (64.3–79.0)	0.789	67.7 (61.4–78.7)	66.9 (56.3–71.7)	66.5 (62.2–79.4)	0.560	72.2 (62.6–78.4)	66.7 (60.2–77.9)	0.120
Work performed during last 20 s, N · s	1,615.4 ± 589.6	1,581.8 ± 717.8	1,326.4 ± 584.0	0.296	1,500.4 ± 421.3	1,559.8 ± 600.9	1,221.8 ± 427.8	0.084	1,506.6 ± 634.5	1,428.6 ± 502.8	0.027
Venous lactate, mmol/l	3.0 (2.5–3.3)	3.2 (2.2–3.4)	2.1* (1.9–2.9)	0.049	2.2 ± 0.6	2.1 ± 0.6	1.9 ± 0.6	0.222	2.8 (2.1–3.2)	2.1 (1.6–2.6)	<0.001‡
Brachial blood flow (ml/min)	192.3 (143.1–331.6)	212.8 (175.5–249.8)	219.4 (142.3–296.3)	0.984	201.5 (151.5–292.1)	224.2 (170.1–296.8)	204.9 (145.7–299.0)	0.910	212.8 (144.0–297.0)	207.5 (163.2–296.8)	0.254
Brachial blood flow (ml/min/kg forearm lean mass)	268.0 ± 103.0	261.1 ± 90.3	313.9 ± 106.8	0.208	270.9 ± 90.8	278.8 ± 104.1	316.4 ± 101.8	0.319	281.4 ± 101.5	288.4 ± 99.2	0.414
Blood gas measurements at maximal effort											
Arterial P_{O_2}, mm Hg	85.9 ± 14.3	85.6 ± 8.4	77.5 ± 8.8	0.031	530.0 (501.0–553.0)	505.0 (462.0–522.0)	483.5 (385.5–592.5)	0.359	84.0 (75.0–89.0)	507.5 (461.0–553.0)	<0.001
Arterial oxygen content, ml oxygen/dl blood	18.4 ± 1.9	18.6 ± 1.8	16.5*† ± 1.3	<0.001	20.3 ± 1.9	20.2 ± 1.8	18.1*† ± 1.5	<0.001	17.9 ± 1.9	19.6 ± 2.0	<0.001
Arterial oxygen delivery, ml oxygen/min	39.4 (23.3–62.6)	38.6 (40.0–50.1)	32.9 (22.1–43.5)	0.438	46.4 ± 22.4	48.1 ± 17.4	41.5 ± 20.3	0.614	38.3 (23.9–50.1)	43.0 (29.6–58.7)	<0.001
Venous P_{O_2}, mm Hg	23.2 ± 3.7	24.2 ± 4.0	24.6 ± 4.8	0.551	26.2 ± 3.7	26.4 ± 4.4	27.6 ± 4.1	0.571	24.0 ± 4.1	26.7 ± 4.0	<0.001
Venous oxygen content, ml oxygen/dl blood	6.6 (6.1–7.5)	7.3 (6.6–8.5)	6.4 (5.9–7.1)	0.101	8.4 ± 2.0	9.0 ± 1.4	8.2 ± 1.8	0.321	6.7 (6.2–7.9)	8.4 (7.8–9.6)	<0.001
ΔAV_{O_2}, ml oxygen/dl blood	11.6 (10.9–12.7)	11.1 (9.8–12.1)	9.6* (9.1–11.2)	0.005	11.9 ± 1.6	11.2 ± 2.1	9.9* ± 1.8	0.011	11.1 (9.7–12.3)	11.3 (9.6–12.6)	0.131
Forearm V_{O_2}, ml oxygen/min	21.6 (15.9–38.6)	21.3 (16.9–33.4)	19.0 (13.1–24.3)	0.216	26.0 16.6–34.5)	25.9 (19.1–37.3)	20.2 (13.1–28.4)	0.438	21.2 (15.3–27.4)	23.3 (16.6–34.5)	0.0499
Forearm V_{O_2}, ml/min/kg forearm lean mass	31.5 ± 12.9	28.4 ± 9.2	29.5 ± 10.8	0.668	31.8 ± 11.7	31.5 ± 11.8	31.5 ± 10.8	0.996	29.8 ± 11.0	31.6 ± 11.3	0.076
Diffusional conductance for oxygen											
Mean capillary DmO_2 (ml/min/mm Hg)	0.54 (0.42–1.04)	0.63 (0.46–0.70)	0.48 (0.32–0.62)	0.140	0.55 (0.37–0.81)	0.57 (0.42–0.75)	0.46 (0.27–0.65)	0.250	0.56 (0.41–0.74)	0.49 (0.40–0.73)	0.018
Mean capillary DmO_2/kg forearm lean mass (ml/min/mm Hg/kg)	0.83 ± 0.34	0.73 ± 0.23	0.77 ± 0.30	0.565	0.70 ± 0.26	0.72 ± 0.26	0.69 ± 0.24	0.915	0.78 ± 0.29	0.70 ± 0.25	0.009
Mean capillary P_{O_2} (mm Hg)	37.5 ± 4.4	38.0 ± 4.6	37.9 ± 4.3	0.932	46.3 (42.3–48.4)	44.1 (40.2–49.6)	47.8 (42.6–50.0)	0.781	37.8 (35.1–40.2)	46.2 (42.3–49.5)	<0.001

