Blood Flow Dynamics in Heart Failure

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Background—Exercise intolerance in heart failure (HF) may be due to inadequate vasodilation, augmented vasoconstriction, and/or altered muscle metabolic responses that lead to fatigue.

Methods and Results—Vascular and metabolic responses to rhythmic forearm exercise were tested in 9 HF patients and 9 control subjects (CTL) during 2 protocols designed to examine the effect of HF on the time course of oxygen delivery versus uptake (protocol 1) and on vasoconstriction during exercise with 50 mm Hg pressure about the forearm to evoke a metaboreflex (protocol 2). In protocol 1, venous lactate and H+ were greater at 4 minutes of exercise in HF versus CTL (P<0.05) despite similar blood flow and oxygen uptake responses. In protocol 2, mean arterial pressure increased similarly in each group during ischemic exercise. In CTL, forearm blood flow and vascular conductance were similar at the end of ischemic and ambient exercise. In HF, forearm blood flow and vascular conductance were reduced during ischemic exercise compared with the ambient trial.

Conclusions—Intrinsic differences in skeletal muscle metabolism, not vasodilatory dynamics, must account for the augmented glycolytic metabolic responses to moderate-intensity exercise in class II and III HF. The inability to increase forearm vascular conductance during ischemic handgrip exercise, despite a normal pressor response, suggests that enhanced vasoconstriction of strenuously exercising skeletal muscle contributes to exertional fatigue in HF.

Key Words: vasodilation ■ vasoconstriction ■ oxygen ■ exercise ■ heart failure

Exertional fatigue is a hallmark of heart failure (HF). In addition to cardiac limitations,1 peripheral mechanisms in the exercising muscle2–6 may contribute to exercise intolerance in HF. Abnormalities in muscle metabolism,2,5–9 blood flow, and muscle oxygen uptake8–10 have been documented in these patients. Others have observed little difference in forearm hyperemic responses between HF and healthy individuals,3,11 suggesting that altered substrate use is responsible for the heightened lactate production in HF.2 However, elevated acidosis could result from a blood flow limitation at exercise onset that normalizes once steady-state conditions develop.12

Additionally, metaboreflex responses in HF are enhanced.13–15 However, this reflex fails to normalize metabolism and/or venous oxygen saturation in HF.15 These observations suggest that the metaboreflex may vasoconstrict active muscle HF.15,16

In this report, we examined whether a blood flow limitation during exercise onset limits oxygen uptake and augments glycolysis in HF. We also examined whether metaboreflex activation would reduce blood flow in exercising muscle of HF patients.

Methods

Subjects
Eighteen men volunteered for the study. Nine healthy control subjects (CTL; mean age, 65.6 years; range, 61 to 75 years) and 9 stable HF patients (mean age, 61.7 years; range, 41 to 70 years) were studied. Seven HF subjects were NYHA class III and 2 were class II HF. HF medications included digoxin (n=7), diuretics (n=7), β-blockers (n=5), ACE inhibitors (n=9), and nitrates (n=2). HF origins included ischemic cardiomyopathy (n=5) and dilated/idio-pathic cardiomyopathy (n=4). Both the CTL and HF groups had 1 subject with non–insulin-dependent diabetes. All subjects signed an Institutional Review Board–approved consent form and had a physical examination and an ECG before testing.

Experimental Procedures

Data Collection
Heart rate (HR) (ECG), mean arterial pressure (MAP; model 2300, Finapres), and brachial artery mean blood velocity (MBV; 4-MHz probe, Multigon Industries) were measured continuously and collected online at 100 Hz. Brachial artery diameter was determined with 2-dimensional echo Doppler imaging (7.5-MHz probe). The echo Doppler images were collected continuously on VHS tape for subsequent analysis. Two separate diameter images, taken during diastole, were obtained within 5 seconds of each required time point (see below), and independent measurements were made of each
Experimental Protocols

Protocol 1

Experimental Design
In protocol 1, we examined blood flow and oxygen uptake dynamics during the transition phase between rest and steady-state exercise. The goals of this protocol were to produce a consistent increase in FBF, to achieve the same level of oxygen uptake in the CTL and HF subjects, and to minimize metaboreflex engagement. Dynamic hand-grip exercise (4.4 kg; 1 second/1 second work/rest ratio for 5 minutes) was performed by all subjects on the nondominant forearm. All CTL and 7 of 9 HF subjects completed 3 trials of this exercise. The remaining 2 HF patients completed 2 trials. Of the 9 HF patients, 2 completed only 4 minutes of exercise before fatigue. One of these patients completed 2 trials; the other completed 3 trials. Subjects rested 20 to 30 minutes between the repeated trials, allowing venous lactate to return to baseline.

