Near-maximal fractional oxygen extraction by active skeletal muscle in patients with chronic heart failure

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1 Division of Circulatory Physiology, Department of Medicine, Columbia University College of Physicians and Surgeons, Columbia Presbyterian Medical Center, New York 10032; and 2 Division of Cardiology, Department of Medicine, The Albert Einstein College of Medicine, Bronx, New York 10461

Katz, Stuart D., Carol Maskin, Guillaume J ondeau, Thomas Cocke, Robert Berkowitz, and Thierry Lejemtel. Near-maximal fractional oxygen extraction by active skeletal muscle in patients with chronic heart failure. J Appl Physiol 88: 2138–2142, 2000.—Systemic oxygen uptake and deep femoral vein oxygen content were determined at peak exercise in 53 patients with chronic heart failure with impaired systolic function (mean left ventricular ejection fraction 0.18; n = 41) or preserved systolic function (mean left ventricular ejection fraction 0.70; n = 12) and in 6 age-matched sedentary normal subjects. At peak exercise, deep femoral vein oxygen content in heart failure patients with impaired systolic function and preserved systolic function were similar, both significantly lower than that of normal subjects (2.5 ± 0.1, 2.9 ± 0.2, and 5.0 ± 0.1 ml/100 ml, respectively; P < 0.05). Deep femoral venous oxygen content was lower in patients with the greater impairment of aerobic capacity, regardless of the underlying systolic function (r = 0.72, P < 0.01). Fractional oxygen extraction in the skeletal muscle at peak exercise is enhanced in patients with chronic heart failure when compared with normal subjects, in proportion to the degree of aerobic impairment.

exercise physiology; vascular physiology; oxygen transport; microcirculation; aerobic performance

ATROPHY AND DECREASED OXIDATIVE enzyme capacity have been documented in the skeletal muscle of deconditioned normal subjects and patients with chronic heart failure (3, 4, 6, 11, 13, 18, 19, 21). In deconditioned normal subjects, these skeletal muscle alterations are associated with less than complete fractional oxygen extraction in skeletal muscle at peak exercise (18). In patients with heart failure, these skeletal muscle alterations are associated with widened systemic arteriovenous oxygen difference when compared with normal subjects, which suggests more complete fractional oxygen extraction by active skeletal muscle (22, 23). Alternatively, widened arteriovenous oxygen difference in heart failure may result from differences in distribution of cardiac output to exercising and nonexercising tissues when compared with normal subjects (27, 28).

Accordingly, the present study was undertaken to measure oxygen content in the venous effluent from active skeletal muscle at peak exercise in normal subjects and patients with chronic heart failure with impaired or preserved systolic function. To ensure selective sampling of venous blood from active skeletal muscle, deep femoral vein catheterization was used to avoid contamination from cutaneous or other circulations (2, 16).

METHODS

Study population. Fifty-three patients with chronic congestive heart failure of at least 3-mo duration associated with impaired left ventricular systolic function (n = 41) or preserved left ventricular systolic function (n = 12) were studied. Patients were recruited into the study according to the following criteria: ages 21–80 yr and stable symptoms of congestive heart failure compatible with functional class II–III according to the criteria of the New York Heart Association. Criteria for exclusion for the study were the presence of noncardiac limitations to exercise related to primary pulmonary, peripheral vascular, joint, or neuromuscular diseases; exercise-limiting angina; clinical instability (hospitalization <1 mo), anemia (hemoglobin <12 mg/dl); or evidence of arterial oxygen desaturation (<97%) at rest or during exercise. No patient was participating in an exercise training program. All patients had an echocardiography-Doppler study within 3 mo before the study. Impaired systolic function (left ventricular ejection fraction (EF) <0.35) was identified in 41 patients. The etiology of left ventricular systolic dysfunction was ischemic heart disease in 14 patients and idiopathic dilated cardiomyopathy in 27 patients. Preserved systolic function (left ventricular EF >0.50, without valvular regurgitation or stenosis, or subaortic outflow obstruction) was identified in 12 patients. Patients with preserved systolic function had increased left ventricular mass index determined by echocardiography (mean 149 g/m2, range 135–191 g/m2; normal range 60–124 g/m2). Coronary heart disease was excluded in patients with preserved systolic function by coronary angiography or thallium perfusion imaging. Patients with impaired and preserved systolic function were analyzed separately because the effect of systolic function on peripheral oxygen utilization in heart failure is unknown.

