Fatigability, Exercise Intolerance, and Abnormal Skeletal Muscle Energetics in Heart Failure

See Editorial by Kitzman et al

BACKGROUND: Among central and peripheral factors contributing to exercise intolerance (EI) in heart failure (HF), the extent to which skeletal muscle (SM) energy metabolic abnormalities occur and contribute to EI and increased fatigability in HF patients with reduced or preserved ejection fraction (HFrEF and HFpEF, respectively) are not known. An energetic plantar flexion exercise fatigability test and magnetic resonance spectroscopy were used to probe the mechanistic in vivo relationships among SM high-energy phosphate concentrations, mitochondrial function, and EI in HFrEF and HFpEF patients and in healthy controls.

METHODS AND RESULTS: Resting SM high-energy phosphate concentrations and ATP flux rates were normal in HFrEF and HFpEF patients. Fatigue occurred at similar SM energetic levels in all subjects, consistent with a common SM energetic limit. Importantly, HFrEF New York Heart Association class II–III patients with EI and high fatigability exhibited significantly faster rates of exercise-induced high-energy phosphate decline than did HFrEF patients with low fatigability (New York Heart Association class I), despite similar left ventricular ejection fractions. HFpEF patients exhibited severe EI, the most rapid rates of high-energy phosphate depletion during exercise, and impaired maximal oxidative capacity.

CONCLUSIONS: Symptomatic fatigue during plantar flexion exercise occurs at a common energetic limit in all subjects. HFrEF and HFpEF patients with EI and increased fatigability manifest early, rapid exercise-induced declines in SM high-energy phosphates and reduced oxidative capacity compared with healthy and low-fatigability HF patients, suggesting that SM metabolism is a potentially important target for future HF treatment strategies.
WHAT IS KNOWN

- Skeletal muscle energetics were studied with $^{31}$P magnetic resonance spectroscopy during plantar flexion exercise in healthy subjects and heart failure (HF) patients with and without exercise intolerance (EI).
- Plantar flexion exercise performance correlated with separate 6-minute walk and peak VO$_2$ testing. Skeletal muscle energetic levels in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction patients were normal at rest.
- HFrEF New York Heart Association class II–III patients with EI and high fatigability exhibited significantly faster rates of exercise-induced high-energy phosphate decline than did HFrEF patients with low fatigability (New York Heart Association class I).
- Heart failure with preserved ejection fraction patients exhibited severe EI, the most rapid rates of high-energy phosphate depletion during exercise and impaired maximal oxidative capacity.

WHAT THE STUDY ADDS

- EI and exertional fatigue are hallmark symptoms of HF with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) and are associated with increased disability and mortality.
- This study showed that symptomatic fatigue during plantar flexion exercise occurs at a common energetic limit in healthy and HF subjects.
- HFrEF and heart failure with preserved ejection fraction patients with EI and increased fatigability manifest early, rapid exercise-induced declines in skeletal muscle high-energy phosphates and reduced oxidative capacity compared with healthy and low-fatigability HF patients.
- These observations suggest that skeletal muscle metabolism may be a potentially important target for future HF-EF and heart failure with preserved ejection fraction treatment strategies.

Exercise intolerance (EI) and exertional fatigue are hallmark symptoms of heart failure (HF) and are associated with increased disability and mortality.
metabolic abnormalities play an important mechanistic role in EI in HFrEF and HFpEF patients.

METHODS
The Johns Hopkins Institutional Review Board approved all human studies. All subjects gave informed written consent after explanation of the study and protocol.

Subjects
Eleven healthy subjects (6 women, age 51±7 years) with no history of hypertension, diabetes mellitus, or of heart or vascular disease served as controls. HF patients had a clinical diagnosis of chronic HF and included 20 subjects with HFrEF (EF ≤40%), 7 of whom had NYHA class I symptoms (2 women, age 43±14 years) and 13 with NYHA class II or III symptoms (7 women, age 52±11 years). Twelve other patients had chronic HFpEF (8 women, age 62±11), as defined by Framingham criteria with EF ≥50%23 (see Data Supplement for additional details).

