

Effect of the Renin-Angiotensin System on Limb Circulation and Metabolism During Exercise in Patients With Heart Failure

JOHN R. WILSON, MD, NANCY FERRARO, RN

Philadelphia, Pennsylvania

The maximal aerobic exercise capacity of patients with chronic heart failure is frequently decreased because of inadequate blood flow to working skeletal muscle. To investigate whether this reduced flow is in part due to interference by angiotensin II with arteriolar dilation in working muscle, the effect of the angiotensin-converting enzyme inhibitor captopril on leg blood flow, leg vascular resistance, leg oxygen consumption ($\dot{V}O_2$) and leg lactate release during maximal upright bicycle exercise was examined in 12 patients with heart failure (maximal $\dot{V}O_2$ 10.7 ± 3.1 ml/min per kg). Captopril decreased leg resistance at rest (258 ± 115 to 173 ± 67 U, $p < 0.01$) and maximal exercise (68 ± 69 to 45 ± 29 U, $p < 0.01$)

associated with proportionately similar decreases in systemic vascular resistance. However, maximal exercise duration and maximal $\dot{V}O_2$ were unchanged and, at identical peak exercise work times, there was no improvement in leg blood flow (2.0 ± 0.9 to 2.0 ± 1.1 liters/min, $p = \text{NS}$), leg $\dot{V}O_2$ (261 ± 104 to 281 ± 157 ml/min, $p = \text{NS}$) or leg lactate release (269 ± 149 to 227 ± 151 mg/min, $p = \text{NS}$). These data suggest that, during exercise in patients with heart failure, angiotensin II does not interfere with blood flow to working skeletal muscle.

(*J Am Coll Cardiol* 1985;6:556-63)

Patients with chronic heart failure are frequently limited during maximal exercise even when they are asymptomatic at rest (1-4). Prior observations (1-7) indicate that this exercise intolerance is frequently due to a decrease in blood flow to working skeletal muscle with consequent muscular fatigue. Therefore, to develop therapeutic strategies for improving the maximal exercise capacity of patients with heart failure, it is important that the mechanism responsible for this decrease in blood flow to muscle be identified.

Previous observations suggest that impaired dilation of resistance vessels within working muscle may be an important contributor to this decreased muscle flow. We have noted (4) that leg vascular resistance does not decrease normally during maximal upright bicycle exercise in patients with severe heart failure. Zelis et al. (7) reported that forearm vascular resistance does not decrease normally during forearm exercise in patients with heart failure.

One potential contributor to impaired vasodilation in working muscle is the renin-angiotensin system. In patients with heart failure, the renin-angiotensin system is frequently more activated than in normal subjects at rest (8,9) and during exercise (10,11). Angiotensin II is a potent vasoconstrictor of skeletal muscle arterioles by a direct effect (12-14) and augmentation of sympathetically mediated vasoconstriction (15). Such vasoconstrictor influences could interfere with the metabolic vasodilation that normally plays a key role in augmenting blood flow to working muscles. The present study was undertaken to investigate this specific hypothesis and to investigate the contribution of the renin-angiotensin system to limb vascular resistance in patients with heart failure.

Methods

Patients. Twelve men with chronic left ventricular dysfunction (ejection fraction $18 \pm 9\%$) were studied. Their mean age was 58 ± 12 years. All patients had exertional breathlessness or fatigue, or both, despite administration of digoxin and diuretic drugs and all were classified in New York Heart Association functional class III. None had peripheral edema, ascites, angina pectoris, intermittent claudication or reduced pulses in his legs at the time of study. Before enrollment in this study, all patients were optimally

From the Cardiovascular Section, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania. This study was supported in part by Clinical Research Center Grant 5-M01-RR00040 from the National Institutes of Health, Bethesda, Maryland. Dr. Wilson is the recipient of New Investigator Award HL30665 from the National Institutes of Health. Manuscript received December 10, 1984; revised manuscript received February 13, 1985, accepted April 16, 1985.

Address for reprints: John R. Wilson, MD, Cardiovascular Section, Hospital of the University of Pennsylvania, 943 West Gates, 3400 Spruce Street, Philadelphia, Pennsylvania 19104.

diuresed by increasing diuretic drug dosage until evidence of fluid retention was gone or until mild prerenal azotemia was noted. All patients had a reduction in maximal oxygen uptake to less than 20 ml/min per kg (average 10.7 ± 3.1 , range 5.3 to 16.3 ml/min per kg). Left ventricular dysfunction was attributed to coronary artery disease in eight patients and to idiopathic dilated cardiomyopathy in four patients. No patient had received any vasodilator for at least 1 week. The protocol was approved by the Committee on Studies Involving Human Subjects at the University of Pennsylvania. Written informed consent was obtained from all subjects.

Protocol. On the day before study, a trial maximal exercise test was performed to acquaint the patient with the exercise protocol. Data accumulated from this trial test were discarded. Exercise was performed on an upright mechanically braked bicycle ergometer (Monarch) and begun at a work load of 20 W. Every 3 minutes the work load was increased by 20 W to symptomatic maximum. All exercise tests were performed at least 4 hours after the patient had eaten a meal.