Data Acquisition and Analysis
In each trial, HR, MAP, and MBV were collected, whereas arterial diameter was measured during the second trial only. During the first trial, 1-mL blood samples were collected from an antecubital vein (20-gauge Angiocath inserted retrograde) in heparinized syringes. These samples were drawn at rest, at 10-second intervals during the first minute of exercise, at 30-second intervals during the second exercise minute, and then every minute thereafter until the end of the trial. Blood samples were analyzed for lactate and pH (model 23L lactate analyzer, Yellow-Springs Instruments), hemoglobin concentration and saturation (SO2), and blood gases (model 510 radiometer, ABL). Blood samples were obtained from all CTL subjects and 8 of 9 HF patients. Three diameter measures were made at rest, with additional measurements made at the time of blood sampling. MBV data were analyzed on a beat-by-beat basis for each trial as described previously. The beat-by-beat data from each trial were then time aligned and ensemble averaged over 2-second time bins to combine a contraction and relaxation phase in each data point. The average MBV values over 60 seconds at rest and over 4 seconds at times corresponding to the blood sampling were obtained to calculate FBF.

Arterial oxygen content (CaO2) was calculated from the venous [Hb] at rest, assuming an arterial So2 of 94% in HPr, and 97% in CTL (commonly observed by ear oximetry). Venous oxygen content (Cvo2) was calculated by use of the measured [Hb] and saturation and the venous Po2. The arteriovenous oxygen difference [(A-V)O2diff] was determined and oxygen extraction was calculated as (A-V)O2diff/CaO2×100. A constant arterial oxygen content was assumed because the intensity of forearm exercise placed a small demand on the cardiovascular system. Forearm muscle oxygen uptake (VO2mus) was calculated at each measured time point as VO2mus=FBE×(A-V)O2diff.

Protocol 2

Experimental Design
All subjects performed protocols 1 and 2. Protocol 2 was designed to examine the muscle metaboreflex effect on FBF and VC. Two exercise trials were performed on the dominant forearm after it was sealed at the elbow in an airtight box. Because ischemic exercise is quite fatiguing, the first trial was performed at atmospheric pressure, whereas box pressure was increased to 50 mm Hg during trial 2. Limb positive pressure limits exercise FBF and evokes a metaboreflex, thereby elevating blood pressure and sympathetic discharge in the exercising arm. The rhythmic isometric exercise load was performed at 25% of maximal voluntary contraction force in a 1 second/1 second work/rest schedule for 5 minutes.

Data Analysis
HR, MAP, FBF, and VC were measured at rest and during each minute of exercise. Values were determined over the first 30 seconds of the baseline period, with a second measurement made 10 seconds before exercise onset. This was done to assess the effect of positive pressure on forearm hemodynamics at rest. Because only 1 trial of each condition was performed, beat-to-beat and contraction-induced MBV variability was minimized by averaging data over 5 contraction/relaxation cycles.

Statistical Analysis
A repeated-measures ANOVA (SAS Institute Inc) with a mixed-effects linear model was used to analyze the data. A step-down Bonferroni adjustment was made to the probability value for the contrasts of interest to adjust for multiple comparisons so that the overall probability of a type I error was 0.05. A two-tailed t test was used to compare differences in age, maximal forearm strength, and work rate between the 2 groups. All values are presented as mean±SE.

Results
Rest
Baseline HRs for CTL (64±3 bpm) and HF (69±4 bpm) subjects were not different. However, compared with CTL (96.9±3.7 mm Hg), MAP at rest was lower in HF (81.1±4.1 mm Hg) (P<0.02). Baseline vascular variables were similar in CTL and HF for both dominant and nondominant arms (the Table). Resting venous So2 was lower in HF (P<0.05), but this did not result in between-group differences for oxygen extraction or muscle oxygen uptake (the Table).

