Failure to augment maximal limb blood flow in response to one-leg versus two-leg exercise in patients with severe heart failure

THIERRY H. LEJEMTEL, M.D., CAROL S. MASKIN, M.D., DAVID LUCIDO, PH.D., AND BRIAN J. CHADWICK, R.N.

ABSTRACT  Lower limb blood flow, oxygen uptake, and femoral vein O_2 content were measured at rest and during maximal bicycle exercise, performed with two legs and one leg, in four normal subjects and in five patients with severe congestive heart failure. While in normal subjects femoral vein blood flow and lower limb vascular conductance were significantly greater during one-leg exercise than during two-leg exercise (6084 ± 745 vs 5370 ± 803 ml/min, p < .05, and 52.3 ± 8.0 vs 45.1 ± 8.2 U × 10^3, p < .05, respectively), in patients with severe congestive heart failure these values were similar during the two forms of exercise (1082 ± 459 vs 1053 ± 479 ml/min and 9.6 ± 3.7 vs 9.4 ± 3.5 U × 10^3, respectively). In five additional patients, one-leg maximal bicycle exercise was performed before and after administration of phentolamine into the femoral artery of the active leg. Regional α-adrenergic blockade with phentolamine did not alter maximal oxygen uptake attained during one-leg bicycle exercise (9.8 ± 1.5 vs 10.3 ± 1.9 ml/kg). Lower limb blood flow and femoral vein O_2 content attained during maximal one-leg exercise were also similar before and after phentolamine. Thus, in contrast with normal subjects, patients with severe congestive heart failure were unable to further increase limb blood flow during one-leg bicycle exercise. Moreover, local α-adrenergic blockade does not augment blood flow to the active limb during maximal one-leg bicycle exercise. This suggests that the ability of the muscular vasculature to vasodilate during exercise is impaired and may be a limiting factor to maximal exercise capacity in such patients.


PATIENTS with congestive heart failure, when compared with normal subjects, have a reduced metabolic arteriolar vasodilatory response after restoration of flow to an ischemic limb. They also do not have an adequate increase in forearm blood flow in response to rhythmic handgrip exercise of increasing intensity. Thus, an inability of the peripheral muscle vasculature to dilate appropriately during dynamic exercise may be a limiting factor to maximal exercise capacity in patients with severe congestive heart failure.

In normal subjects, during graded exercise involving 40% or more of the total muscle mass, such as bicycling with two legs, maximal functional capacity, i.e., oxygen uptake, is limited by the ability of the heart to increase its output. In contrast, when graded exercise involves a smaller percentage of the total muscle mass, such as bicycling with one leg, maximal exercise capacity is attained before maximal cardiac output or VO_2 max is reached, suggesting that a lack of output by the heart is no longer the limiting factor. Of interest, when the effects of one-leg vs two-leg bicycle exercise are compared in normal subjects, the maximal workload per leg is greater during one-leg exercise than during two-leg exercise, suggesting that peak blood flow to the active limb during two-leg exercise can be further augmented. Thus, a comparison of the two forms of exercise may provide a physiologic intervention with which the peripheral vs central components of the exercise response can be evaluated. Accordingly, lower limb blood flow and vascular conductance were measured in normal subjects and in patients with severe congestive heart failure during maximal bicycle exercise performed with two legs and with one leg. In addition, according to the one-leg graded exercise protocol, phentolamine was administered into the femoral artery to evaluate the effect of local adrenergic blockade on limb blood flow during maximal exercise.
Methods

**Patient population.** Four sedentary men without known cardiovascular disorders, ranging in age from 43 to 52 years (mean 47), and 10 patients (nine men and one woman) ranging in age from 45 to 69 years (mean 56) were studied. All patients had severe congestive heart failure consistent with New York Heart Association functional class III or IV, and were markedly limited in exercise capacity by dyspnea and/or fatigue. Clinical, as well as the daily doses of digoxin and diuretics, were stable in all patients for 1 month before the study. No patient had been treated with vasodilator therapy. Cause of heart failure was coronary artery disease in five patients and idiopathic cardiomyopathy in the remaining five. No patient had sustained a myocardial infarction within 3 months of the study, nor was any patient limited by exertional angina. Left ventricular ejection fraction, determined by a gated radionuclide technique, was less than 20% in nine patients and 35% in one. All were in normal sinus rhythm. The study was conducted in the Exercise Physiology Laboratory at the Hospital of the Albert Einstein College of Medicine. All subjects gave written informed consent, and the protocol was approved by the Human Studies Committee of the Albert Einstein College of Medicine.