The following morning, digoxin and diuretic drugs were withheld. A Swan-Ganz catheter was inserted by way of an antecubital vein and positioned in the pulmonary artery. A short polyethylene catheter was inserted in a radial artery. A 5F thermodilution catheter was inserted percutaneously into the left femoral vein and advanced 15 to 16 cm antero-gradely into the iliac vein.

Thirty minutes after instrumentation, hemodynamic measurements were made and blood samples were obtained from the radial artery and femoral vein catheters for oxygen saturation and lactate concentration. Femoral vein blood flow was measured in triplicate. Respiratory gases were measured with a Beckman Metabolic Cart equipped with oxygen and carbon dioxide analyzers and a turbine volume transducer. The patient then mounted the bicycle and, after a 5 minute equilibration period, measurements were repeated.

The patient then began exercise. Respiratory gas and hemodynamic measurements were made continuously. During each 3 minute exercise stage, leg blood flow was measured every 30 seconds starting at 30 seconds and continuing up to 2.5 minutes (total of five measurements). The average of these five measurements was then taken as the mean flow for the exercise stage. Blood sampling was performed during the last 30 seconds of the stage. Leg flow was not measured during this period.

Exercise after captopril. After exercise was terminated, the patient was allowed to rest for 1 hour. Captopril was then administered orally at a dose of 6.25 mg. At the end of 1 hour, repeat supine and upright hemodynamic measurements were made. If the upright systolic blood pressure was decreased by greater than 15 mm Hg, no further captopril was administered. After an additional 1 hour wait to

assure full recovery from the first exercise period, exercise was repeated. If the change in blood pressure was less than 15 mm Hg, an additional 18.75 mg dose of captopril was administered. Hemodynamic data were measured 1 hour after this second dose. If the upright systolic blood pressure was now decreased by greater than 15 mm Hg, exercise was repeated. If the blood pressure change was less than 15 mm Hg, an additional 25 mg dose of captopril was administered. One hour later, exercise was repeated. Total captopril dose averaged 20 ± 14 mg (6.25 mg for five patients, 25 mg for six patients and 50 mg for one patient). The time between the two exercise tests was 3 hours in 11 patients and 4 hours in the 1 patient who received 50 mg of captopril.

During the second exercise test, hemodynamic and metabolic measurements were made at exercise times identical to those during control exercise. If a patient exercised longer after captopril administration, measurements were also made at the new maximal exercise level.

After a single dose of captopril, blood levels and hemodynamic effects peak at 1 to 2 hours (16). Hemodynamic and free captopril levels then decrease progressively over 4 hours. Therefore, when multiple captopril doses are administered over 2 to 3 hours, the effect of the first dose may be dissipating as the effect of the last dose peaks. Hemodynamic measurements, therefore, were made every 30 minutes. At the time of the repeat exercise test, there was no evidence that the hemodynamic effects of captopril had peaked and begun to dissipate. Converting enzyme inhibition should have produced parallel reductions in angiotensin II. The circulating half-life of angiotensin II is approximately 1 minute, so that a steady state level of converting enzyme inhibition should produce a steady state angiotensin II level in a short time.

In three patients, leg blood flow was not measured during exercise because of technical difficulties. Femoral vein effluent, however, was measured in all patients both at rest and during exercise.

Leg blood flow. Leg blood flow was determined by the thermodilution method described by Jorfeldt et al. (17-19) and previously utilized by our laboratory (4,20,21). In brief, femoral vein flow was measured using a 50 cm 5F thermodilution catheter with the thermistor at 2 cm and injection port 12 cm from the tip. Flow was determined using rapid injection of a 2.5 ml iced dextrose bolus injectate and a commercially available thermodilution computer (Elecath). Output curves were displayed on a strip chart recorder to assure an exponential decay curve. Jorfeldt et al. (17) demonstrated that femoral vein flow measured using this technique agrees closely with leg flow determined using injection of indocyanine green into the femoral artery with sampling from the femoral vein.

In our laboratory, flow determined using the bolus in-

jectate technique correlated closely with known flow rates (0.2 to 0.6 liter/min, $r = 0.99$) evaluated using a closed loop system in which 37°C water was continuously circulated through 7 mm polyethylene tubing using a roller pump. In studies in humans, the coefficient of variation of duplicate flow measurements made sequentially in patients during the same exercise test was $9 \pm 10\%$ at rest and $16 \pm 12\%$ during exercise. The variation during exercise is expected given the normal phasic alterations in flow. Therefore, multiple flow measurements are always made during any given work load and the average flow is calculated. During each exercise test in this study, each patient had 13 to 20 leg blood flow measurements made resulting in administration of 32 to 50 ml of iced dextrose. Thermodilution cardiac output determination was not performed, so that the total amount of dextrose administered to each patient during the entire study was small.

