Muscle Blood Flow During Forearm Exercise in Patients With Severe Heart Failure

J. Malcolm O. Arnold, MD, Jorge P. Ribeiro, MD, DSc, and Wilson S. Colucci, MD

Muscle fatigue is a prominent symptom in patients with chronic heart failure (CHF). To determine whether it results from an intrinsic abnormality of vasodilating capacity of the vasculature in exercising muscle, we studied local forearm blood flow (FBF) during exercise in 13 patients with severe CHF and in eight normal untrained subjects of similar age. Intermittent forearm static exercise was performed by squeezing a hand dynamometer for 5 seconds, three times per minute, for 5 minutes at 15%, 30%, and 45% of maximum voluntary contraction. FBF was measured by mercury-in-rubber strain gauge venous plethysmography at baseline before exercise and during the last 3 minutes of each exercise stage. Exercise was repeated after 24 hours of intravenous administration of milrinone in the patients with CHF. FBF increased with forearm exercise in a reproducible manner during 24 hours in the normal subjects: rest, 2.54±0.23 (0 hours); 2.90±0.23, (24 hours); 15%, 7.25±0.92; 5.85±0.56; 30%, 9.20±1.08; 45%, 10.05±0.85; 45%, 14.62±1.64, 13.85±1.09 ml/100 ml/min; p=NS, 0 versus 24 hours. In patients with CHF, FBF was reduced at baseline compared with normal subjects (1.70±0.15 ml/100 ml/min, p<0.05), but no significant differences from normal subjects were observed during exercise (15%, 5.04±0.65; 30%, 7.64±0.99; 45%, 12.56±1.20 ml/100 ml/min). Peak exercise blood flow was correlated negatively with central venous pressure (r=−0.65, p<0.05) and positively with right ventricular ejection fraction (r=0.59, p<0.05). Twenty-four hours of intravenous milrinone administration did not significantly alter FBF during exercise. Similar results were seen for forearm vascular resistance and percent forearm oxygen extraction. The exercise protocol did not significantly increase cardiac output in CHF patients (n=4) (baseline, 3.93±0.77; 45%, 4.05±0.63 l/min; p=NS). Because FBF was not significantly reduced during submaximal forearm exercise in patients with severe CHF or improved by milrinone therapy, we conclude that 1) a reduction in vasodilator capacity is not limiting at submaximal work loads, and 2) an improvement in submaximal functional performance with milrinone may not be secondary to increased intrinsic vasodilation of muscle vasculature during exercise. Alternative explanations for muscle fatigue during whole-body exercise may include inadequate cardiac output response or abnormalities in muscle metabolism. (Circulation 1990;82:465–472)

In patients with chronic heart failure (CHF), exercise capacity is usually limited by symptoms of dyspnea or fatigue. If the exercise is gradual rather than abrupt in its onset and severity, fatigue is more likely to result.1 The specific cause of fatigue remains unclear, but decreases in nutritive blood flow,2,3 changes in muscle metabolism,4,5 and histological muscle fiber atrophy6 have been implicated.

Peripheral blood flow is reduced at rest in patients with CHF.7,8 During upright exercise, blood flow to an exercising limb remains reduced,2 but this could be due to either a reduction in cardiac output and arterial pressure or increased vascular tone. By studying forearm blood flow (FBF) during forearm exercise in patients with CHF, it should be possible to differentiate these two contributions. However, Zelis et al9 in a group of patients with severe rheumatic heart disease and fluid retention (New York Heart Association [NYHA] functional classes III and IV) found an inadequate arteriolar dilation during forearm exercise, whereas Wilson et al10 suggested that vasodilation was not intrinsically impaired in patients with nonedematous CHF (NYHA classes II and III).

Our present study was designed to address two issues: 1) Is blood flow to a single exercising forearm limb reduced in patients with severe CHF? 2) Does...
milrinone, a new positive inotropic vasodilator that improves functional exercise capacity acutely\textsuperscript{11,12} and improve blood flow during exercise because of peripheral vasodilation?

**Methods**

**Study Population**

We studied 13 patients with CHF (11 men and two women) who had a mean age of 54±4 years (range, 32 to 72 years) (Table 1). The etiology of CHF was coronary artery disease in seven and idiopathic dilated cardiomyopathy in six. All had severe left ventricular dysfunction with a mean left ventricular ejection fraction of 13.7±1.5\% (range 6 to 24\%) by radionuclide gated blood pool estimates. All patients had a documented clinical history of CHF (NYHA functional class III \([n=4]\) or IV \([n=9]\)), were receiving digoxin and diuretics, and had been clinically stable for at least 2 weeks. At the time of study, none had decompensated left ventricular failure.

