Resting muscle sympathetic nerve activity and peak oxygen uptake in heart failure and normal subjects

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Aims Exercise intolerance and increased efferent vasoconstrictor traffic to muscle are two characteristics of heart failure that have not been explicitly linked. We tested the hypothesis that peak oxygen consumption is inversely related to resting muscle sympathetic nerve activity in heart failure.

Methods and Results We recorded peroneal muscle sympathetic nerve activity in 17 treated heart failure patients (16 men, 1 woman; mean ejection fraction of 26.0 ± 3.2% (SE)) and 17 age-matched healthy subjects (16 men, 1 woman). Oxygen consumption was measured during cycle ergometry to maximal effort. In heart failure and normal subjects, mean peak oxygen consumption was 20.6 ± 1.7 vs 32.2 ± 2.6 ml·kg⁻¹·min⁻¹ (P < 0.0001) and mean muscle sympathetic activity was 49.3 ± 2.8 vs 33.0 ± 3.3 bursts·min⁻¹ (P < 0.0007) respectively. When age was accounted for by multiple regression analysis, there was a significant relationship between peak oxygen consumption and burst frequency in heart failure (P < 0.02) but not in healthy subjects. The percent of predicted peak oxygen consumption achieved (based on age, sex and body size) was inversely related to muscle sympathetic nerve burst frequency in heart failure (r = −0.71, P < 0.0014) but not in normal subjects (r = −0.44, P < 0.08; P < 0.0001 for this comparison).

Conclusion Reduced exercise capacity in heart failure is related to increased efferent sympathetic traffic to calf muscle. These observations are consistent with the concept of a peripheral neurogenic limit to exercise in heart failure. (Eur Heart J 1999; 20: 880–887)

Key Words: Heart failure, oxygen consumption, sympathetic nerve activity, exercise capacity, ejection fraction.

Introduction

A limited exercise capacity and increased efferent sympathetic vasoconstrictor traffic to muscle are two characteristics of heart failure that have not been explicitly linked. Patients with heart failure usually stop exercise because of fatigue or dyspnoea[1,2], but the onset of these symptoms and peak exercise capacity vary considerably between patients, and are unrelated to left ventricular ejection fraction, or similar clinical measures of disease severity or prognosis[3–5]. This observation has directed attention to peripheral rather than cardiac constraints on exercise in these patients. One such peripheral limitation may be the extent to which vasoconstrictor mechanisms have been activated, and the impact of such activation on oxygen delivery to exercising muscle.

Sympathetic nervous system activation[6], and a reduction in peak oxygen uptake during exercise[7] are two independent risk factors for decreased survival in patients with congestive heart failure. Median plasma noradrenaline concentrations are increased in patients with asymptomatic left ventricular dysfunction, and rise further with the progression to symptomatic congestive heart failure[8,9]. Appearance rates of noradrenaline in plasma are increased[10] owing to increased cardiac and renal adrenergic drive, and augmented sympathetic vasoconstrictor discharge to skeletal muscle[8,11–13]. However, the intensity of muscle sympathetic nerve activity varies considerably between patients and, like peak exercise capacity, bears little or no relationship to left ventricular ejection fraction[13,14]. Whether this increase in sympathetic discharge to skeletal muscle contributes to exercise intolerance, independently of the extent of left ventricular dysfunction, has not been established.
In both healthy subjects and patients with heart failure, the sympathetic nervous system can act as a restraint on increases in skeletal muscle blood flow and on oxygen consumption during severe exercise\[^{15-17}\]. Similar findings have been observed in healthy subjects during reactive hyperaemia\[^{18}\]. As well, a significant inverse relationship exists between resting plasma noradrenaline and peak oxygen consumption during graded exercise\[^{3,19}\]. A recent study reported increased leg blood flow and decreased plasma noradrenaline levels during treadmill exercise in heart failure patients after inhibition of central sympathetic outflow by clonidine\[^{16}\].

The purpose of this study was to determine whether an age-independent relationship exists, in stable, treated heart failure patients, between muscle sympathetic nerve activity at rest and peak oxygen consumption. Age-matched healthy subjects were studied for comparison. Plasma noradrenaline levels are a relatively insensitive index of sympathetic outflow in humans\[^{20}\]. By contrast, the microneurographic technique provides a direct measure of sympathetic vasoconstrictor discharge to the calf muscle, an important vascular bed during bicycle or treadmill exercise. Our hypothesis was that peroneal muscle sympathetic nerve burst frequency, recorded at rest, would be inversely related to peak oxygen consumption during exercise.