Four men and two women without history of chronic medical illness served as normal controls. The control subjects were sedentary nonsmokers, had a normal physical examination, and were not taking chronic medications. The
Table 1. Clinical characteristics of patients with heart failure with impaired systolic function and preserved systolic function

<table>
<thead>
<tr>
<th></th>
<th>Impaired Systolic Function (n = 41)</th>
<th>Preserved Systolic Function (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>61 ± 10</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>Gender, no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (88)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (12)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>NYHA classification, no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>19 (46)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Class III</td>
<td>22 (54)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.21 ± 0.3</td>
<td>0.70 ± 0.10*</td>
</tr>
<tr>
<td>Medications, no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>40 (98)</td>
<td>7 (58)*</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>37 (90)</td>
<td>2 (17)*</td>
</tr>
<tr>
<td>Calcium blockers</td>
<td>3 (7)</td>
<td>8 (67)*</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>3 (7)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>32 (78)</td>
<td>0 (0)*</td>
</tr>
</tbody>
</table>

Values for age and left ventricular ejection fraction (LVEF) are means ± SE, and values within parentheses are %; n, no. of subjects. NYHA, New York Heart Association; ACE, angiotensin-converting enzyme. ∗P < 0.05 vs. patients with impaired systolic function.

The study was approved by the Ethical Review Board of the Albert Einstein College of Medicine and Montefiore Medical Center. All subjects signed written informed consent before participation.

Exercise protocol. Maximal exercise was performed in the fasting state on an electronically braked bicycle ergometer. All subjects exercised at least once within 72 h before the study to ensure familiarization with the testing apparatus. All subjects were instructed to maintain a pedaling rate of 60 rpm. For the patients with heart failure, the exercise protocol consisted of a 2-min warm-up period of unloaded cycling, and subsequent increase in work rate by 25 W every 3 min until exhaustion. Electrocardiogram was monitored continuously throughout exercise. Blood pressure was determined by the cuff method at 2-min intervals during exercise. Mean arterial pressure was calculated by standard formula.

Oxygen uptake determination. Expired gases at rest and during exercise were collected through a mouthpiece attached to a low-resistance three-way valve (Hans Rudolph). Measurements of mixed expired oxygen, mixed expired carbon dioxide, expired volume, expired gas temperature, and barometric pressure were obtained at rest while the subject was seated on the bicycle and every 20 s throughout exercise with the use of a calibrated metabolic measurement cart (SensorMedics). Oxygen uptake (ml·min⁻¹·kg⁻¹), carbon dioxide production (ml·min⁻¹·kg⁻¹), and respiratory exchange ratio were calculated with standard formulas. Peak oxygen uptake was determined as the highest value of oxygen consumption in the last minute of exercise when the respiratory exchange ratio (RER) was >1.0.

Deep femoral venous blood oxygen content measurement. One-half hour before exercise testing, a 5-Fr 6-in. flexible polyethylene catheter was inserted under local anesthesia just below the right inguinal ligament and advanced 10–12 cm distal into the deep femoral vein to ensure specific blood sampling of the venous effluent of exercising skeletal muscle (16). Catheter position in the deep femoral vein was confirmed with two-dimensional ultrasound imaging. Two milliliters of deep femoral venous blood were obtained from the indwelling catheter after 0.5 h of supine rest and at peak exercise. Blood for oxygen content determination was collected in a heparinized syringe, sealed airtight and kept on ice until analysis immediately after test completion. To avoid potential CO-oximetry errors secondary to changes in the hemoglobin oxygen affinity induced by changes in pH and temperature of venous effluent from active muscle, oxygen content (ml/100 ml) was directly measured in triplicate with a platinum electrode (Lex-O-Con Instruments, Waltham, MA) that was calibrated just before each measurement.

