Sympathetic Vasoconstriction During Exercise in Ambulatory Patients With Left Ventricular Failure

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In patients with heart failure, exercise is thought to increase sympathetic vasoconstrictor tone. To investigate the extent of this sympathetic activation, we studied the effect of maximal exercise on nonexercising vascular beds in 35 patients with left ventricular failure (ejection fraction, 21±8%; peak exercise oxygen uptake (VO₂), 12.3±3.5 ml/min/kg). In 28 patients, cardiac output and leg blood flow were measured during maximal upright bicycle exercise. Total flow to nonexercising tissue was then calculated as cardiac output—(2×leg flow). In seven patients and six normal subjects, forearm blood flow was measured during supine bicycle exercise before and after α-adrenergic blockade with intravenous phentolamine. Maximal upright exercise increased the vascular resistance of nonexercising tissue from 34±16 units at upright rest to 45±25 units (p<0.02) but did not affect total flow to nonexercising tissue (rest, 2.9±1.0; maximal exercise, 2.8±1.4 l/min; p=NS). Supine exercise had no significant effect on forearm blood flow or vascular resistance in the normal subjects. In the patients with heart failure, supine exercise increased forearm vascular resistance from 45±17 to 58±25 mm Hg/ml/min/100 ml (p<0.02), again with no change in tissue flow (rest, 2.4±0.1; maximal exercise, 2.4±0.9 ml/min/100 ml; p=NS). The increase in forearm vascular resistance was associated with only a modest increase in plasma norepinephrine levels (rest, 258±129; maximal exercise, 635±188 pg/ml) and was unaffected by prior administration of phentolamine. These findings suggest that exercise does not produce a major increase in sympathetic vasoconstrictor tone in ambulatory patients with left ventricular failure. (Circulation 1989;79:1021–1027)

During exercise, patients with left ventricular failure frequently exhibit greater-than-normal increases in plasma norepinephrine levels.1,2 It is generally believed that this rise reflects augmented sympathetic vasoconstrictor tone,1,2 which shunts blood away from nonexercising portions of the circulation to working skeletal muscle.3–9 In patients with severe exercise intolerance, it has been further speculated that the level of sympathetic vasoconstrictor activity may be sufficiently intense to impair arteriolar vasodilation in working skeletal muscle and thereby contribute to muscle underperfusion.5

There is a growing body of recent evidence, however, that raises the possibility that exercise produces considerably less sympathetic vasoconstriction than previously thought. Francis et al10 have pointed out that, relative to the strenuousness of exercise, plasma norepinephrine levels in patients with left ventricular failure are actually lower than in normal subjects. A number of investigators have observed that sympathetic reflex control of peripheral resistance vessels appears to be impaired by left ventricular failure. For example, attenuated forearm vasoconstrictor responses to orthostatic tilt and lower body negative pressure have been noted in patients with left ventricular failure.11–14 We have observed attenuated hindlimb vasoconstrictor response to lumbar chain stimulation in experimental heart failure.15 Others have demonstrated that elevated resting plasma norepinephrine levels in heart failure to a substantial extent reflect impaired norepinephrine uptake and therefore overestimate sympathetic vasoconstrictor activity.16,17

The present study was undertaken to investigate the degree to which exercise produces sympatheti-
cally mediated vasoconstriction in ambulatory patients with left ventricular failure. To this end, we 
examined the effect of maximal bicycle exercise on nonexercising vascular beds. We reasoned that if 
intense sympathetic vasoconstriction occurs during exercise, this vasoconstriction should reduce flow 
to nonexercising tissue. To assess nonexercising vascular bed flow and resistance, we measured leg 
flow and cardiac output responses to upright bicycle exercise. By subtracting leg blood flow from 
cardiac output, we were able to obtain an estimate of blood flow to nonexercising tissue. In a separate 
group of patients, we measured forearm blood flow and resistance during maximal supine leg exercise. 
Forearm measurements were repeated after α-adrenergic blockade with phentolamine to elucidate 
the extent to which vasoconstrictor effects were due to sympathetic activation.