Values are median (interquartile range) or mean ± SD. RA and 100% represent overall group summary statistics for the transients at the given inspired oxygen concentrations. *HFpEF versus healthy, adjusted $p < 0.05$. †HFpEF versus HTN, adjusted $p < 0.05$. ‡The decrease in lactate at peak effort with oxygen, compared with RA, was significantly greater in healthy individuals than subjects with HFpEF.

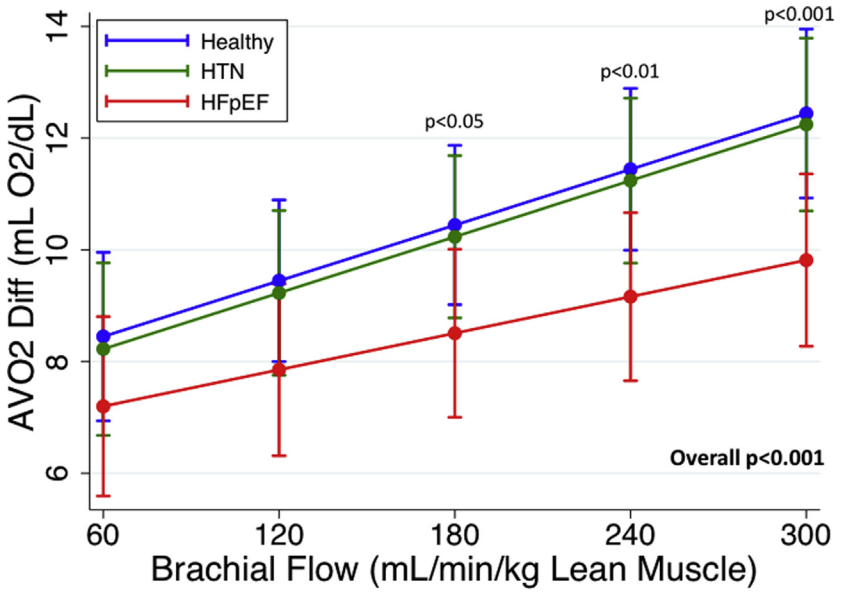
DmO_2 = skeletal muscle diffusional conductance for oxygen; MVC = maximal voluntary contraction force; P_{O_2} = partial pressure of oxygen; other abbreviations as in Tables 1 and 2.

oxygen delivery as opposed to mitochondrial oxidative capacity during the room-air transients. There was no difference in the V_{O_2} response to 100% oxygen between the groups. Brachial blood flow was no different between groups and was unaffected by supplemental oxygen.

