Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction
The Role of Abnormal Peripheral Oxygen Extraction

Bishnu P. Dhakal, MD; Rajeev Malhotra, MD; Ryan M. Murphy, BA; Paul P. Pappagianopoulos, MEd; Aaron L. Baggish, MD; Rory B. Weiner, MD; Nicholas E. Houstis, MD, PhD; Aaron S. Eisman, BS; Stacyann S. Hough, MS; Gregory D. Lewis, MD

Background—Exercise capacity as measured by peak oxygen uptake (\(V_O_2\)) is similarly impaired in patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). However, characterization of how each component of \(V_O_2\) changes in response to incremental exercise in HFpEF versus HFrEF has not been previously defined. We hypothesized that abnormally low peripheral \(O_2\) extraction (arterio-mixed venous \(O_2\) content difference, \(C(a-v)O_2\)) during exercise significantly contributes to impaired exercise capacity in HFpEF.

Methods and Results—We performed maximum incremental cardiopulmonary exercise testing with invasive hemodynamic monitoring on 104 patients with symptomatic NYHA II to IV heart failure (HFpEF, \(n=48\), peak \(V_O_2=13.9±0.5\) mL·kg\(^{-1}\)·min\(^{-1}\), mean±SEM, and HFrEF, \(n=56\), peak \(V_O_2=12.1±0.5\) mL·kg\(^{-1}\)·min\(^{-1}\)) and 24 control subjects (peak \(V_O_2=27.0±1.7\) mL·kg\(^{-1}\)·min\(^{-1}\)). Peak exercise \(C(a-v)O_2\) was lower in HFpEF compared with HFrEF (11.5±0.27 versus 13.5±0.34 mL·dL\(^{-1}\), respectively, \(P<0.0001\)), despite no differences in age, hemoglobin level, peak respiratory exchange ratio, \(Cao2\), or cardiac filling pressures. Peak \(C(a-v)O_2\) and peak heart rate emerged as the leading predictors of peak \(V_O_2\) in HFpEF. Impaired peripheral \(O_2\) extraction was the predominant limiting factor to exercise capacity in 40% of patients with HFpEF and was closely related to elevated systemic blood pressure during exercise (\(r=0.49, P=0.0005\)).

Conclusions—In the first study to directly measure \(C(a-v)O_2\) throughout exercise in HFpEF, HFrEF, and normals, we found that peak \(C(a-v)O_2\) was a major determinant of exercise capacity in HFpEF. The important functional limitation imposed by impaired \(O_2\) extraction may reflect intrinsic abnormalities in skeletal muscle or peripheral microvascular function, and represents a potential target for therapeutic intervention. (Circ Heart Fail. 2015;8:286-294. DOI: 10.1161/CIRCHEARTFAILURE.114.001825.)

Key Words: diastole • exercise • heart failure

Heart failure with preserved left ventricular ejection fraction (HFpEF) is an increasingly common condition with similar incidence and prognosis to heart failure with reduced left ventricular ejection fraction (HFrEF).\(^1\)-\(^4\) A major source of morbidity in both HFpEF and HFrEF is impaired functional capacity, which is best quantified by the degree of impairment in peak \(V_O_2\).\(^5\)-\(^7\) Mechanistic studies of exercise intolerance in HFpEF have primarily focused on central cardiovascular abnormalities, including chronotropic incompetence\(^8\) and impaired stroke volume (SV) augmentation in the setting of decreased left ventricular (LV) compliance.\(^8\) More recently, impaired systolic reserve function and abnormal LV-central vascular coupling have also been implicated in causing impaired exercise capacity in HFpEF.\(^9\)

In assessing the capacity to augment \(V_O_2\) in HFpEF, it is important to consider relative increases in each of the 3 components of \(V_O_2\) (ie, heart rate [HR], SV, and arterio-mixed venous oxygen content difference: \(C(a-v)O_2\)). In normal individuals, the degree to which peripheral oxygen extraction (ie, \(C(a-v)O_2\)) increases in response to exercise (\(\approx 2.5\times\))\(^10\)-\(^12\) is much greater than changes in SV (\(\approx 1.3\times\))\(^11\),\(^13\) and similar to increases in HR (\(\approx 2.5\times\)). Several previous studies have found that patients with HFpEF are not able to increase HR and SV normally during exercise,\(^5\),\(^6\),\(^8\),\(^14\) which implies a greater reliance in the ability to increase \(C(a-v)O_2\) to augment \(V_O_2\). However, the role of \(C(a-v)O_2\) in determining exercise capacity in HFpEF remains incompletely understood.\(^15\)-\(^17\)

In HFpEF, 2 studies\(^5\),\(^6\),\(^16\) that derived \(C(a-v)O_2\) indirectly have suggested that \(C(a-v)O_2\) is abnormally low in HFpEF, whereas a third study found that it was not impaired.\(^17\) To date, no studies
have performed direct serial measurements of C(a-v)O₂ throughout exercise in HFpEF and HFrEF to define O₂ extraction patterns.