Methods

Patient Population

Thirty-five patients with a mean age of 57±10 
years and an average left ventricular ejection frac-
tion of 21±8% were studied. Left ventricular dys-
function was attributed to coronary artery disease 
in 18 patients, to an idiopathic cardiomyopathy in 
12, and to a hypertensive cardiomyopathy in five. 
All patients had a reduced maximal exercise capacity 
(peak exercise oxygen uptake [VO₂] <20 ml/min/kg), 
with an average peak exercise VO₂ of 12.3±3.5 ml/
min/kg. All patients were also receiving chronic ther-
apy with digoxin. However, to avoid digitalis-induced 
vasoconstriction and changes in baroreceptor behav-
ior,13,18–20 digoxin was discontinued 7 days prior 
to studies in all seven patients who underwent fore-
arm blood flow studies. Vasodilator therapy was 
discontinued at least 3 days prior to studies. Forearm 
studies were also performed in six normal male sub-
jects with a mean age of 53±5 years. The protocol was 
approved by the Institutional Research Committee of 
the University of Pennsylvania, and written consent 
for the protocol was obtained from all subjects.

Upright Exercise Protocol

On the day before study, a trial maximal exercise 
test was performed to acquaint the patient with the 
exercise protocol. Exercise was performed on an 
upright bicycle ergometer (Monarch, Varberg, 
Sweden), beginning 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 meals.

The following morning a Swan-Ganz catheter was 
inserted through an antecubital vein and positioned 
in the pulmonary artery. A short polyethylene cath-
eter was inserted into a radial artery. A 5F ther-
modilution catheter was inserted percutaneously 
into the left femoral vein and advanced 15–16 cm 
anterograde into the iliac vein to measure leg blood 
flow, as previously described.21,22

Thirty minutes after instrumentation, hemody-
namic measurements were made and blood samples 
were obtained from the radial artery, femoral vein, 
and pulmonary artery for determination of O₂ satu-
ration. Femoral venous blood flow was measured in 
triplicate. After rapid injection of a 2.5-ml iced 
dextrose bolus, flow was determined by a commer-
cially available thermodilution computer (Elecath, 
Rahway, New Jersey). Output curves were dis-
played on a strip-chart recorder to ensure an expen-
tential decay curve. Respiratory gases were mea-
sured 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 minutes, after 
which all measurements were repeated.

Respiratory gas measurements were made contin-
uously while the patient exercised. Blood sampling 
and hemodynamic measurements were repeated at 
the end of each exercise stage and at peak exercise.

Hemoglobin concentration was measured by Coul-
ter counter, and hemoglobin O₂ saturation was 
measured with a co-oximeter (Instrumentation Lab-
oratories, Lexington, Massachusetts) precalibrated 
with human blood. Blood O₂ content was calculated 
as the product of hemoglobin, 1.34 ml O₂/g hemo-
globin, and percent O₂ saturation. Cardiac output 
was calculated from the Fick principle as VO₂/
arteriovenous O₂ difference. Non-leg blood flow 
was calculated as cardiac output—(2×leg flow). 
Non-leg vascular resistance was calculated as (mean 
arterial blood pressure)/(non-leg blood flow).

Supine Exercise Protocol

Seven patients with heart failure and six normal 
subjects were studied. All subjects had performed 
at least one trial bicycle exercise test before studies. 
On the day of study, the subject came to the labora-
ory in a fasting state. Temperature in the labora-
tory was maintained at 70° F. With the subject 
lying supine on a bed, a right antecubital vein 
intravenous line was inserted. A mercury-in-Silastic 
strain gauge was placed around the left forearm 
approximately 5 cm below the antecubital crease 
and connected to a plethysmograph (Parks Electron-
ics Laboratory, Beaverton, Oregon). A cuff 
was placed around the upper arm and connected to 
a pneumatically powered rapid cuff inflator (D.E. 
cuff was placed around the wrist and inflated to 
suprasystolic pressure at least 1 minute before 
forearm blood flow measurements. The left arm was 
elevated 10 cm above the anterior chest with a sling 
arrangement to ensure that there was no obstruc-
tion to venous return and to minimize forearm 
motion during exercise.

Thirty minutes after instrumentation, five to 10 
forearm flow measurements were made at rest. 
Flow was determined by rapidly inflating the upper 
arm cuff to 60 mm Hg and observing the rate of 
increase in forearm circumference. Flow was
expressed as milliliters per minute per 100 milliliters of forearm volume. The subject then performed supine bicycle exercise with a Quinton Industries bicycle ergometer. In the patients with heart failure, exercise was initiated at a work load of 200 kilopond-meters (kpm) and was increased by 100 kpm every 5 minutes to exhaustion. None of the patients achieved a work load above 400 kpm. Normal subjects were exercised at 200, 300, and 400 kpm. Forearm blood flow measurements were made every 15 seconds during exercise, and all flows obtained during each work load were then averaged. During exercise, the wrist cuff was inflated continuously.

