Effect of hydralazine on perfusion and metabolism in the leg during upright bicycle exercise in patients with heart failure

John R. Wilson, M.D., Jack L. Martin, M.D., Nancy Ferraro, R.N., and Karl T. Weber, M.D.

ABSTRACT The aerobic exercise capacity of patients with chronic heart failure is frequently impaired because of inadequate O2 transport to working skeletal muscle. To determine whether hydralazine improves O2 transport to working muscle, we examined the effect of intravenous hydralazine on blood flow (measured by thermodilution) and metabolism in the leg during maximal upright bicycle exercise in 10 patients with chronic heart failure. Hydralazine increased maximal exercise cardiac output (5.6 ± 0.7 to 6.7 ± 0.6 l/min; p < .01) and decreased systemic O2 extraction (79 ± 3% to 65 ± 2%; p < .01) but did not alter maximal O2 uptake (787 ± 105 vs 779 ± 82 ml/min). Leg blood flow at maximal exercise increased from 1.6 ± 0.2 to 2.1 ± 0.4 l/min (p < .03); the proportion of cardiac output delivered to the leg remained unchanged (59 ± 3% vs 57 ± 9%). This increase in flow was associated with a decrease in O2 extraction in the leg (84 ± 2% to 79 ± 2%; p < .01) and no change in peak femoral venous lactate (59.1 ± 7.4 vs 54.1 ± 5.3 mg/dl), suggesting that there is functional or anatomic shunting of the augmented limb flow rather than delivery to metabolizing muscle. These data suggest that hydralazine augments flow to the exercising limb in patients with heart failure but that this augmented flow does not increase oxygen availability within working muscle.


THE AEROBIC exercise capacity of patients with chronic stable heart failure is frequently impaired.1-3 Recent studies from our laboratory3 and by other investigators4-5 have demonstrated that this impairment in exercise capacity is characteristically associated with increases in systemic lactate concentration and marked O2 extraction, suggesting that there is inadequate O2 availability in exercising skeletal muscle. Studies of blood flow in the forearm during forearm exercise have also shown a markedly attenuated rise in blood flow in patients with heart failure.6-7 Consequently, it has been assumed that the impaired aerobic exercise capacity of such patients is caused by inadequate O2 transport to working skeletal muscle.2-7

Smooth muscle vasodilators such as hydralazine have been shown to increase both resting and exercise cardiac output6,9 and blood flow in the resting limb10 in patients with chronic heart failure. Hydralazine has therefore been viewed as a potentially attractive pharmacologic method of enhancing skeletal muscle O2 transport during exercise in patients with heart failure and thereby of improving their aerobic exercise capacity.8,9

However, whether hydralazine actually improves skeletal muscle blood flow during exercise has not been determined. Moreover, even if hydralazine dilates muscle arterioles during exercise and thereby increases muscle blood flow, muscle O2 availability may not be improved. Tissue O2 delivery is determined by the distribution of capillary flow.11 Previous studies in isolated skeletal muscle preparations suggest that vasodilators can dilate resistance vessels without improving the distribution of capillary flow and tissue O2 delivery.11-13

Accordingly, this study was undertaken to investigate whether hydralazine improves skeletal muscle O2 delivery during upright bicycle exercise in patients with chronic heart failure. Blood flow in the leg, measured with the thermodilution principle, was used to investigate changes in skeletal muscle blood flow. Sampling of femoral venous effluent for O2 content
and lactate concentration was used to assess changes in O2 availability in skeletal muscle.

Methods

Patients. Ten patients (nine men and one woman; mean age 59 ± 9 years) with chronic left ventricular dysfunction (ejection fraction 19 ± 7%) were studied. All patients had histories of exertional breathlessness and/or fatigue despite administration of digoxin and diuretics and were without peripheral edema or ascites at the time of study. No patient had intermittent claudication or reduced pulses in the legs. Each patient had a reduced maximal O2 uptake (VO2max) below the expected normal response (≥ 20 ml/min/kg),3 with an average of 12.3 ± 3.9 ml/min/kg (range 5.3 to 15.4). Left ventricular dysfunction was attributed to coronary artery disease in eight patients, all of whom had sustained large myocardial infarctions, and to idiopathic congestive cardiomyopathy in two patients. The protocol was reviewed and approved by the Human Investigation Review Committee of our institution, and all patients gave written informed consent to the study.

