Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction

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Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction (HFREF and HFPEF, respectively). Evidence to date suggests that the reduced peak pulmonary oxygen uptake (pulm V˙O2) in patients with HFREF compared with healthy controls is due to both central (reduced convective O2 transport) and peripheral factors (impaired skeletal muscle blood flow, decreased diffusive O2 transport coupled with abnormal skeletal morphology, and metabolism). Although central and peripheral impairments also limit peak pulm V˙O2 in HFPEF patients compared with healthy controls, emerging data suggest that the latter may play a relatively greater role in limiting exercise performance in these patients. Unlike HFREF, currently there is limited evidence-based therapies that improve exercise capacity in HFPEF patients, therefore future studies are required to determine whether interventions targeted to improve peripheral vascular and skeletal muscle function result in favorable improvements in peak pulm and leg V˙O2 and their determinants in HFPEF patients.

HEART FAILURE (HF) is a major health care problem with a high morbidity and mortality rate and excessive health care burden (41). An estimated 5.7 million Americans ≥20 years of age have HF, and it is projected that the prevalence of HF will increase by 46% from 2012 to 2030 (41). Approximately 50% of HF patients have reduced ejection fraction with the remainder of patients having preserved ejection fraction (coined HFREF and HFPEF, respectively).

Heart failure with preserved ejection fraction is the fastest growing form of HF and is nearly exclusively found in older persons, particularly women, in whom 90% of new HF cases are HFPEF (14). Unlike HFREF, no medication trials have had a positive effect on improving survival; therefore, there is a lack of evidence-based recommendations for improving clinical outcomes in the growing population of elderly patients with HFPEF.

The primary chronic symptom in both HF phenotypes, even when stable and well compensated, is severe exercise intolerance, which can be measured objectively as decreased oxygen uptake during whole body [pulmonary (pulm) V˙O2] or small muscle mass (peak leg V˙O2) exercise and is associated with reduced quality of life (11, 29). Specifically, previous studies have reported that peak pulm V˙O2 during maximal upright cycle exercise is ~35% lower in HF patients vs. healthy controls (1, 4, 8, 11, 13, 17, 48, 53), and the magnitude of the decline is similar between HFREF and HFPEF patients (29).

During the past three decades, numerous investigators have studied the mechanisms responsible for the reduced peak pulm V˙O2 in clinically stable HFREF patients (8, 10, 11, 21, 33, 38, 42, 46-48, 51–55); however, the pathophysiology of exercise intolerance in patients with HFPEF has not been well studied (1, 4–6, 8, 17, 31). Identification of the mechanisms responsible for the HFPEF-mediated decline in peak pulm V˙O2 could be

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Table 1. Central and peripheral hemodynamic responses during upright maximal large (cycle or treadmill) or small muscle mass (unilateral knee extension) exercise in heart failure patients with reduced or preserved ejection fraction compared to healthy control subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>HFPEF vs. Control</th>
<th>HFREF vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large Muscle Mass</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓ (8, 11, 39, 48)</td>
<td>↓ (1, 8, 17, 28), ≈(4)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑ (8, 48, 53), ≈(11, 39)</td>
<td>↑ (4, 8, 17, 28)</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↓ (8, 11A, 22, 39, 48)</td>
<td>↓ (8, 28), ≈(4, 17)</td>
</tr>
<tr>
<td>End-diastolic volume</td>
<td>↑ (8, 22)</td>
<td>↑ (17, 28), ≈(8)</td>
</tr>
<tr>
<td>End-systolic volume</td>
<td>↑ (BB, 22)</td>
<td>↑ (BB), ≈(17, 28)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>↓ (8, 22)</td>
<td>↓ (8), ≈(17, 28)</td>
</tr>
<tr>
<td>Mean arterial blood pressure</td>
<td>↓ (8, 48)</td>
<td>≈(4, 8)</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>↑ (8C), ≈(39)</td>
<td>↑ (8C), ≈(17)</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>↑ (8, 22, 48)</td>
<td>↑ (8, 28)</td>
</tr>
<tr>
<td>Arterial-mixed venous oxygen difference</td>
<td>≈(8, 48), ↑(39)</td>
<td>↓ (8, 17, 28), ≈(1, 28)</td>
</tr>
<tr>
<td><strong>Small Muscle Mass</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg oxygen uptake</td>
<td>↓ (11, 48, 53)</td>
<td>Not studied</td>
</tr>
<tr>
<td>Leg blood flow</td>
<td>↓ (11, 35, 48, 53)</td>
<td>Not studied</td>
</tr>
<tr>
<td>Leg oxygen delivery</td>
<td>↑ (11)</td>
<td>Not studied</td>
</tr>
<tr>
<td>Leg vascular resistance</td>
<td>↑ (11, 35, 48)</td>
<td>Not studied</td>
</tr>
<tr>
<td>Leg arterial-venous oxygen difference</td>
<td>≈(11, 48, 53)</td>
<td>Not studied</td>
</tr>
<tr>
<td>Muscle oxygen diffusional conductance</td>
<td>↓ (11)</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

