ABSTRACT Recent studies suggest that, in the presence of heart failure, the capability of skeletal muscle to utilize delivered flow may be impaired due to maldistribution of blood flow within working muscle. Similarly, this mechanism could explain the failure of drugs to improve maximal oxygen consumption (VO2max) immediately. Accordingly, we assessed muscular blood flow distribution (ml/min/g, radioactive microspheres, 15 ± 5 μm) among and within working muscle, VO2max, and arterial lactate in a rat preparation of myocardial infarction and heart failure (infarct size 36.0 ± 3.3% of the left ventricle, n = 9), and in sham-operated animals (n = 11). Data were obtained at maximal treadmill exercise during alternate infusions of milrinone and saline. Total skeletal muscle blood flow during exercise was significantly lower in the infarction group (p < .05 vs sham); reduced blood flow was primarily attributed to decreased flow to oxidative working muscle such as soleus and the red portion of gastrocnemius, whereas blood flow to glycolytic muscle portions (e.g., gastrocnemius white, vastus lateralis white) was similar in the infarction and sham-operated groups. Milrinone increased flow to the glycolytic working muscle portions in sham-operated animals (e.g., vastus lateralis white, 0.23 vs 0.29, p < .05); by contrast, blood flow to the oxidative muscle fibers was increased in the infarction group (e.g., gastrocnemius red, 1.45 vs 1.87, p < .05). Arterial lactate levels at similar workloads during exercise were higher in the infarction group (p < .05). Neither lactate nor VO2max were significantly altered with milrinone in either group. We conclude that (1) skeletal muscle underperfusion in heart failure emerges predominantly in oxidative working muscle and therefore early recruitment of glycolytic fibers may increase lactate levels in the early stages of exercise, (2) significant blood flow redistribution (e.g., that induced by drugs) within working muscle may be present without changes in total muscular blood flow, and (3) milrinone increased blood flow to glycolytic fibers in sham-operated animals, suggesting functional shunt, but caused possibly beneficial redistribution of blood flow to more oxidative working muscle in the presence of heart failure.


RECENT STUDIES indicate that the reduced exercise capacity accompanying heart failure is primarily due to impaired nutritional blood flow to skeletal muscle, although the mechanisms responsible for muscle underperfusion remain uncertain. It has been suggested that neurohumoral vasoconstrictor influences, particularly sympathetic activity and angiotensin II, as well as increased vascular stiffness, may impair arterial vasodilatation in working muscle during exercise. Moreover, reduced muscle arteriovenous pressure gradient may contribute to skeletal muscle underperfusion. Abnormally elevated blood lactate levels during exercise and the elevated ratio of inorganic phosphate and phosphocreatine (as determined by magnetic resonance spectroscopy) indicate that abnormal skeletal muscle metabolism may exist in patients with heart failure that cannot simply be explained by decreased muscle blood flow. One possibility is that skeletal muscle cannot efficiently utilize delivered flow due to maldistribution of flow within working muscle related to alterations of local vasomotor responsiveness. Similarly, maldistribution of increased cardiac output has been proposed as a mechanism of the failure of vasodilators to improve maximum oxygen consumption (VO2max) immediately in patients with cardiac
failure, although this issue has never been elaborated upon any further in detail.

In a series of elegant studies, Armstrong and Laughlin have delineated the regional distribution of blood flow within individual and among muscles during slow and prolonged exercise and after training in the normal rat by use of the microsphere technique. However, there are no data on muscular blood flow distribution either in the presence of heart failure and/or after pharmacologic intervention with vasodilators and/or positive inotropes. In contrast to man, the fiber-type distribution in the rat follows a distinctive topography that allows determination of flow to different muscle fiber types. Accordingly, the present study was designed to investigate the muscular blood flow pattern among and within skeletal muscle in a rat preparation of cardiac failure. Furthermore, we sought to examine the effect of milrinone on the intramuscular distribution of blood flow in rats with and without chronic heart failure. This agent was chosen because recent studies have demonstrated potent vasodilator activity of milrinone both in the rat and in patients with congestive heart failure besides its positive inotropic action.

Methods

Experimental preparations. Infarction was produced by left coronary artery ligation, as described previously, using a modification of the method of MacLean et al. In male Sprague-Dawley rats the left coronary artery was ligated approximately 2 mm from its origin with a 6-0 suture. In the sham-operated animals, the suture was tied loosely so as not to obstruct coronary flow. With this method, the 24 hr mortality rate was 40% for the infarction group and 5% for the sham-operated group. Subsequent experimental procedures were started 21 days after surgery. During this postsurgical period, the mortality rate in the infarction group was approximately 15%.