Reproducibility studies. The period between exercise tests was at least 3 hours. To assure that exercise results are reproducible when repeated at this interval, reproducibility measurements were made in six patients. At peak exercise, the following key measurements were found to be reproducible: systemic oxygen consumption ($\dot{V}O_2$) ($1,041 \pm 553$ versus $1,000 \pm 526$ ml/min; first versus second exercise), arterial lactate (35.5 ± 9.4 versus 32.3 ± 9.5 mg/dl), leg flow (3.15 ± 1.40 versus 3.21 ± 1.57 liters/min), femoral vein lactate (44.6 ± 11.5 versus 43.9 ± 16.4 mg/dl) and leg arteriovenous oxygen difference (13.23 ± 1.34 versus 12.94 ± 1.72 ml/dl).

Measured variables. Hemoglobin concentration was measured by Coulter Counter; hemoglobin oxygen saturation was measured with a cooximeter (Instrumentation Laboratories) precalibrated with human blood. Blood oxygen content was calculated as the product of hemoglobin, 1.34 ml oxygen/g hemoglobin and percent oxygen saturation. Oxygen extraction was calculated as the ratio of the arteriovenous oxygen difference and arterial oxygen content. Cardiac output was calculated from the Fick principle as

systemic oxygen uptake/systemic arteriovenous oxygen difference. Systemic vascular resistance was calculated as mean blood pressure/cardiac output.

Leg vascular resistance was calculated as (arterial pressure - femoral vein pressure)/leg flow. Leg oxygen consumption ($\dot{V}O_2$) was calculated as the product of femoral vein flow and the arteriovenous oxygen difference across the leg. Blood for lactate determination was deproteinized with cold perchloric acid and assayed with a spectrophotometric technique (22). Normal values at rest for this technique in our laboratory are 3 to 12 mg/dl. Leg lactate release was calculated as leg blood flow \times (femoral vein - arterial lactate concentration). It should be noted that leg flow, oxygen extraction and lactate data were not obtained simultaneously. Therefore, calculation of leg oxygen uptake and lactate release assumes that leg flow remained relatively constant during exercise. In support of this assumption, we have observed that flow increases abruptly with the onset of exercise and stabilizes within 30 to 45 seconds.

Statistical methods. Values are presented as mean \pm SD. Differences between measurements at rest and maximal exercise were compared using the paired Student's *t* test for all variables except leg resistance. The distribution of leg resistances was nonparametric. Therefore, differences in this variable were compared using the rank sum test, the nonparametric analog of the paired *t* test. A probability of less than 0.05 was considered significant.

Results

The effect of captopril on systemic and regional variables is summarized in Tables 1 and 2 and illustrated in Figures 1 and 2. All the exercise data represent information accumulated at the highest exercise time common to both control and captopril exercise tests.

Effect of captopril at rest. At supine rest before the administration of captopril, the cardiac output was 3.6 ± 1.3 liters/min, pulmonary wedge pressure 24 ± 9 mm Hg,

Table 1. Effects of Captopril on Systemic Hemodynamic and Metabolic Responses to Exercise

	HR (beats/min)	BP (mm Hg)	CO (liters/min)	PWP (mm Hg)	SVR (U)	$\dot{V}O_2$ (ml/min)	Oxygen Extraction (%)	Lactate (mg/dl)
Control								
Supine	87 ± 11	90 ± 7	3.6 ± 1.3	24 ± 9	27 ± 10	253 ± 50	46 ± 12	—
Bicycle	99 ± 16	90 ± 7	3.4 ± 1.1	24 ± 11	29 ± 11	285 ± 58	55 ± 11	12 ± 3
Peak exercise‡	122 ± 15	99 ± 10	5.8 ± 2.2	30 ± 9	20 ± 10	716 ± 189	77 ± 7	27 ± 9
Captopril								
Supine	85 ± 10	$75 \pm 10^\dagger$	$3.9 \pm 1.4^*$	$19 \pm 10^\dagger$	$22 \pm 10^\dagger$	259 ± 37	42 ± 9	—
Bicycle	94 ± 14	$77 \pm 10^\dagger$	3.4 ± 1.0	22 ± 11	$24 \pm 9^\dagger$	300 ± 47	55 ± 8	13 ± 3
Peak exercise‡	116 ± 16	$85 \pm 12^\dagger$	5.7 ± 2.0	$27 \pm 13^*$	$16 \pm 5^*$	702 ± 161	75 ± 6	25 ± 8

* $p < 0.05$ compared with control; $^\dagger p < 0.01$ compared with control; ‡ measured at the highest work time common to both control and captopril exercise. BP = blood pressure; CO = cardiac output; HR = heart rate; PWP = pulmonary wedge pressure; SVR = systemic vascular resistance; $\dot{V}O_2$ = oxygen uptake.

