

# Exertional Fatigue Due to Skeletal Muscle Dysfunction in Patients With Heart Failure

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**Background.** Exertional fatigue in patients with chronic heart failure is usually attributed to skeletal muscle underperfusion. Recently, skeletal muscle atrophy, abnormal muscle metabolic responses, and reduced muscle enzyme levels have been noted in such patients, raising the possibility that some patients may develop muscle fatigue due to intrinsic muscle abnormalities. The present study was undertaken to determine if a subpopulation of patients with heart failure develops exertional fatigue due to skeletal muscle dysfunction rather than to reduced muscle flow.

**Methods and Results.** All exercise hemodynamic studies performed in our laboratory on patients with heart failure were reviewed to identify those who exhibited peak exercise  $\dot{V}O_2$  levels  $\leq 18 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  due to leg fatigue and who underwent insertion of a Swan-Ganz catheter and leg blood flow catheter. Thirty-four patients were identified. Six normal subjects were also studied to define normal leg flow and femoral venous lactate responses to exercise. Patients with peak exercise leg flow levels within the normal mean flow level  $\pm 2$  SEM were considered to have normal skeletal muscle flow during exercise. Nine of the 34 patients with heart failure were found to have normal leg blood flow during exercise. All of these patients terminated exercise due to leg fatigue, and all exhibited abnormal increases in femoral venous lactate concentrations (slope of work load versus femoral venous lactate: normal,  $0.33 \pm 0.07 \text{ mg/W}$ ; heart failure with normal flow,  $0.81 \pm 0.08 \text{ mg/W}$ ;  $p < 0.002$ ). There was no significant difference between patients with normal leg flows and those with reduced flow in age, ejection fraction, and resting hemodynamic measurements. However, patients with normal flows exhibited more normal cardiac output responses to exercise and tended to have higher peak exercise  $\dot{V}O_2$  ( $14.1 \pm 0.9$  versus  $11.5 \pm 0.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ,  $p < 0.05$ ).

**Conclusions.** A substantial percentage of patients with chronic heart failure develop exertional fatigue due to skeletal muscle dysfunction rather than to reduced skeletal muscle blood flow. In such patients, therapeutic interventions probably should be directed at improving the skeletal muscle abnormalities rather than at improving skeletal muscle flow. (*Circulation* 1993;87:470–475)

**KEY WORDS** • heart failure • exercise • muscle, skeletal

Patients with heart failure are frequently limited by exertional fatigue during both normal daily activities and maximal exercise testing.<sup>1–3</sup> This exertional fatigue is usually attributed to skeletal muscle underperfusion, based on observations that patients with heart failure on average exhibit reduced cardiac output and leg blood flow responses to exercise.<sup>1–3</sup> Recently, however, a number of skeletal muscle abnormalities have been detected in patients with heart failure, including abnormal metabolic responses to small muscle exercise,<sup>4–8</sup> reduced mitochondrial-based enzymes,<sup>9,10</sup> reduced mitochondrial volume,<sup>11</sup> and muscle atrophy.<sup>12</sup> It has also been observed that cardiac rehabilitation can improve the exercise capacity of patients with heart failure without improving leg blood

flow.<sup>13,14</sup> These observations suggest that exertional fatigue in at least some patients with heart failure may be due to skeletal muscle changes rather than to inadequate skeletal muscle blood flow.

The present study was undertaken to determine if a subpopulation of patients with heart failure develops exertional fatigue due to skeletal muscle dysfunction rather than to reduced muscle flow. To examine this possibility, we measured cardiac output, leg blood flow, and lactate responses to exercise in a group of patients with heart failure and exertional fatigue. Similar measurements were obtained in a group of normal subjects. Flow and metabolic responses were then compared in the two groups to identify patients with leg fatigue and abnormal muscle lactate release but normal leg flow responses.