Forearm DmO_2 was no different between groups, even when indexed to forearm lean muscle mass (Table 3, Supplemental Figure 1). Forearm DmO_2 correlated with systemic peak V_{O_2} on cycle ergometry ($\rho = 0.51$; $p = 0.0001$). As with cycle ergometry, forearm ΔAV_{O_2}, which was directly measured from arterial and venous blood gases, was lower in patients with HFpEF.

RELATIONSHIP BETWEEN ΔAV_{O_2} AND BLOOD FLOW. Because larger muscle mass necessitates greater blood flow, we analyzed the relationship between ΔAV_{O_2} and estimated brachial blood flow

FIGURE 2 ΔAVo_2 **Versus Brachial Flow**



The relationship between arteriovenous oxygen content difference (ΔAVo_2) and estimated brachial flow, indexed to forearm lean mass, during forearm exercise. Data are displayed as marginal means with 95% confidence intervals. HFpEF = heart failure with preserved ejection fraction; HTN = hypertension.

indexed to forearm lean mass, using more than 800 data points obtained during all forearm exercise studies, and computed estimated marginal means at various blood flow rates. We found a significant difference in this relationship in subjects with HFpEF, with lower ΔAVo_2 for any given estimated indexed blood flow (Figure 2) (overall $p < 0.001$), and a lower slope describing the rate of rise in ΔAVo_2 as blood flow increases (slope comparison: HFpEF vs. hypertension, $p = 0.010$; HFpEF vs. healthy, $p = 0.009$; healthy vs. hypertension, $p = 1.0$).

A similar analysis was performed comparing systemic ΔAVo_2 to estimated CO, indexed to leg lean mass, during cycle ergometry. Because few subjects with HFpEF were able to complete the fourth stage of exercise, analyses were restricted to the first 3 stages of exercise to ensure representation of subjects with HFpEF at each time point. In these analyses, subjects with HFpEF tended to have lower ΔAVo_2 for any given estimated indexed CO (Supplemental Figure 2) ($p = 0.081$).

MODELS PREDICTING ΔAVo_2**.** Univariate predictors of the regional and systemic ΔAVo_2 are presented in Table 4. Multivariate linear models were created to determine the independent correlates of the forearm arteriovenous oxygen content relationship for all subjects (Table 4). For any given DmO_2 and brachial blood flow, forearm tissue composition was a significant predictor of ΔAVo_2, with an increase in forearm fat correlating with a reduced ΔAVo_2.

Similar models were then created for systemic ΔAVo_2, in which local determinants were substituted for their systemic counterparts (i.e., CO was substituted for brachial flow, and whole-body fat was substituted for forearm fat). In these models, body composition significantly predicted systemic ΔAVo_2, with a negative correlation seen for body fat mass, while lean mass was positively correlated with systemic ΔAVo_2.

RELATIONSHIP BETWEEN FOREARM Vo_2 **AND CYCLE ERGOMETRY** Vo_2**.** Despite no difference in peak forearm Vo_2 among groups, forearm Vo_2 was moderately correlated with cycle ergometric peak Vo_2 ($\rho = 0.53$; $p < 0.0001$). Using linear regression, peak forearm Vo_2 predicted 36% of the variability in cycle ergometric peak Vo_2 (Figure 3A) (standardized $\beta = 0.61$; $p < 0.001$; model $R^2 = 0.36$).

We then explored differences in this relationship among groups. Formal interaction testing revealed no differences in the slope of the relationship between

forearm and cycle V_{O_2}; however, there were differences in the main effects (i.e., group). For any given forearm V_{O_2}, the predicted cycle ergometric V_{O_2} was lower in subjects with HFpEF compared with healthy controls, with subjects with hypertension being roughly in the middle of the other groups (Figure 3B). Addition of the grouping variable increased the amount of variability in cycle ergometric V_{O_2} explained by the covariates (model adjusted $R^2 = 0.55$; $p < 0.001$).

