Impact of heart failure and exercise capacity on sympathetic response to handgrip exercise

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Notarius, Catherine F., Deborah J. Atchison, and John S. Floras. Impact of heart failure and exercise capacity on sympathetic response to handgrip exercise. Am J Physiol Heart Circ Physiol 280: H969–H976, 2001.—Peak oxygen uptake (VO2peak) in patients with heart failure (HF) is inversely related to muscle sympathetic nerve activity (MSNA) at rest. We hypothesized that the MSNA response to handgrip exercise is augmented in HF patients and is greatest in those with low VO2peak. We studied 14 HF patients and 10 age-matched normal subjects during isometric [30% of maximal voluntary contraction (MVC)] and isotonic (10%, 30%, and 50% MVC) handgrip exercise that was followed by 2 min of posthandgrip ischemia (PHGI). MSNA was significantly increased during exercise in HF but not normal subjects. Both MSNA and HF levels remained significantly elevated during PHGI after 30% isometric and 50% isotonic handgrip exercise in HF but not normal subjects. HF patients with lower VO2peak (<56% predicted; n = 8) had significantly higher MSNA during rest and exercise than patients with VO2peak > 56% predicted (n = 6) and normal subjects. The muscle metaboreflex contributes to the greater reflex increase in MSNA during ischemic or intense nonischemic exercise in HF. This occurs at a lower threshold than normal and is a function of VO2peak.

muscle sympathetic nerve activity; metaboreflex; VO2peak; left ventricular dysfunction; ischemia

SYMPTOMATIC HEART FAILURE due to left ventricular systolic dysfunction is characterized by limited exercise capacity, impaired peripheral vasodilation, and increases in central sympathetic outflow to hemodynamically important vascular beds (4, 16, 20, 28, 31). Plasma norepinephrine levels and cardiac norepinephrine spillover are increased in asymptomatic left ventricular dysfunction, are further increased in patients with severe heart failure (HF) (24), and are associated with poor prognosis (1, 9).

Several reflex mechanisms may contribute to sympathetic activation in HF (5). One of these is the muscle metaboreflex (18, 27, 29, 30), which in healthy young subjects matches blood flow and metabolism in exercising muscle (23). In animal models this reflex is activated by muscle ischemia (26). In experimental HF, which lowers the threshold for ischemia, the metaboreflex is evoked at moderate workloads (6). Whether this occurs in human HF is controversial; an overactive metaboreflex (18, 19, 29), an intact but ineffective metaboreflex (in that the resulting improvement in perfusion pressure did not enhance either muscle blood flow or oxidative metabolism) (27), and a desensitized metaboreflex (30) have all been described.

There have been no reports comparing sympathetic nerve traffic to muscle in HF and healthy subjects across a range of submaximal work rates under both rhythmic nonischemic (isotonic) and ischemic (isometric) conditions. If present, activation of the muscle metaboreflex at a lower threshold in HF patients could have two important implications: 1) comparisons under resting conditions would underestimate the magnitude and pathophysiological consequences of sympathetic activation (5), and 2) augmented neurogenic vasoconstriction during activity might further compromise exercise capacity (16, 27, 28).

We recently identified a significant inverse relationship between sympathetic outflow to calf skeletal muscle (measured at rest) and exercise capacity in HF patients. This relationship was absent in healthy controls (16). This finding is consistent with the concept that increased sympathetic outflow contributes to active muscle hypoperfusion during exhaustive dynamic exercise in human HF (11, 28, 31) and supports the concept of a peripheral neurogenic limit to exercise in this condition.