Protocol. On the day before study, a trial maximal exercise test was performed to acquaint the patient with the exercise protocol. Patients exercised on an upright bicycle ergometer (Monarch), starting at a workload of 20 W. Every 3 min the workload was increased by 20 W until symptoms prevented further exercise. All exercise tests were performed at least 4 hr after meals.

The following morning, a Swan-Ganz catheter was inserted via an antecubital vein and positioned in the pulmonary artery. A short polyethylene catheter was inserted in a radial artery. A No. 5F thermidilution catheter was inserted percutaneously into a femoral vein and advanced 15 to 16 cm anterograde into the iliac vein.

Thirty minutes after instrumentation, hemodynamic values were determined and blood samples were obtained from the radial artery and femoral vein for measurement of oxygen saturation and lactate concentration and from the pulmonary artery for measurement of oxygen saturation. Femoral venous blood flow was measured in triplicate. Respiratory gases were measured with a Beckman Metabolic Cart equipped with O2 and CO2 analyzers and a turbine volume transducer. The patient then mounted the bicycle and was allowed to equilibrate for 5 min, after which all measurements were repeated.

The patient then began exercise according to the protocol described above. Respiratory gas measurements were taken continuously. Blood sampling and hemodynamic measurements were repeated at the end of each exercise stage and at peak exercise.

After exercise was terminated, the patient was allowed to rest for 2 hr. Hydralazine was then administered intravenously in 5 to 10 mg increments every 15 min until the cardiac output increased ≥ 30% or until the systolic blood pressure was reduced to below 100 mm Hg. The total hydralazine dose averaged 32 ± 12 mg (range 15 to 60). The exercise protocol was then repeated. In all patients, measurements were repeated at the same times as during control exercise. Two patients were able to exercise slightly longer after hydralazine administration, and additional measurements were made at peak exercise in these patients.

Methodologic studies. Femoral vein flow was measured with a 50 cm No. 5F thermidilution catheter (with the thermistor at 2 cm and injection port at 12 cm), a thermidilution computer, and a 2.5 ml bolus of iced dextrose. This system was initially evaluated in a closed-loop system in which 37° C water was continuously circulated through 7 mm polyethylene tubing by a roller pump. Flow determined with the thermidilution system correlated closely with known flow rates (0.2 to 6.0 l/min; r = .99) (figure 1). This correlation was not significantly altered by variation of the injection port–thermistor distance from 10 to 25 cm.

The catheter was then introduced percutaneously into the femoral vein and advanced 15 to 16 cm into the iliac vein in six patients with heart failure and in seven patients without heart failure. Resting flows were 0.23 ± 0.04 l/min in patients with heart failure vs 0.39 ± 0.17 l/min in patients without heart failure (p < .05), whereas corresponding cardiac outputs were 2.9 ± 0.7 and 5.3 ± 0.6 l/min, respectively (p < .01). Eight patients with heart failure and three without (two mild mitral stenosis and one moderate aortic regurgitation) then performed progressive upright bicycle exercise according to the protocol described above. In each patient, a close correlation was observed between flow to the leg and systemic VO2 and between VO2 of the leg and systemic VO2 (figure 2).

The coefficient of variation of duplicate flow measurements made sequentially during the same exercise test was 9 ± 10% at rest and 16 ± 12% during exercise (± SD). This variation is in part due to normal phasic alterations in flow. Therefore flow measurements were routinely made very 30 sec after the first 30 sec of an exercise stage. Measurements at any given stage were then averaged. In three patients, two exercise tests were performed on the same day to evaluate the reproducibility of such averaged flow measurements. Average flow measurements taken during the second exercise test were within 18 ± 10% of those taken during the first test (n = 11). Nine of the 11 measurements were within ± 22% of flow measurements made during the first test.