Study Protocol
All subjects underwent conventional magnetic resonance imaging (for determination of muscle and fat content) and 31P MRS (for energetics) at rest, during graded multistage PFE (Figure I in the Data Supplement), and during the post exercise recovery period in a clinical 3 T magnetic resonance imaging system. Relative and absolute concentrations of high-energy phosphates were measured as were ATP kinetics with 31P magnetization transfer techniques. Fatigue symptoms were recorded at each stage using an 11-point Borg scale. Exercise was terminated when the subject was unable to exercise further. In addition, an upright bicycle ergometry cardiopulmonary exercise test to exhaustion to measure peak VO2 and a 6-minute walk (6MW) were performed (see Data Supplement for details of protocol and statistical analysis).

RESULTS
Patient Characteristics
HFrEF patients were older than NYHA class I HFrEF patients (Table). Symptomatic HF patients (HFrEF NYHA class II–III and HFpEF) were more obese than healthy subjects. As expected, symptomatic HF patients (HFrEF NYHA class II–III and HFpEF) had significant EI with reduced mean 6MW distances and peak VO2 as compared with healthy subjects (Table). However, NYHA class I HFrEF patients had nearly normal functional measures with 6MW and peak VO2 similar to those of healthy subjects despite their significantly lower EF.

PFE Performance and Established Functional Parameters
Mean PFE time, maximum exercise weight, and total work were reduced in HFpEF and HFrEF NYHA class II–III patients compared with healthy subjects and HFpEF patients with NYHA class I symptoms (Figure 1A). HFpEF patients exhibited the most EI during PFE with HFpEF and HFrEF NYHA class II–III patients able to perform only one third to one half of the total work performed by healthy subjects (Figure 1A). Of note, indices of PFE performance (exercise time, maximum exercise weight, and total work) correlated significantly with the more established, global functional indices of 6MW and peak VO2 (Figure 1B). Thus, PFE performance parallels accepted functional measures used in many HF studies. Similar correlations are observed when corrected for ideal body weight (Figure II in the Data Supplement), rather than true body weight, suggesting that the observed differences are not attributable to obesity.

31P MRS Energetic Fatigability Test
Representative images and spectra from a 31P MRS/magnetic resonance imaging energetic fatigability test are shown in Figure 2A through 2C. During exercise, there is depletion of PCr and accumulation of Pi, with intracellular acidification reflected by the change in chemical shift of the Pi resonance (Figure 2C). ATP synthesis through creatine kinase (CK) and that from Pi were calculated from 31P magnetization transfer spectra at rest (Figure 2D through 2G). The time course of energetic changes and fatigue symptoms are shown for a healthy subject with low fatigability (Figure 3A) and a HF patient with high fatigability (Figure 3B). Note that SM energetics can be quantified with a high temporal resolution (2s), PCr is progressively depleted during staged-exercise while ATP is preserved, and, critically, the rate of PCr decline is more rapid in the subject with high fatigability. Note that both subjects reach a similar subjective level of fatigue measured by the Borg scale but at different workloads and exercise durations.

Skeletal Muscle Energetics at Rest, Exercise, and Fatigue
During baseline resting conditions, there were no significant differences in ATP synthesis rates from PCr through CK and from Pi (Figure 2F and 2G) or other SM energetic parameters among the 4 groups (Figure 4A through 4F). Thus, resting SM high-energy phosphates and energetics are normal in HF patients. However, phosphodiester, a byproduct of phospholipid catabolism, are increased. Despite differences in exercise time and work, energetic changes are similar at the point of fatigue in all groups (Figure 4G through 4K) with comparable PCr depletion, Pi, and ADP accumulation, intracellular acidosis, and change in ΔG_ATP. Thus, the SM energetic profile is similar in healthy subjects and HF patients before exercise and at the point of fatigue (Figure 4), although, again, the times to fatigue significantly differ (Figure 1).
Rate of High-Energy Phosphate Decline During Exercise and Postexercise Rate of Recovery