Table 2. Effects of Captopril on Leg Hemodynamic and Metabolic Responses to Exercise

	Leg Flow§ (liters/min)	Leg $\dot{V}O_2$ § (ml/min)	Leg Resistance§ (U)	Leg Oxygen Extraction (%)	Femoral Vein Lactate (mg/dl)	Venous-Arterial Lactate Difference (mg/dl)	Leg Lactate Release (mg/min)
Control							
Supine	0.3 ± 0.1	25 ± 8	258 ± 115	46 ± 15	—	—	—
Bicycle	0.3 ± 0.1	30 ± 14	340 ± 136	63 ± 10	14 ± 3	2 ± 2	8 ± 9
Peak exercise‡	2.0 ± 0.9	261 ± 104	68 ± 69	83 ± 6	41 ± 12	15 ± 6	269 ± 149
Captopril							
Supine	0.4 ± 0.1	22 ± 9	173 ± 67†	37 ± 17*	—	—	—
Bicycle	0.3 ± 0.2	35 ± 18	244 ± 92†	63 ± 10	14 ± 3	1 ± 1	5 ± 6
Peak exercise‡	2.0 ± 1.1	281 ± 157	45 ± 29†	83 ± 5	37 ± 9	12 ± 6	227 ± 151

*p < 0.05 compared with control; †p < 0.01 compared with control; ‡measured at the highest work time common to both control and captopril exercise; §leg flow, $\dot{V}O_2$ and resistance were measured in only 9 of the 12 patients.

systemic vascular resistance 27 ± 10 U, leg flow 0.3 ± 0.1 liters/min and leg vascular resistance 258 ± 115 U. Right atrial pressure was 8 ± 6 mm Hg. Administration of captopril decreased systemic resistance by $20 \pm 15\%$ to 22 ± 10 U ($p < 0.003$) and decreased leg resistance by $25 \pm 36\%$ to 173 ± 67 U ($p < 0.006$) (Fig. 1). This vasodilation was associated with an increase in the cardiac output to 3.9 ± 1.4 liters/min ($p < 0.03$ versus control) and a decrease in the pulmonary wedge pressure to 19 ± 10 mm Hg ($p < 0.005$ versus control) but with no change in leg blood flow.

On mounting the bicycle before administration of captopril, systemic vascular resistance increased from 27 ± 10 to 29 ± 11 U and leg resistance from 258 ± 115 to 340 ± 136 U. Administration of captopril decreased upright systemic and leg resistances to an extent proportional to that observed at supine rest, but did not decrease the upright pulmonary wedge pressure or increase the upright cardiac output.

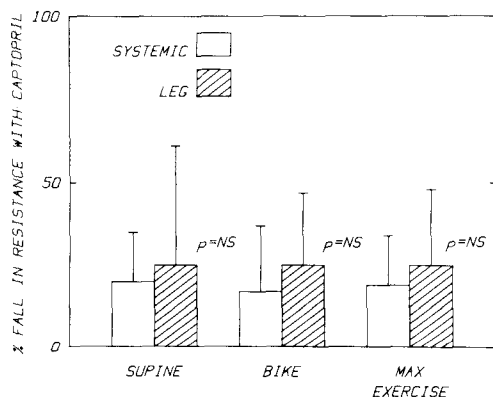
Effect of captopril during exercise. During control exercise, patients exercised for 4.1 ± 2.2 minutes to a maximal $\dot{V}O_2$ of 726 ± 213 ml/min. After captopril adminis-

tration, there was no significant change in either maximal $\dot{V}O_2$ (727 ± 186 ml/min) or maximal exercise duration (4.0 ± 1.7 minutes). Exercise duration was identical in nine patients, increased modestly in one and decreased in two.

To examine the effect of captopril on exercise data, variables were compared at the highest exercise time common to both tests. At this exercise point, captopril decreased systemic vascular resistance by $19 \pm 15\%$ (20 ± 10 to 16 ± 5 U, $p < 0.02$) and decreased leg resistance by $25 \pm 23\%$ (68 ± 69 to 45 ± 29 U, $p < 0.01$) (Fig. 1). Pulmonary wedge pressure was decreased from 30 ± 9 to 27 ± 13 mm Hg ($p < 0.02$). In contrast, there was no change in cardiac output, systemic $\dot{V}O_2$, arterial lactate, leg blood flow, leg $\dot{V}O_2$, leg oxygen extraction, femoral-arterial lactate difference or leg lactate release (Fig. 2).

Subgroup responses to captopril (Table 3). Systemic vascular resistance at the highest work time common to both tests was decreased by 20% or more in five and less than 20% in seven patients. In the five patients with a 20% or greater decrease in systemic resistance, there was no change in maximal $\dot{V}O_2$ (691 ± 247 to 747 ± 255 , $p = NS$). When compared at the highest work time common to both tests, captopril also produced no change in metabolic variables in either group.

Figure 1. Effect of captopril on systemic and leg vascular resistance. Exercise data were obtained at the highest exercise time common to both tests. MAX = maximal.