On the basis of the heterogenous pathogenesis of HFrEF, and the recognized role of peripheral O₂ extraction augmentation in increasing VO₂ during exercise, we hypothesized that patients with HFrEF would be limited primarily by an inability to augment peripheral O₂ extraction appropriately [ie, C(a-v)O₂ <14 mL/dL or CvO₂ >5 mL/dL].18 To address this hypothesis, we measured respiratory gas exchange parameters, arterial and mixed venous O₂ saturations [C(a-v)O₂], as well as HR and SV at 1-minute intervals throughout maximum incremental exercise in patients with symptomatic HFpEF and compared them with patients with HFrEF and normal controls. The primary objective of this study was to delineate the relative contributions of each component of VO₂ to peak exercise capacity in patients with heart failure (HF).

**Methods**

**Patient Population and Study Design**

Consecutive patients who underwent cardiopulmonary exercise testing (CPET) with invasive hemodynamic monitoring at Massachusetts General Hospital and chronic NYHA class II to IV symptoms were included in the study. We classified patients based on left ventricular ejection fraction and resting and exercise pulmonary capillary wedge pressure (PCWP) as (1) HFrEF: Chronic NYHA II to IV LV systolic dysfunction, left ventricular ejection fraction <45% on standard pharmacotherapy; (2) HFrEF: Chronic NYHA II to IV symptoms, left ventricular ejection fraction >50%, and >15 mm Hg PCWP at rest. Exclusion criteria consisted of the following: (1) incomplete pulmonary arterial catheter pressure measurements; (2) documented intracardiac shunting; (3) severe valvular heart disease; (4) known active flow limiting CAD; (5) submaximal exercise (as evidenced by peak respiratory exchange ratio (RER) <1.0); (6) the presence of a pulmonary mechanical limitation to exercise as defined by V̇E/Å/forced expiratory volume in 1 s (FEV₁) ×35% ≥0.7 at the anaerobic threshold.19,20 The control group was included to determine the extent to which hemodynamic measurements and O₂ utilization during exercise in HFrEF subjects differed from normal controls. Controls consisted of subjects referred for CPET to evaluate dyspnea on exertion during the same period of time as the HFrEF group. Controls were required to have normal LV function, normal resting and exercise PCWP and normal exercise capacity as reflected by a peak VO₂ >80% of that predicted on the basis of age, sex, and height.18

**Cardiopulmonary Exercise Testing**

All patients underwent placement of a pulmonary arterial catheter via the internal jugular vein and placement of a systemic arterial catheter via the radial artery. First-pass radionuclide ventriculography of both ventricles was performed immediately before cycle ergometry testing as previously described.21 Subjects then underwent maximum incremental upright cycle ergometry CPET (5–25 Watts/min continuous ramp after an initial 3-minute period of unloaded exercise, MedGraphics, St. Paul, MN) with simultaneous hemodynamic monitoring (Witt Biomedical Inc, Melbourne, FL) as previously described.21,22 None of the subjects developed angina, arrhythmia, hypotension, or significant electrocardiographic changes during exercise. Right atrial pressure, mean pulmonary arterial pressure, PCWP, and systemic arterial pressures were measured in the upright position, at end-expiration, while patients were seated on the cycle, at rest, and at 1-minute intervals during exercise. Fick cardiac outputs (CO)12,23 were also determined at 1-minute intervals throughout exercise by measuring oxygen uptake (VO₂) and simultaneous radial arterial and mixed venous O₂ content to calculate the C(a-v)O₂. Peak VO₂ was defined as the highest O₂ uptake, averaged over 30 s, during the last minute of symptom-limited exercise, as previously described.24,25 Age–predicted maximal HR was defined as 220 minus age in years. Chronotropic response index was derived as the proportion of HR reserve used at peak exercise based on (HRPeak−HRRest)/(220–age–HRRest)×100.24,25 Chronotropic response index <62% and <80% were considered abnormal in the presence and absence of β-blocker use, respectively.24,26,28

**Arterio-Mixed Venous Oxygen Content**

Arterial O₂ content (CaO₂)27 is the amount of O₂ carried by blood to the periphery and was calculated as (hemoglobin×1.39×SaO₂)+(0.003×PaO₂). Similarly mixed venous O₂ content (CvO₂) represents the O₂ content of blood returning from the peripheral tissues to the right heart which was calculated as (hemoglobin×1.39×SvO₂)+(0.003×PvO₂). Given a normal circulating hemoglobin level of ∼15 g/dL, an arterial saturation of 96% and mixed venous saturation of 72%, the normal resting CaO₂ is 20 mL/dL and CvO₂ is 15 mL/dL, which results in a normal resting C(a-v)O₂ value of 5 mL/dL. During exercise, peripheral tissues extract more O₂ to maintain aerobic metabolism, which leads to a decrease in mixed venous saturation to <24% with a resultant reduction in CvO₂ from 15 mL/dL at rest to 5 mL/dL at peak exercise in normal individuals.26 Thus peak exercise C(a-v)O₂ in a normal person with a hemoglobin of 15 g/dL is 15 mL/dL (ie, approximately equal to the hemoglobin level).31 The amount of O₂ extracted by tissues at peak exercise relative to O₂ delivered (ie, extraction ratio, peak C(a-v)O₂/CaO₂) is normally 75%.