Eight normal subjects (seven men and one woman) of similar age (mean, 49±3 years; range, 38 to 66 years) served as our control group. All were untrained, drug-free subjects with a sedentary lifestyle and had no evidence of heart disease by clinical history, physical examination, electrocardiography, or chest radiography.

The protocol was approved by the Human Subjects Review Committee of the institutions, and written, informed consent was obtained.

**Protocol**

CHF patients had been on a 2-g sodium diet and a stable dose of medications for at least 3 days before enrollment. All vasodilators were then withheld for at least 48 hours before study, and digoxin and diuretics were withheld on the morning of the study. A flow-directed triple lumen thermodilution catheter was inserted into the pulmonary artery through the right internal jugular vein on the first morning of the study in the CHF patients only. An intravenous catheter was inserted into an antecubital vein in the dominant arm of all subjects, and the tip was advanced 6 in. proximally to sample mixed venous blood draining the forearm. Maximum voluntary contraction of the dominant forearm was measured with a hand dynamometer (Jamar, Alimed, Boston, Mass.). Arterial pressure was measured in the opposite arm through an intra-arterial line in the CHF patients and with a semiautomated indirect recorder (Dinamap 845XT, Critikon, Tampa, Fla.) in the normal subjects.

All studies were performed in a quiet, temperature-controlled environment (22–24°C) after an overnight fast. Patients and normal subjects were recumbent with head and shoulders comfortably supported. After 30 minutes of rest, baseline measurements of heart rate, blood pressure, cardiac output, pulmonary capillary wedge pressure, and FBF were obtained. FBF was measured with a mercury-in-Silastic rubber strain gauge applied around the dominant forearm, which was comfortably supported above the level of the heart.\textsuperscript{13} A wrist cuff was inflated to 200 mm Hg 1 minute before recordings to exclude hand blood flow.\textsuperscript{14} A venous occlusion pressure of 40 mm Hg was used in the upper arm cuff, and FBF was measured as the slope of the change in forearm volume. The venous cuff was inflated for 5–10 seconds for each flow measurement, then released. The mean of at least six flows was obtained at each measurement time. The mean of two sets of baseline flows was used as the control flow.

After a stable hemodynamic baseline had been obtained, forearm exercise was commenced and consisted of repetitive contractions on the hand dynamometer maintained for 5 seconds and released for

### Table 1. Characteristics of Study Patients With Chronic Heart Failure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Etiology of CHF</th>
<th>NYHA class</th>
<th>LVEF (%)</th>
<th>RVEF (%)</th>
<th>Duration of symptoms (mo)</th>
<th>Evidence of peripheral edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>CAD</td>
<td>IV</td>
<td>7</td>
<td>25</td>
<td>60</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>DCM</td>
<td>IV</td>
<td>24</td>
<td>13</td>
<td>39</td>
<td>+++/4</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>CAD</td>
<td>IV</td>
<td>16</td>
<td>18</td>
<td>36</td>
<td>++/2</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>DCM</td>
<td>IV</td>
<td>15</td>
<td>NA</td>
<td>60</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>CAD</td>
<td>III</td>
<td>17</td>
<td>47</td>
<td>9</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>CAD</td>
<td>III</td>
<td>21</td>
<td>65</td>
<td>68</td>
<td>+/4</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>DCM</td>
<td>IV</td>
<td>16</td>
<td>9</td>
<td>43</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>DCM</td>
<td>IV</td>
<td>6</td>
<td>14</td>
<td>26</td>
<td>+/4</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>DCM</td>
<td>III</td>
<td>13</td>
<td>39</td>
<td>15</td>
<td>+/4</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>CAD</td>
<td>III</td>
<td>16</td>
<td>34</td>
<td>21</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>69</td>
<td>CAD</td>
<td>IV</td>
<td>8</td>
<td>55</td>
<td>11</td>
<td>+/4</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>DCM</td>
<td>IV</td>
<td>9</td>
<td>15</td>
<td>24</td>
<td>+/4</td>
</tr>
<tr>
<td>13</td>
<td>53</td>
<td>CAD</td>
<td>IV</td>
<td>10</td>
<td>35</td>
<td>15</td>
<td>None</td>
</tr>
</tbody>
</table>