DISCUSSION

The main findings of this study are as follows: 1) subjects with HFpEF demonstrated a marked reduction in cycle ergometric exercise capacity; 2) because CO increased in accordance with V_{O_2} (an increase of ~5 l/1 l of oxygen consumed), our findings suggest that abnormalities in ΔAV_{O_2} play a key role in limiting exercise capacity; 3) in line with this, for any given increase in forearm blood flow during local exercise, subjects with HFpEF demonstrated lower forearm ΔAV_{O_2} with a shallower rate of rise as flow increased; 4) however, forearm DmO_2 was not different between groups and thus cannot explain the reduction in forearm ΔAV_{O_2}; 5) after controlling for blood flow, the degree of adiposity, measured using whole-body DEXA, was significantly associated with both the local and systemic ΔAV_{O_2}; and 6) physiological determinants of local oxygen utilization determined during our forearm exercise experiments were able to predict more than one-third of the variability in systemic peak V_{O_2}, suggesting that peripheral limitations to exercise account for an important proportion of systemic aerobic capacity.

Our results are in line with those of prior studies that demonstrated the importance of ΔAV_{O_2} in determining exercise capacity in subjects with HFpEF (5,6,23). However, ΔAV_{O_2} is a complex metric, influenced by: 1) blood flow, arterial oxygen content, and hemoglobin oxygen binding characteristics (convective oxygen transport); and 2) the ability of oxygen to cross the capillary membrane in accordance with the P_{O_2} gradient between the microvasculature and the mitochondria (diffusive oxygen transport). All other things being equal, lower skeletal muscle blood flow might be expected to increase ΔAV_{O_2} because of longer red blood cell capillary transit times, and vice versa (7,24). Consistent with this notion, we found an inverse relationship between blood flow and ΔAV_{O_2} during both small- and large-muscle exercise, highlighting the complexity in assessing ΔAV_{O_2} in isolation and demonstrating that the Fick determinants of V_{O_2} (ΔAV_{O_2} and flow) are not independent (7,24).

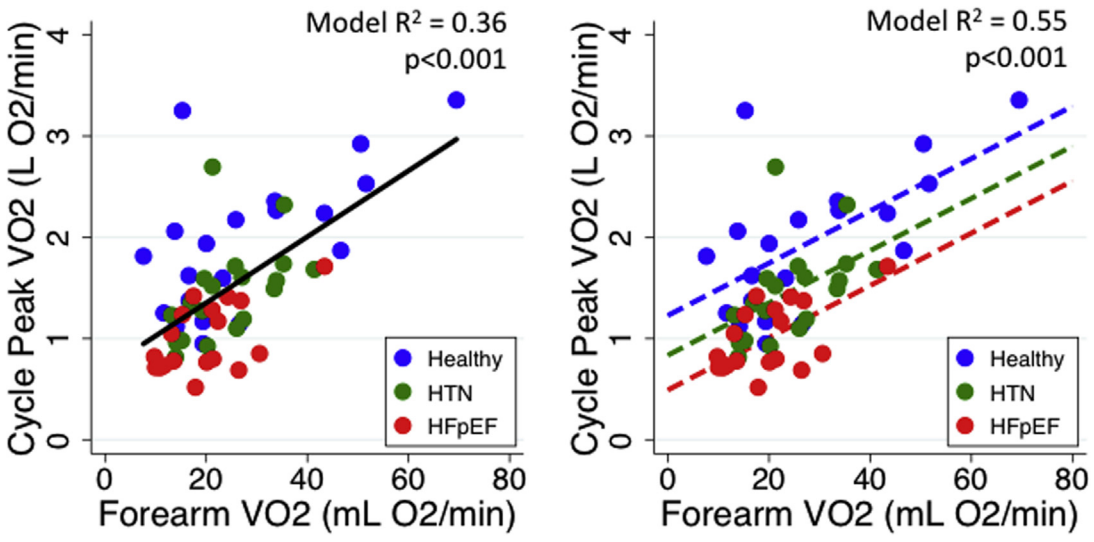
TABLE 4 Univariate and Multivariate Models for Predictors of Regional and Systemic ΔAV_{O_2}