## Methods

### Patient Population

All exercise hemodynamic studies performed in our laboratory on compensated patients with heart failure were reviewed to identify those who exhibited peak exercise  $\dot{V}O_2$  levels  $\leq 18 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  due to leg fatigue and who underwent insertion of a Swan-Ganz catheter and leg blood flow catheter. Most of these

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patients were undergoing investigational studies to examine the effect of acute therapeutic interventions; these studies have been reported previously.<sup>15–18</sup> Patients with peripheral vascular disease were excluded. Patients with a history of excessive alcoholic intake were also excluded as alcohol is known to damage skeletal muscle.

The requirement that patients note marked leg fatigue during exercise did not lead to the exclusion of patients who also experienced dyspnea. During maximal exercise testing, nearly all patients with compensated heart failure report severe leg fatigue at peak exercise with varying levels of dyspnea.<sup>1–3</sup>

A total of 34 patients were identified. This group had an average age of  $57 \pm 2$  years ( $\pm$ SEM), mean left ventricular ejection fraction of  $21 \pm 2\%$ , and peak exercise  $\dot{V}O_2$  of  $12 \pm 1$  ml  $\cdot$  min<sup>-1</sup>  $\cdot$  kg<sup>-1</sup>. All patients reported marked exertional fatigue at maximal exercise; none experienced chest pain. Thirty-one of the patients were male and three were female. Left ventricular dysfunction was attributed to coronary artery disease in 25 patients and to idiopathic cardiomyopathy in nine patients. All patients were taking furosemide, and all except two patients were receiving digoxin. Fourteen patients were taking some form of vasodilator therapy before the study (e.g., isosorbide dinitrate, prazosin, hydralazine, or captopril). All vasodilator therapy was discontinued at least 48 hours before the study. All patients also were optimally diuresed before the study; no patient had peripheral edema.

For comparison, six normal male subjects with normal exercise capacity (peak exercise  $\dot{V}O_2$ ,  $25 \pm 2$  ml  $\cdot$  min<sup>-1</sup>  $\cdot$  kg<sup>-1</sup>) were studied. The average age of the subjects was  $45 \pm 2$  years. These subjects had normal activity levels, were not involved in any training program, and were not taking any medications.

### Protocol

On the day before the study, a trial maximal bicycle exercise test was performed to acquaint the patient with the exercise protocol. Exercise was performed on an upright mechanically braked bicycle ergometer (Monach) and begun at a work load of 20 W. Every 3 minutes, the work load was increased by 20 W to symptomatic maximum. All exercise tests were performed at least 4 hours after meals.

The next morning, a 5F thermodilution catheter was inserted percutaneously into the left femoral vein and advanced 15–16 cm anterograde into the iliac vein. In the patients with heart failure, a Swan-Ganz catheter was inserted through an antecubital vein and positioned in the pulmonary artery.

Thirty minutes after instrumentation, hemodynamic measurements were made and blood samples were obtained from the pulmonary artery and femoral venous catheters for oxygen saturation and lactate concentration. Femoral venous blood flow was measured in triplicate. Respiratory gases were measured with a SensorMedics Metabolic Cart. The patient then mounted the bicycle and was allowed to equilibrate for 5 minutes, after which all measurements were repeated.

The patient then began to exercise. Respiratory gas and hemodynamic measurements were made continuously. During each 3-minute exercise stage, leg blood flow was measured every 30 seconds starting at 30

seconds and continuing for 2.5 minutes for a total of five measurements. Blood sampling was performed during the final 30 seconds of the stage. Leg flow was not measured during this period.