Discussion

Vasoconstrictor and vasodilator influences during exercise. Heart failure is accompanied by a reduction in blood flow to peripheral tissues both at rest and during exercise. This reduced flow leads to the recruitment of a number of compensatory vasoconstrictor mechanisms designed to protect the systemic blood pressure and redistribute blood flow to vital organs. These compensatory mechanisms include activation of the sympathoadrenal (23) and renin-angiotensin systems (8-11).

At rest, when peripheral tissue oxygen demands are small, activation of these vasoconstrictor mechanisms is largely

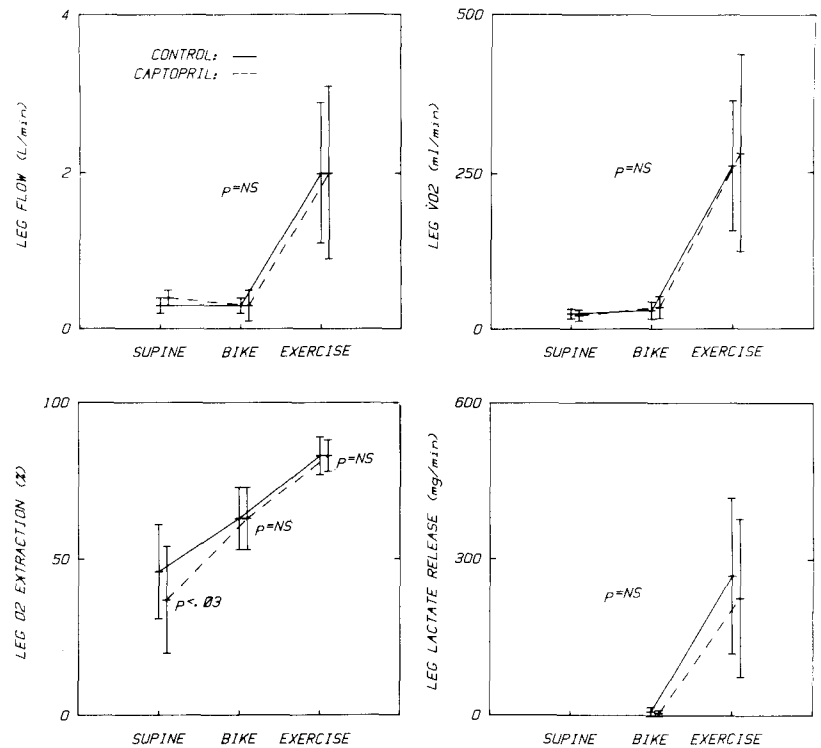


Figure 2. Effect of captopril on leg blood flow and metabolism. Exercise data were obtained at the highest exercise time common to both tests.

beneficial. During exercise, however, these vasoconstrictor mechanisms may be deleterious. Exercise further activates both the sympathoadrenal and renin-angiotensin systems in an attempt to sustain the blood pressure and redistribute flow most efficiently. From the standpoint of the blood flow to working skeletal muscle, this activation on the one hand serves to sustain muscle perfusion pressure, a key determinant of muscle flow. However, this activation also exerts vasoconstrictor influences on arterioles in working muscle and thereby may interfere with muscle vasodilation, the other key determinant of muscle flow.

The extent to which vasodilation is affected is determined by the balance between local vasodilatory factors and vasoconstrictor influences. Studies in humans and experimental animals (14,24,25) have shown that constrictor re-

sponses in muscle to sympathetic nerve activation, norepinephrine administration and angiotensin administration are attenuated during exercise by local vasodilatory factors. In normal subjects, the balance between these two competing influences is such that constrictor influences are markedly attenuated (24). However, abnormally high levels of vasoconstrictor activity, as occur in patients with heart failure, may be sufficient to interfere with metabolic vasodilation and thereby impair blood flow to working skeletal muscle (14,25,26).

Effect of the renin-angiotensin system on muscle vasodilation. In this study, we sought to determine whether the renin-angiotensin system interferes with blood flow to working skeletal muscle in patients with heart failure. Numerous prior observations suggest that the renin-angiotensin

Table 3. Comparison of Systemic and Regional Measurements at the Highest Exercise Work Time Common to Both Control and Captopril Exercise in Patients With a 20% or Greater Decrease in Systemic Vascular Resistance Versus Patients With a Less Than 20% Decrease

Decrease in Systemic Resistance	Systemic VO ₂ (ml/min)	Arterial Lactate (mg/dl)	Femoral-Arterial Lactate (mg/dl)	Leg Lactate Release (mg/min)
20% or greater (n = 5)				
Control	690 ± 246	28 ± 5	11.9 ± 4.4	198 ± 149
Captopril	691 ± 209	26 ± 9	9.4 ± 3.7	204 ± 166
Less than 20% (n = 7)				
Control	737 ± 147	26 ± 9	16.4 ± 5.9	378 ± 105
Captopril	712 ± 129	24 ± 8	14.0 ± 6.9	311 ± 64

All comparisons of control versus captopril data were not significant.

system is frequently more activated in such patients than in normal subjects. Plasma renin levels are frequently higher than normal at rest (8,9) and become even more elevated during exercise (10,11, Mark Creager, personal communication). Blockade of the renin-angiotensin system produces systemic vasodilation at rest and during exercise in such patients (27-30), further supporting the presence of vasoconstrictor influences mediated by angiotensin II. Finally, angiotensin II is known to be a potent vasoconstrictor of skeletal muscle arterioles by both a direct effect (12-14) and augmentation of sympathetically mediated vasoconstriction (15).