**Methods**

**Subjects**

*Heart failure patients*

We studied 17 stable patients (16 men and 1 woman) with moderate to severe impairment of left ventricular function (left ventricular ejection fraction by radionuclide ventriculography 26.0 ± 3.2%, mean ± SE) and a mean age of 48.0 ± 2.8 years. Six patients had ischaemic and 11 had dilated cardiomyopathy. We did not recruit patients with autonomic neuropathy, diabetes, valvular heart disease, angina (>2 attacks a day), a recent myocardial infarction or coronary artery bypass graft surgery (<3 months) or patients requiring frequent adjustment of their medication. For comfort, diuretics were withheld on the morning of the microneurography study. Of the 17 patients, eight (47%) were on beta\(_1\) adrenoceptor blocking drugs; 16 (94%) were taking angiotensin-converting enzyme inhibitors; nine (53%) digitalis; 14 (82%) diuretics and six (35%) anticoagulants.

*Normal subjects*

We recruited 17 healthy volunteers (16 male and 1 female) through local advertisement. All were well by medical history and none was taking medication. The mean age of these subjects was 44.0 ± 3.5 years.

The study protocol was approved by the Human Subjects Review Committee of the University of Toronto and informed written consent was obtained from each subject prior to participation.

**Procedures**

*Sympathetic nerve recordings*

Subjects were studied in the supine position during quiet rest. Blood pressure was monitored from the left arm every minute by an automated device (Physio-Control, model Lifeset 200, Redwood, WA) and heart rate was derived from lead II of the electrocardiogram. Signal output was to an ink recorder (Gould model 2800S, Cleveland, OH) and to computer using a LabVIEW\[^{18}\] software platform (National Instruments, Austin, TX), following analog to digital conversion, for storage and later analysis. In 14 of 17 heart failure patients, an antecubital venous catheter was inserted in the right forearm in order to sample blood for the simultaneous determination of muscle sympathetic nerve activity and plasma noradrenaline concentrations according to methods previously published by our group\[^{21}\].

Multunit recordings of post-ganglionic muscle sympathetic nerve activity were obtained with a unipolar tungsten electrode inserted selectively into a muscle nerve fascicle of the right or left peroneal nerve, posterior to the fibular head, as previously described\[^{22}\]. Acceptable recordings met the following four criteria: (1) spontaneous bursts of neural discharge synchronous with the heart rate; (2) no response to arousal stimuli or skin stroking; (3) an increase in nerve burst frequency with apnoea; (4) a signal to noise ratio of 3:1. After the setup and a stabilization period of 20 min, the subject lay quietly while a 7-10 min baseline recording was made. The average resting heart rate, systolic and diastolic blood pressure, and muscle sympathetic burst frequency were determined over this period. Venous blood was then drawn.

*Exercise tolerance test*

Exercise capacity was assessed on a separate day by means of a graded exercise test performed on a bicycle ergometer. All subjects were studied at least 2 h after a meal and heart failure patients maintained their normal medication schedules. Both patients and normal subjects began exercise at a work rate of 17 watts with step increases of 17 watts every minute until a maximal effort was achieved. The test was terminated when the pedal speed could no longer be maintained and the respiratory exchange ratio exceeded 1:1. Oxygen consumption at peak exercise was obtained by open circuit spirometry (Horizon MMC System or Vmax Series 229, Sensormedics, CA). Heart rate was monitored by a 12-lead electrocardiogram (Quinton, Seattle, WA) and blood pressure was measured with a sphygmomanometer. Peak oxygen consumption was normalized for body weight and expressed both as ml . kg\(^{-1}\) . min\(^{-1}\) and as percent predicted peak oxygen consumption. The predicted value was calculated from a regression...
equation which accounts for age, sex, body weight and height\textsuperscript{[23]}.

