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\textsubscript{O\textsubscript{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\textsubscript{O\textsubscript{2}} changes in response to incremental exercise in HFpEF versus HFrEF has not been previously defined. We hypothesized that abnormally low peripheral \textsubscript{O\textsubscript{2}} extraction (arterio-mixed venous \textsubscript{O\textsubscript{2}} content difference, \textsubscript{C(a-v)}\textsubscript{O\textsubscript{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\textsubscript{O\textsubscript{2}}=13.9±0.5 mL·kg\textsuperscript{-1}·min\textsuperscript{-1}, mean±SEM, and HFrEF, n=56, peak V\textsubscript{O\textsubscript{2}}=12.1±0.5 mL·kg\textsuperscript{-1}·min\textsuperscript{-1}) and 24 control subjects (peak V\textsubscript{O\textsubscript{2}}=27.0±1.7 mL·kg\textsuperscript{-1}·min\textsuperscript{-1}). Peak exercise \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} was lower in HFpEF compared with HFrEF (11.5±0.27 versus 13.5±0.34 mL/dL, respectively, \textit{P}<0.0001), despite no differences in age, hemoglobin level, peak respiratory exchange ratio, Ca\textsubscript{o2}, or cardiac filling pressures. Peak \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} and peak heart rate emerged as the leading predictors of peak V\textsubscript{O\textsubscript{2}} in HFpEF. Impaired peripheral \textsubscript{O\textsubscript{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 (\textit{r}=0.49, \textit{P}=0.0005).

Conclusions—In the first study to directly measure \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} throughout exercise in HFpEF, HFrEF, and normals, we found that peak \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} was a major determinant of exercise capacity in HFpEF. The important functional limitation imposed by impaired \textsubscript{O\textsubscript{2}} extraction may reflect intrinsic abnormalities in skeletal muscle or peripheral microvascular function, and represents a potential target for therapeutic intervention. (\textit{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).\textsuperscript{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\textsubscript{O\textsubscript{2}}.\textsuperscript{5-7} Mechanistic studies of exercise intolerance in HFpEF have primarily focused on central cardiovascular abnormalities, including chronotropic incompetence\textsuperscript{8} and impaired stroke volume (SV) augmentation in the setting of decreased left ventricular (LV) compliance.\textsuperscript{5,8} More recently, impaired systolic reserve function and abnormal LV-central vascular coupling have also been implicated in causing impaired exercise capacity in HFpEF.\textsuperscript{9}

In assessing the capacity to augment V\textsubscript{O\textsubscript{2}} in HFpEF, it is important to consider relative increases in each of the 3 components of V\textsubscript{O\textsubscript{2}} (ie, heart rate [HR], SV, and arterio-mixed venous oxygen content difference: \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}}). In normal individuals, the degree to which peripheral oxygen extraction (ie, \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}}) increases in response to exercise (≈2.5\texttimes) is much greater than changes in SV (≈1.3\texttimes)\textsuperscript{10-12} and similar to increases in HR (≈2.5\texttimes). Several previous studies have found that patients with HFpEF are not able to increase HR and SV normally during exercise,\textsuperscript{5,8,13} which implies a greater reliance in the ability to increase \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} to augment V\textsubscript{O\textsubscript{2}}. However, the role of \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} in determining exercise capacity in HFpEF remains incompletely understood.\textsuperscript{15-17}

In HFpEF, 2 studies\textsuperscript{5,16} that derived \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} indirectly have suggested that \textsubscript{C(a-v)}\textsubscript{O\textsubscript{2}} is abnormally low in HFpEF, whereas a third study found that it was not impaired.\textsuperscript{17} To date, no studies

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Correspondence to Gregory D. Lewis, MD, Heart Failure and Cardiac Transplantation Unit, Massachusetts General Hospital, Bigelow 800, 55 Fruit St, Boston, MA 02114. E-mail glewis@partners.org


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From the Cardiology Division (B.P.D., R.M., R.M.M., A.L.B., R.B.W., N.E.H., A.S.E, G.D.L.) and the Pulmonary and Critical Care Unit (P.P.P., S.S.H., G.D.L.), Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.

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have performed direct serial measurements of C(a-v)O₂ through-out exercise in HFpEF and HFrEF to define O₂ extraction patterns.