	Forearm ΔAV_{O_2}			Systemic ΔAV_{O_2}	
	Standardized β	p Value	Univariate	Standardized β	p Value
Univariate					
Age	−0.23	0.081	Age	−0.27	0.055
Male	0.24	0.075	Male	0.39	0.005
HFpEF	−0.43	0.001	HFpEF	−0.50	<0.001
Forearm fat	−0.32	0.014	Body fat mass, kg	−0.60	<0.001
Forearm lean mass	0.21	0.110	Body lean mass	0.11	0.438
Forearm % fat	−0.36	0.006	Body % fat	−0.62	<0.001
Forearm DmO_2	0.45	<0.001	Forearm DmO_2	0.18	0.220
Peak brachial flow	−0.003	0.984	Peak cardiac output	−0.19	0.185
Multivariate		Model $R^2 = 0.74$			Model $R^2 = 0.69$
Age	−0.14	0.066	Age	−0.32	0.002
Forearm fat	−0.21	0.005	HFpEF	−0.22	0.028
Peak brachial flow	−1.30	<0.001	Body fat mass	−0.54	<0.001
DmO_2	1.45	<0.001	Body lean mass	0.57	<0.001
			Peak cardiac output	−0.75	<0.001

Abbreviations as in Tables 1 to 3.

In contrast, DmO_2 across the skeletal muscle capillary membrane is expressed per unit of time (milliliters of oxygen *per minute* per millimeter of mercury) and therefore is independent of differences in capillary transit time (9). Recently, an elegant modeling study raised the possibility for reduced DmO_2 in subjects with HFpEF (7). That study focused on estimations of DmO_2 based on pulmonary artery blood gas samples obtained during cycle exercise. Although intriguing, large-muscle exercise, such as cycle ergometry, might be influenced by central (i.e., cardiac) limitations, reaching a "ceiling" on skeletal muscle oxygen supply (9). Moreover, as the investigators noted, the degree to which mixed venous blood in the pulmonary artery reflects the blood draining from the skeletal muscle may be variable between patients with HFpEF and control subjects, in part because of the abnormalities in systemic blood flow distribution and the vasodilatory reserve in patients with HFpEF (25). In contrast, in the present investigation, we estimated DmO_2 during forearm exercise, a small-muscle modality that is not dependent upon peak CO, and we used local deep venous blood sampling, leading to measurements that focus exclusively on the factors driving local skeletal muscle oxygen utilization in the forearm. In our measurements, we did not find a reduction in

FIGURE 3 Relationship Between Local Exercise and Systemic Aerobic Capacity



Cycle ergometric oxygen consumption (V_{O_2}) versus forearm V_{O_2}. Among all subjects, forearm V_{O_2} significantly correlated with peak V_{O_2} on cycle ergometry (model $R^2 = 0.36$; **left**). For any given forearm V_{O_2}, subjects with HFpEF had lower peak V_{O_2} on cycle ergometry (model $R^2 = 0.55$; **right**). Abbreviations as in Figure 2.

forearm DmO_2 during maximal-effort forearm exercise.

Our study answers the central question as to why subjects with HFpEF do not simply extract more oxygen to balance the forearm ΔAV_{O_2} during exercise: given that forearm DmO_2 was the same between groups, increasing forearm ΔAV_{O_2} would drive mean capillary P_{O_2} lower in subjects with HFpEF. By Fick's law of diffusion, lower mean capillary P_{O_2} would actually reduce V_{O_2} for a given DmO_2 (26) by decreasing mitochondrial oxygen availability. This imposes a limit below which capillary oxygen content cannot be reduced. Strategies that either increase arterial oxygen content (i.e., increase hemoglobin) such that more total oxygen can be extracted for any given DmO_2 or increase forearm DmO_2 and allow greater fractional extraction (or ideally both; see the following discussion) need to be undertaken to improve ΔAV_{O_2} in patients with HFpEF (27).