Following completion of the exercise protocol, the subject was allowed to rest for 2 hours. The entire exercise protocol was then repeated.

At rest and at each work load, blood pressure was measured in the right arm with a sphygmomanometer. During one of the two exercise protocols in the randomized sequence, exercise was immediately preceded by administration of a phentolamine bolus (5 mg i.v.) with a subsequent continuous infusion of phentolamine. The infusion rate was 0.4 mg/min in the first four patients and all normal subjects. In the remaining three patients, the rate was increased to 1 mg/min to ensure that a higher infusion rate would not produce more blockade of forearm vasoconstrictor responses than did the lower infusion rate. No difference in forearm vascular responses to exercise were observed in patients with the lower versus the higher infusion rates. During the exercise protocol without phentolamine, blood samples were obtained from the antecubital vein at rest and during each level of exercise for determination of plasma noradrenaline levels and plasma renin activity.

Samples were immediately spun in a refrigerated centrifuge and analyzed later for norepinephrine with a radioenzymatic assay (CAT-A-KIT, Amer- sham, Arlington Heights, Illinois) and for renin with a radiolmmunooassay kit (GammaCoat Kit, Dade-Baxter Travenol Diagnostics, Cambridge, Massachusetts).

Mean arterial blood pressure was calculated as the diastolic pressure plus one third of the pulse pressure. Forearm vascular resistance was calculated by dividing mean arterial blood pressure by forearm blood flow.

To ensure that intravenous phentolamine produced forearm sympathetic blockade, forearm blood flow and resistance were measured in two normal subjects before and while they immersed a hand in ice water for 1½ minutes. The cold pressor test was then repeated after infusion of a 5-mg bolus of phentolamine followed by a continuous infusion of 0.4 mg/min. In the first subject, the cold pressor test increased forearm vascular resistance from 25.7 to 68.5 mm Hg/ml/min/100 ml before phentolamine but to only 27.3 mm Hg/ml/min/100 ml during phentolamine infusion. In the other subject, forearm resistance increased from 42.7 to 81.0 mm Hg/ml/min/100 ml before phentolamine but to only 43.7 mm Hg/ml/min/100 ml during phentolamine infusion.

**Statistical Analysis**

All data are expressed as mean±SD. Comparison of exercise values with rest values was performed with paired Student's t test. A p value of <0.05 was considered statistically significant.

**Results**

**Upright Bicycle Exercise**

As shown in Table 1, at supine rest, VO₂ averaged 249±39 ml/min, cardiac output 3.7±1.1 l/min, pulmonary wedge pressure 23±8 mm Hg, and leg blood flow 0.3±0.1 l/min. Exercise increased VO₂ to 850±307 ml/min, cardiac output to 6.8±2.5 l/min, pulmonary wedge pressure to 31±9 mm Hg, and leg blood flow to 2.0±1.0 l/min.

At upright rest, non–leg blood flow was 2.9±1.0 l/min, whereas non–leg vascular resistance averaged 34±16 units. With exercise, non–leg vascular resistance increased approximately 45% above resting levels to 45±25 units, indicating vasoconstriction. However, mean arterial blood pressure also increased, from 86±10 to 98±14 mm Hg, counterbalancing the increase in vascular resistance so that non–leg blood flow at maximal exercise, 2.8±1.4 l/min, remained unchanged from resting levels.

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**Table 1. Effect of Maximal Bicycle Exercise on Blood Flow to Nonexercising Tissues**

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Upright</th>
<th>20 W</th>
<th>Maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-leg flow (l/min)</td>
<td>3.1±1.1</td>
<td>2.9±1.0</td>
<td>3.1±1.3</td>
<td>2.8±1.4</td>
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<tr>
<td>Non-leg vascular resistance (units)</td>
<td>31±12</td>
<td>34±16</td>
<td>40±25</td>
<td>45±25*</td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>249±39</td>
<td>283±42</td>
<td>637±124*</td>
<td>850±307*</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.7±1.1</td>
<td>3.4±0.9</td>
<td>5.6±1.6*</td>
<td>6.8±2.5*</td>
</tr>
<tr>
<td>Leg flow (l/min)</td>
<td>0.3±0.1</td>
<td>0.3±0.1</td>
<td>1.3±0.5*</td>
<td>2.0±1.0*</td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>23±8</td>
<td>21±10</td>
<td>27±10*</td>
<td>31±9*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>86±10</td>
<td>86±10</td>
<td>94±12*</td>
<td>98±14*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>86±12</td>
<td>93±16</td>
<td>111±19*</td>
<td>121±20*</td>
</tr>
</tbody>
</table>

(n=28). Exercise data is given for the 20-W work load, a submaximal work load achieved by all patients, and the maximal work load.