The measured leg blood flow levels in this study are comparable to those reported for other methods.14,15 The validity of the thermidilution technique to measure blood flow in the leg during upright bicycle exercise has also been confirmed by other investigators.16

Measured variables. Hemoglobin concentration was measured with a Coulter counter; hemoglobin O2 saturation was measured with a co-oximeter (Instrumentation Laboratories) precalibrated with human blood. Blood O2 content was calculated as the product of hemoglobin, 1.34 ml O2/g of hemoglobin, and percent O2 saturation. O2 extraction was calculated as the ratio of the arteriovenous O2 difference and arterial O2 content. Cardiac output was calculated from the Fick principle as VO2max/arteriovenous O2 difference. Vascular resistance in the leg was calculated as (arterial pressure minus femoral venous pressure)/leg blood flow (unit, U). O2 consumption was calcu-
Results

The effect of hydralazine on systemic and regional parameters are summarized in tables 1 and 2 and illustrated in figures 3 to 6.

Control systemic hemodynamic and metabolic measurements (figures 3 and 4). With patients at supine rest, the cardiac output was 3.2 ± 0.3 l/min, pulmonary wedge pressure was 22 ± 3 mm Hg, and systemic O₂ extraction was 43 ± 3%, consistent with left ventricular pump dysfunction. When patients mounted the bicycle, both the cardiac output and pulmonary wedge pressures dropped slightly to 3.0 ± 0.3 l/min and 18 ± 3 mm Hg, respectively. Patients exercised to exhaustion for an average of 6 ± 1 min to a VO₂ max of 787 ± 105 ml/min (VO₂ max = 12.3 ± 1.2 ml/min/kg). Exercise increased the cardiac output to 5.6 ± 0.7 l/min and the pulmonary wedge pressure to 29 ± 3 mm Hg. At the termination of exercise, systemic O₂ extraction was 79 ± 3% because of a decrease in mixed venous O₂ content; arterial O₂ content remained constant or increased slightly with exercise. Exercise increased arterial lactate concentration from 12.8 ± 1.3 mg/dl to 38.0 ± 4.8 mg/dl, consistent with the presence of anaerobic metabolism.

Effects of hydralazine on systemic O₂ transport (figures 3 and 4). Administration of intravenous hydralazine increased the resting cardiac output from 3.2 ± 0.3 to 5.3 ± 0.3 l/min (p < .01) while decreasing systemic O₂ extraction from 43 ± 3% to 27 ± 2% (p < .01). When patients reached peak exercise, the cardiac output increased from 5.6 ± 0.7 to 6.7 ± 0.6 l/min (p < .01) while systemic O₂ extraction decreased from 79 ± 3% to 65 ± 2% (p < .01). VO₂ max was unchanged (control, 787 ± 105 ml/min; hydralazine, 779 ± 82 ml/min) as was the peak pulmonary wedge pressure (control, 29 ± 3 mm Hg; hydralazine, 25 ± 2 mm

![Figure 2: Relationship between systemic VO₂ max and leg blood flow during progressive upright exercise in three control patients and eight patients with heart failure (HF).](http://circ.ahajournals.org/doi/10.1161/01.CIR.68.2.827)