The purpose of the present study was to examine systematically the effect of ischemic and rhythmic handgrip exercise at different intensities on muscle sympathetic nerve activity (MSNA) in HF and age-matched normal subjects. In addition, we determined whether the sympathoneural response to handgrip exercise is augmented further in those HF patients with markedly reduced exercise capacity. To relate such changes in sympathetic activity to the stimulus of ischemic metabolites generated locally during handgrip exercise, responses to posthandgrip ischemia (PHGI) were also examined (13). We hypothesized that: 1) sympathetic traffic to muscle during both isometric and rhythmic ischemic handgrip exercise would...
be greater in HF patients, 2) sympathetic activation would be detected at a lower intensity of isotonic exercise in HF, and 3) patients with mildly to moderately impaired exercise tolerance would display a sympathetic response intermediate between that of age-matched healthy subjects and patients with severely reduced exercise capacity.

METHODS

Subjects

HF patients. We studied 14 stable patients (13 males and 1 female) aged 51.4 ± 3.7 (mean ± SE) yr with moderate to severe left ventricular systolic dysfunction (ejection fraction by radionuclide ventriculography 19 ± 2%). Seven patients had ischemic and seven had dilated cardiomyopathy. Within this population, 12 patients (86%) were taking angiotensin-converting enzyme inhibitors; 13 (92%) were taking diuretics; 10 (71%) were taking β1-adrenoceptor blocking drugs; 8 (57%) were taking digitalis; and 5 (36%) were taking anticoagulants. Clinical management also included dietary sodium and fluid restriction. Patients were free of congestion, significant edema, or orthopnea.

Healthy subjects. We recruited and screened 10 healthy volunteers (9 males and 1 female, ages 48.0 ± 3.9 yr). None were taking medication.

This protocol was approved by the Human Subjects Review Committee of the University of Toronto. Informed written consent was obtained from each subject before participation.

Procedures

All studies were performed while patients were supine in a quiet, temperature-controlled laboratory under similar conditions. Blood pressure was monitored from the left arm every minute by an automated device (Lifestat 200, Physio-conditions). MAP that was sustained during PHGI (P 0.05; Fig. 1). Protocol

For subject comfort, diuretics were withheld the morning and a 20-min stabilization period, 7–10 min of baseline values were obtained. The following tests were then performed in random order: sustained handgrip (isometric or ischemic exercise) at 30% MVC and rhythmic handgrip (isotonic or nonischemic exercise) at 10, 30, and 50% MVC. Two minutes of handgrip were followed by 2 min of PHGI. An upper-arm cuff was inflated to 200 mmHg to trap metabolites released by the muscle contraction and to dissociate the biochemical from the mechanical effects of muscle contraction. Variables were averaged for the 2-min baseline, each minute of handgrip, the 2 min of PHGI, and the subsequent 2 min of recovery. To assess the integrity of efferent sympathetic responsiveness to a nonmetaboreflex-mediated stimulus, one hand was immersed in ice water for 1.5 min. Subjects rested for 10–12 min between handgrip tasks until heart rate and blood pressure were observed to return to preexercise levels.

Low VO2 peak versus high VO2 peak. The median for VO2 peak in these HF patients was 56% of that predicted by age, sex, and body size. Patients were allocated to a high (n = 6) or low (n = 8) VO2 peak group, depending on whether their values were above or below this median.

Statistical Analysis

Data are presented as means ± SE. Unpaired t-tests were performed to test for differences between group means. Two-way ANOVA with repeated measures (SigmaStat for Windows 1.0, Jandel Scientific; San Rafael, CA) was performed with groups (HF patients and normal subjects) and intervention (prehandgrip, 1- and 2-min handgrip, PHGI, and recovery) as the two factors. A post hoc Student-Newman-Keuls test was applied to assess the effects of specific interventions.

RESULTS

Comparison of HF and Normal Subjects

The two groups of subjects were similar in age, height, weight, resting heart rate, blood pressure, and resting forearm blood flow, which suggested optimal medical management of their HF (Table 1). However, HF patients had significantly higher resting sympathetic nerve burst frequency and burst incidence (P < 0.0001) and lower VO2 peak and percentage of predicted VO2 peak (P < 0.0001; Table 1).