**Statistical analysis**

All data are summarized as mean ± standard error. Unpaired t-tests were performed to test for differences between group mean values for normally distributed variables. If data for a particular variable did not follow a normal Gaussian distribution, a Mann–Whitney rank sum test was applied. To confirm that any sympathetic activation observed in heart failure subjects was not simply a consequence of their higher resting rates, muscle sympathetic nerve activity was expressed as bursts per minute (burst frequency) and as bursts per 100 heart beats (burst incidence) when comparing baseline values between groups. Multiple regression analysis (SigmaStat\textsuperscript{[29]} for Windows, Ver. 1.0, Jandel Scientific Corp., San Rafael, CA) was used to determine the extent to which the dependent variable, peak oxygen consumption during exercise, could be predicted from the two independent variables, resting muscle sympathetic nerve activity burst frequency and age, in both heart failure patients and normal subjects. Linear regression was performed to describe the relationship between the percent of predicted peak oxygen consumption achieved (dependent variable) and resting muscle sympathetic nerve activity burst frequency (independent variable) for the two groups. A t-test was used to test the hypothesis that the two samples were drawn from populations with the same slope of the line of means.

**Results**

There was no significant difference between the heart failure group and the normal subjects with respect to mean age, height and resting systolic or diastolic blood pressure. However, when compared with healthy subjects, the heart failure group had a significantly higher body mass (\(P<0.01\)), mean resting heart rate (\(P<0.005\)), muscle sympathetic nerve activity burst frequency (\(P<0.0007\)) and incidence (\(P<0.02\)), a significantly lower peak oxygen consumption (\(P<0.0002\)) and percent of predicted peak oxygen uptake achieved (\(P<0.0002\)). These comparisons are shown in Table 1.

Heart failure patients were able to exercise to a mean peak heart rate of 154.7 ± 6.2 beats . min\(^{-1}\), which was 92 ± 3.3\% of their age-predicted maximal heart rate. This was not significantly different from the normal subjects who reached a mean peak heart rate of 162.2 ± 6.1 beats . min\(^{-1}\) or 95.0 ± 2.8\% of predicted, suggesting that these patients were not limited by chronotropic incompetence or beta\(_2\) adrenergic blockade and that both groups had a similar maximal effort. Of the 17 patients, nine (53\%) stopped exercise because of fatigue, seven (41\%) owing to dyspnoea and one because of chest discomfort; whereas of the 17 normal subjects, 15 (88.2\%) complained of fatigue at the test endpoint, only one (5.9\%) reported dyspnoea and one (5.9\%) was stopped because of a marked rise in blood pressure. There was no difference in the respiratory exchange ratio at peak exercise in heart failure patients (1.17 ± 0.02) as compared with normal subjects (1.18 ± 0.04).

In heart failure patients, there was no significant relationship by multiple regression analysis between left ventricular ejection fraction and either muscle sympathetic nerve activity burst frequency or peak oxygen uptake (\(r=0.13\)). Peak oxygen consumption (ml . kg\(^{-1}\) . min\(^{-1}\)) could be predicted from a linear combination of resting muscle sympathetic nerve activity burst frequency and age by the regression equation:

\[
\text{Peak oxygen consumption} = 40.5 - (0.347 \times \text{MSNA}) - (0.0570 \times \text{age})
\]

In this equation, only the slope of the muscle sympathetic nerve activity (MSNA) variable was significantly different from zero (\(P<0.02\)) (Fig 1).

In contrast, in the normal subjects peak oxygen consumption could be described by the regression equation:

\[
\text{Peak oxygen consumption} = 57.8 - (0.246 \times \text{MSNA}) - (0.375 \times \text{age})
\]

In this equation, only the slope of the variable, age, was statistically significant (\(P<0.04\)) (Fig. 2).

When the relationship between exercise limitation (i.e. percent of predicted peak oxygen consumption achieved) and muscle sympathetic nerve activity burst frequency was examined by linear regression, a significant correlation (\(r= -0.71, P<0.0014\)) was observed in heart failure patients, but not in normal subjects (\(r= -0.44, P<0.08\)). The slope of this relationship in