**Study design.** In normal subjects and in the first five patients with severe congestive heart failure, oxygen uptake, mean systemic arterial pressure, femoral vein blood flow, and oxygen content were determined at rest and during maximal bicycle exercise performed with two legs and one leg. The order in which two-leg and one-leg bicycle exercise was performed was alternated sequentially in the normal subjects and patients. The two-leg and one-leg maximal exercise tests were separated by at least 4 hr.

In the remaining five patients, values for the parameters listed above were obtained at rest and during maximal one-leg bicycle exercise performed before and after administration of phentolamine.

**Exercise protocol.** Two-leg exercise testing was performed with the subject sitting upright on an electronically braked bicycle ergometer with feet secured to the pedals. During one-leg exercise, the nonexercising leg rested in a sling suspended adjacent to the ergometer, while the active foot was secured to the pedal. In normal subjects, the initial workload during two-leg bicycle exercise was 50 W and it was increased by 25 W every 3 min. In normal subjects during one-leg bicycle exercise, and in patients during both two-leg and one-leg bicycle exercise, the initial workload was 12.5 W and it was increased by 12.5 W every 3 min. When a higher workload could not be performed due to severe leg fatigue, subjects were considered to have achieved peak oxygen uptake if the respiratory quotient had reached a value equal to or greater than 1.1. All subjects exercised at least twice within 72 hr of the study to ensure familiarization with the apparatus and to establish reproducibility. All patients were tested in the postabsorptive state a minimum of 8 hr after their last dose of diuretic. Digitalis was not administered by the day of the study.

**Oxygen uptake.** 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 sitting on the bicycle and every 30 sec throughout the exercise with the use of a metabolic measurement cart (Beckman Instruments). Oxygen uptake was calculated by standard formulas. Subjects breathed through a mouthpiece and a low-resistance, nonrebreathing, three-way valve with a nose clamp. The oxygen analyzer (LB-2 Beckman Instruments) was calibrated with an analyzed mixture of approximately 4% carbon dioxide and 16% oxygen in nitrogen. This calibration was made within 1 hr of testing.

**Systemic arterial pressure.** In all subjects an indwelling catheter was inserted percutaneously into a radial artery for measurement of systemic arterial pressure. Systemic arterial pressures were determined with a Gould Statham P23 ID transducer and recorded on an Electronics for Medicine photographic recorder. Mean systemic arterial pressure was derived electronically. Heart rate was recorded continuously throughout the study.

**Femoral vein blood flow.** Femoral vein blood flow was determined by the continuous thermodilution technique with a No. 7F dual thermistor catheter (Webster Laboratories). The external dilution thermistor was located 35 mm proximal to the indicator injection orifice. The second indicator thermistor was located inside the nylon tubing adjacent to the injection orifice. On the day of the study, the catheter was introduced into the femoral vein via the Seldinger technique 1 to 2 cm below the inguinal ligament. The catheter was advanced in a retrograde manner 8 to 10 cm into the femoral vein and then secured with a suture to the skin. For each determination of blood flow, 5% dextrose at room temperature was infused through the catheter with a Harvard pump (Model 921) at a constant rate of 50 ml/min until the resistance deflection of both thermistors was stable. A standard three-channel thermodilution Wheatstone Bridge (Webster Laboratories) was used to convert the resistance changes into calibrated voltages, which were recorded on photographic paper. Blood flow was then calculated with the formula derived by Ganz et al. and Fronek and Ganz with a modification to correct for thermotransport within the Webster catheter at blood flow greater than 300 ml/min. Femoral vein blood flow was determined in triplicate in subjects at rest with less than 10% variation, while the subject was sitting on the bicycle, every 30 sec during the second and third minute of each workload, and at peak exercise. Derived hemodynamic parameters were calculated as follows: lower limb vascular conductance (U x 10³) = femoral vein blood flow (liters/min)/mean systemic arterial pressure (mm Hg).

**Femoral vein oxygen content.** Femoral vein blood was withdrawn from the end hole of the thermodilution catheter at rest and at each minute during exercise. All samples were evaluated in triplicate and then averaged to calculate oxygen content (ml/100 ml) with a Lex O₂ Con oxygen analyzer (Lexington Instruments). The blood sample obtained at the highest workload reached during exercise was considered to represent the femoral vein O₂ content at maximal exercise.