*p<0.02 versus upright rest.
TABLE 2. Effect of Leg Exercise and α-Adrenergic Blockade on Forearm Vascular Resistance in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mm Hg)</th>
<th>Forearm blood flow (ml/min/100 ml)</th>
<th>Forearm vascular resistance (mm Hg/ml/min/100 ml)</th>
<th>Norepinephrine (pg/ml)</th>
<th>Renin activity (pg/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rest</td>
<td>69±8</td>
<td>94±9</td>
<td>2.6±1.2</td>
<td>43±22</td>
<td>181±125</td>
<td>1.3±0.7</td>
</tr>
<tr>
<td>200 kpm</td>
<td>96±11*</td>
<td>110±7*</td>
<td>2.6±0.7</td>
<td>47±17</td>
<td>384±304</td>
<td>1.1±0.7</td>
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<tr>
<td>300 kpm</td>
<td>100±8*</td>
<td>113±9*</td>
<td>2.5±0.7</td>
<td>48±17</td>
<td>336±306</td>
<td>1.5±1.0</td>
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<tr>
<td>400 kpm</td>
<td>104±9*</td>
<td>115±9*</td>
<td>3.0±0.7</td>
<td>41±13</td>
<td>749±375*</td>
<td>1.0±0.8</td>
</tr>
<tr>
<td>Phentolamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>84±15†</td>
<td>89±6†</td>
<td>3.4±1.3</td>
<td>30±12</td>
<td></td>
<td></td>
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<tr>
<td>200 kpm</td>
<td>104±14*</td>
<td>99±10**†</td>
<td>3.1±1.0</td>
<td>35±12**†</td>
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<td></td>
</tr>
<tr>
<td>300 kpm</td>
<td>109±15*</td>
<td>104±8**†</td>
<td>3.3±1.1</td>
<td>35±12**†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 kpm</td>
<td>119±12**†</td>
<td>107±11**†</td>
<td>3.5±1.0</td>
<td>33±12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=6.
*tp<0.05 versus rest.
†p<0.05 versus control.

Supine Bicycle Exercise in Normal Subjects

The six normal subjects exercised at all three work loads without problems (Table 2). During the control exercise test, blood pressure increased from 94±9 to 115±9 mm Hg and heart rate from 69±8 to 104±9 beats/min. Exercise had no effect on forearm blood flow (rest, 2.6±1.2; 400-kpm work load, 3.0±0.7 ml/min/100 ml), forearm vascular resistance (rest, 43±22; 400-kpm work load, 41±13 mm Hg/ml/min/100 ml), or plasma renin activity. Plasma norepinephrine levels increased significantly at the 400-kpm work load (from 181±125 pg/ml at rest to 749±375 pg/ml, p<0.03).

Phentolamine administration decreased arterial blood pressure both at rest and throughout exercise. Compared with control exercise, forearm blood flow tended to be higher at rest and during exercise, but this difference did not reach statistical significance. However, exercise again had no effect on blood flow. Forearm vascular resistance increased slightly at the 200- and 300-kpm level but not at the 400-kpm work load.

Supine Bicycle Exercise in Patients With Heart Failure

Five patients exercised to 400 kpm, whereas two patients discontinued exercise at 300 kpm (Table 3). Without α-adrenergic blockade, resting mean arterial pressure was 96±11 mm Hg, forearm blood flow 2.4±1.0 ml/min/100 ml, and forearm vascular resistance 44.6±16.6 mm Hg/ml/min/100 ml. Plasma norepinephrine averaged 258±129 pg/ml and renin activity 2.8±1.7 pg/ml. These values were not significantly different from values in the normal subjects.

Exercise was associated with higher heart rates in patients with heart failure than in control subjects but blood pressures were comparable. Forearm blood flow increased slightly at the 200-kpm work load but subsequently was unchanged from resting levels. In contrast to that in the control subjects,
forearm vascular resistance in patients increased significantly during exercise to a level of 58±25 mm Hg/ml/min/100 ml, or approximately 30% above resting levels. This change in forearm vascular resistance was associated with plasma norepinephrine levels not significantly greater than those in the control subjects. However, plasma renin activity in the patients with heart failure was markedly higher during exercise, reaching at peak exercise 44.5±13.3 pg/ml/hr versus only 1.0±0.8 pg/ml/hr in the control subjects.