**Statistical Methods**

STATA 10 (Statacorp, College Station, TX) was used for statistical analysis. The Wilk–Shapiro test was used to assess the normality of
distribution of the data. All continuous, normally distributed measurements are presented as the mean±SEM. Categorical data are reported as percentages. Group baseline characteristics were compared using either the Student t test, Mann–Whitney U test, or Fisher exact test, as appropriate. For clinical characteristics, comparisons between groups for continuous variables were performed using ANOVA with post hoc pairwise comparisons, unpaired 2-sample t tests or the Wilcoxon signed rank test, as appropriate. Pearson or Spearman correlation coefficients were calculated, based on whether the data were either normally or not normally distributed, respectively. Partial R² values were obtained from a multiple linear regression model that included age, sex, HRmax, SVmax, and C(a-v)O₂max. Subgroup analysis was performed comparing HF patients with higher and lower CvO₂. A P<0.05 was considered significant. This study was approved by the Partners Healthcare Institutional Review Board, the authors had full access to the data and take responsibility for its integrity and for the article as written.

**Results**

**Population Characteristics**

Baseline characteristics for all HFP EF (n=48), HFr EF (n=56), and control subjects (n=24) are reported in Table 1. All patients surpassed their ventilatory anaerobic thresholds and demonstrated an average peak RER of 1.15 to 1.16 in all 3 groups, indicating maximum or near maximum exercise effort across the 3 groups. HFP EF subjects had more elevated body mass index and a female predominance (60%) compared with patients with HFr EF, consistent with the known distinct demographic characteristics of HFp EF and HFr EF populations.

**Arterial and Mixed Venous Oxygen Content at Rest and at Peak Exercise**

All 3 groups had similar CaO₂ values at rest and at peak exercise, reflecting mildly reduced hemoglobin levels and normal systemic arterial O₂ saturations (Tables 1 and 2). Resting CvO₂ was lowest in HFr EF (9.4±0.3 mL/dL), and similar in HFP EF and controls (11.6±0.3 and 12.1±0.36 mL/dL, P=0.70, 

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**Table 2. Hemodynamic, Gas Exchange, and Ventriculography Measurements of HF and Control Subjects**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rest</th>
<th>Exercise</th>
<th>Controls</th>
<th>Rest</th>
<th>Exercise</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂, mL/min</td>
<td>307±11</td>
<td>281±9</td>
<td>298±9</td>
<td>1227±61</td>
<td>1021±50</td>
<td>2049±122</td>
</tr>
<tr>
<td>VO₂, mLkg⁻¹min⁻¹</td>
<td>3.4±0.1</td>
<td>3.4±0.1</td>
<td>3.7±0.12</td>
<td>13.9±0.5</td>
<td>12.1±0.5</td>
<td>27.0±1.7</td>
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<tr>
<td>CO, L/min</td>
<td>5.1±0.2</td>
<td>3.7±0.1</td>
<td>5.3±0.2</td>
<td>10.7±0.5</td>
<td>7.7±0.3</td>
<td>15.2±0.7</td>
</tr>
<tr>
<td>Ci, Lmin⁻¹m⁻²</td>
<td>2.7±0.1</td>
<td>1.9±0.1</td>
<td>2.7±0.1</td>
<td>5.2±0.2</td>
<td>3.8±0.1</td>
<td>7.8±0.4</td>
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<tr>
<td>SV, mL</td>
<td>69±2.6</td>
<td>51±2†</td>
<td>74±2.8</td>
<td>88±3.6</td>
<td>68±2.8†</td>
<td>103±4.28</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>36.6±1.3</td>
<td>25.6±1.0†</td>
<td>38.1±1.6</td>
<td>42.7±1.2</td>
<td>34.3±1.2‡</td>
<td>52.4±2.0</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>75±2</td>
<td>75±0.5</td>
<td>73±1.8</td>
<td>121±3.6</td>
<td>113±3.2</td>
<td>148±3.47</td>
</tr>
<tr>
<td>CaO₂, mL/dL</td>
<td>17.8±0.3</td>
<td>17.1±0.4</td>
<td>17.8±0.38</td>
<td>18.3±0.28</td>
<td>18.3±0.37</td>
<td>19.0±0.34</td>
</tr>
<tr>
<td>CaO₂, mL/dL</td>
<td>11.6±0.3</td>
<td>9.4±0.3†</td>
<td>12.1±0.4</td>
<td>6.8±0.3</td>
<td>4.7±0.2‡</td>
<td>5.7±0.2</td>
</tr>
</tbody>
</table>
| Ci indicates cardiac index; CO, cardiac output; DBP, diastolic blood pressure; HFP EF, heart failure with preserved ejection fraction; HFr EF, heart failure with reduced ejection fraction; HR, heart rate; LVEDV, left ventricular end diastolic volume; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; SBP, systolic blood pressure; SV, stroke volume; and SVI, stroke volume index.

