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Vasodilatory behavior of skeletal muscle arterioles in patients with nonedematous chronic heart failure

JOHN R. WILSON, M.D., DAVID H. WENER, M.D., LOUIS I. FINK, M.D., AND NANCY FERRARO, R.N.

ABSTRACT During maximal upright exercise, blood flow to working skeletal muscle is frequently reduced in patients with nonedematous chronic heart failure. It has been speculated that this reduced muscle flow may be caused in part by an intrinsic impairment of skeletal muscle vasodilator capacity. To test this hypothesis, forearm blood flow and resistance were compared during forearm exercise and in response to transient forearm ischemia (10 min) in 22 patients with heart failure and in 11 normal subjects. During forearm exercise, both groups exhibited comparable forearm blood flows (ml/min/100 ml) (0.2 W: normal 5.9 ± 3.1, heart failure 6.5 ± 2.8; 0.4 W: normal 8.2 ± 5.5, heart failure 8.2 ± 3.6; 0.6 W: normal 11.5 ± 6.8, heart failure 11.8 ± 4.8 [all p = NS]) and forearm vascular resistances (mm Hg/ml/min/100 ml) (0.2 W: normal 23.1 ± 12.4, heart failure 18.5 ± 7.8; 0.4 W: normal 16.9 ± 7.7, heart failure 14.7 ± 6.4; 0.6 W: normal 13.1 ± 7.7, heart failure 10.3 ± 4.1 [all p = NS]). Ten minutes of forearm ischemia, an intervention that produces maximal forearm vasodilation, also resulted in comparable forearm vascular resistances in both groups (normal 4.1 ± 2.4, heart failure 3.8 ± 1.3 mm Hg/ml/min/100 ml/ p = NS). These data suggest that skeletal muscle vasodilatory capacity is not intrinsically impaired in patients with nonedematous chronic heart failure.

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PATIENTS WITH CHRONIC, compensated heart failure are frequently limited during maximal exercise even when they are asymptomatic at rest.1–5 Prior studies from this and other laboratories suggest that this exercise intolerance is in large part caused by inadequate skeletal muscle blood flow with consequent muscular fatigue.1,2,4 However, the mechanism responsible for this muscle underperfusion remains uncertain.

During exercise, blood flow to working skeletal muscle is increased because of augmentation of the arterial blood pressure coupled with skeletal muscle arteriolar vasodilation. Consequently, muscle underperfusion in heart failure could be produced by an attenuated blood pressure response to exercise and/or by a inability of muscle arterioles to dilate normally. Impaired muscle arteriolar vasodilation could in turn be caused by neurohumoral vasoconstrictor influences and/or by an intrinsic abnormality of muscle arterioles.

This study was undertaken to determine whether an intrinsic abnormality of skeletal muscle arteriolar vasodilation is present in patients with compensated, nonedematous heart failure. With plethysmography, forearm vascular resistance during progressive forearm exercise was compared in normal subjects and in patients with heart failure. Forearm resistance after 10 min of forearm ischemia, an intervention that has previously been shown to produce maximal vasodilation of forearm muscle,6–8 was also compared in the two groups. It was hypothesized that if impaired muscle vasodilation contributes to muscle underperfusion in nonedematous heart failure, forearm vascular resistance during exercise and/or after temporary ischemia should decrease less in the patients than in the normal subjects.

Methods

Patients. Twenty-two patients with chronic nonedematous heart failure (age 60 ± 8 years) and 11 normal subjects (age 56 ± 13 years) were studied. Heart failure was attributed to coronary artery disease in 11 patients and to idiopathic or alcoholic cardiomyopathy in 11. All of the patients had severe left ventricular dysfunction as assessed by gated nuclear blood pool analysis (n = 20; ejection fraction 22 ± 8%) or by two-dimensional echocardiography (n = 2). Peak exercise VO2 during maximal bicycle or treadmill exercise averaged 14.7 ± 4.5 ml/min/kg (normal >20 to 25). All patients were ambulatory,
were in NYHA functional class II or III, and were receiving digoxin and diuretics. Patients receiving vasodilators (hydralazine and/or nitrates) had the drug withheld 24 hr before study. No patient was receiving angiotensin-converting enzyme inhibitors, and no patient had peripheral edema, ascites, angina, peripheral necrosis, intermittent claudication, or reduced pulses in his legs at the time of study. Before enrollment in the study, optimal diuresis was achieved in all patients. The normal subjects had no history of heart disease, no cardiac abnormalities on physical examination, and no exercise intolerance.