Protocol 1
Forearm volumes were 1147±52 and 1152±71 mL for HF and CTL subjects, respectively. Compared with CTL (35.1±1.8 kg), the smaller maximal contraction strength of the nondominant arm in the HF group (29.2±1.8 kg, P<0.04) led to a 2% difference in relative workload between groups. No between-group differences were observed for the exercise-induced increase in HR and MAP (Figure 1) or FBF and VC (Figure 2). The reduction in So2 with exercise tended to be greater in HF than in CTL (group main effect, P<0.06; Figure 3). However, the time courses of increase in oxygen extraction, (A-V)O2diff and VO2mus (P<0.05), were not different between groups (Figure 3). Despite the similar time courses of FBF and VO2mus, venous lactate (P<0.003) and hydrogen ion concentration (P<0.02) after 4 minutes of exercise (the duration that all subjects completed) were greater in HF (Figure 4).

Protocol 2
For both groups, HR increased more during ischemic hand-grip exercise than during ambient conditions (P<0.05); however, no between-group differences were observed (Figure 5). Specifically, the increase in MAP (ie, the pressor response) during ischemic exercise in HF was 12.2±2.4 and 16.5±3.1 mm Hg in CTL (P=NS).

As with protocol 1, FBF during ambient exercise achieved a new steady-state level by 1 minute of exercise with little difference between groups (Figure 6). Compared with the
ambient trial, positive pressure reduced FBF during the first minute of exercise in both groups ($P<0.05$) (Figure 6). Thereafter, FBF increased toward the ambient trial levels in the CTL subjects, but blood flow remained depressed in the HF group ($P<0.05$; Figure 6).

The similar MAP but diminished FBF with 50 mm Hg forearm pressure resulted in an attenuated total forearm VC in the HF group for the duration of the ischemic trial ($P<0.05$; Figure 6). Total forearm VC did not rise above baseline levels in the HF group during ischemic exercise, whereas the CTL group defended both FBF and VC so that the 50 mm Hg and ambient responses were similar beyond 2 minutes of exercise.

### Discussion

These experiments demonstrated that peripheral vascular responses at the initiation of exercise were not impaired in this group of HF patients. Nonetheless, the HF response was characterized by greater acidosis and lactate production, indicating differences intrinsic to the active skeletal muscle. In contrast, when mild-intensity exercise was made ischemic with forearm positive pressure, the same HF patients demonstrated a reduced ability to increase blood flow and VC despite a normal pressor response.

### Protocol 1

In both the HF and CTL groups, the increase in muscle oxygen uptake during the first 30 seconds of exercise was
mediated primarily by an increase in FBF because there was a lag of 20 to 30 seconds for oxygen extraction to increase. Oxygen extraction and (A-V)O$_2$diff were not reduced during the early moments of exercise despite large increases in blood flow and oxygen uptake, indicating that extraction was keeping pace with oxygen delivery. Although pulmonary oxygen uptake kinetics during cycling exercise are slowed in HF,25,26 the current data suggest that HF per se does not slow the adaptation of FBF and V˙O$_2$mus during small muscle mass exercise that minimize contributions from central hemodynamics.

The current data do not support our initial hypothesis that blood flow and oxygen uptake kinetics during forearm exercise would be slowed in HF. In part, this hypothesis was based on earlier observations of attenuated blood flow and oxygen uptake responses to handgrip contractions in HF.4,10 The explanation for these differences is unclear but may involve differences in disease severity and fluid retention. Unlike patients in the present study, the subjects of earlier reports4,10 had evidence of right-sided decompensation and fluid retention. Forearm edema reduces vascular dilation capacity27 and may alter blood flow distribution and oxygen diffusion. In addition, these earlier studies4,10 used workloads greater than those used in the present study protocol, with consequent increases in metabolic and vasodilatory requirements. Thus, our findings agree with other investigations showing normal steady-state exercise FBF responses in class II and III patients.11 Additionally, our data concur with recent magnetic resonance spectroscopy measures of deoxymyoglobin that suggest that small muscle mass exercise in HF patients is not limited by tissue hypoxia.28 Our data add to these earlier findings by indicating that blood flow and muscle oxygen uptake are not altered during the rest-to-exercise transition in well-compensated HF patients. The greater reliance on glycolytic metabolism in HF is consistent with earlier findings that intramuscular alterations may predispose HF individuals to early fatigue independent of changes in tissue perfusion.2,29,30

The cause of the predilection to elevated lactic acidosis in HF is not entirely clear. Muscle atrophy in HF may alter the muscle metabolic adaptation to exercise.31 However, it is unlikely that the 2.7% difference in maximal handgrip strength between the HF and CTL groups indicates sufficient muscle atrophy to account for the $\approx$30% greater venous lactate levels in the HF patients. The comparable blood flow and oxygen uptake responses strongly suggest that flow distribution within the forearm muscle was similar in the 2 groups. Therefore, it is unlikely that fiber-type alterations toward a greater proportion of the more glycolytic type II fibers8,31 can explain the predisposition toward elevated lactic acidosis in HF in the present study.