**Cold pressor test and phentolamine administration.** Before administration of phentolamine, one hand of each patient was immersed in a bucket of ice for 1 to 2 min; femoral blood flow was measured every 30 sec and systemic arterial pressure and heart rate were recorded continuously. Phentolamine, at a dose of 1 mg, was then administered into the femoral artery of the exercising leg with a 21-gauge needle and with the patient in the resting, supine position. Subsequent to administration of phentolamine, femoral vein blood flow was again measured and the cold pressor test was repeated to assess the efficacy of phentolamine-induced alpha-adrenergic blockade. If this manipulation induced a 20% or greater reduction in femoral vein blood flow, an additional 1 mg bolus of phentolamine was administered into the femoral artery.

**Statistical analysis.** The results are expressed as mean ± SD and were considered significant at p < .05. Exercise responses during two-leg and one-leg exercise were analyzed by a two-within factor repeated-measures analysis of variance design. Each subject was evaluated under four conditions: rest and peak two-leg bicycle exercise, rest and peak one-leg bicycle exercise. Subsequent to the overall analysis of variance, tests of the single main effects were conducted to test the effects of each form of exercise (two-leg vs one-leg). The exercise responses to one-leg bicycle exercise tests performed during the control peri-
TABLE 1

Hemodynamic and metabolic parameters during two-leg and one-leg maximal exercise in normal subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Type of exercise</th>
<th>VO₂</th>
<th>SAP</th>
<th>FVBF</th>
<th>FVO₂</th>
<th>LLVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>WL</td>
<td>R</td>
<td>Exh</td>
<td>R</td>
<td>Exh</td>
<td>R</td>
<td>Exh</td>
</tr>
<tr>
<td>1</td>
<td>2-leg</td>
<td>225</td>
<td>3.4</td>
<td>42.8</td>
<td>90</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>1-leg</td>
<td>137.5</td>
<td>3.2</td>
<td>30.6</td>
<td>85</td>
<td>113</td>
</tr>
<tr>
<td>2</td>
<td>2-leg</td>
<td>200</td>
<td>2.9</td>
<td>38.0</td>
<td>88</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>1-leg</td>
<td>125</td>
<td>2.9</td>
<td>26.9</td>
<td>90</td>
<td>116</td>
</tr>
<tr>
<td>3</td>
<td>2-leg</td>
<td>200</td>
<td>3.2</td>
<td>36.0</td>
<td>85</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>1-leg</td>
<td>125</td>
<td>3.3</td>
<td>27.0</td>
<td>86</td>
<td>123</td>
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<tr>
<td>4</td>
<td>2-leg</td>
<td>225</td>
<td>3.3</td>
<td>40.4</td>
<td>92</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>1-leg</td>
<td>137.5</td>
<td>3.1</td>
<td>29.8</td>
<td>90</td>
<td>115</td>
</tr>
<tr>
<td>Mean</td>
<td>2-leg</td>
<td></td>
<td>3.2</td>
<td>39.3</td>
<td>89</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>1-leg</td>
<td></td>
<td>3.1</td>
<td>28.6</td>
<td>87</td>
<td>117</td>
</tr>
<tr>
<td>SD</td>
<td>2-leg</td>
<td></td>
<td>0.2</td>
<td>2.9</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1-leg</td>
<td></td>
<td>0.2</td>
<td>1.9</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

p value (1-leg vs 2-leg) <.05 NS <.05 NS <.05

WL = workload (W); VO₂ = oxygen uptake (ml/kg/min); SAP = mean systemic arterial pressure (mm Hg); FVBF = femoral vein blood flow (ml/min); FVO₂ = femoral vein oxygen content (ml/100 ml); LLVC = lower limb vascular conductance (U x 10⁶); R = rest; Exh = exhaustion.

Results

Hemodynamic and metabolic parameters measured at rest and during bicycle exercise with two legs and one leg are detailed for the normal subjects in table 1. Parameters at rest before one-leg and two-leg exercise were similar. Maximum oxygen uptake was greater during two-leg exercise than during one-leg exercise (39.3 ± 2.9 vs 28.6 ± 1.9 ml/kg/min, p < .05). However, during one-leg exercise, normal subjects attained higher femoral vein blood flow and lower limb vascular conductance than during two-leg exercise (6084 ± 745 vs 5370 ± 803 ml/min, p < .05, and 52.3 ± 8.0 vs 45.1 ± 8.2 U x 10⁶, p < .05, respectively). Mean systemic arterial pressure and femoral vein oxygen content were similar during two-leg and one-leg bicycle exercise (119 ± 4 vs 117 ± 4 mm Hg and 4.6 ± 0.6 vs 4.7 ± 0.6 ml/100 ml, respectively).