* P<0.05 between HFP EF and controls.
† P<0.05 between HFr EF and controls.
‡ P<0.05 between HFp EF and HFr EF.
CO/VO₂ slope, also termed exercise factor, was 5.6±0.2 in controls consistent with the values reported by previous investigators. CO/VO₂ slope was 6.1±0.2 in HFpEF (P=0.068 compared with controls, P<0.0001 compared with HFrEF) and 5.0±0.17 in HFrEF (P=0.02 compared with controls). Higher CO/VO₂ slope in HFpEF compared with HFrEF is indicative of a reduced relative contribution of C(a-v)O₂ to VO₂ in HFpEF throughout exercise. Among patients in whom peak C(a-v)O₂ was below predicted and constituted the primary cause of reduced peak VO₂, the CO/VO₂ slope was 8 (Figure I in the Data Supplement), indicating a disproportionate reliance on CO increment throughout exercise to compensate for abnormal C(a-v)O₂.

Chronotropic Response During Exercise
HR at rest was similar in all 3 groups (Table 2). Failure to reach 85% of predicted HR was similarly common in HFpEF (67%) and HFrEF (75%, P=0.35). After accounting for β-blocker use, 73% of patients with HFpEF and 75% in patients with HFrEF met diagnostic criteria for chronotropic incompetence, consistent with findings from previous studies of exercise response patterns in HF.6,15,35,36

SV and Filling Pressures During Exercise
Resting SV in HFpEF was higher than resting SV in HFrEF and similar to that in controls (Table 2). At peak exercise, patients with HFpEF achieved higher SV than HFrEF subjects (88±3.6 mL versus 68±2.8 mL; P<0.001) but lower than controls (103±4.3 mL; P=0.03 compared with HFpEF; Table 2). The observed differences in SVs in HFpEF and HFrEF occurred in the setting of similar resting and exercise PCWP.
Integrated Responses: CO Versus Extraction Reserve Capacity During Exercise

We examined reserve capacity of each component of VO2, independently of resting values by assessing change in HR, SV, and C(a-v)O2 from rest to peak exercise in the 3 groups (Figure 2). In normal middle-aged controls in our study, VO2 increased 592±42% from rest to peak exercise, consistent with previous studies. This increase was because of a 109±8% increase in HR, a 39±4% increase in SV, and a 138±9% increase in C(a-v)O2 during exercise. In contrast, patients with HFpEF had a 311±20% increase in resting VO2 during exercise because of a 63±5% increase in HR, a 32±5% increase in SV, and a 91±6% increase in C(a-v)O2. Patients with HFrEF had a 264±14% increase in VO2 attributable to a 53±4% increase in HR, a 40±5% increase in SV, and a 77±5% increase in C(a-v)O2 (Figure 2). Notably, in all groups the magnitude of increase in C(a-v)O2 in response to exercise was greater than the magnitude of increase in HR or SV; thereby highlighting the important contribution of increase in C(a-v)O2 to augmenting VO2 during exercise.

Assessment of convective oxygen delivery (ie, CO×CaO2) and diffusive oxygen transport (represented by fall in CvO2) is an alternative, mechanistic way to analyze components of O2 utilization.7 Multipoint plots of CvO2 versus VO2 in the 3 groups indicate that diffusive O2 transport is most impaired in HFpEF, whereas convective O2 delivery is lowest in HFrEF (Figure 3). The extent to which VO2 would increase upon normalization of convective O2 delivery and diffusive O2 utilization in HFpEF is illustrated in Figure 3 and highlights the greater relative abnormality in diffusive O2 transport than in convective O2 delivery in HFpEF.

Predictors of Peak VO2

Partial R2 values describing age and sex-adjusted relationships between peak VO2 and individual components of peak VO2 are displayed in Table 3. In HFpEF, peak VO2 related to maximum C(a-v)O2 (partial R2=0.28; P=0.0002) and peak HR (partial R2=0.35; P<0.0001) and there was a trend toward association with maximum SV (partial R2=0.07, P=0.077). In normal controls, by way of contrast, peak C(a-v)O2 tended to be more constant (mean 13.3±0.3 mL/dL) and predictably related to hemoglobin levels (mean 13.2g/dL),18 with a lower, partial R2 value (0.19, P=0.056) relative to peak VO2.