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**Table 1 Physical characteristics of heart failure patients and normal subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heart failure (n=17)</th>
<th>Normal (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.0 ± 2.8</td>
<td>44.0 ± 3.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176.7 ± 2.0</td>
<td>177.1 ± 1.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92.6 ± 4.0*</td>
<td>77.1 ± 3.1</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125.5 ± 3.8</td>
<td>118.0 ± 3.7</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74.4 ± 1.8</td>
<td>69.7 ± 2.6</td>
</tr>
<tr>
<td>HR (beats . min(^{-1}))</td>
<td>74.9 ± 3.5*</td>
<td>63.0 ± 1.8</td>
</tr>
<tr>
<td>Peak oxygen consumption (ml . min(^{-1}))</td>
<td>1925.0 ± 166.2*</td>
<td>2477.6 ± 123.0</td>
</tr>
<tr>
<td>(ml . kg(^{-1}) . min(^{-1}))</td>
<td>20.6 ± 1.7*</td>
<td>33.2 ± 2.6</td>
</tr>
<tr>
<td>(predicted)</td>
<td>63.7 ± 5.1*</td>
<td>91.6 ± 4.0</td>
</tr>
<tr>
<td>MSNA (bursts . min(^{-1}))</td>
<td>49.3 ± 2.8*</td>
<td>33.0 ± 3.3</td>
</tr>
<tr>
<td>(bursts . 100 beats(^{-1}))</td>
<td>66.5 ± 3.2*</td>
<td>52.2 ± 4.7</td>
</tr>
</tbody>
</table>

Values are given as mean ± SE. SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; MSNA=muscle sympathetic nerve activity. *\(P<0.001\).
heart failure patients was significantly steeper than that in normal subjects ($P<0.0001$) (Fig. 3). This demonstrates that peak exercise capacity in normal subjects is unrelated to resting muscle sympathetic nerve activity, whereas in heart failure, as resting muscle sympathetic nerve activity burst frequency increases, exercise capacity becomes increasingly limited.

In 14 of these 17 heart failure patients, there was no relationship between resting plasma noradrenaline levels and peak oxygen consumption ($r=-0.41$, $P<0.14$) or percent of predicted peak oxygen consumption achieved ($r=-0.45$, $P<0.01$).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No beta-blockade (n=9)</th>
<th>Beta blockade (n=8)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.1 ± 3.5</td>
<td>50.3 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Rest HR (beats . min$^{-1}$)</td>
<td>75.3 ± 4.3</td>
<td>74.4 ± 6.0</td>
<td>NS</td>
</tr>
<tr>
<td>MSNA (bursts . min$^{-1}$)</td>
<td>50.3 ± 3.3</td>
<td>48.3 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Rest SBP (mmHg)</td>
<td>128.4 ± 5.6</td>
<td>122.2 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Rest DBP (mmHg)</td>
<td>73.5 ± 2.9</td>
<td>75.1 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Peak exercise HR</td>
<td>160.2 ± 4.9</td>
<td>149.1 ± 10.4</td>
<td>NS</td>
</tr>
<tr>
<td>% of predicted peak HR</td>
<td>94.6 ± 2.5</td>
<td>87.9 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td>VO$_2$ peak (ml . kg$^{-1}$ . min$^{-1}$)</td>
<td>21.8 ± 2.3</td>
<td>19.3 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>% predicted VO$_2$ peak</td>
<td>67.9 ± 6.4</td>
<td>61.0 ± 8.3</td>
<td>NS</td>
</tr>
<tr>
<td>Correlation r-value</td>
<td>MSNA vs VO$_2$ peak</td>
<td>$-0.72$</td>
<td>$-0.64$</td>
</tr>
<tr>
<td></td>
<td>MSNA vs % predicted VO$_2$ peak</td>
<td>$-0.63$</td>
<td>$-0.81$</td>
</tr>
</tbody>
</table>

Values are means ± SE.
HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; VO$_2$=oxygen uptake; NS=no statistically significant difference between groups.

Patients taking the beta$_1$-adrenoceptor antagonist, metoprolol, for heart failure displayed similar baseline characteristics and response to exercise as those not prescribed this class of medication (Table 2).

**Discussion**

Limited exercise capacity, impaired peripheral vasodilation, and marked increases in sympathetic outflow to haemodynamically important vascular beds are present in most patients with symptomatic heart failure$^{8–13,19}$.
Noradrenaline spillover across the leg has been reported as more than double that of age-matched normal subjects\(^{[10]}\). Noradrenaline spillover increases further when heart failure patients exercise\(^{[24]}\). In experimental preparations, and in healthy humans, metabolic vasodilation and reactive hyperaemia can be attenuated by neurogenic vasoconstriction, but at the expense of limiting peripheral oxygen delivery\(^{[15,17,18,25–27]}\). However, in a recent study in heart failure patients, acute reduction in central sympathetic outflow by clonidine caused leg blood flow during exercise to increase, and plasma noradrenaline concentration and mixed venous lactate concentration to decrease\(^{[16]}\). In studies comprising young subjects with dilated cardiomyopathy and age-matched healthy volunteers, we documented a significant positive relationship between peroneal nerve muscle sympathetic nerve activity, and resistance in the calf, the vascular bed distal to the recording electrode\(^{[12]}\). When muscle sympathetic nerve activity in heart failure was reduced chronically by long-term beta\(_1\) selective blockade (metoprolol), there was a concordant fall in calf vascular resistance\(^{[28]}\). Whether increased sympathetic nerve discharge to muscle acts as a peripheral constraint on exercise capacity in heart failure remains controversial.