On the basis of the heterogeneous 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]. 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 <0.45 on standard pharmacotherapy; (2) HFpEF: Chronic NYHA II to IV symptoms, left ventricular ejection fraction >0.50, 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 V̇/forced expiratory volume in 1 s (FEV₁)×35>0.7 at the anaerobic threshold. 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.

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. 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. 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) 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. 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

### Table 1. Demographics of Heart Failure and Control Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HFpEF (48)</th>
<th>HFrEF (56)</th>
<th>Controls (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±12*</td>
<td>59±12</td>
<td>55±18</td>
</tr>
<tr>
<td>Male (number, %)</td>
<td>20 (40)*</td>
<td>45 (81)†</td>
<td>15 (62)</td>
</tr>
<tr>
<td>Race (White, %)</td>
<td>46 (96)</td>
<td>50 (88)</td>
<td>23 (96)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.7±7.6*</td>
<td>27.8±6*</td>
<td>27.6±3.0</td>
</tr>
<tr>
<td>Comorbidities %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (60)*</td>
<td>34 (61)†</td>
<td>9 (37)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (25)*</td>
<td>12 (21)†</td>
<td>0</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>25 (52)*</td>
<td>32 (57)†</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (26)*</td>
<td>11 (19)†</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure pharmacotherapy %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>30 (63)*</td>
<td>48 (86)†</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>14 (29)</td>
<td>45 (80)†</td>
<td>7 (29)</td>
</tr>
<tr>
<td>β-adrenergic receptor blocker</td>
<td>25 (52)*</td>
<td>51 (91)†</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>4 (8)</td>
<td>30 (54)†</td>
<td>0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>6 (12)*</td>
<td>28 (50)†</td>
<td>0</td>
</tr>
<tr>
<td>LVEF %</td>
<td>62±7*</td>
<td>29±6†</td>
<td>67±6</td>
</tr>
<tr>
<td>Resting Supine PCWP, mm Hg</td>
<td>20±2.7*</td>
<td>22±8.9†</td>
<td>10±3.9</td>
</tr>
<tr>
<td>Hemoglobin, gm/dL</td>
<td>13.2±1.4</td>
<td>12.9±2.2</td>
<td>13.2±1.5</td>
</tr>
<tr>
<td>Peak VO₂, mL·kg⁻¹·min⁻¹</td>
<td>13.9±3.5*</td>
<td>12.1±3.7*</td>
<td>27.0±8.3</td>
</tr>
<tr>
<td>Max watts achieved</td>
<td>82±32&quot;</td>
<td>75±37&quot;</td>
<td>166±57</td>
</tr>
<tr>
<td>Peak exercise RER</td>
<td>1.15±0.07</td>
<td>1.16±0.14</td>
<td>1.15±0.05</td>
</tr>
<tr>
<td>Peak exercise lactate, mM</td>
<td>5.3±2.7*</td>
<td>4.8±1.5*</td>
<td>7.6±1.5</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; HFrEF, heart failure with preserved ejection fraction; HFpEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; RER, respiratory exchange ratio.

*P<0.05 between HFpEF and controls.
†P<0.05 between HFpEF and HFrEF.
‡P<0.05 between HFrEF and controls.

Arterio-Mixed Venous Oxygen Content

Arterial O₂ content (CaO₂) 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. 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). 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 $R^2$ 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 HFpEF (n=48), HFrEF (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.$^{1,20}$ HFpEF subjects had more elevated body mass index and a female predominance (60%) compared with patients with HFrEF, consistent with the known distinct demographic characteristics of HFpEF and HFrEF populations.$^{1,15,16,32}$

Functional capacity as indicated by peak VO2 was reduced in HFpEF (13.9±0.5 mL kg$^{-1}$ min$^{-1}$) and in HFrEF (12.1±0.5 mL kg$^{-1}$ min$^{-1}$) compared with controls (27.0±1.7 mL kg$^{-1}$ min$^{-1}$, $P<0.05$ for both comparisons, Table 1). The measurement of VO2, HR, CaO2, and CvO2 during each minute of exercise and application of the Fick Principle [ie, $VO_2=HR\times SV \times C(a-v)O_2$] permitted analysis of each component of VO2 during exercise in the 3 groups.