Blood Pressure and Diffusive Oxygen Transport in HFpEF

To further investigate impaired diffusive O2 transport in HFpEF in isolation, we stratified patients with HFpEF into 2 groups based on median peak exercise CVO2 of 6.8 mL/dL. The higher CVO2 subgroup did not differ from the lower CVO2 subgroup in age, sex, left ventricular ejection fraction, CO, or cardiac filling pressures but hemoglobin was slightly higher in the higher CVO2 group (Table 1 in the Data Supplement). The subset of patients with HFpEF with higher CVO2 had similar lactate and peak RER to the lower CVO2 group, which argues against reduced effort during exercise as an explanation for the attenuated fall in CVO2 during exercise in the high CVO2 group. The most striking difference between HFpEF CVO2 subgroups was that elevated CVO2 was associated with a disproportionate hypertensive response during exercise with elevation of diastolic blood pressure (DBP) (93±4 mmHg versus

Table 3. Heart Rate, Stroke Volume, and C(a-v)O2 Association With Peak VO2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HFpEF</th>
<th>HFrEF</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR max</td>
<td>0.350</td>
<td>&lt;0.0001</td>
<td>0.307</td>
</tr>
<tr>
<td>SV max</td>
<td>0.072</td>
<td>0.077</td>
<td>0.379</td>
</tr>
<tr>
<td>C(a-v)O2 max</td>
<td>0.281</td>
<td>0.0002</td>
<td>0.253</td>
</tr>
</tbody>
</table>

HR, SV, and C(a-v)O2 are adjusted for age and sex both and VO2 is indexed to body weight. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; and SV, stroke volume.

Figure 3. Illustration of the convective and diffusive components that interact to determine exercise capacity (VO2) in heart failure and controls. Mean values for CVO2 and VO2 at rest, 30 W, and peak exercise are used to construct Fick principal lines, which indicate convective O2 delivery and are curvilinear because they directly reflect the hemoglobin dissociation curve. The vertical lines extending from the origin to the VO2-CvO2 plot at peak exercise indicate maximum diffusive oxygen delivery as determined by the Fick law, with a steeper relationship indicating better O2 diffusion. Black arrow indicates the increment in peak VO2 in heart failure with preserved ejection fraction (HFpEF) if convective O2 delivery was corrected to that of normal controls. White arrow indicates the increment in peak VO2 if O2 diffusion was normalized in HFpEF.

Figure 4. Diastolic blood pressure (BP) at rest and during incremental exercise in 2 subgroups of heart failure with preserved ejection fraction stratified by median mixed venous oxygen content at peak exercise.
76±3; P=0.001), systolic blood pressure (196±7 versus 171±7 mm Hg; P=0.01), and mean arterial pressure (127±4 versus 107±4 mm Hg; P=0.001) at peak exercise (Figure 4; Table I in the Data Supplement). Among patients with peak exercise DBP in excess of 100 mm Hg, **CvO₂** was 8.5±0.3 mL/dL, compared with **CvO₂** of 6.5±0.4 mL/dL (P=0.005) in patients with exercise DBP≤100 mm Hg. When analyzed as a continuous variable, **CvO₂** was directly correlated with peak exercise DBP (Pearson r=0.49; P=0.0005) and extraction ratio was inversely related to exercise DBP (Pearson r=-0.41; P=0.004).

**Discussion**

In comprehensively characterized cohorts with HFrEF, HFrEF, and controls, we found that relative augmentation in peripheral oxygen extraction [C(a-v)O₂] exceeded that of HR or SV during maximum incremental exercise in all 3 groups. Impaired peripheral **O₂** extraction was present in 75% of HFrEF subjects in our study and was attributable to impaired diffusive **O₂** transport and utilization (Figures 1 and 3). In contrast to the close association that we observed between peak VO₂ and C(a-v)O₂ in HFrEF, we found relatively modest or absent associations between peak VO₂ and LV filling pressures or LV SV in HFrEF. Taken together, our findings highlight the potentially important role of targeting peripheral **O₂** extraction to augment impaired exercise capacity in HFrEF; particularly in light of failure of other interventions directed at central cardiac function to improve exercise capacity in HFrEF.12,38–40

The validity of our findings defining relative components of VO₂ augmentation in HFrEF, HFrEF, and normals is supported by (1) rigorous entry criteria with confirmation of diagnoses with invasive hemodynamic assessment and ventriculography on the day of enrollment; (2) direct repeated measurements of CaO₂, **CvO₂**, and CO at 1-minute intervals throughout exercise; (3) use of physiologically relevant upright exercise with maximum effort confirmed by mean RERs ≥1.15 in each group; and (4) consistency of our findings with other studies with regard to demographic variables of HF subgroups and absolute levels of peak C(a-v)O₂ during exercise in normals.

**Exercise Capacity in HF**

Limitation in exercise capacity is a cardinal manifestation of HF that is closely related to poor quality of life and mortality.41,42

The degree of reduction in exercise capacity in HFrEF in our study was similar to that reported in previous studies,5,15,16,32 and was intermediate between 2 recent interventional trials in HFrEF with rigorous entry criteria.23,44 In HFrEF, exercise capacity was also similar to that reported in previous studies,45,46 confirming that the peak VO₂ values measured in our study were representative of the broader HF populations.