Our purpose in conducting the present study was to determine whether in patients with impaired left ventricular systolic function there is a relationship between the magnitude of central sympathetic outflow to muscle, at rest, as assessed by muscle sympathetic nerve activity burst frequency, and peak oxygen consumption during exercise. This goal was achieved. Our key and novel observation was the presence of a significant inverse relationship between the prevailing level of muscle sympathetic nerve activity and peak oxygen uptake in heart failure patients. This relationship was independent of age and was absent in age-matched subjects with normal ventricular systolic function. When considered as a percentage of predicted peak oxygen uptake achieved, exercise capacity in these heart failure patients was also inversely related to efferent sympathetic discharge to their calf muscle. The slope of this relationship was significantly steeper than in healthy subjects \((P<0.0001; \text{Fig. 3})\).

Could these correlations between muscle sympathetic nerve activity and peak oxygen consumption simply reflect, indirectly, the severity of heart failure? In clinical practice, left ventricular ejection fraction remains the most practical marker of prognosis\(^{[29]}\) and the benchmark used to develop standards of care based on evidence arising from mortality trials. If severity of illness were the sole explanation for these observations in heart failure patients, by this criterion significant relationships between left ventricular ejection fraction and muscle sympathetic nerve activity, and left ventricular ejection fraction and peak oxygen consumption should also be present. However, there was no relationship between left ventricular ejection fraction and either muscle sympathetic nerve activity or peak oxygen consumption, as in previously published reports\(^{[3,4,13,30]}\). Although such correlations in themselves cannot prove causality, they add to the above body of evidence implicating neurogenic vasoconstriction as an important constraint on exercise blood flow in heart failure patients that is independent of ventricular systolic function.

Several groups have reported an inverse correlation between resting venous plasma noradrenaline concentrations and peak oxygen uptake in patients with heart failure\(^{[3,4,19]}\) and have suggested that neurohormonal stimulation may modulate exercise capacity in this population. Others, using similar methods, have concluded the opposite\(^{[31]}\). Because elevated plasma catecholamine concentrations in chronic heart failure are a function of reduced clearance, as well of increased release, it is difficult to draw firm conclusions from these conflicting reports. Indeed, in a subgroup of 14 patients in whom plasma noradrenaline concentrations were measured, we observed significant correlations between muscle sympathetic nerve activity and peak oxygen consumption, but no relationship between resting plasma noradrenaline concentrations and either the absolute, or the percentage of predicted peak oxygen uptake achieved. This underscores the importance of acquiring direct measurements of muscle sympathetic nerve activity in studies of this nature.

Our findings in healthy subjects are consistent with previous reports describing a decrease in peak oxygen uptake and an increase in muscle sympathetic nerve activity with age\(^{[23,32]}\). However, muscle sympathetic nerve activity is not associated with peak oxygen uptake or the level of physical training in normal individuals\(^{[33]}\).

During dynamic exercise in healthy, conscious dogs, intra-arterial infusion of the alpha, adrenoceptor antagonist, prazosin, caused graded increases in

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**Figure 3** Relationship between percent of predicted peak oxygen uptake (VO\(_2\) peak) and muscle sympathetic nerve activity (MSNA) burst frequency in normal subjects (open circles) and patients with heart failure (closed circles). Regression lines are significantly different from one another \((P<0.0001)\). Heart failure patients: VO\(_2\) peak (%) = -1.28 MSNA + 127.6; \(r= -0.71, P<0.0014\). Normal subjects: VO\(_2\) peak (%) = -0.515 MSNA + 108.6; \(r= -0.44, P<0.08\).
terminal aortic or selective iliac blood flow, and in vascular conductance even at heavy workloads, indicating progressively greater restraint of muscle vasodilation by the sympathetic nervous system with increasing levels of exercise\(^{25,27}\). In healthy humans, the sympathetic nervous system is also capable of countering metabolic vasodilation\(^{13,17}\).