Instrumentation. Animals were anesthetized with halothane (1% in oxygen) and catheters (PE 50) were inserted into the right jugular vein, tail artery, and left ventricle; the latter was monitored by pressure wave detection (Statham P23ID pressure transducers) on a recorder screen (Siemens Elema, Mingograf). Animals were allowed to recover from anesthesia for a minimum of 3 hr before experimental procedures were initiated. This recovery period has been found to be of sufficient duration to ensure a return to steady-state conditions in the rat.

Regional blood flow measurements. Radioactive microspheres (tSc, 95Nb, 141Ce, 103Ru, New England Nuclear, Dreieich, West Germany), 15 ± 5 μm in diameter, were used to measure regional blood flow according to the reference sample technique as adapted for use in the rat. A detailed presentation of the radioactive microsphere technique as used in this study has been previously described. In brief, the microsphere suspension was thoroughly mixed by agitation and sonication (Branson Sonifier B-30, Danbury, CT) immediately before each injection. Approximately 250,000 microspheres (0.5 ml) were then injected into the left ventricle immediately after the reference sample, arterial blood was withdrawn (beginning 15 sec before and continuing over 1.5 min during the injection of microspheres) via the tail artery at a rate of 0.35 ml/min with the use of a Harvard constant flow pump (model 906). Immediately before withdrawal of the reference sample 0.15 ml of blood was collected for determination of arterial lactate concentrations.

The animals were killed by phenobarbital injection in the ventricle and all samples were immediately plotted, weighed, and transferred to a two-channel Gamma scintillation counter (Kontron 480 AR) for determination of radioactivity levels. A Digital Equipment Professional 350 computer was used to calculate regional blood flow as well as total cardiac output. For regions in which total flow was not measured (skin, skeletal muscle, intestines), estimates for each animal were made based on representative samples. The following muscle samples were removed from both the right and left hindlimbs as previously described by Armstrong and Laughlin (with Green's Anatomy of the Rat used as a reference for the dissection: soleus, the deep red portion of the gastrocnemius, the superficial white portion of the gastrocnemius, the mixed portion of the gastrocnemius, the tibialis anterior, the deep red portion of vastus lateralis, the superficial white portion of vastus lateralis, and the rectus femoris. To ensure a sufficient number of microspheres per sample (particularly in the heart failure group), we combined tissue from the right and left sides of the muscle samples to obtain accurate blood flow measurements. The lowest numbers of spheres were observed in superficial white portions, ranging approximately from 150 to 300. Adequacy of microsphere mixing in the blood was monitored in each experiment by comparison of the blood flow values to the same muscles from the right and left sides and from the right and left kidney. Blood flow to the free wall of the right ventricle was used as a measure of noninfarcted coronary blood flow, since microspheres trapping in noninfarcted left ventricular tissue were not determined separately. Forty-two rats were instrumented as described above. Animals were excluded from the study for the following reasons: catheter problems (n = 3), poor exercise performance (e.g., disturbance by microsphere infusion) (n = 5), evidence of poor mixing of microspheres in left and right muscle portions (n = 4), sudden death of instrumented animals with infarction (n = 2), and small infarcts with almost normal exercise tolerance in animals in the infarction group (n = 8).

Hemodynamics. Tracings from the left ventricular and caudal catheter were used to obtain heart rate, left ventricular peak systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), and mean arterial pressure (MAP) (by electronic integration). Stroke volume was calculated from cardiac output and heart rate. Total vascular resistance was determined from cardiac output and mean arterial pressure data. With the exception of cardiac output, hemodynamic data were collected immediately before the microsphere injection.

Determination of infarct size. The left ventricle and the ventricular septum were separated, weighed, and fixed in 10% formalin and finally cut in eight transverse slices (5 μm) from apex to base and stained with van Gieson stain and mounted. With a planimeter Digital Image Analyzer (Leica), the endocardial and epicardial circumference of the infarcted and noninfarcted portions of the left ventricle were determined. The infarcted mean circumference (mean of epicardial and endocardial circumference) of all eight slices was summed and then expressed as ratio of the summed circumference of the left ventricle. Area measurements of infarct size were not made because these have been shown to underestimate infarct size as a result of resorption of necrotic tissue and subsequent wall thinning and late development of compensatory myocardiopathy.