A, calculated from published mean cardiac output and heart rate data from Esposito et al. (11); B, calculated from published mean ejection fraction and end-diastolic volume data from Dhakal et al. (8); C, calculated from published mean cardiac output and mean arterial pressure data from Dhakal et al. (8).

The aim of this mini-review is to highlight the salient mechanisms underpinning the reduced peak pulm and leg VO2 during upright maximal large (cycle or treadmill) and small muscle mass (one-leg knee extension) exercise in both HF phenotypes compared with healthy controls. In addition, we also briefly discuss future research opportunities pertaining to HF exercise physiology studies.

**PATHOPHYSIOLOGY OF EXERCISE INTOLERANCE IN HFREF PATIENTS VS. HEALTHY SUBJECTS**

**Role of impaired convective and diffusive oxygen transport.** Previous studies incorporating invasive central and peripheral hemodynamic monitoring with simultaneous expired gas analysis have compared peak pulm VO2 and leg VO2 and their determinants in HFREF patients and healthy control subjects (8, 11, 48, 53). Based on the Fick principle [VO2 = cardiac output (CO) × arterial-venous oxygen content difference, AVO2Diff (42, 49)], the decreased peak pulm VO2 in HFREF patients vs. healthy controls was due to a lower maximal heart rate (HR), stroke volume (SV), and CO, as maximal AVO2Diff (oxygen extraction) was not significantly different between groups (Table 1) (7, 8, 11, 48). Given that maximal left ventricular end-diastolic volume (EDV) is higher and the percent change in EDV from rest to peak exercise is similar or greater in HFREF patients compared with healthy controls, these findings suggest that the attenuated maximal SV is due to impaired inotropic and/or systemic vascular resistance reserve (peak exercise minus rest change) (45, 50).

In accordance with Fick’s law of diffusion [VO2 = muscle oxygen diffusion capacity (DMO2) × constant (K) × muscle capillary to venous O2 pressure, which is ~2) × muscle venous partial pressure of O2, assuming intracellular PO2 is close to zero] (42, 49), impaired diffusive O2 transport between the muscle microvascular red blood cells and muscle mitochondria may also limit exercise capacity in HFREF patients (11, 12).

Sullivan et al. (48) and Esposito et al. (11) have shown that the significant and marked decline in peak leg VO2 during maximal normoxic upright cycle exercise or one-leg knee extension exercise in patients with HFREF vs. healthy subjects was due to a lower maximal leg oxygen delivery, as maximal leg A-VO2Diff was not different between groups (Fig. 1, arrow 1) (11, 48, 53). In turn, the reduced maximal leg oxygen delivery was due to a lower maximal leg blood flow and hemoglobin concentration because maximal arterial O2 partial pressure and arterial oxygen saturation were not significantly different between groups (11). Finally, the finding that maximal leg O2 extraction is similar between HFREF and controls during large or small muscle exercise despite the former having longer capillary transit time and thus greater time for O2 extraction (due to decreased maximal leg blood flow) suggests that diffusion of O2 from hemoglobin establishes potential targeted therapies to improve overall functional capacity and quality of life in these patients.
to muscle mitochondria is reduced in HFREF patients (11). Indeed, Esposito et al. (11, 12) reported that DMO$_2$ was 30% lower in HFREF than healthy controls during maximal cycle exercise (Fig. 1, arrow 2).