### Techniques

Leg blood flow was determined as previously described.<sup>1,15–18</sup> In brief, femoral vein flow was measured using a 50-cm 5F thermodilution catheter with the thermistor at 2 cm and the injection port at 12 cm. Flow was determined using rapid injection of a 2.5-ml iced dextrose bolus injectate and a commercially available thermodilution computer (Elecath). Output curves were displayed on a strip-chart recorder to ensure an exponential decay curve. Flow determined using this system correlated closely with known flow rates (0.2–6.0 l/min,  $r=0.99$ ) when evaluated using a closed-loop system in which 37°C H<sub>2</sub>O was continuously circulated through 7-mm polyethylene tubing using a roller pump. Coefficients of variation of duplicate flow measurements and reproducibility of measurements made during repeat exercise tests have been reported previously.<sup>1,18</sup>

### Measured Variables

Hemoglobin concentration was measured by Coulter counter. Hemoglobin oxygen saturation was measured with an IL 282 Co-Oximeter. Arteriovenous oxygen difference was calculated using standard formulas. Blood for lactate determination was deproteinized with cold perchloric acid and assayed with a spectrophotometric technique. Normal values at rest for this technique in our laboratory are 3–12 mg/dl.

### Statistical Methods

Values are presented as mean  $\pm$  SEM. Differences between measurements at rest were compared using nonpaired Student's *t* test. Exercise measurements were compared using repeated-measures ANOVA and linear regression analysis. If statistical significance was noted in the initial ANOVA, subsequent comparisons were performed using Scheffe's method to correct for multiple comparisons. A value of  $p < 0.05$  was considered significant.

## Results

### Normal Subjects

The control subjects were able to exercise to a peak  $\dot{V}O_2$  of  $25.1 \pm 1.6$  ml  $\cdot$  min<sup>-1</sup>  $\cdot$  kg<sup>-1</sup>. Hemodynamic, metabolic, and leg flow responses to exercise are summarized in Tables 1 and 2 and Figure 1. Exercise resulted in progressive increases in systemic  $\dot{V}O_2$ , leg blood flow, and leg arteriovenous oxygen difference. Femoral venous lactate concentration typically increased in an exponential fashion, with levels increasing only modestly at 20–60 W followed by a more rapid increase at higher work loads. This pattern was paralleled by changes in the respiratory gas exchange ratio.

### Heart Failure Patients

As a group, the patients with heart failure were able to exercise to a peak  $\dot{V}O_2$  of only  $12.2 \pm 0.6$  ml  $\cdot$  min<sup>-1</sup>  $\cdot$  kg<sup>-1</sup>, significantly less than in the normal subjects ( $p < 0.001$ ). All patients experienced marked exertional fatigue at peak exercise.

TABLE 1. Systemic Hemodynamic and Metabolic Responses to Exercise

Response	Group	Upright rest	Work load (W)			Maximal exercise
			20	40	60	
Heart rate (bpm)	Controls	91±4	107±4	119±6	138±5	170±4
	HF-1	85±5	100±6	112±7	115±10	118±7*
	HF-2	94±3	114±3	120±4	122±9	122±3*
Blood pressure (mm Hg)	Controls	95±4	103±3	107±3	116±4	130±5
	HF-1	84±3	88±3*	91±4*	90±4*	92±3*
	HF-2	85±2	94±2	96±3	100±7	97±2*
$\dot{V}O_2$ (ml/min)	Controls	304±14	864±52	1,087±44	1,329±27	1,941±96
	HF-1	275±11	658±31*	876±44	1,158±43	1,008±82*
	HF-2	277±10	631±24*	881±48*	1,183±46	802±54*
RER	Controls	0.85±0.01	0.86±0.02	0.94±0.03	1.03±0.03	1.19±0.03
	HF-1	0.83±0.02	0.92±0.02	1.07±0.05	1.09±0.03	1.11±0.04
	HF-2	0.84±0.03	1.01±0.04	1.08±0.05	1.18±0.05*	1.12±0.04
Cardiac output (l/min)	Controls	...	...	...	...	...
	HF-1	4.1±0.3†	7.0±0.5†	8.7±6.9†	9.7±0.2	8.6±0.8†
	HF-2	3.1±0.2	5.1±0.3	6.5±0.4	8.2±0.5	6.0±0.4
Systemic lactate (mg/dl)	Controls	...	...	...	...	...
	HF-1	13±1	19±2	32±3	39±2	37±3
	HF-2	12±1	22±2	31±2	47±5	34±3
Pulmonary wedge pressure (mm Hg)	Controls	...	...	...	...	...
	HF-1	13±2†	20±2†	24±3	26±3	25±2
	HF-2	20±2	27±2	27±3	26±4	30±2
No. of subjects	Controls	6	6	6	6	6
	HF-1	9	9	8	5	9
	HF-2	25	25	15	6	25