Although SM high-energy phosphates are comparable at rest and at the time of fatigue in the 4 groups, the rates of PCr decline and Pi accumulation differ significantly. Specifically, the normalized rates of PCr decline during PFE were greater in HFpEF (P < 0.001) and HFrEF NYHA class II–III patients (P < 0.005) than in healthy subjects (Figure 5A). Because the rate averaged over all of exercise could be impacted by reduced cardiac-derived SM perfusion in HF patients at peak exercise, we also measured high-energy phosphate decline during the earliest 4 minutes of low-level exercise (Figure 5B). The initial rates of high-energy phosphate decline were still significantly greater in HFrEF II–III (P < 0.05) and HFpEF patients (P < 0.001) than in healthy subjects. There is a strong correlation between the average rate of PCr decline during PFE and the maximum exercise time (Figure 5C; R²=0.83; P<0.001), indicating that the accelerated exercise-induced SM high-energy phosphate loss in symptomatic HFrEF and HFpEF patients is closely related to their EI.

The rate of PCr recovery after exercise directly reflects oxidative resynthesis of creatine and is related to maximal mitochondrial oxidative capacity. The time for PCr recovery was significantly delayed (Figure 6A) and maximum oxidative capacity reduced (Figure 6B) in HFpEF and HFrEF II–III patients compared with healthy subjects, indicating impaired mitochondrial function in the former 2 HF groups. In addition, maximum oxidative capacity in HFrEF patients with EI (NYHA class II–III) was half that of the NYHA class I HFrEF patients despite comparable mean EFs. This indicates that impaired SM mitochondrial function is more closely related to EI and HF
symptoms than is EF in these HFrEF patients. Thus, symptomatic HFrEF patients with EI and HFpEF patients exhibit an accelerated loss of SM high-energy phosphates commencing during early exercise, before we expect blood flow to be limiting during small muscle exercise. These patients also exhibited impaired mitochondrial oxidative capacity compared with healthy subjects and with HFrEF patients with nearly normal exercise tolerance.

Skeletal Muscle Fat Content

Because obesity is associated with the development of both HFpEF and HFrEF and because obesity-associated lipid accumulation and lipotoxicity are thought to adversely affect cardiac muscle function,25 we also measured fat content in SM. Muscle fat fraction is non-significantly increased in HFrEF patients compared with that of healthy subjects and did not differ between HFrEF NYHA class I and class II–III patients (Figure 7).

In contrast, SM fat fraction is increased almost 3-fold in HFpEF patients compared with healthy subjects (Figure 7). However, no correlations between muscle fat content and muscle mass and high-energy phosphate decline during exercise or during post exercise recovery are observed (Figure IV in the Data Supplement).

DISCUSSION

SM High-Energy Phosphate Metabolism and EI in HF

We evaluated SM fatigability in HF patients with and without EI using an approach that allowed simultaneous assessment of fatigue symptoms, lower-extremity exercise capacity, and SM energetics at rest, matched workloads and fatigue. Exercise duration and work performed with this energetic fatigability stress test correlated with conventional functional measures.
of 6MW and exercise peak VO$_2$ (Figure 1). The novel findings are that all subjects fatigue at a common SM energetic level but that a faster rate of energetic decline distinguishes HF patients with EI from those with normal exercise tolerance. Of the cohorts studied, HFpEF patients exhibit the most dramatic SM energetic changes (Figures 3, 5, and 6).