In patients with severe congestive heart failure, resting hemodynamic and metabolic parameters measured were similar before one- and two-leg exercise. Systemic oxygen uptake and mean arterial pressure were 3.7 ± 0.5 vs 3.7 ± 0.6 ml/kg/min and 81 ± 10 vs 82 ± 11 mm Hg, respectively. Resting lower limb blood flow and femoral vein O₂ content were also similar (302 ± 96 vs 297 ± 71 ml/min and 5.5 ± 1.9 vs 5.7 ± 2.1 ml/100 ml, respectively).

During two-leg bicycle exercise, maximal workload was 37.5 W in two patients and 25 W in the remaining three. During one-leg exercise, maximal workload was considered to be 12.5 W because no patient could sustain exercise after a further increment in workload.

As shown in figures 1 and 2, maximal oxygen uptake was significantly higher during two-leg exercise than during one-leg exercise (10.8 ± 3.5 vs 7.8 ± 1.7 ml/kg/min, p < .05), but femoral vein blood flow and O₂ content were similar (1082 ± 459 vs 1053 ± 479 ml/min).

FIGURE 1. Changes in oxygen uptake and femoral vein blood flow during maximal two-leg and one-leg bicycle exercise. *p < .05; **p < .01 exercise vs rest.
ml/min and 2.1 ± 1.0 vs 2.0 ± 0.7 ml/100 ml, respectively). Mean systemic arterial pressure and lower limb conductance were also similar during maximal exercise performed with two legs and one leg (114 ± 22 vs 110 ± 21 mm Hg and 9.6 ± 3.7 vs 9.4 ± 3.5 U × 10³, respectively). The contrast between the changes in lower limb vascular resistance during one-leg and two-leg exercise in normal subjects and in patients with congestive heart failure is illustrated in figure 3.

Resting leg blood flow was 390 ± 80 ml/min and decreased to 269 ± 64 ml/min (p < .001) after the cold pressor test, as depicted in figure 4. Resting mean systemic arterial pressure and heart rate increased after the cold pressor test from 81 ± 9 to 91 ± 9 mm Hg (p < .05), and from 88 ± 13 to 99 ± 13 beats/min (p < .05), respectively. After intra-arterial administration of phentolamine, resting limb blood increased from 390 ± 80 to 809 ± 115 ml/min (p < .001), while mean systemic arterial pressure and heart rate did not change (81 ± 9 vs 83 ± 12 mm Hg and 88 ± 13 vs 93 ± 15 beats/min, respectively). However, after administration of phentolamine, the cold pressor test failed to decrease leg blood flow (809 ± 115 vs 822 ± 145 ml/min) or significantly change systemic arterial pressure (83 ± 12 to 79 ± 21 mm Hg, NS), while heart rate increased from 93 ± 15 to 101 ± 13 beats/min (p < .05).

Maximal oxygen uptake during one-leg exercise performed after administration of phentolamine was not statistically different from that attained during control one-leg exercise (9.8 ± 1.5 vs 10.3 ± 1.9 ml/min).

**FIGURE 2.** Changes in femoral vein oxygen content and lower limb vascular conductance during maximal two-leg and one-leg bicycle exercise. *p < .05; **p < .01 exercise vs rest.

**FIGURE 3.** Absolute changes in lower limb vascular conductance during one-leg vs two-leg bicycle exercise in patients with severe congestive heart failure (CHF) and in normal sedentary subjects (N).

**FIGURE 4.** Effect of the cold pressor test on resting femoral vein blood flow in patients lying supine. Under control conditions, resting femoral vein blood flow decreases significantly during immersion of the hand in ice. Administration of phentolamine substantially increases resting femoral vein blood flow and blocks its decrease during immersion of the hand in ice.
In ml/kg/min). In addition, as shown in figures 5 and 6, lower limb blood flow and femoral vein O₂ content were similar during maximal control and phentolamine one-leg exercise (1322 ± 187 vs 1311 ± 164 ml/min and 3.0 ± 0.8 vs 2.9 ± 0.6 ml/100 ml). Since there were also no statistical differences between mean systemic arterial pressure and heart rate reached during maximum control and phentolamine one-leg exercise (114 ± 11 vs 114 ± 12 mm Hg and 133 ± 24 and 136 ± 127 beats/min), there was no change in lower limb vascular conductance.

Discussion

During graded bicycle exercise performed to exhaustion with two legs, normal subjects increase cardiac output to a maximum and consequently attain a plateau in oxygen uptake. When bicycling is performed with one leg only, normal subjects do not maximally increase cardiac output, and oxygen uptake at exhaustion is below their previously determined maximum. Moreover, as suggested by previous investigators, our data demonstrate that blood flow and vascular conductance in the working limb at maximal effort are greater during one-leg than during two-leg bicycle exercise. Thus, bicycling with one leg is a particularly interesting physiologic intervention in which the peripheral response (i.e., ability of skeletal muscle vasculature to dilate or to extract oxygen) may be differentiated from the central (i.e., cardiac performance) response to exercise.