**Association of Central Cardiac Function With Exercise Capacity in HF**

Our finding that 73% of patients with HFrEF and 75% of patients with HFrEF had chronotropic incompetence, after accounting for β-blocker use, and that peak HR was strongly associated with peak VO₂ in HFrEF, confirms previous studies demonstrating an important influence of chronotropic response on exercise capacity in HF.6,15,16,47,48 By confining our study to individuals who exceeded their ventilatory anaerobic threshold and an RER of 1.0, we can be confident that impaired chronotropic responses did not reflect lack of maximum effort or premature cessation of exercise because of pulmonary or orthopedic limitations.

SV in patients with HFrEF compared with controls was similar at rest but lower at peak exercise. Previous elegant studies have elucidated mechanisms by which SV is impaired in HFrEF at rest and during exercise, including abnormal ventriculo-vascular coupling,4 impaired relaxation,8,46 and impaired augmentation in systolic function.5,49 However, not all studies to date have found impaired SV responses to exercise in HFrEF29,51 and we found that within patients with HFrEF, peak SV was not significantly related to peak VO₂. Furthermore, the percentage increases in SV from rest to peak exercise within the groups were modest and similar between patients with HF and controls (39±4% in controls, 32±5% in HFrEF, and 40±5% in HFrEF; Figure 2).13,30 The modest increments in SV in response to exercise (32% to 40%) across the 3 groups indicate that the range of SV reserve capacity is more narrow than that for HR (53% to 109%) or C(a-v)O₂ (77% to 138%; Figure 2). Hence, targeting impaired SV augmentation in response to exercise may be of limited benefit in a broad population of patients with HFrEF.

**Peripheral Oxygen Extraction in HFrEF**

Reduced C(a-v)O₂ was the leading cause of impaired exercise capacity (ie, the degree of impairment in C(a-v)O₂ was greater than that in CO as a % of predicted) in 40% of patients with HFrEF in our study and in only 2% of patients with HFrEF. Furthermore, in patients with HFrEF, we found that normalization of impaired **O₂** diffusion would result in a greater increment in peak VO₂ than normalization of convective **O₂** delivery (Figure 3).

After convective delivery of **O₂** to skeletal muscle, diffusive **O₂** transport and utilization is dependent on the pathway consisting of skeletal muscle tissue microcirculatory **O₂** exchange vessels (ie, arterioles, venules, capillaries) and muscle units. **O₂** is transported passively by diffusion in this physically short pathway.52,53 In light of the large-scale blood flow redistribution to skeletal muscles during exercise, our finding that impaired diffusive **O₂** transport in HFrEF was closely related to an exaggerated systemic blood pressure increment during exercise (Figure 4), suggesting a potential role of impaired skeletal muscle vasodilatory capacity in small resistance vessels in mediating reduced peak C(a-v)O₂ in HFrEF. Vasocostricor sympathetic tone and intrinsic microvascular control mechanisms have been shown to modulate the balance between **O₂** delivery an **O₂** demand within organs,40 which suggests that skeletal muscle sympatholysis during exercise may be dysregulated in patients with HFrEF with impaired **O₂** extraction. In further support of sympathetic dysregulation and poorly co-ordinated vasoconstriction, elevated norepinephrine levels have been reported in patients with HFrEF at rest. Alternatively, diffusing capacity of the microvascular network may be limited by heterogeneity in microcirculatory blood flow recognized to occur in proinflammatory states. Finally, morphological and histochemical changes in skeletal muscle have also been described in HFrEF53,54 including marked abnormalities in skeletal muscle mass, composition, capillary density, fiber type, oxidative metabolism, mitochondrial mass, and mitochondrial function as reviewed by Clark et al.15 These pathological peripheral abnormalities are distinct from the influence of deconditioning alone.56,57 Detailed
investigations of skeletal muscle in HFpEF are limited, although intriguing in that Bhella et al15 first reported reduced oxidative metabolism by MRI in 2 patients with HFpEF and more recently abnormal skeletal muscle mass, adiposity, fiber type, and capillary density have been observed in HFpEF.15,56

Previous HFpEF studies in which C(a-v)O2 was estimated via noninvasive CO measurement have led to widely variable estimates of C(a-v)O2 levels in normals and in HFpEF.15,16 Peak exercise C(a-v)O2 values should be equal to hemoglobin levels in normal individuals.18,31 In 1 previous study that directly measured C(a-v)O2, in a subset of patients studied, C(a-v)O2 levels in controls and HFpEF were similarly low (10.1±0.3 versus 9.9±0.3 mL/dL; P=0.7).17 However, the study by Abudiah et al relied on exercise in a semisupine position and control subjects only exercised to 80 Watts, which may not have elicited maximum C(a-v)O2 as we observed C(a-v)O2 to increase in a linear fashion throughout maximum incremental exercise in our study (data not shown). In other HFpEF studies with a control group, the peak C(a-v)O2 values in controls3,15,17 were also 30% lower than their hemoglobin levels, which is much lower than to the ≈6% reduction in C(a-v)O2 expected with deconditioning alone.18 In previous small studies in HFpEF that deployed maximum upright exercise, C(a-v)O2 is consistently depressed.5,50,51 Our findings of an inverse initial relationship between C(a-v)O2 and CO that is no longer present at peak exercise points to the importance of performing maximum effort exercise to ascertain peak O2 extraction capacity in study populations.