Reduced skeletal muscle PCr/ATP and PCr/Pi ratios were previously observed with $^{31}$P MRS in HFrEF patients during submaximal steady-state exercise in most, but not all, prior studies. To our knowledge, the present study is the first to noninvasively quantify absolute concentrations of skeletal muscle ATP and PCr in these patient populations and to do so throughout a graded exercise regimen performed to fatigue. Importantly, because the high-energy phosphate ratio of PCr/ATP may not change with concomitant depletion in both PCr and ATP, the present absolute HEP results demonstrate that SM ATP and PCr are not reduced in HFrEF or HFpEF patients at rest. Because the CK reaction is the primary muscle energy reserve reaction and because ATP flux through myocardial CK is reduced in human HF and predicts future clinical HF events, we also tested whether reduced skeletal muscle CK ATP synthesis is present in HF and contributes to EI. However, skeletal muscle ATP synthesis through CK at rest is not reduced in HF patients (Figure 2). Thus, resting skeletal muscle high-energy phosphate stores and CK reserve are not reduced and cannot account for EI in HFrEF or in HFpEF patients.

**Framework for Energetic Fatigability in HF**

Although fatigue is typically defined as a subjective sense of tiredness, fatigability is an arguably more useful term because it relates the symptom of tiredness to the level, duration, and intensity of the activity that induced the symptom. Fatigability is an important concept in HF because it can distinguish individuals who experience identical levels of symptomatic fatigue after different amounts of activity (eg, walking 5 m versus running a 10k race).

Because originally described by Eldadah, a healthy subject with low fatigability (Figure 8A, blue line)
achieves a higher level, duration, and intensity of work than does a subject with high fatigability (Figure 8A, red line) who experiences the same level of fatigue symptoms (fatigue limit) at less activity. Here, we expand the fatigability construct to include an energetic dimension (Figure 8B). If there was no energetic basis for increased fatigability in HF, then fatigue would be independent of SM high-energy phosphate stores (eg, less depletion, Figure 8B red line 1 if skeletal muscle energetics are not limiting). However, if an energetic component to HF fatigue exists, then those patients with high fatigability (Figure 8B red lines 2 and 3) and those with low fatigability (Figure 8B blue line) would fatigue at a comparable energetic limit or metabolic index. The current findings of a common energetic limit in HF patients and healthy subjects (Figure 4) that is reached more rapidly in HF

Figure 3. Time course of energetic changes and fatigue symptoms for a healthy subject with low fatigability (A) and for a heart failure (HF) patient with high fatigability (B).

In both cases, PCr is progressively depleted and Pi accumulates during staged-exercise while ATP is preserved. The rates of creatine phosphate (PCr) decrease and inorganic phosphate (Pi) increase are more rapid in the subject with high fatigability. Both subjects reached a similar subjective level of fatigue (Borg scale) and PCr depletion but at different workloads and exercise durations.

Figure 4. Skeletal muscle (SM) energetic parameters (PCr, Pi, pH, ADP, ΔG~ATP) and phosphodiester (PDE) during baseline resting conditions (A–F, left column) and at the point of fatigue (G–K, right column).

There are no significant differences in the SM energetic parameters among the 4 groups at rest or at the point of fatigue (although PDE differed at baseline). Comparisons vs healthy subjects: §P<0.005, §§§P<0.001.
patients with increased fatigability because of a more rapid rate of SM energetic depletion (Figure 5 and red line 2 in Figure 8B) support the hypothesis that high-energy phosphate energetics is an important contributor to HF fatigability. In theory, a significant increase in [ADP], [Pi], or change in ΔG~ATP could impair myofilament function before ATP is fully depleted, as observed here. Note that the present observation of a common energetic limit involves exercise of a relatively small muscle group not likely limited by central hemodynamics in subjects studied and suggest the possibility that new interventions to delay or slow the SM energetic decline during exercise could reduce EI in both HFrEF and HFpEF.

Furthermore, the rates of high-energy phosphate decline during exercise are significantly faster in HFrEF patients with EI and high fatigability (NYHA class II–III) than are the rates in HFrEF patients with low fatigability (NYHA class I), despite similarly low EFs (Figure 5). HFpEF patients with severe EI exhibit the most rapid rates of high-energy phosphate depletion during exercise. Their maximal oxidative capacity, reflected in delayed high-energy phosphate recovery, is comparable to that of HFrEF NYHA class II–III patients (Figure 6). Indeed, the rate of high-energy phosphate decline during PFE is inversely related to exercise duration (Figure 5C). All of these observations are consistent with normal baseline energetics but a faster exercise-induced decline to a common energetic limit in symptomatic HF (Figure 8B, red line 2).