The protocol was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania. Written informed consent was obtained from all subjects.

Forearm blood flow. Forearm blood flow was measured by plethysmography with the subject seated in a quiet room kept at 70°F. Care was taken to position the arm at the height of the shoulder to ensure that there was no obstruction to venous return. A mercury-in-Silastic strain gauge was placed approximately 5 cm below the antecubital crease. Flow was determined by rapidly inflating a cuff around the upper arm to 40 mm Hg with a pneumatically powered rapid cuff inflator (D.E. Hokanson, Issaquah, WA).9 Forearm blood flow was calculated from the rate of increase in forearm circumference during venous occlusion measured on a plethysmograph (Parks Electronics Laboratory, Beaverton, OR) and expressed as ml/min/100 ml forearm volume. The blood pressure was measured in the other arm with a sphygmanometer. Circulation to the hand was arrested by inflating a cuff around the wrist to suprasystolic pressure at least 1 min before determination of forearm blood flow. During exercise, the wrist cuff was inflated continuously.

Four to five forearm flow measurements were made at rest. The subject then performed wrist flexion every 5 sec for 7 min at a workload of 1 J (average power output 0.2 W). Exercise consisted of depressing a handle that elevated a bar. The workload was varied by hanging different weights from the end of the bar. The workload was determined from the weight lifted and the distance moved by the weight with standard formulas. Duration of flexion was monitored and held as close to 1 sec as possible. Flow was determined after each minute of exercise by rapidly inflating the venous occlusion cuff while the subject paused for 5 to 10 sec. Data for the last 6 min of exercise were averaged to calculate the mean forearm blood flow at each workload. The subject then rested for 10 min. Flow was remeasured at the end of the rest period to ensure full recovery to baseline. Return to previous resting flow values was always noted before the next exercise level began. The exercise protocol was repeated at 0.4 and 0.6 W.

After a 20 min rest period, blood flow to the forearm was occluded by inflating a cuff on the upper arm to suprasystolic pressure for 10 min. The cuff was then rapidly deflated and forearm blood flow was measured at 8 to 10 sec after release and every 15 sec thereafter for 2 min. Peak blood flow after release was then identified and used to calculate minimal forearm vascular resistance.7,8

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 pressure by forearm blood flow.

Reproducibility studies. To investigate the reproducibility of forearm blood flow data, three normal subjects and three patients with heart failure underwent duplicate flow studies on the same day. Thus each subject exercised twice at all three loads, yielding a total of nine duplicate exercise measurements in normal subjects and nine duplicate measurements in the patients with heart failure. In the normal subjects, forearm blood flow measurements varied by 9.2 ± 7.2% (n = 9). In the patients with heart failure, forearm blood flow varied by 19 ± 11% (n = 9).

Statistical analysis. All data are expressed as mean ± SD. Group comparisons were made with the nonpaired Student’s t test. A p value <.05 was considered significant.

Results

Results are summarized in Table 1.

Forearm vascular behavior during exercise. In the normal subjects, resting forearm blood flow averaged 2.9 ± 1.4 ml/min/kg and increased progressively with exercise to a peak level of 11.5 ± 6.8 ml/min/kg. These flow changes were associated with a progressive decrease in forearm vascular resistance and an increase in arterial blood pressure.