To determine whether the renin-angiotensin system interferes with blood flow to working skeletal muscle, we examined the effect of captopril, an angiotensin converting enzyme inhibitor, on leg resistance, leg blood flow and leg lactate release during maximal upright bicycle exercise. Leg resistance and blood flow were used as indexes of skeletal muscle resistance and flow, respectively; flow to nonmuscular tissue makes up only a small portion of leg blood flow during exercise (31). Systemic and leg oxygen uptake and leg lactate release were used as indexes of the adequacy of oxygen delivery to working muscle (32,33). To evaluate changes in these variables during exercise, the variables were compared at the highest work time common to both control and captopril exercise. Exercise level influences muscle blood flow and metabolism. Therefore, comparison of data at different work times would leave uncertain whether any change observed is due to captopril or differences in work load.

During control exercise, all patients developed metabolic changes suggesting impaired blood flow to working skeletal muscle. Specifically, patients were limited by fatigue at reduced maximal oxygen uptakes of 10.7 ± 3.1 ml/min per kg, the normal maximal oxygen uptake being greater than 20 to 25 ml/min per kg (34). The leg oxygen extraction and leg lactate release noted at maximal exercise were markedly increased above levels observed in normal subjects at comparable work loads (35,36). The limb vascular resistance noted at maximal exercise was also higher than levels observed by us in patients with normal exercise capacity (4), suggesting reduced limb vasodilation.

Administration of captopril reduced systemic and limb vascular resistance both at rest and during exercise. This vasodilation was accompanied by improved pump function at rest as evidence by a reduction in the pulmonary wedge pressure and increase in the cardiac output. However, we found no evidence that flow or metabolic responses to exercise were improved. Maximal exercise duration and maximal oxygen uptake were not increased and the arterial lactate response to exercise was not decreased. When measured at identical peak exercise times, cardiac output, leg blood flow, leg oxygen uptake and leg lactate release were all unchanged.

These findings reinforce prior observations indicating that the renin-angiotensin system frequently contributes to systemic vascular resistance both at rest and during exercise in patients with heart failure (27-30). This vasoconstrictor effect in turn supports the arterial blood pressure at rest and during exercise. Of greater interest, however, is that our findings suggest that this vasoconstrictor effect of the renin-angiotensin system does not interfere with blood flow to working skeletal muscle. If angiotensin II did interfere with muscle flow, one would expect that captopril would increase muscle flow and oxygen uptake and reduce muscle lactate release. These changes were not observed in either the total study group or the subgroup of patients with the greatest decrease in systemic vascular resistance with captopril and presumably, therefore, the highest angiotensin II levels. A prior study by Kugler et al. (30) also failed to demonstrate any acute change in maximal oxygen uptake after captopril administration in patients with heart failure.

The decrease in leg vascular resistance noted during exercise after captopril administration most likely represented an autoregulatory response on the part of active muscle. Captopril produced a substantial decrease in mean arterial pressure during exercise. Because muscle flow and muscle $\dot{V}O_2$ apparently remained constant, metabolic factors in working muscle most likely produced arteriolar dilation to keep muscle flow commensurate with muscle oxygen demand. The decrease in leg resistance may also at least in part have been due to a reduction in vasoconstriction in nonexercising tissues of the leg.

During exercise, the overall circulatory effect of the renin-angiotensin system in patients with severe heart failure is, therefore, probably not detrimental with respect to nutritional blood flow to skeletal muscle and may in some respects be beneficial. During exercise, this system helps to increase vascular resistance in nonexercising vascular beds and thereby optimize the perfusion pressure of exercising muscle. This beneficial systemic effect appears to occur without adverse regional effects on blood flow to working skeletal muscle.

Potential limitations. This conclusion must be viewed within the context of several potential limitations. The use of skeletal muscle glycolysis as a marker of blood flow to working muscle is supported by prior observations that reducing muscle flow augments glycolysis (32,33). Nevertheless, glycolysis occurs normally in well oxygenated working muscle and is affected by pH and substrate availability (37,38). We cannot totally exclude the possibility that changes in these other variables affected our results but doubt that such changes occur. Another limitation is that captopril inhibits an enzyme responsible for the degradation of bradykinin (39). Because bradykinin is a potent vasodilator, it is possible that accumulation of this hormone contributed to the observed effects of captopril. A further potential concern with captopril relates to the dosing sched-

ule utilized in this study. To avoid marked hypotension, we chose to administer captopril in sequential doses depending on the hemodynamic response rather than to administer a single fixed dose. This approach was taken to avoid marked hypotension, which would have precluded repeat exercise and, more important, might offset a potentially beneficial regional effect of converting enzyme inhibition by reducing muscle perfusion pressure. Therefore, it is possible that angiotensin-converting enzyme inhibition was not complete in all patients.