**Potential Mechanistic Factors Underlying Impaired SM Energetics in HF**

The more rapid decline of high-energy phosphate during exercise in HF patients with EI could be because of reduced ATP production and/or increased ATP utilization during exercise. Reduced SM mitochondrial number and enzyme activity were previously reported in HFrEF and HFpEF. We observed reduced maximal oxidative capacity in HFrEF and HFpEF patients (Figure 6), consistent with most 16,27,29 but not all 15 pre-

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**Figure 5. A** Normalized rate of creatine phosphate (PCr) decline during plantar flexion exercise (PFE). B, Initial normalized rate of PCr decline during the first 4 min of PFE. C, Correlation of maximal PCr decline. Significant differences are indicated: *P < 0.05, §P < 0.005, §§§P < 0.001.

**Figure 6. A** The rate of creatine phosphate (PCr) recovery after plantar flexion exercise (PFE) is significantly delayed in heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) II–III patients compared with HFrEF class I and healthy subjects. B, Indices of maximal oxidative capacity (VmaxO₂) are lower in New York Heart Association (NYHA) class II–II HFrEF and HFpEF patients than in the other 2 groups without exercise intolerance. Comparisons vs healthy subjects: §§§P < 0.005. Comparisons vs HFrEF NYHA class I patients: ***P < 0.001.
...previous reports in HFrEF patients. We think these to be the first findings of significantly reduced maximal oxidative capacity in HFpEF. Although increased ATP consumption during exercise could occur at a matched workload in HF because of reduced muscle mass or inefficiency, we did not observe significant reductions in muscle mass in these patients (Figure III in the Data Supplement).

Reduced SM blood flow in HF patients could contribute to the more rapid energetic decline, catabolite accumulation, and mitochondrial dysfunction during exercise in HF patients. Although early studies showed reduced blood flow in HFrEF,30–32 subsequent studies during upper or lower-extremity exercise in HFrEF patients did not demonstrate reductions in extremity blood flow, tissue oxygenation, or myoglobin desaturation during exercise sufficient to cause SM energetic abnormalities.12,13,33,34 Such observations reduce the likelihood of deficiencies in oxygen delivery as an underlying cause and suggest instead a SM mitochondrial metabolic abnormality in HF. This is consistent with the present observation of a rapid PCr decline during the earliest minutes of small muscle group exercise when the workload is low (2 to 4 lbs; Figures 3 and 5B), and blood flow may not be limiting. Intrinsic SM energetic abnormalities that are closely related to EI in HF patients are consistent with the hypothesis that the myopathy of HF may not be driven so much by hemodynamic abnormalities but rather by changes in SM mitochondrial function, perhaps related to the milieu of neurohormonal factors, metabolites, and cytokines that bathe the skeletal muscle.35 Alternatively, if HF patients become sedentary because of reduced cardiac reserve,36 the inactivity, per se, may contribute to EI and SM mitochondrial abnormalities.

Although these are the first 31P MRS findings showing statistically significant skeletal muscle energetic abnormalities during exercise in HFpEF patients, Bhella et al22 described delayed PCr recovery in 2 HFpEF patients, a sample size that precluded quantitative comparisons. Although cardiac dysfunction is a significant contributor to EI in HFpEF patients,37,38 there is also evidence that peripheral factors contribute.22,39,40 Recently,
reduced peripheral oxygen extraction was identified as a major determinant of upright bicycle exercise capacity in HFrEF patients. This was attributed to limited diffusive oxygen transport, possibly because of greater diffusion distances or heterogeneity in the matching of regional flow to metabolic demand. However, the deficit in SM maximal oxidative capacity observed here in HFrEF patients could also contribute to reduced peripheral oxygen extraction during exercise. A meta-analysis of 6 randomized trials indicated that exercise training in HFrEF patients improves cardiorespiratory fitness, but this occurs without measurable changes in systolic or diastolic function. In 1 randomized trial, exercise training improved peak VO₂ in HFrEF patients with only a minimal effect on cardiac output but with a significant increase in peak arterial-venous oxygen difference. Those findings indicate that peripheral factors contribute to improved exercise capacity with exercise training in HFrEF and by inference that peripheral mechanisms contribute to EI in HFrEF. All of these studies are consistent with the concept that HFrEF is a systemic syndrome affecting multiple organs, including SM.