In the patients with heart failure, resting arterial blood pressure was significantly lower than that in the normal subjects (88 ± 9 vs 97 ± 9 mm Hg; p < .01). However, forearm blood flow and vascular resistance were comparable to levels noted in the normal subjects. During exercise, arterial blood pressure was also lower in the patients with heart failure at 0.4 and 0.6 W. However, again forearm blood flow and resistance

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Comparison of forearm blood flow and vascular resistance in normal subjects and in patients with heart failure</th>
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<tr>
<td></td>
<td>Forearm blood flow (ml/min/100 ml)</td>
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<tr>
<td>Normal (n = 11)</td>
<td>Rest 2.9 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>0.2 W 5.9 ± 3.1</td>
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<td></td>
<td>0.4 W 8.2 ± 5.5</td>
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<td></td>
<td>0.6 W 11.5 ± 6.8</td>
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<tr>
<td>Ischemia 33.8 ± 17.8</td>
<td>4.1 ± 2.4</td>
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<tr>
<td>Heart failure (n = 22)</td>
<td>Rest 2.6 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>0.2 W 6.5 ± 2.8</td>
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<td></td>
<td>0.4 W 8.2 ± 3.6</td>
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<td></td>
<td>0.6 W 11.8 ± 4.8</td>
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<tr>
<td>Ischemia 31.7 ± 18.1</td>
<td>3.8 ± 1.3</td>
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<tr>
<td>Heart failure: peak VO2,14 ml/min/kg (n = 13)</td>
<td>Rest 2.5 ± 1.0</td>
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<td></td>
<td>0.2 W 6.2 ± 2.5</td>
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<td></td>
<td>Heart failure: peak VO2,14 ml/min/kg (n = 9)</td>
</tr>
<tr>
<td></td>
<td>0.2 W 7.0 ± 3.1</td>
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<td></td>
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<td>0.6 W 11.4 ± 3.9</td>
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</table>

*p < .05 vs normal; b p < .01 vs normal.
were comparable with levels noted in the normal subjects.

To determine whether vascular behavior was impaired in patients with more severe exercise intolerance but not in those with less exercise intolerance, patients were divided into those with peak VO2 levels of 14 ml/min/kg or greater and those with levels of less than 14 ml/min/kg. Neither subgroup had forearm blood flow or resistance significantly different from the levels noted in the normal subjects. However, arterial blood pressure responses to exercise were more impaired in the patients with the peak VO2 levels under 14 ml/min/kg.

Forearm vascular behavior after forearm ischemia. Changes in forearm blood flow and vascular resistance after 10 min of forearm ischemia were comparable in the normal subjects and in the patients with heart failure. Moreover, no significant differences were observed when the patients were subdivided according to peak VO2.

Discussion

The performance of patients with chronic heart failure is frequently limited during maximal upright exercise.1–5 Recent evidence suggests that this exercise intolerance is in large part caused by skeletal muscle underperfusion. Specifically, this exercise intolerance is typically associated with severe muscular fatigue, reduced systemic and leg blood flow, and earlier-than-normal lactate release from working muscle.1–5 Moreover, the degree of exercise intolerance usually parallels the extent of a patient’s flow and lactate abnormalities.1, 2, 4 Consequently, identification of the mechanism responsible for skeletal muscle underperfusion in heart failure is a clinically important objective.

In this study we sought to investigate one potential contributor to muscle underperfusion in heart failure: an intrinsic abnormality of skeletal muscle vasodilatory capacity. In exercising skeletal muscle, metabolically induced vasodilation of muscle arterioles plays a key role in ensuring that muscle flow closely matches muscle metabolic demand. Consequently, any abnormality of muscle arterioles that impairs their ability to dilate could cause a significant reduction in muscle flow.