One last concern relates to our not having obtained plasma renin levels during exercise. An alternative approach to this study would have been to measure renin levels at rest and during exercise in patients with heart failure and then to perform studies only on those subjects who showed high renin levels during exercise. We elected not to take this approach for several reasons. First, prior investigators (8,9) have demonstrated that the hemodynamic response to captopril correlates with plasma renin levels. Second, it remains uncertain to what extent plasma renin activation during exercise provides a valid reflection of the impact of the renin-angiotensin system on the muscle vasculature. Angiotensin II has different vasoactive effects depending on vascular sodium content and adrenergic activity (13,15). Therefore, even normal angiotensin II levels may have adverse vasoconstrictor effects during exercise depending on the accompanying neurohumoral and vascular environment. In addition, measurement of renin levels during exercise may not necessarily reflect either systemic or local vascular angiotensin II levels. During the brief exercise periods undertaken in this study, a steady state of angiotensin may not have been achieved.

Clinical Implications

The maximal aerobic exercise capacity of patients with heart failure is frequently limited by reduced skeletal muscle blood flow. Therefore, to be able to design methods for improving the maximal exercise capacity of such patients, it is important to identify the mechanism responsible for this reduced flow. The present study suggests that direct interference by angiotensin II with vasodilation in working muscle is probably not an important contributor. Prior observations from our laboratory (2) suggest that the reduced cardiac output noted during exercise in patients with heart failure is also not a key contributor. Blood flow to working muscle is increased during exercise as a result of vasodilation within muscle coupled with augmentation of muscle perfusion pressure, produced by vasoconstriction in nonexercising tissues and an increase in cardiac output. Therefore, reduced flow to working skeletal muscle in patients with heart failure is probably due to an intrinsic impairment of vasodilation in muscle, impaired vasodilation produced by sympathetic nerve activation or an abnormality of blood

pressure regulation during exercise. Studies are needed to determine which of these abnormalities is operative. Studies will also be needed to clarify the factor or factors that produce the abnormality. In this regard, the renin-angiotensin system still may prove to contribute indirectly to altered muscle flow in heart failure.

In summary, this study suggests that the renin-angiotensin system contributes to systemic vascular resistance both at rest and during exercise in patients with severe heart failure but does not directly interfere with blood flow to working skeletal muscle.

References

1. Franciosa JA, Ziesche S, Wilen M. Functional capacity of patients with chronic left ventricular failure. Relationship of bicycle exercise performance to clinical and hemodynamic characterization. *Am J Med* 1979;67:460-6.
2. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982;65:1218-23.
3. Wilson JR, Ferraro N. Exercise intolerance in patients with chronic left heart failure: relation to oxygen transport and ventilatory abnormalities. *Am J Cardiol* 1983;51:1358-63.
4. Wilson JR, Martin JL, Schwartz D, Ferraro N. Exercise intolerance in patients with chronic heart failure: role of impaired skeletal muscle nutritive flow. *Circulation* 1984;69:1079-87.
5. Zelis R, Longhurst J, Capone RJ, Mason DT. A comparison of regional blood flow and oxygen utilization during dynamic forearm exercise in normal subjects and patients with congestive heart failure. *Circulation* 1974;50:137-43.
6. Longhurst J, Gifford W, Zelis R. Impaired forearm oxygen consumption during static exercise in patients with congestive heart failure. *Circulation* 1976;54:477-80.
7. Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. *J Clin Invest* 1968;47:960-70.
8. Levine TB, Cohn JN. Determinants of acute and long-term response to converting enzyme inhibitors in congestive heart failure. *Am Heart J* 1982;104:1159-64.
9. Cody RJ, Laragh JH. Use of captopril to estimate renin-angiotensin-aldosterone activity in the pathophysiology of chronic heart failure. *Am Heart J* 1982;104:1184-9.
10. Kirklin P, Grekin R, Ballor E, Das S, Pitt B. Neuroendocrine activation in response to exercise in congestive heart failure (abstr). *J Am Coll Cardiol* 1984;3:533.
11. Hesse B, Christensen NJ, Anderson ED. Renin release in relation to plasma noradrenaline during supine exercise in cardiac patients. *Acta Med Scand* 1978;204:185-9.
12. Wood JF. Peripheral venous and arteriolar responses to infusions of angiotensin in normal and hypertensive subjects. *Circ Res* 1961;9:768-72.
13. Abboud FM. Effects of sodium, angiotensin, and steroids on vascular reactivity in man. *Fed Proc* 1974;33:143-9.
14. Burcher E, Garlick D. Antagonism of vasoconstrictor responses by exercise in the gracilis muscle of the dog. *J Pharmacol Exp Ther* 1973;187:78-85.
15. Imai Y, Abe K, Seino M, et al. Captopril attenuates pressor responses to norepinephrine and vasopressin through depletion of endogenous angiotensin II. *Am J Cardiol* 1982;49:1537-9.
16. Cody RJ, Covit A, Schaefer G, Williams G. Captopril pharmacokinetics