Data analysis. The results are expressed as means ± SE. Measurements of cardiovascular and metabolic parameters at rest and during exercise were compared with one-way ANOVA among patients with heart failure with impaired systolic function, patients with preserved systolic function, and normal subjects. Tukey’s multiple-comparison test was used for post hoc between-group comparisons. Correlations among variables of interest were analyzed with simple linear regression. Differences were considered to be statistically significant if the two-tailed P value was <0.05.

RESULTS

Clinical characteristics. Clinical characteristics of the patients with heart failure with impaired systolic function and preserved systolic function are presented in Table 1. Clinical characteristics were similar with the exception of left ventricular EF and background medications. The mean age and gender distribution of the two patient populations did not differ significantly from those of the normal subjects.

Exercise performance. Table 2 provides data on heart rate, mean arterial pressure, oxygen uptake, and RER at rest and at peak exercise.

Table 2. Heart rate, mean arterial pressure, oxygen uptake, and respiratory exchange ratio at rest and at peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Peak Exercise</th>
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<tbody>
<tr>
<td></td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
<tr>
<td></td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>89 ± 2.2†</td>
<td>77 ± 4.1</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>87 ± 1.7†</td>
<td>97 ± 2.9</td>
</tr>
<tr>
<td>Work rate, w</td>
<td>47 ± 5*</td>
<td>43 ± 3*</td>
</tr>
<tr>
<td>VO₂, ml·kg⁻¹·min⁻¹</td>
<td>3.7 ± 0.1</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>RER</td>
<td>0.82 ± 0.01</td>
<td>0.81 ± 0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE for 41 heart failure patients with impaired systolic function, 12 heart failure patients with preserved systolic function, and 6 normal subjects. HR, heart rate; MAP, mean arterial pressure; RER, respiratory exchange ratio; VO₂, oxygen uptake. *P < 0.05 vs. normal subjects. †P < 0.05 vs. preserved systolic function.
at rest and at peak exercise for patients with heart failure with impaired systolic function, patients with heart failure with preserved systolic function, and normal subjects. At rest, heart rate was significantly higher in patients with impaired systolic function when compared with patients with preserved systolic function and normal subjects. Resting mean arterial pressure was significantly lower in patients with impaired systolic function when compared with patients with preserved systolic function. At peak exercise, heart rate and oxygen uptake in patients with impaired systolic function and in patients with preserved systolic function were similar, both significantly lower than those of normal subjects. Peak RER was significantly lower in patients with impaired systolic function when compared with normal subjects. No patient had Hb <12 mg/dl or oxygen saturation <97% by transcutaneous monitoring during exercise.

Deep femoral vein oxygen content. At rest, deep femoral vein oxygen content was significantly lower in patients with impaired systolic function and with normal subjects (7.2 ± 0.4, 9.6 ± 0.4, and 11.3 ± 0.5 ml/100 ml, respectively; P < 0.05). At peak exercise, deep femoral vein oxygen content was similar in patients with impaired systolic function and in patients with preserved systolic function and was significantly lower than that in normal subjects (2.5 ± 0.1, 2.9 ± 0.2, and 5.0 ± 0.1 ml/100 ml respectively; P < 0.05; Fig. 1). Deep femoral venous oxygen content was lower in patients with the greater impairment of aerobic capacity, regardless of the underlying systolic function (r = 0.72, P < 0.01; Fig. 2). The lowest deep femoral vein oxygen content was observed in patients with impaired systolic function and peak oxygen uptake <14 ml·min⁻¹·kg⁻¹, with near-complete oxygen extraction (≤1 ml/100 ml oxygen content) in two patients (Fig. 3).

**DISCUSSION**

The present data demonstrate that deep femoral vein oxygen concentration at peak exercise in patients with heart failure with impaired or preserved systolic function is significantly less than that of normal subjects. This finding indicates that widened systemic arteriovenous oxygen difference at peak exercise in patients with heart failure is at least partially attributable to increased fractional oxygen extraction in exercising skeletal muscle.