To investigate intrinsic muscle arteriolar behavior, two forms of vasodilatory stimuli were used: mild forearm exercise and 10 min of forearm ischemia. Forearm exercise places minimal demands on the circulation and therefore is unlikely to exhaust cardiac reserve or, more importantly, to activate major neurohumoral vasococontractor influence; such activation could influence muscle arterioles and thereby obscure intrinsic vasodilatory behavior. Transient forearm ischemia was used to assess maximal forearm vasodilatory capacity based on prior observations suggesting that this intervention produces maximal forearm vasodilatation.6–8

Forearm blood flow was measured by plethysmography. Total forearm flow was taken as an index of muscle flow, since most of the forearm is made up of muscle. Nevertheless, it should be recognized that the forearm also includes nonmuscular tissue such as skin, making our flow values only an approximation of muscle flow.

For this study, a relatively well-defined group of patients was studied: patients with compensated, nonedematous heart failure. The syndrome of heart failure encompasses a wide spectrum of clinical states ranging from patients with minimal pump dysfunction and fluid retention to patients with severe pump dysfunction and marked fluid retention. Findings in patients located at one point on this spectrum may differ in important ways from patients at another point, making it imperative in small studies to focus on a relatively homogeneous group of patients.

We focused on patients with nonedematous chronic heart failure for several reasons. First, such patients represent a substantial proportion of all patients with heart failure, and are frequently limited during maximal exercise.1–4 Second, it has been our experience and that of others that nonedematous patients are primarily limited by fatigue during exercise,1, 2, 4 making investigation of their muscle behavior particularly important. Third, we have previously documented that muscle flow is reduced during maximal exercise in nonedematous patients, as evidenced by reduced leg blood flow and heightened leg lactate release.1 Finally, very little is currently known about intrinsic muscle vasodilatory behavior in such patients.

In the normal control subjects, forearm exercise was associated with a progressive increase in forearm blood flow, mediated by both a progressive rise in muscle perfusion pressure (arterial blood pressure) and a progressive decrease in forearm vascular resistance. The changes in flow and resistance were similar to those previously reported by Zelis et al.10, 11 for normal subjects performing a different form of mild forearm exercise. Reactive hyperemia after 10 min of forearm ischemia was also in a range similar to levels previously reported by Zelis et al.6

In the patients with heart failure, forearm exercise produced a progressive increase in forearm blood flow
to levels nearly identical to those noted in the normal subjects. This flow increase was again mediated by a rise in arterial blood pressure and a decrease in forearm vascular resistance. However, the arterial blood pressure response to exercise was lower than normal. In contrast, forearm vascular resistance decreased to levels not significantly different from levels noted in the normal subjects but with a trend favoring greater than normal dilation in the patients; in the presence of a reduced muscle perfusion pressure, augmented vasodilation would have to occur to preserve normal forearm blood flow.

Flow and vascular resistance responses to forearm ischemia were also similar to responses noted in the normal subjects. Subgrouping of patients according to peak exercise VO$_2$ into those with mild and those with more severe exercise intolerance also failed to identify a subgroup with abnormal forearm flow and resistance behavior.

These findings suggest that patients with nonedematous chronic heart failure exhibit normal intrinsic skeletal muscle vasodilatory behavior. This conclusion is in general consistent with recent experimental animal studies. Using radioactive microspheres, Flaim and Minteer$^{12}$ measured skeletal muscle blood flow and resistance during exercise in a nonedematous experimental rat preparation of heart failure produced with an arteriovenous fistula. Vascular resistance at rest was normal in all of six muscles examined, and only two of the six muscles exhibited higher-than-normal vascular resistance during treadmill exercise.

More recently, we measured femoral bed vascular resistance during treadmill exercise in a mildly edematous dog preparation of heart failure produced by 3 weeks of rapid ventricular pacing.$^{13}$ Femoral bed vascular resistance during exercise was comparable to levels noted in control dogs. To further analyze muscle vasodilatory behavior, gracilis muscle in the dogs was vascularity and neurally isolated and then studied during exercise induced by stimulating the obturator nerve. Again, no evidence of altered muscle vasodilatory behavior was found.