**TABLE 1**

Effects of hydralazine on systemic hemodynamic and metabolic parameters

<table>
<thead>
<tr>
<th></th>
<th>HR (bpm)</th>
<th>BP (mm Hg)</th>
<th>CO (l/min)</th>
<th>PWP (mm Hg)</th>
<th>VO₂ (ml/min)</th>
<th>O₂ extraction (%)</th>
<th>Lactate (mg/dl)</th>
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<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Supine rest</td>
<td>82 ± 4</td>
<td>81 ± 3</td>
<td>3.2 ± 0.3</td>
<td>22 ± 3</td>
<td>235 ± 6</td>
<td>43 ± 3</td>
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<tr>
<td>Bike</td>
<td>85 ± 5</td>
<td>81 ± 3</td>
<td>3.0 ± 0.3</td>
<td>18 ± 3</td>
<td>254 ± 15</td>
<td>52 ± 3</td>
<td>12.8 ± 1.3</td>
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<tr>
<td>Submaximal exercise</td>
<td>95 ± 6</td>
<td>90 ± 3</td>
<td>5.9 ± 0.4</td>
<td>24 ± 4</td>
<td>731 ± 61</td>
<td>68 ± 4</td>
<td>22.0 ± 2.4</td>
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<tr>
<td>Peak exercise</td>
<td>113 ± 7</td>
<td>103 ± 6</td>
<td>5.6 ± 0.7</td>
<td>29 ± 3</td>
<td>787 ± 105</td>
<td>79 ± 3</td>
<td>38.0 ± 4.8</td>
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<td>Hydralazine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Supine rest</td>
<td>85 ± 4</td>
<td>74 ± 3</td>
<td>5.3 ± 0.3</td>
<td>17 ± 2</td>
<td>239 ± 7</td>
<td>27 ± 2</td>
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<tr>
<td>Bike</td>
<td>87 ± 3</td>
<td>75 ± 3</td>
<td>4.6 ± 0.3</td>
<td>15 ± 1</td>
<td>270 ± 17</td>
<td>35 ± 2</td>
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<td>Submaximal exercise</td>
<td>99 ± 5</td>
<td>83 ± 5</td>
<td>6.9 ± 0.5</td>
<td>19 ± 3</td>
<td>718 ± 84</td>
<td>56 ± 3</td>
<td>22.7 ± 1.3</td>
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<tr>
<td>Peak exercise</td>
<td>110 ± 6</td>
<td>96 ± 5</td>
<td>6.7 ± 0.6</td>
<td>25 ± 2</td>
<td>779 ± 82</td>
<td>65 ± 2</td>
<td>37.3 ± 3.5</td>
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</table>

Statistical comparisons (vs control): ^p < .05; ^p < .01.
Hg). Two patients were able to exercise longer after hydralazine administration but did not have increased VO₂max above control values. Maximal lactate levels during exercise were also unchanged (control, 38.0 ± 4.8 mg/dl; hydralazine, 37.3 ± 3.5 mg/dl).

Control leg blood flow and metabolic measurements (figures 5 and 6). With patients at supine rest, blood flow was 0.25 ± 0.02 l/min, VO₂ was 18.4 ± 2.4 ml/min, vascular resistance was 286 ± 21 U, and O₂ extraction was 42 ± 4%. When patients mounted the bicycle, vascular resistance increased, associated with an increase in VO₂max to 23.2 ± 1.5 ml/min and in O₂ extraction to 63 ± 3%. There was a small but significant amount of lactate output from the leg, with a positive lactate gradient across the leg of 1.9 ± 0.6 mg/dl. Seven of the 10 patients exhibited gradients greater than 1.0 mg/dl.

With exercise, blood flow increased progressively to a peak of 1.55 ± 0.19 l/min, whereas vascular resistance decreased to 55 ± 7 U. Leg VO₂ increased to 229 ± 30 ml/min, mediated by both the increase in flow and an increase in O₂ extraction to 84 ± 2%. Femoral venous lactate levels increased from 14.7 ± 1.6 to 59.1 ± 7.4 mg/dl whereas the femoral-arterial lactate difference increased from 1.9 ± 0.6 to 21.4 ± 3.7 mg/dl, reflecting augmented anaerobic activity in the leg.

Effect of hydralazine on leg blood flow and metabolism (figures 5 and 6). Administration of hydralazine increased the supine resting blood flow from 0.25 ± 0.02 to 0.43 ± 0.05 l/min (p < .01); calculated leg VO₂ remaining unchanged. Vascular resistance decreased from 286 ± 21 to 174 ± 24 U (p < .01). When patients mounted the bike, O₂ extraction remained lower than that during control exercise (43 ± 4%), whereas blood flow declined toward control levels. Lactate gradients across the leg were comparable to the control gradients.

Hydralazine increased peak blood flow from 1.55 ± 0.19 to 2.14 ± 0.37 l/min (p < .03) because of a reduction in vascular resistance from 55 ± 7 to 42 ± 8 U (p < .03). O₂ extraction at peak exercise decreased from 84 ± 2% to 79 ± 2% (p < .01). Peak calculated leg VO₂ increased from 229 ± 30 to 291 ± 50 ml/min (p < .03) because of the increase in blood flow. However, only five patients exhibited an increase in leg VO₂. Three patients had no change in leg VO₂, while one patient had a modest decrease. Hydralazine did not affect the rate of increase or peak femoral venous lactate concentration (control, 59.1 ± 7.4 mg/dl; hydralazine, 54.1 ± 5.3 mg/dl), the femoral-arterial lactate difference, or the lactate output.