VO2 and VO2max was measured by the flow-through mask...
Room air was drawn through the mask at 4 liters/min, as controlled by a precision flowmeter (Rota, Wehr, West Germany). A fraction of expired flow (250 ml/min) was drawn through a flowmeter (Model R-1, Applied Electrochemistry, Metek, Pittsburgh) and connected to an oxygen analyzer (N-22M S 3A-unit, Applied Electrochemistry), which was calibrated with room air. Both H₂O and CO₂ absorbents were imposed in the line before the flowmeter and analyzer. Thus, VO₂ was calculated by the equation

\[
VO₂ = V_E \times (FIO₂ - FEO₂) \times (1 - FIO₂)^{-1}
\]

where \(V_E\) = expired minute volume; \(FIO₂\) = fraction of inspired O₂; \(FEO₂\) = fraction of expired O₂.

Experimental protocol. Milrinone (Sterling-Winthrop Laboratories, Guildford, U.K.) was prepared by dissolving 10 mg in 0.5 ml 0.5N lactic acid and diluting to the appropriate concentration with 0.9% saline.

The exercise protocol was performed as described previously. 27 Maximal exercise capacity of all animals was determined during progressive treadmill exercise (15, 20, 25 . . . 50 m/min), with increasing workload every 2 min. Exercise duration averaged 552 ± 32 sec for the sham-operated group and 425 ± 39 sec for the infarction group and correlated significantly with VO₂max determined the following day (r = 81, p < .005).

After a 24 hr recovery period, a PE 50 catheter was placed in the right jugular vein during light anesthesia with halothane. 18 Either milrinone (6 μg/kg bolus followed by 2.5 μg/kg/min) or 0.9% saline were infused first in random order. This dosage has recently been found to increase cardiac output by 25% to 30% in normal rats. 13 Ten minutes after starting the infusion of milrinone or saline, VO₂max was determined during progressive treadmill exercise. The initial speed of the treadmill was 30% of the maximal exercise capacity (determined the day before) and was increased after 2 min each to 55%, 80%, and 105%. This protocol was applied to ensure similar exercise time for all rats. Muscular blood flow distribution is a function of both the running speed and exercise duration/workload. 9, 10 The objective of the present study was to compare hemodynamics and muscular blood flow distribution during maximal exercise workload in both groups, and therefore, measurements were made during individual maximal workload as estimated by measurements of VO₂. In contrast, comparisons between sham-operated and infarction groups during similar workloads would represent measurements during maximal workload for the infarction group but at submaximal exercise workload for the sham-operated rats (or significantly longer exercise duration), and would result in questions that were not subject of the present study being addressed.

The protocol was repeated with the alternate infusion (milrinone or saline) after a recovery period of 3 hr. The selection of animals with infarction was based on a VO₂max of less than 70 ml/kg/min, a criterion that has been noted to indicate impaired left ventricular function and large myocardial infarction. 27 Eight animals that did not meet this inclusion criterion were excluded from blood flow measurements.

After 24 hr, PE 50 catheters were placed in the left ventricles and caudal arteries of animals under light halothane anesthesia (similar to the day before) and, after recovery, milrinone or saline was again administered in random order as administered the day before and described above. Preliminary sequential exercise tests (without drug intervention), including measurements of regional blood flow and arterial blood gas analysis, did not reveal significant differences (table 1). These findings are supported by the good reproducibility of arterial lactate levels during repeated maximal exercise in a separate group of both sham-operated rats and animals with infarction (sham-operated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test 1</th>
<th>Test 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>92 ± 7</td>
<td>89 ± 9</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>458 ± 23</td>
<td>464 ± 16</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>24 ± 5</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>133 ± 8</td>
<td>127 ± 11</td>
</tr>
<tr>
<td>Cardiac output (ml/min/kg)</td>
<td>328 ± 30</td>
<td>308 ± 21</td>
</tr>
<tr>
<td>Kidney BF</td>
<td>3.3 ± 0.4</td>
<td>3.0 ± 0.5</td>
</tr>
<tr>
<td>Liver BF</td>
<td>0.19 ± 0.07</td>
<td>0.23 ± 0.08</td>
</tr>
<tr>
<td>Right ventricular BF</td>
<td>7.6 ± 0.8</td>
<td>7.9 ± 0.7</td>
</tr>
<tr>
<td>Intestines BF</td>
<td>1.7 ± 0.4</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Sk-muscle BF</td>
<td>0.84 ± 0.14</td>
<td>0.79 ± 0.11</td>
</tr>
<tr>
<td>pH</td>
<td>7.329 ± 0.018</td>
<td>7.316 ± 0.016</td>
</tr>
<tr>
<td>Po₂ (mm Hg)</td>
<td>113 ± 6.3</td>
<td>115 ± 7.0</td>
</tr>
<tr>
<td>Po₂ (mm Hg)</td>
<td>29.7 ± 1.2</td>
<td>30.3 ± 1.5</td>
</tr>
</tbody>
</table>