- and the acute hemodynamic and hormonal response in patients with severe chronic congestive heart failure. *Am Heart J* 1982;104:1180-3.
17. Jorfeldt L, Jublin-Dannefelt A, Pernow B, Wassen E. Determination of human leg blood flow: a thermodilution technique based on femoral venous bolus injection. *Clin Sci Mol Med* 1968;54:517-23.
 18. Jorfeldt L, Wahren J. Leg blood flow during exercise in man. *Clin Sci* 1971;41:459-73.
 19. Wahren J, Saltin B, Jorfeldt L, Pernow B. Influence of age on the local circulatory adaptation to leg exercise. *Scand J Clin Lab Invest* 1974;33:79-86.
 20. Wilson JR, Martin JL, Ferraro N, Weber KT. Effect of hydralazine on perfusion and metabolism in the leg during upright bicycle exercise in patients with heart failure. *Circulation* 1983;68:425-32.
 21. Wilson JR, Martin JL, Ferraro N. Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: role of cardiac pump dysfunction as determined by the effect of dobutamine. *Am J Cardiol* 1984;53:1308-15.
 22. Weissman N, Pileggi VJ. Inorganic ions. In: Henry RJ, ed. *Clinical Chemistry, Principles and Techniques*. New York: Harper & Row, 1974:655.
 23. Francis GS, Goldsmith SR, Ziesche SM, Cohn JN. Response of plasma norepinephrine and epinephrine to dynamic exercise in patients with congestive heart failure. *Am J Cardiol* 1982;49:1152-6.
 24. Strandell T, Shepherd JT. The effect in humans of increased sympathetic activity on the blood flow to active muscles. *Acta Med Scand* 1967;472(suppl):146-67.
 25. Thompson LP, Mohrman DE. Blood flow and oxygen consumption in skeletal muscle during sympathetic stimulation. *Am J Physiol* 1983;245:H66-71.
 26. Flaim SF, Crede W, Beech A, Nellis SH, Zelis R. The effects of norepinephrine on active hyperemia in the canine gracilis muscle. *Circ Res* 1979;44:660-6.
 27. Faxon DP, Creager MA, Halperin JL, Gavras H, Coffman JD, Ryan TJ. Central and peripheral hemodynamic effects of angiotensin inhibition in patients with refractory congestive heart failure. *Circulation* 1980;61:925-30.
 28. Faxon DP, Halperin JL, Creager MA, Gavras H, Schick EC, Ryan TJ. Angiotensin inhibition in severe heart failure: acute central and limb hemodynamic effects of captopril with observations on sustained oral therapy. *Am Heart J* 1981;101:548-56.
 29. Awan NA, Evenson MK, Needham KE, Win A, Mason DT. Efficacy of oral angiotensin-converting enzyme inhibition with captopril therapy in severe chronic normotensive congestive heart failure. *Am Heart J* 1981;101:22-31.
 30. Kugler J, Maskin C, Frishman WH, Sonnenblick EH, LeJemtel TH. Regional and systemic metabolic effects of angiotensin-converting enzyme inhibition during exercise in patients with severe heart failure. *Circulation* 1982;66:1256-61.
 31. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev* 1974;54:75-159.
 32. Walker PM, Idstrom J, Schersten T, Bylund-Fellenius A. Metabolic response in different muscle types to reduced blood flow during exercise in perfused rat hindlimb. *Clin Sci* 1982;63:293-9.
 33. Bylund-Fellenius A, Walker PM, Elander A, Holm S, Holm J, Schersten T. Energy metabolism in relation to oxygen partial pressure in human skeletal muscle during exercise. *Biochem J* 1981;200:247-55.
 34. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973;85:546-62.
 35. Pirnay F, Lamy M, DuJardin J, Deroanne R, Petit JM. Analysis of femoral venous blood during maximal muscular exercise. *J Appl Physiol* 1972;33:289-92.
 36. Doll E, Keul J, Maiwald C. Oxygen tension and acid-base equilibria in venous blood of working muscle. *Am J Physiol* 1968;215:23-9.
 37. Connett RJ, Gayeski TEJ, Honig CR. Lactate accumulation in fully aerobic, working dog gracilis muscle. *Am J Physiol* 1984;246:H120-8.
 38. Holloszy JO, Booth FW. Biochemical adaptations to endurance exercise in muscle. *Ann Rev Physiol* 1976;18:273-91.
 39. Engel SL, Schaeffer TR, Gold BI, Rubin B. Inhibition of pressor effects of angiotensin I and augmentation of depressor effects of bradykinin by synthetic peptides. *Proc Soc Exp Biol Med* 1972;140:240-4.