Clinical Implications

Within the constraints of currently applied definitions of HFpEF,2,60 a single dominant pathophysiological mechanism governing exercise intolerance in HFpEF is unlikely to exist. The heterogeneity of the HFpEF population poses a major challenge to development of therapies to treat the entire HFpEF population.32,38–40 A potential pathway forward is to carefully identify subjects in whom the majority of reduction in peak VO2 is attributable to an abnormality in 1 component of peak VO2. In this study, CPET with invasive hemodynamic measurements permitted us to probe the reserve capacity of each component of VO2 to subphenotype patients on the basis of the dominant mechanism limiting exercise capacity. This approach may refine patient selection for targeted HFpEF therapeutics, for example, HFpEF could be subclassified into those with primarily impaired peripheral O2 extraction, chronotropic incompetence, or impaired SV among patients able to complete maximum incremental exercise without orthopedic or pulmonary mechanical limitation.

This study highlights the significant role of impaired C(a-v)O2 augmentation in contributing to exercise intolerance in ≈40% of an HFpEF population similar to those recently studied in HFpEF trials. Further studies are needed to determine the relative effect of targeting different aspects of the O2 diffusion unit. A recent study by Haykowsky et al41 found that improved peripheral function [estimated C(a-v)O2] primarily accounted for observed improvements in peak VO2 after exercise training in an HFpEF cohort. In light of the plasticity of skeletal muscle, targeting oxygen diffusion abnormalities in HF is particularly attractive. Positive studies with iron repletion in HFrEF, which promotes aerobic enzymatic activity and O2 storage in myoglobin offer promise for the possibility of extending this intervention to HFpEF.52 With regard to improving diffusional O2 transport to muscle in HF, decreasing O2 affinity (right shifting the O2 dissociation curve) has been shown to improve exercise capacity in mice with HFrEF.50 Alternatively, patients with HFpEF with an exaggerated blood pressure response to exercise and impaired O2 diffusion may be particularly amenable to treatment with vasodilator interventions (ie, with nitrates, such as the NHLBI Heart Failure Network NEAT Trial, NCT02053493) to target skeletal muscle resistance vessels.

In contrast, patients in whom the dominant component of VO2 impairment is chronotropic incompetence,49 pacing or reduction in heart rate–lowering medications may promote improved exercise capacity, as will be tested in the RAPID Trial (NCT21415351). Finally, while SV emerged as the least dynamic of the 3 Fick variables, if SV remains fixed because of a noncompliant ventricle, then attempting to promote improvement in myocardial relaxation properties during exercise may be warranted.

Limitations

Our study has several limitations. Results were derived from small patient cohort referred to a tertiary care center, which may not be representative of the general patients with HFpEF found in the community, and we tested multiple hypotheses regarding associations between C(a-v)O2 and physiological parameters, increasing the chance of type 1 error. Our control population was limited in size (n=24) because of the infrequency with which subjects without significant cardiopulmonary disease undergo CPET with invasive hemodynamic monitoring. Using clinically referred patients who were physiologically normal as controls may underestimate differences between patients with HF and controls. The sampling of systemic venous blood does not permit localization of the peripheral abnormality in oxygen utilization in HFpEF. However, the majority of blood is directed to skeletal muscle during exercise and splanchnic and renal vasoconstriction have been shown to occur normally in HFrEF.10 Although none of the patients with HFpEF in our study had a known diagnosis of a mitochondrial disease or muscular dystrophy, it is possible that some of these patients may have had underlying conditions other than HFpEF that impaired skeletal muscle oxygen extraction. Finally, direct assessments of skeletal muscle and its perfusion were not available in our study to investigate potential histopathologic correlates of impaired O2 diffusion. This will be an important topic of future investigations aimed at further characterizing impaired O2 diffusion in HFpEF.

Conclusions

Patients with HFpEF demonstrated abnormally low peripheral oxygen extraction [C(a-v)O2] during exercise compared with HFrEF subjects and normal controls. This finding highlights the importance of looking beyond impairments in LV function and CO in evaluating functional limitations in patients with HFpEF. Our findings further indicate that improving abnormal O2 extraction may be an important therapeutic target in the notoriously difficult-to-treat patients with HFpEF.
SOURCES OF FUNDING
This work was supported by K23 HL091106, R01 HL119154, the Hassenfeld Clinical Scholars Program (Dr Lewis and A.S. Eisman), and the Massachusetts General Hospital Cardiac Performance Program (Drs Baggish, Weiner, and Lewis).

DISCLOSURES
None.