ROLE OF IMPAIRED VASCULAR FUNCTION

The attenuated ability of skeletal muscle vasculature to dilate during whole body exercise may be due to impaired peripheral arterial endothelial function (2, 9, 24, 26, 32, 43, 56). Specifically, Hambrecht et al. (15) found that resting and acetylcholine-mediated (an endothelial dependent stress) superficial femoral artery blood flow was 35% and 63% lower, respectively, in HFREF patients compared with healthy controls. Hundley et al. (24), using phase contrast magnetic resonance imaging, compared superficial femoral artery flow mediated arterial dilation (FMAD) in response to lower limb cuff ischemia (an endothelial-dependent stimulus) in elderly HFREF ($n = 10$; mean age: 73 yr; mean EF: 26%) and HFPEF ($n = 9$; mean age: 74 yr; mean EF: 63%) patients and healthy controls ($n = 11$; mean age: 71 yr; mean EF: 62%). As depicted in Fig. 2, superficial femoral artery FMAD was significantly reduced in HFREF compared with HFPEF and healthy controls, and was positively associated with peak pulm $V_O_2$ in patients with HFREF ($r^2 = 0.8, P = 0.02$) and controls ($r^2 = 0.5, P = 0.05$) but not in those with HFPEF ($r^2 = 0.07, P = 0.6$) (24). Alternatively, increased sympathetic nervous system activity may also attenuate the increase in maximal leg blood flow and leg vascular conductance in HFREF patients (12).

ROLE OF SKELETAL MUSCLE DYSFUNCTION

Patients with HFREF have multiple skeletal muscle abnormalities, including reduced percent type I (oxidative) fibers and oxidative enzymes (10, 36, 40, 44, 47), reduced volume density of mitochondria and surface density of mitochondrial cristae (10), decreased capillary-fiber ratio (36, 47), and these alterations are associated with their severely reduced exercise tolerance (10, 36, 37, 40).

In summary, in HFREF patients, both central (reduced CO and convective O$_2$ transport) and peripheral factors (impaired skeletal muscle blood flow, decreased diffusive O$_2$ transport coupled with abnormal skeletal morphology, and metabolism) contribute to the reduced pulm and leg $V_O_2$ during maximal whole body exercise (11, 12, 48, 53).

DETERMINANTS OF EXERCISE INTOLERANCE IN HFPEF PATIENTS VS. HEALTHY SUBJECTS

Role of impaired convective and diffusive oxygen transport. A series of studies by Kitzman et al. (17, 28) and Dhakal and colleagues (8) have shown that the reduced pulm $V_O_2$ during maximal upright cycle exercise in HFPEF patients vs. healthy subjects was due both to a decreased maximal CO and AVO$_2$Diff (Table 1). In turn, the lower peak exercise CO appears to be due to a greater extent to a lower peak HR than peak SV (8, 17). Indeed, Dhakal et al. (8) recently demonstrated that 73% of HFPEF patients had chronotropic incompetence (defined as a failure to achieve 85% of age predicted HR) after accounting for beta blocker use. Importantly, “non-cardiac” peripheral factors also limit exercise tolerance as Haykowsky et al. (17) reported that the change in calculated AVO$_2$Diff from rest to maximal exercise was the strongest independent predictor of peak pulm $V_O_2$ in HFPEF patients and controls, whereas Dhakal et al. found that peak pulm $V_O_2$ was positively related to maximal AVO$_2$Diff (8). Bhella et al. (4) confirmed that peripheral factors play an important role in limiting exercise capacity, because the reduced peak pulm $V_O_2$ during maximal treadmill exercise in older HFPEF patients vs. age-matched healthy controls occurred despite no significant difference in maximal exercise SV or CO between groups.