CHF, chronic heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; CAD, coronary artery disease; DCM, dilated cardiomyopathy; NA, could not be analyzed.
15 seconds, similar to that described by Zelis et al. Measured Variables

Exercise was performed for 5 minutes at 15%, 30%, and 45% of maximum voluntary contraction. All patients and normal subjects were able to complete the full protocol, but some required encouragement because of fatigue. No patients complained of painful muscles, although some normal subjects complained of discomfort in the hand during the last minute of exercise after inflation of the wrist cuff. Hemodynamics and FBF were measured during the last 3 minutes of each exercise stage, and FBF was measured during relaxation between contractions as described and validated by Longhurst et al. Oxygen saturation of mixed venous blood (Hemoximeter OSM2, Radiometer, Copenhagen) draining the exercising forearm was measured before and at the end of each exercise stage (immediately after the last flow measurement, during muscle relaxation). Arterial oxygen saturation was measured from the intra-arterial line in CHF patients and from a warmed earlobe capillary sample in the normal subjects. In five CHF patients, arterial samples were taken before exercise and at the end of each stage of exercise, but no significant change in oxygen saturation was observed with this forearm exercise protocol (rest, 95.5±0.9%; 15%, 94.7±1.2%; 30%, 94.1±1.3%; 45%, 95.0±0.7%). Therefore, in subsequent patients and normal subjects, arterial oxygen saturation was measured before exercise only.

Normal subjects were restudied in an identical fashion 24 hours later. Intravenous and arterial lines were left in situ in the CHF patients who received a 48-hour intravenous infusion of milrinone (50 μg/kg during 10 minutes, 0.25 or 0.5 μg/kg/min for 6 hours, 0.5 μg/kg/min to 48 hours) during which repeat forearm exercise testing was performed at 24 hours. Plasma milrinone concentration between 24 and 48 hours of infusion was 166±18 ng/ml. The full hemodynamic effects of a 48-hour infusion of milrinone in these patients are reported elsewhere in the results of a multicenter trial.

Neurohormones were assayed at rest in eight CHF patients. Plasma norepinephrine concentration was measured by a standard radioenzymatic technique and was 472±76 pg/ml. Plasma renin activity was measured by radioimmunoassay and was 11.0±3.0 ng/ml/hr.

by thermodilution from the mean of at least three injections differing by less than 10%, and cardiac index was calculated as (l/min/m²). Pulmonary capillary wedge pressure was measured at end expiration. Systemic vascular resistance (dyne·sec/cm²) was calculated as 80 multiplied by (mean blood pressure minus right atrial pressure) divided by cardiac output.

Statistical Analysis

Increases in FBF during exercise in normal subjects were compared by analysis of variance for repeated measures with contrasts performed with Tukey's method. Hemodynamic data at 0 and 24 hours were compared with paired t tests. A p value less than 0.05 was considered significant. Data from CHF patients before milrinone therapy were compared by unpaired t tests with normal subjects at day 1 and CHF patients after milrinone therapy at each level of exercise and p<0.025 was considered significant. Linear regression was performed with the least-squares method. All values are expressed as mean±SEM.

Results

To assess the reproducibility of the exercise protocol, the results from the normal subjects on the two consecutive days are shown in Figure 1. With each stage of exercise, there was a progressive increase in FBF, but no significant differences were seen between the FBFs of the two days at any level of exercise, confirming good reproducibility. Therefore, for clarity, the subsequent figures show only the normal results from day 1.

To confirm that the forearm exercise protocol was producing local vascular changes without a change in
central pump function, hemodynamics were measured before and at peak forearm exercise before milrinone therapy in 12 CHF patients. Forearm exercise in CHF patients resulted in no significant changes in heart rate (89±3 and 90±3 beats/min), mean blood pressure (75±3 and 77±3 mm Hg), pulmonary artery diastolic pressure (27±3 and 28±2 mm Hg), right atrial pressure (10±2 and 10±2 mm Hg), or cardiac output (3.93±0.77 and 4.05±0.63 l/min, n=4). In normal subjects, the protocol did not increase heart rate (65±4 and 69±4 beats/min), and mean blood pressure tended to increase slightly (rest, 94±4; 15%, 97±4; 30%, 102±3; 45%, 107±3 mm Hg; p=0.06).