Regional distribution of blood flow (figure 5). With patients at supine rest before hydralazine administration, total blood flow in the leg was 18 ± 3% of the total cardiac output. This proportion did not change when the patient mounted the bicycle. Blood flow increased to 59 ± 3% of the cardiac output at peak exercise, consistent with a redistribution of flow to the legs during exercise. Administration of hydralazine did not significantly alter the proportion of flow to the legs.

Discussion

In the present study, we combined measurements of femoral venous flow determined by the thermodilution principle with sampling of femoral venous effluent to investigate the effect of hydralazine on perfusion and O₂ availability of working muscle. The thermodilution principle has been successfully applied previously by several investigators to the measurement of both fem-
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Figure 3. Effect of hydralazine on cardiac output and pulmonary wedge pressure (PWP) responses to exercise. The apparent drop of the cardiac output from submaximal to maximal exercise is caused by inclusion of submaximal data from only six patients, not to a plateau of the cardiac output response. Significant differences between control and hydralazine data are noted by asterisks.

Figure 4. Effect of hydralazine on systemic VO₂max, systemic O₂ extraction, and arterial lactate concentrations. Significant differences between control and hydralazine data are noted by asterisks.

oral venous and femoral arterial blood flow in exercising subjects. The main advantage of this approach is that it permits repeated measurements of flow during continuous exercise and during exercise with large muscle groups. This is not possible with the plethysmographic technique previously used to study limb blood flow in patients with heart failure. One disadvantage common to both approaches, however, is that they measure flow from nonexercising tissue as well as from exercising muscle. Therefore, when the patient is at rest and flow from nonmuscular tissue makes up a significant proportion of femoral venous flow, this technique provides only a general estimate of muscle flow. However, femoral venous flow during exercise should provide a reliable index of flow to working muscle, since flow to nonexercising tissue either does not change or decreases with exercise.

A second potential shortcoming relates to the use of combined flow and venous effluent measurements to assess O₂ uptake in the leg during exercise. Femoral venous effluent samples may not necessarily assess venous drainage from the same total muscle mass.
tributing to the leg blood flow measurement. This could occur, for example, if the sampling port is close to a sizable vein draining into the femoral or iliac vein. In addition, flow measurement represent the average of measurements made over 3 min, whereas O$_2$ extraction is measured only once every 3 min; changes in O$_2$ extraction occurring during the 3 min are not taken into account in the calculation of O$_2$ uptake. These two factors could result in modest quantitative errors in calculated O$_2$ uptake in the leg. Nevertheless, femoral venous flow and effluent measurements provide useful information concerning directional changes in blood flow, O$_2$ extraction, and anaerobic activity in muscle.

The results of this study indicate that hydralazine significantly decreases resting leg vascular resistance and increases resting leg blood flow in patients with heart failure. This finding is consistent with the direct vasodilatory effect of hydralazine on vascular smooth muscle. In addition, this finding confirms previous results obtained by plethysmographic techniques in patients with heart failure.\textsuperscript{10}

Of more importance, this study also demonstrates that hydralazine significantly increases blood flow in the leg during exercise. It is likely that this augmented limb flow primarily reflects increased flow to skeletal muscle, since, as mentioned above, almost all of the increase in limb blood flow that occurs during exercise in caused by arteriolar vasodilation in muscle.\textsuperscript{20} Moreover, experimental animal studies have demonstrated that hydralazine increases blood flow to skeletal muscle.\textsuperscript{21} The increase in limb blood flow may be the result of accentuation of the normal metabolic vasodilation produced by exercise. Alternatively, hydralazine may improve blood flow in the leg by counteracting abnormal local vasoconstrictor influences. In patients with heart failure, exercise is associated with excessive sympathetic activity and elevated concentrations of circulating norepinephrine, angiotensin II and vasopressin.\textsuperscript{22, 23} These neurohumoral abnormalities may impair exercise-induced vasodilation of muscle arterioles.\textsuperscript{23-25}