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 HFrEF (9.4±0.3 mL/dL), and similar in HFpEF and controls (11.6±0.3 and 12.1±0.36 mL/dL, $P=0.70$, indicating maximum or near maximum exercise effort across the 3 groups.$^{1,20}$ HFpEF subjects had more elevated body mass index and a female predominance (60%) compared with patients with HFrEF, consistent with the known distinct demographic characteristics of HFpEF and HFrEF populations.$^{1,15,16,32}$

Functional capacity as indicated by peak VO2 was reduced in HFpEF (13.9±0.5 mL kg$^{-1}$ min$^{-1}$) and in HFrEF (12.1±0.5 mL kg$^{-1}$ min$^{-1}$) compared with controls (27.0±1.7 mL kg$^{-1}$ min$^{-1}$, $P<0.05$ for both comparisons, Table 1). The measurement of VO2, HR, CaO2, and CvO2 during each minute of exercise and application of the Fick Principle [ie, $VO_2=HR\times SV \times C(a-v)O_2$] permitted analysis of each component of VO2 during exercise in the 3 groups.
Compared to controls and patients with HFrEF, patients with HFpEF had the lowest average C(a-v)O₂ and highest peak exercise CvO₂, indicating relatively impaired maximum peripheral O₂ extraction in HFpEF (Table 2; Figure 1). Maximum C(a-v)O₂ was less than the predicted value [i.e., maximum C(a-v)O₂=hemoglobin level,¹⁸ and CvO₂ >5 mL/dL, see Methods Section] in 75% of HFpEF versus 21% of HFrEF and 33% of controls (P<0.001). Peak C(a-v)O₂ was not related to peak CO in any of the groups, indicating that at peak exercise these variables are dissociated, and not reciprocally related as they are at rest and during low-level exercise.

**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 59±4±2% from rest to peak exercise, consistent with previous studies.13,31 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 HFrEF had a 31±1±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 26±4±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.37 Multipoint plots of CvO2 versus VO2 in the 3 groups indicate that diffusive O2 transport is most impaired in HFrEF. Patients with HFrEF had a 26±4±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.

To further investigate impaired diffusive O2 transport in HFrEF, we stratified patients with HFrEF into 2 groups based on median peak exercise C(a-v)O2 of 6.8 mL/dL. The higher C(a-v)O2 subgroup did not differ from the lower C(a-v)O2 subgroup in age, sex, left ventricular ejection fraction, CO, or cardiac filling pressures but hemoglobin was slightly higher in the higher C(a-v)O2 subgroup (Table I in the Data Supplement). The subset of patients with HFrEF with higher C(a-v)O2 had similar lactate and peak RER to the lower C(a-v)O2 group, which argues against reduced effort during exercise as an explanation for the attenuated fall in C(a-v)O2 during exercise in the high C(a-v)O2 group. The most striking difference between HFrEF C(a-v)O2 subgroups was that elevated C(a-v)O2 was associated with a disproportionate hypertensive response during exercise with elevation of diastolic blood pressure (DBP) (93±4 mmHg versus displayed in Table 3. In HFrEF, 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 13.2±g/dL).18 with a lower, partial R2 value (0.19, P=0.056) relative to peak VO2.

Blood Pressure and Diffusive Oxygen Transport in HFrEF

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

Exercise capacity is a cardinal manifestation of HF that is closely related to poor quality of life and mortality.1,2 The degree of reduction in exercise capacity in HFpEF in our study was similar to that reported in previous studies,3,5,15,32 and was intermediate between 2 recent interventional trials in HFpEF with rigorous entry criteria.43,44 In HFrEF, exercise was intermediate between 2 recent interventional trials study was similar to that reported in previous studies,3,5,15,32 thereby suggesting that skeletal muscle sympatholysis during exercise may be significantly important role of targeting peripheral O2 extraction to augment impaired exercise capacity in HFpEF; particularly in light of failure of other interventions directed at central cardiac function to improve exercise capacity in HFpEF.6,38,40

The validity of our findings defining relative components of O2 augmentation in HFpEF, 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 CaO2 in HFpEF during exercise in normals.