Decreased femoral vein oxygen content has been previously reported in patients with decompensated heart failure due to rheumatic heart disease and other types of organic heart disease (5, 10, 24). The present study extends the findings of these previous studies to a well-characterized population of patients with chronic heart failure with impaired or preserved systolic function. Taken together with previous studies, the present findings suggest that peripheral adaptations of oxygen utilization in response to diminished cardiac output reserve are similar regardless of the underlying cardiac pathology. The present study also extends the findings of previous reports because it is the first to utilize retrograde catheterization of the femoral vein to obtain deep femoral venous blood directly draining the exercising skeletal muscle bed without contamination from cutaneous drainage via the saphenous vein (16).
Oxygen utilization in skeletal muscle during exercise is determined by the factors that regulate the delivery of oxygen to the mitochondria in the myocyte: limb blood flow, capillary volume, capillary diffusion capacity, myoglobin concentration, and mitochondrial respiratory rate (8, 20, 25). The present study cannot directly determine which of these mechanisms contributed to increased fractional oxygen extraction in heart failure. Capillary density in limb skeletal muscle vasculature in experimental heart failure is not altered when compared with control animals, but it appears to be decreased in the skeletal muscle of patients with heart failure (7, 26). Because fractional oxygen extraction is determined by the ratio of oxygen diffusion capacity to regional blood flow, a likely explanation of our findings is that capillary recruitment outstripped limb blood flow at peak exercise, with resultant increase in capillary transit time and increased fractional extraction of oxygen (17). This interpretation is supported by the recent findings of Kindig and colleagues (9), who observed increased capillary transit time without change in oxygen diffusion capacity in the spinotrapezius muscle microcirculation of rats with heart failure due to left anterior descending coronary artery ligation when compared with sham-operated control animals. It is also possible, but unlikely, that capillary recruitment in heart failure is adapted to specifically distribute available limb blood flow to motor units with high oxidative capacity (12). The near-complete extraction of oxygen in patients with most severe limitation of aerobic capacity suggests that reduced capacity of oxidative enzymes in exercised skeletal muscle does not limit maximal exercise capacity in these patients (10). The linear relationship between systemic oxygen consumption and femoral vein oxygen content observed in our study is consistent with previous studies that demonstrated a close proportional relationship between fractional oxygen extraction and oxygen uptake in isolated canine muscle preparations, normal human subjects, and patients with cardiovascular disease (8, 10, 16).

Our finding of increased oxygen utilization in patients with heart failure is not consistent with expected findings of deconditioning (4, 18, 19). In normal subjects, deconditioning induced by bed rest is associated with decreased maximal cardiac output with no change in maximal arteriovenous oxygen difference (19). Diffusion capacity in the skeletal muscle microcirculation does not change in response to deconditioning because capillary-to-fiber ratio and fiber cross-sectional area decrease in proportion to one another (4, 18, 19). Physical training increases maximal aerobic performance in normal subjects, in part, by increasing fractional oxygen extraction in exercising skeletal muscle (15). Increased fractional oxygen extraction in response to physical training is likely attributable to increased capillary density of the skeletal muscle bed, which increases diffusion capacity without change in transit time, and possibly to enhanced distribution of blood to high oxidative capacity motor units (1, 15). The oxygen content in the femoral blood at peak exercise in our patients with the most severe aerobic impairment is comparable to that reported in endurance-trained athletes (14). Because fractional oxygen extraction in exercising skeletal muscle of patients with severe aerobic impairment is nearly complete, training-induced improvement in maximal aerobic capacity in these patients must be primarily mediated by increased skeletal muscle perfusion.

In conclusion, oxygen content in the deep femoral vein blood at peak exercise is decreased in patients with heart failure when compared with sedentary normal subjects. Increased fractional oxygen extraction, likely attributable to an increase in capillary transit time without change in oxygen diffusion capacity, may function as an adaptive mechanism to optimize oxygen utilization in heart failure and other pathophysiological states characterized by chronic reductions in skeletal muscle perfusion. Biochemical abnormalities in skeletal muscle present in patients with heart failure likely contribute to decreased submaximal endurance but do not appear to be limit oxygen utilization in skeletal muscle at peak aerobic capacity.

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REFERENCES