bpm, Beats per minute;  $\dot{V}O_2$ , systemic oxygen consumption; RER, respiratory gas exchange ratio; HF, heart failure.

\* $p < 0.05$  vs. controls.

† $p < 0.05$  vs. HF-2.

To identify patients with normal leg blood flow responses, leg blood flow measurements in the normal subjects were analyzed to determine mean±2 SEM. Patients whose peak exercise leg blood flow fell within this range were considered to have a normal flow response.

Using this definition, nine of the 34 patients were found to have normal leg blood flow responses to exercise. Flow responses in these subjects are illustrated in Figure 1. All flow responses fell within the normal range. In addition, the leg arteriovenous oxygen differences in the patients (Table 2) were comparable to levels noted in the normal subjects, further confirming the presence of normal leg flow.

Despite normal leg blood flow responses to exercise, all of the nine patients discontinued exercise due to leg fatigue and exhibited markedly reduced peak exercise

$\dot{V}O_2$  ( $14.1 \pm 0.9 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ). One of the patients was able to exercise to a maximal work load of only 20 W. Three were able to exercise to only 40 W, and five were able to exercise to only 60 W.

Despite the presence of normal leg flow, all nine of these patients exhibited abnormal increases in femoral venous lactate concentration (Figure 1). Lactate concentrations were significantly elevated at both 40 and 60 W in the subjects. To further characterize lactate response both in the normal subjects and in the patients with normal flow, femoral venous lactate was correlated with work load using linear regression analysis. Only values obtained at 0–60 W were used in the analysis because no patient exceeded a work load of 60 W. Over these work loads, femoral venous lactate responses were essentially linear in both groups, with all correlation coefficients  $> 0.90$ . The slope of the work load versus

TABLE 2. Leg Hemodynamic and Metabolic Responses to Exercise

Response	Group	Upright rest	Work load (W)			Maximal exercise
			20	40	60	
Leg flow (l/min)	Controls	0.5±0.1	2.6±0.2	3.4±0.4	4.1±0.4	5.6±0.6
	HF-1	0.3±0.1*	2.3±0.2†	3.0±0.2†	4.0±0.2†	3.5±0.2†*
	HF-2	0.3±0.1*	1.1±0.1*	1.7±0.1*	2.2±0.2*	1.6±0.1*
Femoral lactate (mg/dl)	Controls	9±1	17±3	22±2	30±4	71±10
	HF-1	13±1	25±3	42±3*	52±1*	49±3
	HF-2	14±1*	36±3*	46±3*	67±8*	53±4
Leg arteriovenous oxygen difference (mg/dl)	Controls	10.2±0.9	12.2±0.8	12.6±0.8	12.8±0.7	13.7±1.0
	HF-1	9.1±0.5	11.6±0.6†	11.7±0.7†	12.4±0.5†	11.9±0.6†
	HF-2	10.7±0.4	14.1±0.4*	15.0±0.6*	16.1±0.7*	14.7±0.4

HF, heart failure.

\* $p < 0.05$  vs. controls.

† $p < 0.05$  vs. HF-2.