Peripheral Oxygen Extraction in HFpEF

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 HFpEF in our study and in only 2% of patients with HFrEF. Furthermore, in patients with HFpEF, 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 HFpEF 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 HFpEF. Vasoconstrictor sympathetic tone and intrinsic microvascular control mechanisms have been shown to modulate the balance between O2 delivery and O2 demand within organs,40 which suggests that skeletal muscle sympatholysis during exercise may be dysregulated in patients with HFpEF with impaired O2 extraction. In further support of sympathetic dysregulation and poorly co-ordinated vasoconstriction, elevated norepinephrine levels have been reported in patients with HFpEF 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 HFrEF,51 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.55 These pathological peripheral abnormalities are distinct from the influence of deconditioning alone.56,57 Detailed

Association of Central Cardiac Function With Exercise Capacity in HF

Our finding that 73% of patients with HFpEF 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 HFpEF, confirms previous studies demonstrating an important influence of chronotropic response on exercise capacity in HF.6,53,16,47,48 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 HFpEF compared with controls was similar at rest but lower at peak exercise. Previous elegant studies have elucidated mechanisms by which SV is impaired in HFpEF at rest and during exercise, including abnormal ventriculo-vascular coupling,4 impaired relaxation,4,46 and impaired augmentation in systolic function.5,49 However, not all studies to date have found impaired SV responses to exercise in HFpEF,50,51 and we found that within patients with HFpEF, peak SV was not significantly related to peak VO2. Furthermore, the percentage increase 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 HFpEF, and 40±5% in HFrEF; Figure 2).13,50 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 HFpEF.

Discussion

In comprehensively characterized cohorts with HFpEF, 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 HFpEF 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 HFpEF, we found relatively modest or absent associations between peak VO2 and LV filling pressures or LV SV in HFpEF. Taken together, our findings highlight the potentially important role of targeting peripheral O2 extraction to augment impaired exercise capacity in HFpEF, particularly in light of failure of other interventions directed at central cardiac function to improve exercise capacity in HFpEF.6,38,40

The validity of our findings defining relative components of O2 augmentation in HFpEF, 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.1,2 The degree of reduction in exercise capacity in HFpEF in our study was similar to that reported in previous studies,3,5,15,32 and was intermediate between 2 recent interventional trials in HFpEF with rigorous entry criteria.43,44 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.

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Peripheral Oxygen Extraction in HFpEF

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 HFpEF in our study and in only 2% of patients with HFrEF. Furthermore, in patients with HFpEF, 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 HFpEF 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 HFpEF. Vasoconstrictor sympathetic tone and intrinsic microvascular control mechanisms have been shown to modulate the balance between O2 delivery and O2 demand within organs,40 which suggests that skeletal muscle sympatholysis during exercise may be dysregulated in patients with HFpEF with impaired O2 extraction. In further support of sympathetic dysregulation and poorly co-ordinated vasoconstriction, elevated norepinephrine levels have been reported in patients with HFpEF 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 HFrEF,51 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.55 These pathological peripheral abnormalities are distinct from the influence of deconditioning alone.56,57 Detailed
investigations of skeletal muscle in HFrEF are limited, although intriguing in that Bhella et al\textsuperscript{15} first reported reduced oxidative metabolism by MRI in 2 patients with HFrEF and more recently abnormal skeletal muscle mass, adiposity, fiber type, and capillary density have been observed in HFrEF.\textsuperscript{55,56}

Previous HFrEF studies in which C(a-v)O$_2$ was estimated via noninvasive CO measurement have led to widely variable estimates of C(a-v)O$_2$ levels in normals and in HFrEF.\textsuperscript{15,16} Peak exercise C(a-v)O$_2$ values should be equal to hemoglobin levels in normal individuals.\textsuperscript{15,17} In 1 previous study that directly measured C(a-v)O$_2$ in a subset of patients studied, C(a-v)O$_2$ levels in controls and HFrEF were similarly low (10.1±0.3 versus 9.9±0.3 mL/dL; \(P=0.7\)).\textsuperscript{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)O$_2$ as we observed C(a-v)O$_2$ to increase in a linear fashion throughout maximum incremental exercise in our study (data not shown). In other HFrEF studies with a control group, the peak C(a-v)O$_2$ values in controls\textsuperscript{14,15,17} were also 30% lower than their hemoglobin levels, which is much lower than to the ≈6% reduction in C(a-v)O$_2$ expected with deconditioning alone.\textsuperscript{18} In previous small studies in HFrEF that deployed maximum upright exercise, C(a-v)O$_2$ is consistently depressed.\textsuperscript{50,51} Our findings of an inverse initial relationship between C(a-v)O$_2$ and CO that is no longer present at peak exercise points to the importance of performing maximum effort exercise to ascertain peak O$_2$ extraction capacity in study populations.