BF = blood flow (ml/min/g); Sk-muscle = skeletal muscle.

There were no significant differences by paired t test between exercise tests 1 and 2.
11 sham-operated animals and in nine animals with infarction are listed in tables 2 to 4. The average infarct size was 36 ± 3.3% of the left ventricular (midmyocardial) circumference. Depressed cardiac performance in the infarction group (heart failure) was documented by elevated LVEDP and depressed LVSP, cardiac output, MAP, and stroke volume as well as lower skeletal muscle and skin blood flow values during exercise. Table 4 and figures 1 and 2 depict the effect of myocardial infarction on individual skeletal muscles during exercise. Blood flow to the soleus and the red portion of the gastrocnemius was reduced in the infarction group as compared with the sham-operated group and tended to be reduced in the red portion of the vastus lateralis. No significant differences in blood flow to muscles with predominant white glycolytic (FG) fibers (e.g., vastus lateralis white or gastrocnemius white) were observed.

Effect of milrinone on systemic hemodynamics, blood flow to different organs, and muscle fibers during exercise (table 2). In the control group, milrinone decreased mean arterial and left ventricular systolic pressure as well as systemic vascular resistance. Cardiac output tended to increase, although not statistically significantly so. In the infarction group, milrinone reduced LVEDP (−16%) and systemic vascular resistance (−17%) and increased output (+18%), stroke volume (+22%), and stroke work (+21%) during exercise significantly. The infusion of milrinone during exercise increased blood flow to the right ventricle in the sham-operated and infarction groups. No other significant changes in regional blood flow per gram of tissue were observed in any of the other tissues investigated (table 3).

Milrinone increased flow to the white portions of the vastus lateralis and gastrocnemius in the sham-operated group. By contrast, blood flow to the red portion of the gastrocnemius and to the soleus was enhanced by milrinone in the infarction group; as a result, blood flow to the soleus was similar in the infarction and sham-operated groups.

Lactate values. In the sham-operated group the arterial lactate concentration during exercise averaged 2.7 ± 0.17 mmol/liter before and 3.00 ± 0.24 mmol/liter after drug administration. In the infarction group the values were 4.13 ± 0.33 mmol/liter before and 3.94 ± 0.22 mmol/liter after milrinone. The differences

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham (n = 11)</th>
<th>Milrinone</th>
<th>Infarct (n = 9)</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Milrinone</td>
<td>Control</td>
<td>Milrinone</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>123 ± 3.0</td>
<td>112 ± 4.7A</td>
<td>86 ± 4.8B</td>
<td>83 ± 4.2</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>536 ± 14</td>
<td>518 ± 13A</td>
<td>440 ± 17D</td>
<td>427 ± 21</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>172 ± 3.6</td>
<td>154 ± 4.3B</td>
<td>112 ± 4.9E</td>
<td>108 ± 5.1</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>8.1 ± 0.8</td>
<td>8.4 ± 0.8</td>
<td>27.8 ± 2.7D</td>
<td>23.3 ± 2.8C</td>
</tr>
<tr>
<td>CO (ml/min/kg)</td>
<td>516 ± 42</td>
<td>548 ± 42</td>
<td>366 ± 24D</td>
<td>431 ± 36A</td>
</tr>
<tr>
<td>SV (ml/beat/kg)</td>
<td>0.97 ± 0.05</td>
<td>1.06 ± 0.09</td>
<td>0.83 ± 0.03D</td>
<td>1.01 ± 0.06A</td>
</tr>
<tr>
<td>SVR (mm Hg/ml)</td>
<td>0.25 ± 0.01</td>
<td>0.21 ± 0.01A</td>
<td>0.23 ± 0.01</td>
<td>0.19 ± 0.01A</td>
</tr>
<tr>
<td>SW (g/kg)</td>
<td>2.07 ± 0.15</td>
<td>1.99 ± 0.16</td>
<td>0.95 ± 0.06D</td>
<td>1.16 ± 0.10A</td>
</tr>
</tbody>
</table>

HR = heart rate; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; SW = stroke work.