The increase in flow to the working leg produced by hydralazine does not, however, appear to increase O$_2$ availability in working muscle. During control exercise, maximal systemic O$_2$ uptake was reduced in association with high femoral venous lactate concentrations and marked O$_2$ extraction by the leg, suggesting that there is impaired O$_2$ delivery to working muscle. Administration of hydralazine did not increase systemic O$_2$ uptake or reduce femoral venous lactate concentrations either at submaximal or maximal workloads. Moreover, hydralazine produced a reduction in limb O$_2$ extraction, further suggesting that the O$_2$ delivered by the increased limb flow was not made available to ischemic muscle.

Our observation that hydralazine did not alter lactate release during exercise is consistent with prior studies from this laboratory. We have examined the effect of hydralazine on brachial venous lactate and O$_2$ content during forearm exercise in patients with heart failure.\textsuperscript{26} Brachial venous lactate during exercise was not sig-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Effect of hydralazine on blood flow, vascular resistance, and the percentage of cardiac output delivered to the leg. Significant differences between control and hydralazine data are noted by asterisks.}
\end{figure}
significantly changed. In contrast to the present study, however, O2 extraction by the forearm was also unchanged. This difference probably reflects the form of exercise used. The forearm exercise protocol consisted of intermittent isometric exercise, whereas bicycle exercise is dynamic. Isometric exercise results in substantially more compression of arterial vessels than does dynamic exercise, and this compression may have counteracted the vasodilatory effects of hydralazine.

The failure of hydralazine to alter O2 availability in working muscle while producing a decrease in O2 extraction suggests that hydralazine causes functional shunting of blood within working muscle. This could occur if hydralazine causes a maldistribution of capillary flow within working muscle. Alternatively, capillary flow to ischemic muscle may be enhanced without an increase in cellular O2 uptake caused by a defect in O2 extraction and/or utilization.

There is considerable experimental evidence to support the concept that vasodilators can dilate resistance vessels without improving O2 delivery to working muscle. Isoproterenol, a vasodilator by virtue of its β2-agonist activity, and acetylcholine have both been shown to improve flow to isolated skeletal muscle either without altering or actually impairing O2 availability at a cellular level.

The only evidence provided by this study that hydralazine may improve O2 delivery to working muscle is the significant increase in calculated leg O2 uptake observed after hydralazine administration. However, an increase in O2 uptake was observed in only five patients and was not accompanied by any other evidence of improved O2 delivery. As noted above, calculated leg O2 uptake is subject to more errors than measurement of arteriovenous lactate differences, leg O2 extraction and systemic VO2 max. Therefore, leg O2 uptake may not have been significantly increased by hydralazine. Nevertheless, we cannot exclude the possibility that hydralazine improves leg O2 uptake in a
subgroup of patients but that systemic VO_2 max is not improved because of a reduction in oxygen uptake by nonexercising tissues.

The fractional distribution of cardiac output to the leg during rest and exercise was unchanged by hydralazine. Therefore hydralazine does not appear to preferentially increase flow to working muscle vs nonworking tissue. Magorien et al. have also previously noted in patients with heart failure that hydralazine increases resting limb, renal, and hepatic blood flow in proportion to the increase in cardiac output.

The failure of hydralazine to augment O_2 availability in working muscle in patients with chronic heart failure suggests that direct smooth muscle vasodilators may not be useful in the treatment of exercise intolerance in patients with chronic heart failure. This conclusion is supported by the results of recent studies, which have failed to demonstrate a short-term effect of hydralazine on exercise capacity in patients with heart failure. In fact, it could be argued that an agent that produces substantial vascular shunting places a volume load on the failing ventricle and thereby could accelerate the rate of deterioration of ventricle function. It is possible that long-term administration of hydralazine enhances O_2 availability because of a readjustment in peripheral circulatory control. However, a recent study suggests that such improvement does not occur. Hopefully, vasodilators with other modes of action—α-adrenergic blocking agents and angiotensin II-converting enzyme inhibitors—and/or positive inotropic agents may augment O_2 availability in working muscle more effectively than direct smooth muscle vasodilators. Studies are currently underway in our laboratory to investigate this possibility.

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