**Clinical Implications**

Within the constraints of currently applied definitions of HFrEF,\textsuperscript{2,60} a single dominant pathophysiological mechanism governing exercise intolerance in HFrEF is unlikely to exist. The heterogeneity of the HFrEF population poses a major challenge to development of therapies to treat the entire HFrEF population.\textsuperscript{2,38-40} A potential pathway forward is to carefully identify subjects in whom the majority of reduction in peak VO$_2$ is attributable to an abnormality in 1 component of peak VO$_2$. In this study, CPET with invasive hemodynamic measurements permitted us to probe the reserve capacity of each component of VO$_2$ to subphenotype patients on the basis of the dominant mechanism limiting exercise capacity. This approach may refine patient selection for targeted HFrEF therapeutics, for example, HFrEF could be subclassified into those with primarily impaired peripheral O$_2$ 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)O$_2$ augmentation in contributing to exercise intolerance in ≈40% of an HFrEF population similar to those recently studied in HFrEF trials. Further studies are needed to determine the relative effect of targeting different aspects of the O$_2$ diffusion unit. A recent study by Haykowsky et al\textsuperscript{41} found that improved peripheral function [estimated C(a-v)O$_2$] primarily accounted for observed improvements in peak VO$_2$ after exercise training in an HFrEF 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 O$_2$ storage in myoglobin offer promise for the possibility of extending this intervention to HFrEF.\textsuperscript{52} With regard to improving diffusional O$_2$ transport to muscle in HF, decreasing O$_2$ affinity (right shifting the O$_2$ dissociation curve) has been shown to improve exercise capacity in mice with HF.\textsuperscript{50} Alternatively, patients with HFrEF with an exaggerated blood pressure response to exercise and impaired O$_2$ 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 VO$_2$ impairment is chronotropic incompetence,\textsuperscript{48} pacing or reduction in heart rate–lowering medications may promote improved exercise capacity, as will be tested in the RAPID Trial (NCT02145351). 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 HFrEF found in the community, and we tested multiple hypotheses regarding associations between C(a-v)O$_2$ 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 HFrEF. 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.\textsuperscript{10} Although none of the patients with HFrEF 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 HFrEF 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 O$_2$ diffusion. This will be an important topic of future investigations aimed at further characterizing impaired O$_2$ diffusion in HFrEF.

**Conclusions**

Patients with HFrEF demonstrated abnormally low peripheral oxygen extraction [C(a-v)O$_2$] 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 HFrEF. Our findings further indicate that improving abnormal O$_2$ extraction may be an important therapeutic target in the notoriously difficult-to-treat patients with HFrEF.
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Disclosures
None.

References
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Krogh 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.


CLINICAL PERSPECTIVE
Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: 
The Role of Abnormal Peripheral Oxygen Extraction
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Gregory D. Lewis

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**SUPPLEMENTAL MATERIAL**

Supplemental Table 1: Demographics and hemodynamics of HFpEF subclasses*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Higher CvO₂ (n=24)</th>
<th>Lower CvO₂ (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 VO₂, ml/kg/min</td>
<td>14.2±0.7</td>
<td>13.5±0.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Peak VO₂ % predicted</td>
<td>70±3.3</td>
<td>72±3.9</td>
<td>0.74</td>
</tr>
<tr>
<td>Resting C(a-v)O₂, 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)O₂, 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>
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<tr>
<td>Peak HR, % predicted</td>
<td>80±3</td>
<td>73±3</td>
<td>0.11</td>
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<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 CvO₂ of 6.8 mg/dl
Supplemental Figure 1: Graphical representation of the linearity of the cardiac output-VO\textsubscript{2} relationship during exercise in 2 HFpEF subgroups.

**Figure Legend:** The group with impaired peak C(a-v)O\textsubscript{2} demonstrates a steep CO-VO\textsubscript{2} slope upon initiation of exercise in comparison to other patients with HFpEF.