*p < .05; **p < .001; *p < .01 vs respective control; *p < .05; **p < .005 vs corresponding sham values.

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham (n = 11)</th>
<th>Milrinone</th>
<th>Infarct (n = 9)</th>
<th>Milrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>3.38 ± 0.41</td>
<td>3.32 ± 0.30</td>
<td>2.70 ± 0.48</td>
<td>2.79 ± 0.42</td>
</tr>
<tr>
<td>Liver</td>
<td>0.17 ± 0.03</td>
<td>0.15 ± 0.02</td>
<td>0.14 ± 0.04</td>
<td>0.21 ± 0.07</td>
</tr>
<tr>
<td>RV</td>
<td>8.88 ± 0.70</td>
<td>10.4 ± 1.01A</td>
<td>7.06 ± 0.47D</td>
<td>9.10 ± 0.68A</td>
</tr>
<tr>
<td>Skin</td>
<td>0.075 ± 0.011</td>
<td>0.09 ± 0.009</td>
<td>0.042 ± 0.004C</td>
<td>0.058 ± 0.006</td>
</tr>
<tr>
<td>Intestine</td>
<td>1.89 ± 0.19</td>
<td>1.96 ± 0.19</td>
<td>1.36 ± 0.29</td>
<td>1.56 ± 0.20</td>
</tr>
<tr>
<td>Sk-muscle</td>
<td>1.02 ± 0.07</td>
<td>1.04 ± 0.06</td>
<td>0.75 ± 0.10C</td>
<td>0.86 ± 0.08</td>
</tr>
</tbody>
</table>

RV = right ventricle; Sk-muscle = skeletal muscle.

*p < .05; **p < .005 vs control values; *p < .05; **p < .001 vs sham control values.
between pretreatment and posttreatment values in the two groups were not statistically significant.

At similar workloads arterial lactate levels were significantly higher in animals with infarction and heart failure (figure 3), indicating an earlier onset of anaerobic metabolism in the heart failure group (similar observations have been reported in patients with heart failure).30, 31 There was no significant difference between maximal lactate values during the standardized protocol and those during the exercise test using the exercise program with stages relative to $\dot{V}O_2$max (6.9 ± 0.65 vs 6.6 ± 0.76 mmol/liter). The resting lactate levels before each exercise test were similar (1.12 ± 0.12, 1.19 ± 0.14, and 1.03 ± 0.10 mmol/liter).

$\dot{V}O_2$max. $\dot{V}O_2$max did not change after administration of milrinone in the sham-operated group (sham control/milrinone, 81.8 ± 3.2/84.1 ± 2.9 ml/min/kg). Milrinone increased $\dot{V}O_2$max by 11.6% in the infarction group (control/milrinone, 62.2 ± 3.9/69.4 ± 4.6 ml/min/kg); however, this difference was not statistically significant as compared with control. $\dot{V}O_2$max was a major selection criterion for inclusion of animals in the infarction group, and therefore, $\dot{V}O_2$max was significantly reduced in the infarction group as compared with that in the sham-operated group (p < .005).

**Discussion**

The major purpose of the present study was to determine the muscular blood flow distribution in the presence of congestive heart failure and to investigate the
LVEDP was markedly increased, similar to the case in previous studies with this preparation.\textsuperscript{16, 20} Furthermore, estimated total cutaneous and skeletal muscle flow per gram of tissue were reduced. These findings indicate that heart failure was present. Although reduced blood flow to skeletal muscle in cardiac failure is well documented,\textsuperscript{4, 7} we are not aware of any report investigating the blood flow distribution within and among skeletal muscles in this setting. In the comparison of individual muscular blood flow data from the sham-operated and infarction groups, it is evident that blood flow is compromised in the presence of heart failure primarily in the red portions of skeletal muscles, i.e., in oxidative working muscle portions predominantly activated during this kind of exercise.