To our knowledge, prior studies of intrinsic skeletal muscle arteriolar behavior have not been done in patients with nonedematous heart failure. However, in a series of elegant studies, Zelis and co-workers$^{6, 10, 11, 14}$ measured forearm vascular resistance in severely edematous patients both during forearm exercise and in response to transient forearm ischemia. They observed that, during both interventions, forearm resistance decreased less in the patients than in normal control subjects, suggesting that such patients have an intrinsic abnormality of their muscle arterioles. Zelis et al.$^{9}$ also demonstrated that diuresis of patients partially normalized forearm vasodilatory behavior. This finding, coupled with related studies in normal subjects and experimental animals,$^{14}$ led these investigators to propose that impaired muscle vasodilation in edematous heart failure is due to an adverse effect of sodium and water retention on vascular function. Our finding that nonedematous patients appear to have normal muscle vasodilatory behavior is consistent with this conclusion.

These observations do not necessarily indicate, of course, that sodium and water retention is the only factor that can influence intrinsic skeletal muscle arteriolar behavior. Neurohumoral factors such as sympathetic activity, norepinephrine, renin, and arginine vasopressin all are potent vasoconstrictors. Therefore it is possible that some nonedematous patients with marked elevations of neurohumoral vasoconstrictor influences could have impaired arteriolar behavior. However, our results suggest that, in general, nonedematous patients exhibit normal arteriolar behavior.

If muscle vasodilation is in general not impaired in nonedematous patients, what then is responsible for the reduced skeletal muscle blood flow noted in such patients during maximal upright exercise? During exercise, skeletal muscle blood flow is increased because of an augmented muscle perfusion pressure (arterial blood pressure) coupled with muscle arteriolar vasodilation. If intrinsic muscle arteriolar vasodilation is normal, then the only two remaining likely contributors to the muscle underperfusion are an attenuated arterial blood pressure during exercise and/or impaired vasodilation produced by neurohumoral vasoconstrictor influences. Recently, we investigated the contribution to muscle underperfusion of the two most important potential vasoconstrictor influences: excessive sympathetic activation$^{15}$ and angiotensin II.$^{16}$ Our results failed to demonstrate a critical contribution to muscle underperfusion of either of these neurohumoral vasoconstrictor influences. Taken together, these various observations suggest that a reduced arterial blood pressure is the most likely mechanism responsible for muscle underperfusion in nonedematous heart failure. In support of such a conclusion, prior studies of patients with heart failure have almost invariably noted reduced arterial blood pressure response to exercise in patients with reduced maximal exercise capacity.$^{1-3}$

If an inadequate muscle perfusion pressure is the principal contributor to muscle underperfusion, why was forearm blood flow during forearm exercise normal in the patients in the present study despite their reduced arterial blood pressures? This apparent discre-
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pancy could be due simply to differences in the degree of arterial blood pressure attenuation during maximal upright vs forearm exercise. However, an alternative explanation is that the different flow responses to forearm vs maximal exercise are caused by differences in the ability of muscle arterioles to compensate for reduced muscle pressures under these two conditions. During forearm exercise, muscle vasodilation is only modest, as evidenced by the much lower forearm vascular resistances observed after forearm ischemia than during exercise. Therefore, during forearm exercise there is considerable vasodilatory reserve available to compensate for a low arterial pressure. In contrast, during maximal upright exercise, active leg muscles are probably working at a level of vasodilation much closer to their maximal vasodilatory capacity. Consequently, muscle arterioles would be less able to compensate for a reduced arterial pressure.

In any event, if a reduced arterial blood pressure is the principal mechanism responsible for muscle underperfusion in nonedematous patients with heart failure, it may be necessary to modify current approaches to treating exertional fatigue in such patients. Until now, much attention has been focused on overriding skeletal muscle arteriolar vasoconstriction with vasodilators and thereby augmenting muscle flow. If in fact muscle vasodilation is not impaired during exercise, administration of vasodilators may only serve to decrease arterial blood pressure, an effect that potentially could worsen muscle flow. In fact, if muscle vasodilation is normal, the optimal agent for improving muscle flow theoretically would be one that augments arterial blood pressure, such as an inotropic agent with partial α-agonist properties.

References