FBF responses to forearm exercise in the CHF patients are shown in Figure 2A. Before milrinone therapy, FBF was reduced at rest in the CHF patients compared with the normal subjects (p<0.05); however, FBF progressively increased with exercise and was not significantly different from that in normal subjects. After milrinone therapy, FBF was significantly increased at rest, but exercise blood flow was not altered. Similar changes were seen with forearm vascular resistance (Figure 2B) and percent forearm oxygen extraction (Figure 2C), which were both increased at rest in patients with CHF. Milrinone therapy decreased forearm vascular resistance and percent oxygen extraction at rest but did not alter either variable from that seen in normal subjects at each stage of exercise. Indeed, because forearm vascular resistance was higher at rest in patients with CHF than in normal subjects, yet the same at peak exercise, the reduction in forearm vascular resistance achieved during forearm exercise by patients with CHF (41.1±4.0 units) tended to be greater than that in normal subjects (31.4±3.5 units), although it did not reach statistical significance. Forearm oxygen consumption (Figure 2D) was normal in CHF patients at rest and was not altered by milrinone at rest or during exercise.

Because the control group completed more physical work than the CHF group, the results are also shown in Figure 3 as the force developed with each contraction. This illustrates that the points for the control group have moved to the right and that differences from the CHF group are further reduced for FBF, forearm vascular resistance, and oxygen consumption. Percent forearm oxygen extraction remains increased in the CHF group to maintain normal oxygen consumption because hemoglobin was lower in the CHF patients (12.4±0.5 versus 14.3±0.4 g%, p<0.01).

FBF during exercise at 45% of maximum voluntary contraction was found to correlate negatively with resting central venous pressure and positively with resting right ventricular ejection fraction (Figure 4). No correlation was seen between exercise blood flow and resting plasma norepinephrine levels or plasma renin activity.

At rest, milrinone significantly improved cardiac index (2.92±0.28 at 24 hours versus 2.12±0.25
l/min/m² preinfusion, p<0.005) with a reduction in systemic vascular resistance (1,061±110 at 24 hours versus 1,382±143 preinfusion, p<0.01). Milrinone therapy tended to reduce pulmonary capillary wedge pressure (20.4±1.4 versus 23.7±1.8 mm Hg) and right atrial pressure (7.0±1.3 versus 8.4±1.9 mm Hg), with small increases in mean blood pressure (72.1±2.5 versus 70.9±3.9 mm Hg) and heart rate (90.2±3.4 versus 86.1±3.0 beats/min), but these changes were not significant.

**Discussion**

Using a reproducible protocol of forearm exercise that did not cause significant central hemodynamic changes in patients with severe CHF, we showed no difference between CHF patients and normal subjects of similar age in the ability of their forearm vasculature to dilate and increase blood flow during exercise. This occurred even though their exercise functional capacity by clinical assessment was significantly reduced and suggests that the development of fatigue during exercise may not primarily result from an intrinsic defect in the vasodilating capacity of the muscle vasculature. This conclusion is supported by the observation that milrinone, a drug known to improve exercise capacity acutely in patients with CHF, although producing vasodilation at rest, did not improve vasodilation during forearm exercise.

The protocol used in this study required exercise to 45% of maximum voluntary contraction for 5 minutes, and the end point was not chosen to be maximum symptom-limited exercise capacity. However, all patients and normal subjects complained of fatigue during the protocol, and submaximal exercise may be more relevant to a patient’s performance of activities of daily living than maximal exercise. The protocol was designed to be similar to that described by Zelis et al, except that we adjusted the strength of contraction to allow for different muscle mass in individual patients. If the present results are considered as force developed, then the patients with CHF generated less force but had a similar vasodilation to normal subjects, further supporting the conclusion that the ability of their forearm muscle vasculature to dilate was not impaired.
Increased central venous pressure could be associated with increased tissue sodium and water retention and a decrease in vasodilator capacity, in an experimental animal model of heart failure induced by rapid atrial pacing, modest increases in mean right atrial pressure with evidence of some fluid retention and increased muscle water content were not associated with a decrease in peripheral arterial vasodilation. The degree of fluid retention was variable among the animals, and the investigators did not report a correlation between degree of fluid retention or central venous pressure and vasodilator capacity. Thus, it remains possible that the decrease in exercise blood flow seen by Zelis et al.2 reflected local tissue edema secondary to the very high venous pressures present in their patients.24,25

Severe heart failure is also associated with neurohormonal activation,26,27 and plasma norepinephrine has been shown to correlate positively with right atrial pressure.28 This neurohormonal activation could be a further independent influence on vasodilator capacity, although we found no association with plasma norepinephrine levels or plasma renin activity in our patients. Another consideration is that venous plethysmography assumes the veins are empty at rest. With high right atrial pressures, this may not be so, and thus, further small increments in forearm volume during intermittent venous occlusion may be operating on a flattened portion of the venous pressure-volume curve,29 thus underestimating forearm blood flow. However, significant flattening of the curve does not occur until pressures higher than 20 mm Hg, and this elevation of right atrial pressure was present in only one of our patients.