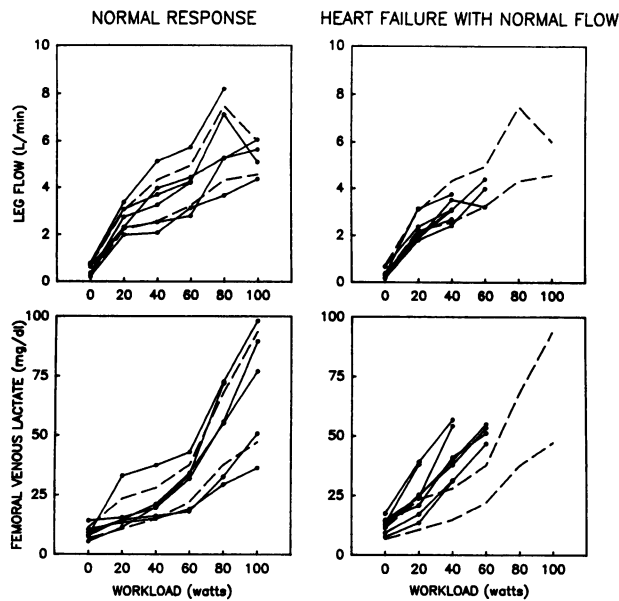


FIGURE 1. Plots of leg blood flow and femoral venous lactate responses in the control subjects (normal response) and in the patients with heart failure and normal leg blood flow responses to exercise (heart failure with normal flow). The dashed lines indicate the mean  $\pm$  2 SEM for responses in the control subjects.

femoral venous lactate relations was almost threefold steeper in the patients than in the normal subjects ( $0.81 \pm 0.08$  versus  $0.33 \pm 0.07$   $\text{mg} \cdot \text{dl}^{-1} \cdot \text{W}^{-1}$ ,  $p < 0.002$ ), whereas the intercepts were similar in the two groups ( $11 \pm 4$  versus  $9 \pm 1$   $\text{mg/dl}$ ,  $p = \text{NS}$ ). These early increases in femoral venous lactate in the patients were also associated with early increases in systemic lactate and in the respiratory gas exchange ratio (Table 1).

The remaining 25 patients with heart failure exhibited reduced leg blood flow responses, increased leg arteriovenous oxygen differences, early lactate release, and reduced exercise capacity (Tables 1 and 2). Compared with these 25 patients, the nine patients with normal flow exhibited comparable ejection fractions (normal flow,  $26 \pm 4\%$ ; low flow,  $19 \pm 2\%$ ), supine resting cardiac indices (normal flow,  $2.1 \pm 0.2$   $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ; low flow,  $1.9 \pm 0.1$   $\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ), supine resting pulmonary wedge pressure (normal flow,  $19 \pm 2$   $\text{mm Hg}$ ; low flow,  $23 \pm 2$   $\text{mm Hg}$ ), ages (normal flow,  $58 \pm 3$  years; low flow,  $57 \pm 2$  years), duration of heart failure (normal flow,  $21 \pm 8$  months; low flow,  $24 \pm 7$  months), and time to the most recent hospitalization (normal flow,  $7 \pm 2$  months; low flow,  $6 \pm 2$  months) (all  $p = \text{NS}$ ). Of particular note, femoral venous, systemic lactate, and respiratory gas exchange ratio responses to exercise were similar in the two groups (Tables 1 and 2). Patients with normal leg flow did exhibit lower pulmonary wedge pressures when they were at rest sitting on the bicycle (normal flow,  $13 \pm 2$   $\text{mm Hg}$ ; low flow,  $20 \pm 2$   $\text{mm Hg}$ ) ( $p < 0.05$ ), better cardiac output responses to exercise, and a tendency toward higher peak exercise  $\dot{V}\text{O}_2$  (normal flow,  $14.1 \pm 0.9$   $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ; low flow,  $11.5 \pm 0.7$   $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ ) ( $p = 0.0503$ ). In addition, patients with normal leg flow tended to have lower levels of nonleg flow at peak exercise (normal flow,  $2.0 \pm 0.7$   $\text{l/min}$ ; low flow,  $2.8 \pm 0.3$

$\text{l/min}$ ) ( $p = 0.17$ ); nonleg flow was calculated as the difference between the cardiac output and twice the leg flow measurement.