Recent studies indicate\textsuperscript{33, 35} that blood flows are fairly proportional to the oxidative capacity of muscle fibers. This may support the interpretation that the oxidative capacity of FOG red muscles is reduced in heart failure. In support of this contention there is evidence (both in man and animals such as the rat) that training increases oxidative capacity of skeletal muscle and that detraining results in a marked decrease in mitochondrial enzyme activity levels.\textsuperscript{36, 37} Thus, heart failure may limit muscular activity in rats and thereby lead to reduced oxidative capacity of skeletal muscle. Alternatively, the reduced blood flow to the FOG fibers might simply reflect a given running speed similar to the findings in normal rats,\textsuperscript{9} since the rats with infarction tolerated a significantly lower treadmill speed as compared with the sham-operated group. However, this appears to be unlikely since an early increase in arterial lactate values (earlier onset of anaerobic metabolism) during exercise over those in sham-operated rats was observed in the infarction group and skeletal muscle flow was also lower, consistent with skeletal muscle underperfusion. This early onset of anaerobic metabolism suggests that increased recruitment of FG fibers emerged in the infarction group, with the consequences that lactate production increased. This is similar to findings by Saltin and Gollnick\textsuperscript{38} concerning fiber recruitment in man. Thus, the increased recruitment of FG fibers may be somewhat linked to the limited flow to the oxidative working fibers in the infarction group. In the face of regional vasoconstriction within exercising (oxidative) muscle (as opposed to the metabolic vasodilation in the face of underperfusion),\textsuperscript{39} less flow-dependent (FG) muscles appear to be activated. Since blood pressure during exercise was significantly reduced in the infarction group, such regional sympathetically mediated vasoconstriction (compared with that in the sham-operated animals) is likely to occur by

**FIGURE 3.** Arterial lactate concentrations during stepwise increased treadmill exercise in sham-operated (triangles) and infarction groups (squares). Maximal lactate values are given at mean maximal treadmill speed of each group (n = 6). *p < .05, **p < .01 vs sham.

Effect of a pharmacologic intervention that has been shown to increase skeletal muscle blood flow in this setting.\textsuperscript{15} To this end we used an established rat preparation of myocardial infarction and heart failure.\textsuperscript{20, 32} Recent studies of Armstrong and Laughlin\textsuperscript{9, 10} have demonstrated that in normal rats the distribution of blood flow both within and among muscles is markedly heterogeneous during exercise, both as a function of the fiber type composition and of the spatial recruitment pattern of the fibers in the muscles. These data from conscious rats as well as observations during anesthesia and nerve stimulation\textsuperscript{33} suggest that skeletal muscle blood flow during exercise is coupled to the active slow-twitch oxidative (SO) and fast-twitch, oxidative-glycolytic (FOG) muscles. Data obtained from the exercising dog and indirectly from studies in man also support the view that the arrangement of the vascular bed and blood supply differ in FOG and SO muscle fibers.\textsuperscript{34} In contrast to man or the dog, the fiber type distribution in the rat follows a distinct topography,\textsuperscript{12, 33} that allows the determination of blood flow to muscles containing, to a large degree, a specific fiber type. According to results obtained with the method of individual muscle preparation described by Armstrong and Laughlin,\textsuperscript{9, 12} the blood flow values for the individual muscles investigated compare reasonably well with those reported by these authors when corresponding running speeds are compared\textsuperscript{11} (for example, for the gastrocnemius white and soleus 23 and 168 ml/min/100 g as compared with 19 and 191 ml/min/100 g\textsuperscript{11}).

**Muscular blood flow distribution in the presence of heart failure.** In the infarction group cardiac output and stroke volume were significantly reduced during exercise and
activation of arterial baroreceptors, although total peripheral vascular resistance for control and heart failure groups during exercise was similar.

**Effect of milrinone on muscular blood flow distribution.** The effects of milrinone on central hemodynamics in the heart failure group during exercise included increases in cardiac output and stroke volume and reduction of LVEDP and systemic vascular resistance, consistent with recent observations in patients with congestive heart failure. Blood flow to FG fibers was unchanged by milrinone, whereas flow to oxidative working muscle did increase (similar to findings observed after exercise training in normal rats). In the sham-operated group milrinone did not alter total muscular blood flow during exercise. However, blood flow to muscles with a large percentage of FG fibers increased with milrinone, whereas flow to the oxidative working SO and FOG fibers (for example, red portion of gastrocnemius, figure 2) remained unaffected by milrinone.