Interestingly, we found that body composition, particularly the degree of adiposity, was correlated with ΔAV_{O_2}, with increasing fat associated with reduced ΔAV_{O_2}. Three possible explanations exist for this finding. First, the adipose tissue within and around the myocytes could "steal" blood away from the exercising skeletal muscle (28,29). As the fat is less metabolically active, especially during exercise, the adipocytes would extract less oxygen than exercising muscle for any given flow, leading to a greater venous oxygen content in the draining vein. Second, the adipose tissue may have an impact on skeletal muscle metabolism and the mitochondria (29). Obesity is associated with impairments in skeletal muscle fuel utilization (30–32), mitochondrial content (33,34), and an increase in inflammation and reactive oxygen species (3,35,36), which can also decrease mitochondrial function. The lower slope of the relationship between the change in forearm ΔAV_{O_2} as a function of indexed brachial flow in subjects with HFpEF suggests abnormalities in oxygen utilization at the skeletal muscle (37,38). Third, obesity, as a source of chronic inflammation, may be an important contributor to the anemia commonly seen in HFpEF (39,40), leading to a lower arterial content, which may influence ΔAV_{O_2}. Although erythropoiesis-stimulating agents increase hemoglobin concentration in patients with HFpEF, their use did not improve submaximal exercise capacity, as measured using the 6-min walk test (41), though changes in peak V_{O_2} were not assessed.

Perhaps the links between adiposity, mitochondrial function, and aerobic capacity in patients with

HFpEF explain recent findings in clinical trials that: 1) adiposity inversely correlates with peak aerobic capacity in subjects with HFpEF (42); 2) weight loss decreases systemic inflammation (43); and 3) when combined with exercise training, weight loss leads to additive benefits in increasing aerobic capacity in subjects with HFpEF beyond those garnered from exercise alone (44). Our findings may help reinforce the importance of weight loss and exercise training in patients with HFpEF and point toward a novel mechanistic link between obesity and reduced aerobic capacity in patients with HFpEF.

Peak forearm V_{O_2} significantly correlated with whole-body aerobic capacity, even though forearm V_{O_2} was not different among groups, whereas cycle ergometric peak V_{O_2} was. Notwithstanding this finding, that small-muscle exercise was able to predict more than a third of the variability in whole-body exercise is noteworthy, reinforcing the importance of local peripheral factors on systemic aerobic capacity. However, for any given forearm V_{O_2}, cycle ergometric peak V_{O_2} was systematically lower in subjects with HFpEF, suggesting that additional factors not addressed in the small-muscle forearm exercise (including cardiac abnormalities) further constrain V_{O_2} in subjects with HFpEF.

We did not measure central filling pressures in our studies, and it is possible that although the CO-to-V_{O_2} relationship was preserved in patients with HFpEF (~5 l of CO/1 l of oxygen consumed), the increase in CO came at the cost of higher filling pressures and shortness of breath (4). It is also possible that other noncardiovascular limitations to exercise, such as increased work of breathing, might be present during whole-body exercise that requires greater muscle mass. Of note, the well-known effect of excess leg weight in obesity could not explain the additional decrement in systemic V_{O_2}, because the excess weight in subjects with HFpEF would be expected to increase systemic V_{O_2} for any given forearm V_{O_2} because of the increased work required to move the larger mass (45).

It is tempting to speculate that simply a reduction in absolute muscle mass could explain many of our findings. However, we found no difference in the absolute amount of lean mass across groups (data not shown) on DEXA (29,38), and the differences in whole-body exercise persisted, even when indexing systemic V_{O_2} to lean leg mass (38,42). Instead, the amount of fat mass, and the ratio of fat mass to total mass (which takes lean mass into account), were strikingly divergent among groups (29,38,42). Importantly, we show that the degree of adiposity correlated with the reductions in ΔAV_{O_2}.

Although cycle ergometric V_{O_2} was markedly different among groups, we did not find a difference in forearm V_{O_2}. This was unexpected, as prior work suggested abnormalities in blood flow distribution during small-muscle exercise in patients with HFpEF (46), along with reduced grip strength, which was recapitulated in our study (47). One would have expected this to translate into lower forearm V_{O_2}; however, this was not found. Instead, the reduced ΔAV_{O_2} across the forearm at peak exercise was counterbalanced by numerically greater (though not statistically significant) brachial blood flow, keeping forearm V_{O_2} relatively preserved. Importantly, our estimates of forearm V_{O_2}, brachial blood flow, and forearm ΔAV_{O_2} are similar in magnitude to those observed in prior work (15,18). Our data are at odds with prior work in patients with HFpEF that demonstrated reduced blood flow redistribution to exercising muscle during small-muscle mass movements (46), perhaps because of differences in the muscle bed studied and/or whether the exercise paradigm was isotonic rather than isometric as herein.