### Discussion

Exertional fatigue in heart failure traditionally has been attributed to inadequate skeletal muscle blood flow, based on observations that cardiac output and leg blood flow responses to maximal exercise are on average reduced in patients with heart failure.<sup>1-3</sup> Recently, we and others<sup>4-12</sup> have described a number of skeletal muscle changes in patients with heart failure, including skeletal muscle atrophy, reduced mitochondrial-based enzymes, reduced mitochondrial size, increased type II fibers, and abnormal metabolic responses to forearm and calf exercise despite normal flow responses. Such observations have led many investigators to speculate that skeletal muscle changes may contribute to exercise intolerance in heart failure. However, it has also been reported that these muscle changes parallel changes in muscle flow and exercise capacity,<sup>11,19</sup> leading to the assumption that muscle abnormalities occur concurrently with flow abnormalities and therefore primarily compound the effects of muscle underperfusion.

Results of the present study suggest that a significant proportion of patients with heart failure and typical exertional fatigue are in fact not limited by skeletal muscle underperfusion. Using a conservative estimate of normal leg flow, 26% of our patients with heart failure and significant exercise intolerance did not exhibit skeletal muscle underperfusion, as evidenced by a normal leg blood flow. Nevertheless, these patients exhibited abnormal lactate responses to exercise and leg fatigue, suggesting that they were limited by intrinsic skeletal muscle abnormalities.

The etiology of these muscle abnormalities was not specifically examined in the present study. However, it seems likely that muscle deconditioning and, possibly, malnutrition are important contributors; these conditions could trigger abnormal lactate release by a variety of mechanisms, including muscle atrophy with increased loading of each muscle fiber; increased activation of fast-twitch, glycolytic fibers; and heightened glycolytic activity due to enzymatic changes within muscle. Patients are frequently inactive. The muscle changes noted in patients have been observed in deconditioning normal subjects.<sup>20</sup> Cardiac rehabilitation has been shown to improve the maximal exercise capacity of patients and to improve muscle metabolic responses to exercise.<sup>13,14</sup> Total caloric intake of patients is frequently reduced,<sup>12</sup> and classic evidence of malnutrition is not uncommon.<sup>21</sup>

The fact that one fourth of our patients appeared to be limited by skeletal muscle changes rather than by muscle underperfusion has several major clinical implications. First, it suggests that the presence of exertional fatigue, a reduced peak exercise  $\dot{V}\text{O}_2$ , and an early anaerobic threshold should no longer be considered indicative of skeletal muscle underperfusion in patients with heart failure. How does one reconcile this conclusion with prior observations that both the anaerobic threshold and peak  $\dot{V}\text{O}_2$  correlate with cardiac output and leg blood flow responses to exercise in patients with heart failure<sup>1-3</sup>? Results of the present study are not inconsistent with these prior observations. The majority of patients examined in this study also exhibited re-

duced leg blood flow and cardiac output responses to exercise. Our findings simply indicate that not all patients exhibit reduced leg blood flow. In fact, if one examines reported correlations between leg blood flow and peak exercise  $\dot{V}O_2$ ,<sup>1,2</sup> a relatively wide range of flows is noted at any given level of peak exercise  $\dot{V}O_2$ . This range overlaps flow responses noted in normal subjects, supporting the concept that some patients with reduced exercise exhibit normal leg blood flow responses to exercise.

Our conclusion that increased lactate release can occur in the presence of normal leg blood flow is also consistent with a number of recent observations demonstrating that muscle lactate release is not necessarily an indication of muscle ischemia. Connett et al,<sup>22</sup> for example, noted lactate accumulation in exercising dog gracilis muscle despite normal muscle oxygenation, as assessed by myoglobin saturation. It has also been observed that diet, glycogen levels, and muscle enzymatic levels can influence lactate production during exercise.<sup>23</sup>

In patients with normal leg flow, the management of exertional fatigue probably should be different than that in patients with reduced flow. At present, patients with a limited maximal exercise capacity due to leg fatigue and premature onset of the lactate threshold are presumed to have circulatory dysfunction and therefore are usually treated with additional pharmacological agents and sometimes with cardiac transplantation. In patients with normal leg flow, therapeutic interventions should probably be directed at improving skeletal muscle function rather than at improving muscle blood flow. Precisely what interventions should be used remains to be determined. At present, enrollment in a cardiac rehabilitation program and treatment of nutritional abnormalities probably represent the best therapeutic approach.