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Within the constraints of currently applied definitions of heart failure with preserved left ventricular ejection fraction (HFpEF), a single dominant pathophysiological mechanism governing exercise intolerance is unlikely to exist. A potential pathway forward is to carefully identify subjects in whom the majority of reduction in peak VO$_2$ is attributable to an abnormal response during dynamic exercise in patients with heart failure and preserved left ventricular ejection fraction at rest. J Card Fail. 2008;14:475–480.


Krog A. The number and distribution of capillaries in muscles with calculations of the oxygen pressure head necessary for supplying the tissue. J Physiol. 1919;52:409–415.


Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: The Role of Abnormal Peripheral Oxygen Extraction
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Circ Heart Fail. 2015;8:286-294; originally published online October 24, 2014; doi: 10.1161/CIRCHEARTFAILURE.114.001825
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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**SUPPLEMENTAL MATERIAL**

Supplemental Table 1: Demographics and hemodynamics of HFpEF subclasses*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Higher CvO$_2$ (n=24)</th>
<th>Lower CvO$_2$ (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years</td>
<td>60±3</td>
<td>66±3</td>
<td>0.10</td>
</tr>
<tr>
<td>Male Sex %</td>
<td>42</td>
<td>37</td>
<td>0.60</td>
</tr>
<tr>
<td>BMI</td>
<td>34.2±1.5</td>
<td>33.1±1.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Heart Failure Pharmacotherapy %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>65</td>
<td>71</td>
<td>0.04</td>
</tr>
<tr>
<td>ACE Inhibitor or ARB</td>
<td>42</td>
<td>24</td>
<td>0.6</td>
</tr>
<tr>
<td>β-Adrenergic Receptor Antagonist</td>
<td>54</td>
<td>50</td>
<td>0.79</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0</td>
<td>21</td>
<td>0.02</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>0</td>
<td>21</td>
<td>0.02</td>
</tr>
<tr>
<td>Resting Supine PCWP, mm Hg</td>
<td>20±0.6</td>
<td>20±0.6</td>
<td>0.68</td>
</tr>
<tr>
<td>LVEF at rest %</td>
<td>63±1</td>
<td>62±1</td>
<td>0.56</td>
</tr>
<tr>
<td>Mean Hb, gm/dl</td>
<td>13.9±0.2</td>
<td>12.6±0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak VO$_2$, ml/kg/min</td>
<td>14.2±0.7</td>
<td>13.5±0.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Peak VO$_2$ % predicted</td>
<td>70±3.3</td>
<td>72±3.9</td>
<td>0.74</td>
</tr>
<tr>
<td>Resting C(a-v)O$_2$, ml/dl</td>
<td>6.0±0.2</td>
<td>6.4±0.3</td>
<td>0.23</td>
</tr>
<tr>
<td>Peak Exercise C(a-v)O$_2$, ml/dl</td>
<td>10.8±0.3</td>
<td>12.2±0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Extraction ratio</td>
<td>57±1.2</td>
<td>69±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting CO, liters/min</td>
<td>5.2±0.3</td>
<td>4.6±0.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Peak CO, liters/min</td>
<td>11.7±0.7</td>
<td>9.6±0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak CO, % predicted</td>
<td>88±3.5</td>
<td>77±4.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>72±3</td>
<td>78±3</td>
<td>0.11</td>
</tr>
<tr>
<td>Peak HR, beats/min</td>
<td>129±5</td>
<td>113±5</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak HR, % predicted</td>
<td>80±3</td>
<td>73±3</td>
<td>0.11</td>
</tr>
<tr>
<td>DBP rest, mm Hg</td>
<td>78±2</td>
<td>70±3</td>
<td>0.02</td>
</tr>
<tr>
<td>SBP rest, mm Hg</td>
<td>156±5</td>
<td>143±6</td>
<td>0.10</td>
</tr>
<tr>
<td>MAP rest, mm Hg</td>
<td>104±3</td>
<td>94±3</td>
<td>0.02</td>
</tr>
<tr>
<td>DBP max, mm Hg</td>
<td>93±4</td>
<td>76 ±3</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP max, mm Hg</td>
<td>196±7</td>
<td>171±7</td>
<td>0.01</td>
</tr>
<tr>
<td>MAP max, mm Hg</td>
<td>127±4</td>
<td>107±4</td>
<td>0.001</td>
</tr>
<tr>
<td>Peak exercise Lactate</td>
<td>5.7±0.5</td>
<td>4.8±0.5</td>
<td>0.21</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.15±0.03</td>
<td>1.15±0.02</td>
<td>0.96</td>
</tr>
<tr>
<td>Peak pH</td>
<td>7.38±0.01</td>
<td>7.40±0.01</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Stratification based on median CvO$_2$ of 6.8 mg/dl*
Supplemental Figure 1: Graphical representation of the linearity of the cardiac output-VO₂ relationship during exercise in 2 HFpEF subgroups.

**Figure Legend:** The group with impaired peak C(a-v)O₂ demonstrates a steep CO-VO₂ slope upon initiation of exercise in comparison to other patients with HFpEF.