Phentolamine significantly decreased arterial blood pressure at rest but did not change it during exercise. Exercise again increased the forearm vascular resistance from 39±13 at rest to 48±16 mm Hg/ml/min/100 ml (p<0.04) at peak exercise but without change in forearm blood flow.

There was no significant difference between forearm vascular resistance and flow measurements made before and those made after phentolamine administration.

Discussion

In normal subjects, strenuous exercise is associated with a generalized increase in sympathetic vasoconstrictor activity and angiotensin II.25,26 These neurohumoral responses serve to increase vascular resistance in nonworking tissues and thereby augment the arterial blood pressure and redistribute blood from nonworking tissues to exercising muscle.27 In working skeletal muscle, local metabolic factors override these neurohumoral influences and produce vasodilation.

It has been postulated that this normal pattern of responses is accentuated in patients with left ventricular failure, possibly to a deleterious extent. According to this hypothesis, sympathetic activation is substantially elevated above normal at low work levels, producing both intense vasoconstriction and flow reductions in nonworking tissues.4–9 It has been further suggested that the degree of vasoconstriction may be sufficiently intense to override local metabolic factors in working skeletal muscle and thereby interfere with muscle flow.5

Results of the present study confirm that vasoconstriction occurs in nonexercising vascular beds during maximal exercise in patients with heart failure. However, several observations suggest that the degree of sympathetic vasoconstriction produced by exercise is considerably less than previously thought. First, the observed vasoconstriction had no significant affect on blood flow to nonexercising tissues. Second, the forearm vasoconstriction noted during supine exercise was associated with abnormal increases in plasma renin activity rather than in plasma norepinephrine levels, suggesting that this vasoconstriction may be caused by production of angiotensin II rather than by heightened sympathetic tone. Third, the forearm vasoconstriction was not blocked by phentolamine, further implicating a mechanism other than heightened sympathetic tone.

Blood Flow to Nonexercising Tissues

During exercise, the main regions which can redistribute significant quantities of blood to working muscle are the splanchnic beds, the renal vascular beds, and nonexercising skeletal muscle. In normal man, maximal exercise reduces blood flow to these areas by 50–80%.27 This flow reduction is associated with plasma norepinephrine levels in excess of 2,000 pg/ml, leading to the general presumption that the flow change is due to a marked elevation in sympathetic vasoconstrictor activity.

In the present study, maximal bicycle exercise produced a significant increase in both forearm and total non-leg vascular resistance of our patients, indicating substantial vasoconstriction in nonexercising tissue. However, because this vasoconstriction was accompanied by a concurrent rise in arterial blood pressure, blood flow to nonexercising tissues remained unchanged. No change was noted in either forearm flow or vascular resistance in the normal subjects, a finding consistent with prior observations in normal subjects performing mild exercise.28,29

Results of the present study therefore suggest that, in contrast to normal subjects performing maximal exercise, patients with heart failure do not develop major redistributions of blood flow from nonexercising beds to exercising muscle. Although vasoconstriction occurs, this effect is counterbalanced by an increase in blood pressure. Thus, in contrast to the widely held view that patients with heart failure exhibit during exercise intense vasoconstriction that reduces flow to nonexercising beds, our results suggest that the degree of vasoconstriction may in fact be substantially less than that in normal subjects exercising maximally.

Our finding that non–leg and forearm blood flow do not decrease during exercise in patients with left ventricular failure contrasts with findings in patients with heart failure caused by rheumatic valvular disease. In the latter group, prior observations indicate that exercise-induced flow redistribution occurs. Specifically, exercise in such patients has been demonstrated to decrease forearm blood flow; forearm, renal, and hepatic venous O2 saturation6–8; and hepatic clearance of indocyanine green.9

There are several potential explanations for the differences between results of the present study and findings in patients with rheumatic heart disease. The patients in the present study were ambulatory and may not have been as hemodynamically compromised as patients with rheumatic valvular disease. The different responses may be due to differences in the underlying cardiac disease; most of the patients with rheumatic valvular disease had mitral stenosis. In addition, we discontinued digoxin in our patients prior to forearm studies. In previous studies, digitalis preparations were continued and may have augmented sympathetic vasoconstrictor responses to exercise by increasing baroreceptor
sensitivity. Furthermore, digitalis is known to be a direct vasoconstrictor and to increase the vasoconstrictor effects of angiotensin II and norepinephrine, properties that would also tend to augment exercise-induced vasoconstriction.