We found that ΔAV_{O_2} was reduced during forearm exercise, as it was systemically during whole-body exercise, but the absence of any concomitant decrease in forearm DmO_2 removed compromised oxygen diffusion as a candidate mechanism to explain the reduced forearm ΔAV_{O_2}. Although previous work on DmO_2 has focused largely on the legs (9,20), our forearm technique allowed DmO_2 measurements in a much greater number of subjects because of its less invasive nature. How leg DmO_2 compares with forearm measurements in the same subject is unknown and should be the focus of future work. Indeed, in the only prior study of local DmO_2 in heart failure, Esposito et al. (9) measured DmO_2 during leg extension exercise, estimating DmO_2 to be 5.1 ml oxygen/min/mm Hg/kg leg muscle, which is a much greater value than we observed across the forearm. This suggests that differences exist between the forearm muscles and those involved in locomotion, which is certainly not unexpected. Regardless, our data argue against a circulating factor that impairs microcirculatory function throughout the body.

STUDY LIMITATIONS. We used an isometric exercise protocol consisting of forearm handgrip exercise, as opposed to dynamic exercise such as arm cranking. This may have led to differences in the peak forearm V_{O_2} measurements achieved in our study compared with other studies (48) and may also have affected our DmO_2 estimations (48). However, handgrip exercise more likely reflects the type of forearm exercise encountered by patients with HFpEF during routine activities of daily living, as opposed to arm cranking. We recognize, though, that the type of exercise and its characteristics (e.g., duty cycle) could affect forearm DmO_2 estimations (49). Future studies on DmO_2 and oxygen transport in patients with HFpEF should consider the exercise paradigm, in addition to the muscle bed interrogated, to reach the most clinically relevant findings.

We did not randomize the order in which subjects exercised while breathing FI_{O_2} = 0.21 versus FI_{O_2} = 1.00. Consequently, the decrease in work performed during the FI_{O_2} = 1.0 transients may have been due to fatigue, as these represented the average of the third and fourth exercise bouts. However, that forearm peak V_{O_2} increased with FI_{O_2} = 1.00, despite the lower work load, supports the contention that maximal forearm V_{O_2} was reached during FI_{O_2} = 0.21. Finally, our DmO_2 measurements assume homogeneity of V_{O_2} and flow within the exercising muscle; however, we now know that this is not always the case (50). When better techniques become available, future studies examining DmO_2 during exercise will be needed to clarify the physiological importance of flow and V_{O_2} heterogeneity within the muscle in subjects with HFpEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with HFpEF are markedly limited in terms of functional capacity. Although cardiac abnormalities have been described, our work suggests that additional "peripheral" factors further conspire to constrain exercise capacity. Here, we found that although ΔAV_{O_2} was reduced in patients with HFpEF during both peak whole-body and local (forearm) exercise, forearm DmO_2 was no different compared with both healthy subjects and those with hypertension and is therefore unable to explain the reduced forearm ΔAV_{O_2} seen in patients with HFpEF. Yet ΔAV_{O_2} increased more slowly in subjects with HFpEF, suggesting intrinsic abnormalities within the skeletal muscle itself. We found strong associations between the degree of adiposity and ΔAV_{O_2}, suggesting that adipocytes may play a detrimental role in limiting exercise capacity.

TRANSLATIONAL OUTLOOK: Accumulating evidence suggests that the adipose tissue may play an active role in limiting exercise capacity in patients with HFpEF. Future research investigating the potential mechanism(s) through which the adipocytes may negatively affect skeletal muscle function is warranted.

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KEY WORDS adiposity, aerobic capacity, exercise, HFpEF, oxygen transport

APPENDIX For an expanded Methods section and supplemental figures, please see the online version of this paper.