In contrast to the above findings, a series of cross-sectional studies by Borlaug et al. (1, 5, 6) showed that the lower peak pulm $V_O_2$ in HFPEF vs. healthy subjects or comorbidity-matched controls without HF was due entirely to a lower peak and reserve CO secondary to impaired chronotropic, inotropic, and systemic vascular resistance reserve as peak AVO$_2$Diff was not significantly different between groups. The finding of a similar peak AVO$_2$Diff may be due to the inclusion of severely deconditioned control subjects. Indeed, in one of these studies (5), the healthy controls peak pulm $V_O_2$ (14.4 ml·kg$^{-1}$·min$^{-1}$ equal to 70% predicted peak pulm $V_O_2$) is lower than one would expect during maximal upright cycle exercise. Importantly, as discussed above for HFREF patients, the finding of a similar peak AVO$_2$Diff between patients with HFPEF and controls despite the former having greater time for $O_2$ extraction by the active muscles (due to a lower maximal CO and muscle blood flow) suggests that decreased DMO$_2$ contributes to exercise intolerance in HFPEF patients (8, 19).

Role of impaired vascular function. Kitzman et al. (25, 27) demonstrated that carotid arterial and proximal thoracic aortic distensibility are reduced in HFPEF patients compared with healthy controls, and this correlates with their reduced exercise tolerance. Balmain et al. (3) also reported that aortic pulse wave velocity was significantly higher in coronary heart disease patients (CHD) with HFPEF compared with both CHD patients with HFREF or CHD patients with preserved systolic...
function with no evidence of heart failure (10.7 ± 1.1 vs. 8.9 ± 1.7 vs. 8.6 ± 2.1 m/s, respectively). A consequence of increased aortic stiffness and systemic vascular resistance is that it may result in a blunted increase in oxygen delivery and nutrients to the active muscles (16, 19).

To our knowledge, no study has measured leg blood flow during maximal whole body exercise in HFPEF patients. However, preliminary data by Lee et al. (34), in a small sample of HFPEF patients (n = 6, mean age: 68 yr) and age- and sex-matched controls (n = 6), revealed that leg blood flow was 30 to 40% lower in HFPEF vs. controls during knee extensor exercise performed at 5, 10, and 15 W.

The mechanism responsible for the decreased leg blood flow does not appear to be due to impaired lower extremity conduit arterial endothelial function, because Hundley et al. (24) reported that superficial femoral artery FMAD is not significantly different than age-matched healthy controls (Fig. 2). However, it is possible that the HFPEF-mediated impairment in microvascular endothelial function may result in decreased O2 transport at the vasculomuscular interface (6, 19).

Role of skeletal muscle dysfunction. Given that a majority of the O2 consumed during exercise occurs in the working muscles (11, 12), it is possible that a reduction in metabolically active tissue may result in reduced exercise tolerance. Haykowsky et al. (18), using dual energy X-ray absorptiometry and cardiopulmonary cycle exercise testing, compared lean body mass and peak pulm V02 in older HFPEF patients and age-matched healthy subjects. These investigators reported three novel findings: 1) the percent total lean body and leg lean mass was significantly lower in HFPEF patients than healthy subjects (18); 2) peak pulm V02 indexed to total lean body mass or leg lean mass was significantly lower in patients with HFPEF than healthy subjects (18); and 3) the change in peak pulm V02 with increasing percent leg lean mass was markedly reduced in HFPEF patients vs. healthy subjects (healthy mean slope: 36 ± 5 ml O2/min vs. HFPEF mean slope: 11 ± 5 ml O2/min, P < 0.001, Fig. 3) (18). This latter finding indicated that the O2 utilization (muscle quality) was impaired in HFPEF.