It should be noted that our findings do not exclude the possibility that some blood flow redistribution occurred within nonexercising tissues in our patients. For example, splanchnic blood flow could have decreased while cardiac and thoracic wall muscle flow could have increased, resulting in no overall change in flow.

**Contribution of Sympathetic Activation to Exercise Vasoconstriction**

To investigate the contribution of sympathetic activity to the exercise-induced forearm vasoconstriction noted in our patients, plasma norepinephrine levels were obtained during exercise, and forearm vascular responses were reexamined after \( \alpha \)-adrenergic blockade with phentolamine. At rest, plasma norepinephrine levels tended to be higher in the patients with heart failure, although not to a significant extent. During exercise, plasma norepinephrine levels increased over twofold in all patients, consistent with an increase in sympathetic activity. Although the levels again tended to be higher than in the normal subjects, this trend was not significant, suggesting that sympathetic activation did not produce the forearm vasoconstriction. Further supporting this conclusion, the forearm vasoconstriction was not blocked by phentolamine administration.

Kirlin et al. also noted comparable norepinephrine levels in normal subjects and in ambulatory patients with heart failure both at rest and during exercise. In contrast, Chidsey et al. and Francis et al. demonstrated higher-than-normal norepinephrine levels in patients with heart failure. This apparent discrepancy between the results of different studies is probably related to differences in study populations. Both in the present study and in the study of Kirlin et al., patients with moderate exercise intolerance were compared with age-matched normal subjects. The studies of Chidsey et al. and Francis et al. compared patients with both severe and moderate exercise intolerance with somewhat younger, normal volunteers. Patients with severe exercise intolerance exhibit more abnormal norepinephrine levels than patients with less-severe exercise intolerance. In normal subjects, norepinephrine levels at rest and in response to a variety of stimuli, including exercise, are directly related to age. Therefore, Chidsey et al. and Francis et al. probably would not have observed as striking a difference in norepinephrine levels if they had compared patients with only moderate exercise intolerance with age-matched normal subjects.

The exact mechanism by which exercise increased forearm vascular resistance in our patients cannot be determined from the present study. We cannot exclude a role for sympathetic activation because phentolamine does not totally block \( \alpha \)-receptors. Interestingly, the increase in plasma renin activity noted during exercise was much greater in the patients than in the normal subjects. Kirlin et al. observed a similar pattern in their study. This increase in renin activity may have produced sufficient angiotensin II to augment forearm vascular resistance. Local autoregulation of forearm blood flow also could contribute to the increase in forearm resistance.

**Modulation of Sympathetic Activity in Heart Failure**

Results of this study suggest that ambulatory patients with left ventricular failure develop relatively little sympathetic vasoconstrictor activity during bicycle exercise. This conclusion is consistent with a growing number of observations which suggest that sympathetic vasoconstrictor effects are considerably less pronounced in left ventricular failure than previously thought. Attenuated forearm vasoconstrictor responses to orthostatic tilt and lower body negative pressure have been noted in such patients, suggesting impaired sympathetic reflex control of peripheral resistance vessels. We have recently noted that hindlimb vascular responses to lumbar sympathetic chain stimulation are impaired by experimental heart failure. Other observations suggest that heart failure may impair sympathetic neurotransmitter production and/or release.

**Clinical Implications**

The apparent failure of sympathetic vasoconstrictor tone to increase more markedly in our patients has important clinical implications. Previous therapeutic interventions designed to influence sympathoadrenal activity in heart failure have focused exclusively on blocking this activity. Results of the present study suggest that such an approach may have little or no long-term benefit in ambulatory patients with moderate exercise intolerance, a conclusion supported by the failure of chronic \( \alpha \)-adrenergic blocking agents to improve the clinical status of such patients. One might even argue that an intervention designed to enhance sympathetic activity might be beneficial in increasing cardiac inotropy and shunting blood from nonexercising tissues to working skeletal muscle. However, such an approach might also increase cardiac afterload, reduce cardiac output, and impair muscle perfusion. Enhancing sympathetic activity, therefore, may not improve skeletal muscle performance. In support of this conclusion, Maskin et al. observed no acute beneficial effect of dopamine infusion on the exercise capacity of patients with heart failure.

**References**


**KEY WORDS** • vasoconstriction • heart failure • exercise • sympathetic nervous system
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