The in vivo SM energetic abnormalities in HFrEF patients (ie, accelerated rate of PCr decline and of Pi and H⁺ accumulation during exercise in Figure 5 and reduced in vivo maximal oxidative capacity in Figure 6) are similar or more marked in the HFpEF, than in the HFrEF, group. Remarkably, the intermuscular (not subcutaneous) fat was increased an average 3- to 4-fold over that in healthy subjects (Figure 7), possibly reflecting common HFpEF comorbidities of obesity, diabetes mellitus, and dyslipidemia. An earlier study reported that increased intermuscular fat in HFpEF patients correlated with reduced peak VO₂.

Limitations
The cohort size was small and derived from patients referred to a tertiary care center and so may not represent the more general population. Nonetheless, highly significant differences in SM energetics between those HF patients with, and without, EI were detected. The 31P MRS PFE fatigability examination is not intended to replace standard 6MW or peak VO₂ testing but instead to provide insight into the role of SM energetic fatigue in HF patients. The correlation of these plantar flexion findings with conventional measures of total body exercise capacity is of interest because it cannot be assumed that capacity of a small muscle mass and total body exercise are necessarily limited by the same processes. Lower-extremity blood flow, endothelial function, and muscle perfusion were not measured with magnetic resonance imaging during PFE because of motion artifacts, and systemic lactate measures were not obtained. Thus, we cannot exclude the possibility that reduced perfusion during exercise contributed to the observed metabolic declines during exercise in HF subjects with EI. It seems unlikely, though, that reduced perfusion alone is responsible for energetic decline during the first minutes of low-level exercise or reduced maximal oxidative capacity (Vmax₃⁵) during recovery. HFpEF patients in many studies including this one tend to be older, be more obese, and have greater NYHA symptoms and EI. These data do not demonstrate whether the more dramatic energetic changes in HFpEF patients are because of HFpEF per se or to these other factors. It will be important in future studies to study older, obese subjects without HF, asymptomatic HFpEF patients and to match NYHA symptoms and exercise tolerance in HFpEF and HFrEF populations.

Conclusions
To evaluate whether SM energetic abnormalities exist and contribute to EI in HF patients, we exploited a SM energetic fatigability test that is noninvasive, correlates with established functional measures (6MW and peak VO₂), and allows studies of SM energetics at matched workloads and at fatigue. HFrEF patients with increased fatigability and EI exhibit more rapid exercise-induced declines in SM high-energy phosphates than do HFrEF patients with no EI, despite matched left ventricular ejection fractions. HFpEF patients in this study exhibit the most profound EI, energetic abnormalities, and rapid PCr depletion during exercise as well as increased muscle lipids. On average, all subjects fatigue at the same mean SM energetic state, suggesting a common energetic limit. Because of the relatively high plasticity and remodeling potential of skeletal muscle to respond to multiple stimuli, compared with cardiac muscle, these studies offer a new approach to quantify SM energetics in HF and suggest that interventions that augment SM metabolism may offer another treatment target for the EI and disability that markedly impair quality of life for both HFrEF and HFpEF patients.

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DISCLOSURES
After the study was completed, Dr K. Weiss became an employee of Philips Healthcare at which time he performed data analysis and article preparation. No financial support from Philips Healthcare was received for the study.

AFFILIATIONS
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FOOTNOTES

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