The other major implication of our research concerns the evaluation of investigational vasodilator and inotropic agents designed to improve the exercise capacity of patients with heart failure. Such agents are currently evaluated by randomizing patients with reduced maximal exercise capacity to active versus placebo therapy. Our findings suggest that this approach leads to the randomization of a substantial number of patients not limited by circulatory dysfunction and therefore not likely to respond to active agent. This "contamination" of the study population may explain, at least in part, why responses to drug interventions may vary widely among patients and why some trials of an investigational agent but not others detect significant effects on exercise capacity.

How can clinicians identify patients primarily limited by skeletal muscle dysfunction? Evaluation of leg blood flow is an investigational technique currently available in only a few institutions. Nevertheless, insertion of a femoral venous catheter is a relatively simple technique with little morbidity, and the equipment required to measure flow is commercially available and easy to operate. Physicians interested in identifying patients limited by muscle dysfunction should probably obtain the expertise and equipment to measure leg blood flow.

One method of estimating leg blood flow during exercise is to measure cardiac output responses to exercise using a Swan-Ganz catheter. However, this approach has a higher complication rate than femoral

venous catheterization and may provide misleading information. In addition, the patients in this study who exhibited normal leg blood flows also tended to deliver a greater proportion of their cardiac output to the legs during exercise, as evidenced by a lower nonleg blood flow at peak exercise. In such patients, evaluation of the cardiac output response to exercise would underestimate the actual leg blood flow response. Why such patients appear to have enhanced flow distribution to the leg is unclear, although one might speculate that arteriolar vasodilation in skeletal muscle is less impaired in these patients than in patients with reduced leg flow.

Ideally, a noninvasive technique should be available to identify patients with normal flow. One potential technique is near-infrared spectroscopy, a noninvasive method of assessing skeletal muscle hemoglobin oxygenation using near-infrared light.<sup>24</sup> We are currently evaluating the utility of this technique.

Whatever technique is developed, one key issue that will need to be addressed is the definition of normal leg blood flow. We used a conservative criterion to define normal leg blood flow during exercise. If a different criterion were used, such as mean normal flow  $\pm 2$  SD, close to 50% of the patients would have been identified as having normal leg flow. Further work is needed to define the optimal criteria for identifying patients with preserved muscle flow, i.e., flow levels that ensure adequate muscle oxygen delivery at a cellular level.

Several limitations of this study are worth noting. Leg blood flow is an index of flow flow to working skeletal muscle but also includes flow to nonmuscular tissue and to inactive muscle. Therefore, it is possible that flow to working muscle was actually reduced in the patients with normal flow, although this seems very unlikely. Second, it should be emphasized that demonstration of abnormal increases in femoral venous lactate with concurrent leg fatigue in the patients with normal flow does not prove that skeletal muscle metabolic abnormalities limit exercise. Abnormal release of lactate from the legs indicates abnormal muscle metabolism but not that lactate causes fatigue. In fact, reports from this and other laboratories suggest that lactate does not directly cause fatigue.<sup>25</sup> Nevertheless, the demonstration of fatigue and lactate abnormalities in the presence of normal leg flow strongly suggests that muscle rather than flow abnormalities are limiting exercise.

In summary, results of this study suggest that  $\geq 25\%$  of patients with chronic heart failure and exertional fatigue are limited by skeletal muscle abnormalities rather than by skeletal muscle underperfusion.

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