In human heart failure, blood flow in both small and large muscle groups is reduced at rest, and during dynamic exercise\(^{34,35}\). Arterial blood pressure and blood flow to non-exercising muscle are preferentially maintained, at the expense of hypoperfusion in exercising muscle\(^{36}\). As a consequence, there is less muscle oxygen consumption during exercise in these patients\(^{34}\). Those with the lowest peak oxygen uptake exhibit the greatest impairment in blood flow\(^{37}\). However, inhibition of the sympathetic nervous or renin–angiotensin vasoconstrictor systems does not immediately increase exercise performance\(^{16,35,38}\). A number of explanations have been proposed to account for this. Any increase in peripheral blood flow elicited by these interventions may be distributed to metabolically inactive tissues\(^{16,35}\) or may not be effectively utilized owing to intrinsic alterations in skeletal muscle, e.g., a reduction in the proportion of oxidative fibres\(^{31}\). Post-junctional alpha adrenergic receptors may not be accessed by blood-borne antagonists or blockade may be incomplete\(^{39}\).

Co-release, from sympathetic nerve endings, of vasoconstrictors such as adenosine triphosphate or neuropeptide Y, which are capable of restraining vasodilation during exercise, would not be affected by beta-blockade or angiotensin-converting enzyme inhibition\(^{40,41}\). Sympathetic outflow may be only one of several factors contributing to impaired vasodilation in heart failure. Others include endothelial dysfunction, vascular stiffness from increased vascular sodium content, deconditioning or structural alterations of the vessel wall, and additional neural, humoral or local vascular factors not measured in the present study\(^{42}\). Redundancy in these systems could prevent exercise capacity from increasing acutely following sympatholytic therapy, and these mechanisms may differ in the time course required for their reversal. For example, there is a lag period between improvements in haemodynamics and increases in exercise tolerance after institution of vasodilator therapy\(^{30,38}\) or after heart transplantation\(^{43}\), but muscle sympathetic nerve activity will normalize as cardiac function and symptoms improve following transplantation\(^{44}\). Exercise training reduces independent markers of adrenergic activity as symptoms and peak oxygen uptake improve\(^{45,46}\).

Almost half of the patients were provided chronic beta\(_1\) adrenoceptor blockade with metoprolol. Had we been unable to demonstrate a relationship between muscle sympathetic nerve activity and peak oxygen uptake, beta adrenoceptor blockade might be proposed as a potential confounding variable. However, this subgroup did not differ from the remainder with respect to any principal study variable (Table 2). Previous studies of long-term metoprolol therapy for heart failure have documented increases in peak oxygen uptake\(^{47,48}\), decreases in peroneal muscle sympathetic nerve activity, and concurrent decreases in calf vascular resistance\(^{28}\). The mechanism by which chronic metoprolol therapy increases peak oxygen consumption in heart failure has not been established, but a plausible hypothesis, and one supported by the results of the present study, is that a fall in central sympathetic outflow to skeletal muscle contributes to this increase.

Because microneurographic recordings cannot be sustained during maximal bicycle exercise, our study was neither designed nor intended to address the issue of how exercise-induced sympathetic activation correlates with peak oxygen consumption. However, in subjects both with normal and with impaired ventricular systolic function, there is a significant positive relationship between venous plasma noradrenaline concentrations and muscle sympathetic nerve activity\(^{11,13}\), and in patients with heart failure of varying degrees of severity, basal levels of plasma noradrenaline correlate significantly with those achieved during maximal exercise\(^{49}\).

In summary, we conclude that there is a significant inverse relationship between peak oxygen uptake and resting sympathetic nerve traffic to muscle in human heart failure that is independent of age and absent in normal subjects. Although this demonstration does not infer causality, it implies that approximately one-half of the variance in exercise capacity in these patients relates to resting sympathetic outflow to muscle. By contrast, there was no relationship between muscle sympathetic nerve activity, at rest, and left ventricular ejection fraction. When expressed as a percentage of peak oxygen uptake, as predicted by age, sex and body size, the extent of exercise limitation is also inversely related to resting muscle sympathetic nerve traffic; the slope of this relationship is significantly steeper in heart failure than in healthy subjects \(P<0.0001\). These results support the concept of a peripheral limit to exercise which may be related to the degree of sympathetic outflow in heart failure, and suggest that interventions that specifically inhibit central sympathetic outflow, over time, may improve both exercise capacity and survival in these patients.

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