Our results support the observations of Wilson et al.10 who studied a group of nonedematous patients with less severe clinical heart failure (NYHA classes II and III) than our population, but they used a different protocol of forearm exercise. Blood flow responses in the forearm30 and biochemical alterations within the muscle31 can be dependent on the exercise protocol used. However, Wilson et al.10 also found increases in blood flow to be similar between normal subjects and patients, suggesting that the reduced vasodilation seen by Zelis et al.9 is more likely to be due to the edematous condition of the patients they studied rather than to differences in exercise protocol. In addition, our observations on the effects of milrinone further support the conclusion that improvements in exercise capacity of patients with compensated severe heart failure may not be mediated through alterations in the intrinsic vasodilator capacity of muscle blood vessels. Our results differ from those of LeJemtel et al.,3 who compared one-leg with two-leg maximal bicycle exercise and concluded that the ability of the muscle vasculature to vasodilate is impaired in patients with CHF. However, oxygen uptake was significantly increased in their model, and thus, changes in cardiac output could have influenced their measurements of blood flow. Sullivan et al.32 also studied leg blood flow
during maximal upright bicycle exercise and found evidence of reduced perfusion at rest and during exercise. Because nonleg blood flow and arterial pressure were preferentially maintained during exercise at the expense of leg hypoperfusion, they concluded that a reflex-mediated peripheral vasoconstriction may occur in the exercising limb in the setting of an inadequate cardiac output response. Our findings complement the results of this study, because we studied a small muscle mass, without a change in cardiac output, and found no intrinsic abnormality in vasodilator capacity with exercise.

Improved functional capacity after vasodilator therapy in CHF could occur through other mechanisms such as increased cardiac output. During whole-body upright exercise, this could maintain muscle perfusion and perhaps performance. Thus, our results are not inconsistent with previous observations during upright exercise that blood flow to exercising skeletal muscle is reduced in CHF3 and improved by long-term administration of drugs such as captopril that increase maximum oxygen uptake.33 Muscle fatigue and decreased performance may also involve alterations in skeletal muscle metabolism with increased phosphocreatine depletion and low pH.4,5 Two studies in patients with heart failure have suggested that these changes do not appear to be secondary to impaired blood flow or muscle atrophy.34,35 Also, of interest, in a rat model of myocardial infarction and acute heart failure, milrinone preferentially increased blood flow to oxidative rather than glycolytic working muscle during maximal treadmill exercise.36 Hence, although total FBF was not increased in our patients, milrinone may improve the distribution between oxidative and glycolytic muscle fibers. If oxidative muscle fibers were to have better resistance to fatigue compared with glycolytic fibers, then this would be clinically helpful.

In summary, we found no impairment in the ability of the local vasculature to dilate during submaximal, intermittent forearm static exercise in patients with compensated severe CHF despite the presence of mild-to-moderate peripheral edema in some patients. Milrinone did not further increase exercise forearm blood flow. We conclude that impairment of functional exercise capacity in patients with CHF is unlikely to be due primarily to an intrinsic vasodilator abnormality of muscle blood vessels.

Acknowledgments

We acknowledge the expert help of Diane Gauthier, BSc, RN, Gail Burton, RN, Gordon Marchiori, PhD, and the excellent secretarial assistance of Paula Hugin and Dale Arts.

References

13. Whitney RJ: The measurement of volume changes in human limbs. J Physiol (Lond) 1953;121:1
29. Wood JE: Factors of basic importance to the study of veins as capacitance vessels, in The Veins, Normal and Abnormal Function. Little, Brown & Co, Boston, 1965

KEY WORDS • heart failure • exercise, forearm • blood flow, muscle • milrinone
Muscle blood flow during forearm exercise in patients with severe heart failure.
J M Arnold, J P Ribeiro and W S Colucci

Circulation. 1990;82:465-472
doi: 10.1161/01.CIR.82.2.465
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/2/465

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/