Thus, it appears that milrinone did not augment vasodilation caused by metabolic factors in the sham-operated group but increased flow to FG fibers not yet fully activated. As a result VO₂max did not rise in the sham-operated group. In the presence of heart failure, however, increased flow to the oxidative fibers within skeletal muscle occurred with milrinone. Muscle blood flow is believed to be controlled by alterations in sympathetic nervous activity, circulating vasoactive agents, local metabolites, and/or local reflexes. During exercise, the overall elevation in sympathetic tone decreases blood flow to less active muscle fibers, whereas flow to active muscles preferentially increases due to the effects of local factors that allow these vascular beds to “escape” the influence of the elevated sympathetic activity. In heart failure, reduced skeletal muscle flow during exercise may be in part due to increased sympathetic tone (e.g., that stimulated by low exercise blood pressure, see table 2). Interestingly, it has been demonstrated in a clinical study that milrinone reduces plasma norepinephrine levels during exercise in patients with heart failure. Thus, the withdrawal of sympathetic activity elicited by milrinone may contribute to the improvement in perfusion of oxidative fibers within FOG and SO muscles.

Our results indicate that pharmacologic intervention with milrinone alters the pattern of blood flow distribution among and within working muscle. The elevated flow to white portions of muscles in the control group probably reflects increased functional shunt without improvement in oxygen availability within working muscle. Increased blood flow to oxidative fibers within muscles in the heart failure group along with a tendency to increased VO₂max may indicate improved nutritional blood flow in part due to favorable blood flow redistribution within working muscle by withdrawal of sympathetic activity. In fact, improved VO₂max after short-term administration of milrinone has been observed in patients with congestive heart failure, supporting this contention. The overall inability of milrinone to significantly increase VO₂max immediately in the present study (although it did so in the majority of infarcted animals) may be explained by intrinsic skeletal muscle abnormalities. Recent studies using nuclear magnetic resonance spectroscopy have suggested that the abnormal skeletal muscle metabolism accompanying heart failure is not simply due to reduced blood flow and that intrinsic muscle abnormalities may be present. Skeletal muscle itself appears to be altered, as indicated by skeletal muscle taken at biopsy from patients with heart failure, in part due to deconditioning with reduction in oxidative capacity of working muscle. In keeping with these findings, several investigators have shown that interventions that improve hemodynamics do not necessarily alter exercise capacity immediately, and that improved functional capacity is time dependent. Thus, changes in exercise capacity (and VO₂max) may be in part related to peripheral mechanisms.

Recent experimental and clinical studies suggest that reduced arterial driving pressure during exercise may contribute to muscle underperfusion in nonedematous heart failure, contrary to the widespread belief that neurohumoral factors and vascular stiffness (“increased vascular resistance”) are involved. In fact, arterial blood pressure during exercise was significantly lower in the heart failure group (as compared with the control group) in our study. This, in turn, may have evoked baroreceptor-mediated regional vasoconstriction within skeletal muscle, thereby causing a significant redistribution of blood flow among and within skeletal muscle of the heart failure group. Thus, vasoconstrictor mechanisms may be “regionally” active within working muscle in heart failure, causing a distinctive muscular blood flow distribution, although systemic or total femoral vascular resistance is not increased. Failure of pharmacologic interventions such as α-adrenergic blockade and converting-enzyme inhibition to alter total femoral flow or metabolism immediately may not indicate that excessive sympathetic activation or angiotensin II do not contribute to the pattern of muscular blood flow distribution. As a matter of fact, total skeletal flow was not significantly altered by milrinone in the present study, although
important effects of this pharmacologic intervention on skeletal muscle flow distribution occurred.

Limitations of the study. The quantitative composition and enzyme activities of skeletal muscle fiber types in man differ somewhat from the features observed in rodents. Thus, the present detailed studies of blood flow distribution in rats should provide clinically important insight regarding distribution and control of blood flow within skeletal muscle in patients with heart failure as well as information about how drugs may interfere in this setting.

In conclusion, the present study demonstrated a distinctive muscular blood flow distribution during exercise in experimental heart failure. It appears that skeletal muscle underperfusion emerges predominantly in oxidative working muscle fibers, and therefore early recruitment of glycolytic fibers may occur, leading to increased lactate levels in the early stages of exercise. Significant blood flow redistribution among and within working muscle can be present without changes in total femoral or total skeletal muscle blood flow. Pharmacologic intervention with milrinone alters the pattern of skeletal muscle blood flow distribution. In particular, milrinone improves flow to oxidative muscle fibers in rats with heart failure, which may indicate that it would increase nutritional flow and VO$_2$max after the prolonged therapy observed in clinical studies.

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