Abnormalities in skeletal muscle circulation have previously been described in patients with severe chronic heart failure by Zelis et al. They have shown a substantial reduction in metabolic arteriole-dilator response after restoration of blood flow to an ischemic forearm when compared with normal subjects. Inadequate vasodilatation of forearm arterioles during rhythmic grip exercise has also been noted in patients with chronic heart failure. In addition, the inability of forearm blood flow to be augmented sufficiently during static exercise results in an early shift from aerobic to anaerobic metabolism.

Our data in patients with severe congestive heart
failure extend these observations to a larger muscle mass (i.e., lower limb) during dynamic exercise performed up to maximal workload. The capacity of skeletal muscle vasculature to dilate during exercise appeared to be considerably limited in our patients. Since they were unable to further augment blood flow to the working limb during one-leg exercise when compared with two-leg exercise, impairment of vasodilative capacity, independent of cardiac performance, seemed to be a limiting factor to maximal exercise capacity.

We have previously reported that short-term inotropic stimulation with dobutamine failed to substantially improve exercise capacity in patients with severe congestive heart failure despite an increase in the maximal cardiac index. However, dobutamine, which activates peripheral \( \alpha \)-adrenergic vascular receptors, may have preferentially increased blood flow to vascular beds other than that of active skeletal muscles. In the present study the nonexercising peripheral circulation was not altered by exogenous interventions, and thus, the failure of the active limb blood flow to increase during one-leg exercise suggests a fixed vasodilative capacity that may limit exercise capacity in patients with severe heart failure.

Our results differ from those of Wilson et al., who have reported that maximum lower limb blood flow during exercise could be increased over the short term by administration of dobutamine or hydralazine. However, in these studies, limb blood flow was measured in the external iliac vein by a bolus thermodilution injection technique. Since the external iliac vein drains blood from the lower limb, the anterior abdominal wall, and the great saphenous vein, these investigators may have measured not only blood flow from the exercising skeletal muscles, but also blood flow from inactive skeletal muscles and other nonexercising tissues as well. Such admixture of blood flow may also explain the changes in iliac vein oxygen content induced by hydralazine or dobutamine during maximal exercise. In contrast, during maximal exercise, the femoral vein contains, almost exclusively, blood from the active skeletal muscles characterized by an extremely low oxygen saturation.

During maximal bicycle exercise performed with one or two legs, femoral vein oxygen content decreased in our patients with severe congestive heart failure to an average of 2 ml/100 ml, which is substantially lower than that attained in normal subjects. The magnitude of the reduction in oxygen content of the venous blood returning from the exercised muscles indicates almost complete oxygen extraction by the skeletal muscles in patients with severe congestive heart failure. This degree of oxygen extraction has also been observed in a similar population by Donald et al. Moreover, preliminary data from our laboratory suggest that the femoral vein oxygen content measured during maximal exercise is linearly related to peak oxygen uptake in patients with chronic heart failure. Thus, maximal oxygen extraction can be seen as a compensatory mechanism in response to the inadequate rise in limb blood flow that occurs during exercise in patients with severe congestive heart failure.

Administration of phentolamine into the femoral artery of the exercising leg did not alter maximal limb blood flow in our patients during one-leg bicycle exercise. Failure of regional \( \alpha \)-adrenergic blockade to augment blood flow to exercising muscle during a maximal metabolic stimulus has been well established. In addition, since maximal femoral vein oxygen content was also unchanged after phentolamine, it appears that \( \alpha \)-adrenergic blockade had little effect on blood flow distribution within the skeletal muscle in our patients. In fact, shunting of blood away from the more actively metabolizing tissues secondary to the administration of phentolamine would be expected to result in a higher maximal femoral vein \( O_2 \) content than was observed.

In summary, in patients with severe congestive heart failure, the failure of maximal limb blood flow to increase in response to one-leg vs two-leg exercise, or after regional administration of phentolamine during one-leg exercise, suggests that the ability of the muscle vasculature to vasodilate is impaired. This inability to adequately augment limb blood flow may represent an important limiting factor to maximal exercise capacity in patients with severe congestive heart failure.

References
PATHOPHYSIOLOGY AND NATURAL HISTORY—CONGESTIVE HEART FAILURE

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