In possible conjunction with altered fiber types, reductions in intramuscular high-energy phosphates and mitochondrial oxidative enzyme concentrations2,31 might combine to augment glycolytic ATP contributions during mild exercise. These changes would be comparable to deconditioned skeletal muscle in healthy individuals. Under conditions of reduced oxidative capacity in which oxygen availability is not limiting, an increased cytosolic reduction (ie, NADH/NAD)}
would be required to maintain a higher flux through the diminished concentration of electron transport chain enzymes. Cytosolic lactate accumulation would result.

Protocol 2
For the CTL group, the similar FBF responses between ambient and positive pressure trials suggest that in healthy older subjects, factors associated with a metaboreflex-induced exercise pressor response act to maintain flow to active skeletal muscle. Whether the inability to observe an increased VC during ischemic exercise in the HF group indicates reduced vasodilation or augmented metaboreflex-induced sympathetic vasoconstriction cannot be determined from the current data. However, the normal dilator response in HF subjects during protocol 1 would suggest that an enhanced vasoconstrictor response contributed importantly to the reduced blood flow response in protocol 2.

In the present study, blood flow was normal during ischemic exercise in CTL subjects. However, the same protocol did not result in improved venous markers of muscle metabolism in our previous study. The explanation for this may be the slowed adaptation of blood flow during positive pressure in the present study.

Methodological Considerations
In our hands, the between-day reproducibility for Doppler ultrasound measures is 2% to 4% for diameter and 10% to 12% for velocity. Interobserver variation for measurements of vessel diameter, as performed in the present study, was <5%. These data provide confidence in the estimate of both volumetric blood flow and its time course. Beat-to-beat variability in blood velocity measures was minimized by convergent averaging of data from 2 or 3 repeated trials (protocol 1) or by averaging velocity data over 5 contraction/relaxation cycles (protocol 2).

Maintaining patient pharmacological therapy may have normalized an otherwise compromised vascular response to rhythmic exercise during protocol 1. We chose this approach...
over withdrawing treatment before the test because it is unclear what effect drug withdrawal has on vascular responses and how long these effects may persist. Regardless, the attenuated increase in VC during ischemic exercise indicates that despite pharmacological interventions, the HF group does not defend muscle blood flow as well as CTL subjects during metaboreflex engagement.

Finally, we observed previously that HF patients generate a significantly greater pressor response to ischemic exercise compared with normal CTL subjects. This is in contrast to the present study, in which pressor responses were comparable. As addressed above, cardiovascular responses to fatiguing exercise may depend on the severity of HF. Although the patients studied previously were largely class III, the degree of HF was more severe, as indicated by ejection fractions that were on average ≈15% less than those observed in the present patients. Additionally, metaboreflex studies were performed on the dominant forearm in the present report. Dominant forearm exercise evokes less acidosis and metaboreflex engagement.

It is unlikely that the test sequence influenced results because protocols 1 and 2 were performed on different arms.

Conclusions
In the present study, greater glycolytic metabolism was evident in the HF patients during rhythmic handgrip exercise when the time courses of FBF, oxygen extraction, and oxygen uptake were not different from CTL subjects. Therefore, altered muscle metabolism appears to be independent of blood flow and oxygen delivery in HF. Whether this mechanism plays a role in limitations to whole-body exercise cannot be extrapolated from these data. Under more strenuous exercise conditions imposed by muscle ischemia, the same HF patients displayed an attenuated increase in both FBF and VC. The inability of these HF patients to increase forearm VC during ischemic exercise, despite a normal pressor response, suggests that enhanced vasoconstriction occurred in the strenuously contracting skeletal muscle. We speculate that limited cardiac output during whole-body exercise in HF results in relative muscle ischemia that, when coupled with muscle abnormalities, produces greater metaboreflex engagement, heightened sympathoexcitation, and greater muscle vasoconstriction, which contribute to early exertional fatigue.

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