Haykowsky et al. (20), using magnetic resonance imaging, examined thigh muscle composition and its relationship to peak pulm V02 in older patients with HFPEF compared with age-matched healthy subjects. Although there were no significant intergroup differences in total thigh area or subcutaneous adipose, HFPEF patients had significantly increased intermuscular adipose area (35.6 ± 11.5 vs. 22.3 ± 7.6 cm2, P = 0.01) and ratio of intermuscular adipose to skeletal muscle area (0.38 ± 0.10 vs. 0.28 ± 0.09, P = 0.007) (20). Moreover, multivariate analyses showed that intermuscular adipose area and intermuscular adipose to muscle area (partial r = −0.51 and r = −0.45 respectively, P < 0.01 for both) were independent predictors of peak pulm V02 (20). Taken together, abnormalities in skeletal muscle composition contribute significantly to the severely reduced exercise capacity in older HFPEF patients.

Finally, using needle biopsy of the vastus lateralis, Kitzman et al. (30) recently found that older HFPEF patients exhibited a shift in skeletal muscle fiber type distribution with reduced percent slow-twitch type I (oxidative) fibers, type IIa/type II fiber ratio, and capillary-to-fiber ratio, and these alterations are associated with their decreased peak pulm V02 (30). The importance of the fiber type shift from oxidative to glycolytic fibers coupled with abnormal mitochondrial function is that it may impair oxidative metabolism during exercise (19). Indeed, Bhella et al. (4) found reduced leg muscle oxidative metabolism by magnetic resonance imaging during exercise in the small number of HFPEF patients that were studied.

In summary, given the heterogenous nature of HFPEF both central and peripheral impairments also may limit peak pulm V02 in HFPEF patients compared with healthy controls (23); however, emerging data suggest that the latter may play a relatively greater role in limiting exercise performance in these patients (8, 17, 19).

FUTURE DIRECTIONS

Prior studies that examined the pathophysiology of exercise intolerance in both HF phenotypes are based on comparisons with age-matched or comorbidity-matched controls without HF (16, 19). However, it is possible that the contribution of central and peripheral limits to exercise may differ between HFREF and HFPEF patients. Indeed, a recently published study by Dhakal et al. (8) using invasive central hemodynamic monitoring during incremental cardiopulmonary (cycle) exercise testing found that the lower absolute and relative peak pulm V02 in HFREF compared with HFPEF patients (1,021 vs. 1,227 ml/min, P < 0.05, and 12.1 vs. 13.9 ml·kg−1·min−1, P < 0.05, respectively) was primarily due to a significantly lower maximal SV (68 vs. 88 ml, P < 0.05) and CO (7.7 vs. 10.7 l/min, P < 0.05), because maximal exercise AVO2Diff was significantly higher in HFREF than HFPEF patients (13.5 vs. 11.5 ml·dl, P < 0.05).

These direct group comparisons suggest that reduced exercise tolerance in HFREF patients may be more centrally driven (decreased CO and convective O2 delivery), whereas peripheral abnormalities may play a greater limiting role in HFPEF patients. Although novel, a limitation of the Dhakal et al. study was that invasive peripheral hemodynamic measures were not performed; therefore, it is unknown whether leg V02 and its determinants (leg blood flow, DMO2Diff) differ between HFREF and HFPEF patients. Accordingly, future studies are required to compare peak pulm V02 and leg V02 and their determinants in HFREF and HFPEF during whole body exercise.
SUMMARY

Heart failure patients have severe and marked exercise intolerance that is associated with reduced quality of life (29). Evidence to date suggests that the decreased peak VO2 in clinically stable HFPEF patients vs. healthy controls is due to central (decreased cardiac output and convective oxygen delivery) and peripheral factors (decreased leg blood flow, vascular conductance, and DMO2 with or without abnormalities in skeletal muscle metabolism) (8, 11). Although central and peripheral impairments also limit peak pulm VO2 in HFPEF patients compared with healthy controls, emerging data suggest that the latter may play a relatively greater role in limiting exercise performance in these patients (8, 19).

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