Mean arterial blood pressure (MAP) at baseline and during handgrip exercise was similar in both HF and normal subjects. In both groups, MAP increased significantly during the second minute of 30% ischemic and 50% isotonic handgrip and remained elevated during PHGI after isometric handgrip. In HF subjects only, 10% isotonic exercise elicited a significant increase in MAP that was sustained during PHGI (P < 0.05; Fig. 1).

Mean heart rates at baseline and during handgrip exercise were similar in both groups. There were significant increases in heart rate during the second minute of 30% isometric handgrip and the first and second minutes of 50% rhythmic handgrip (P < 0.05).
However, in contrast to normal subjects, heart rate in HF patients did not return to baseline values during PHGI after these two exercise tasks (P < 0.05; Fig. 2).

MSNA burst frequency was significantly greater in HF patients under all experimental conditions (main effect of group, all P < 0.001; Fig. 3), and in contrast to normal subjects, each of these exercise protocols evoked a significant increase in MSNA above baseline (P < 0.05). Moreover, in HF patients MSNA remained elevated during PHGI after both 30% isometric and 50% isotonic handgrip (P < 0.05) and during the recovery period after sustained handgrip exercise (P < 0.05; Fig. 3).

A similar pattern was noted for the integrated MSNA response in HF patients. Normal subjects demonstrated an increase in the integrated MSNA response to 50% isotonic handgrip (P < 0.05) and a nonsignificant trend toward higher integrated MSNA during the second minute of 30% isometric handgrip exercise. However, integrated MSNA during PHGI was elevated only in HF patients and only at the highest intensity of isotonic handgrip (P < 0.05).

The increase in heart rate and MSNA with the cold pressor test was similar in HF and normal subjects (15.0 ± 6.1 beats/min and 11.1 ± 2.6 bursts/min; 15.5 ± 2.4 beats/min and +6 ± 2 bursts/min, respectively; P = 0.77 for heart rate, and P = 0.15 for MSNA).

Influence of VO₂peak

Subdivision of the HF patients on the basis of their VO₂peak values resulted in two groups of similar age, body size, and blood pressure (Table 2). Mean heart rate was significantly higher in HF subjects with low VO₂peak (P < 0.03), even though seven of eight patients in this group versus three of six patients in the high-VO₂peak group were receiving β-adrenoceptor antagonists. There was a trend, not significant, toward lower

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (n = 10)</th>
<th>Heart Failure (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>48.0 ± 4.0</td>
<td>51.4 ± 3.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>176.0 ± 3.0</td>
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<tr>
<td>Weight, kg</td>
<td>75.5 ± 5.8</td>
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<tr>
<td>SBP, mmHg</td>
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<td>DBP, mmHg</td>
<td>72.8 ± 2.5</td>
<td>73.6 ± 4.0</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>67.8 ± 3.1</td>
<td>67.8 ± 4.0</td>
</tr>
<tr>
<td>FBF, ml·min⁻¹·100 g⁻¹</td>
<td>3.3 ± 0.5</td>
<td>3.5 ± 0.4</td>
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<tr>
<td>MSNA bursts/min</td>
<td>33.0 ± 2.5</td>
<td>52.7 ± 2.6*</td>
</tr>
<tr>
<td>bursts/100 beats</td>
<td>50.3 ± 4.6</td>
<td>78.9 ± 2.6*</td>
</tr>
<tr>
<td>VO₂peak, ml·kg⁻¹·min⁻¹</td>
<td>34.4 ± 2.0</td>
<td>18.6 ± 1.6*</td>
</tr>
<tr>
<td>VO₂peak, % predicted</td>
<td>104.0 ± 7.2</td>
<td>57.3 ± 4.6*</td>
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</table>

Values are means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; FBF, forearm blood flow; MSNA, muscle sympathetic nerve activity; VO₂peak, peak oxygen uptake; P < 0.0001.

Fig. 1. Mean arterial pressure (MAP) response to handgrip (HG) exercise in heart failure (HF, ◦) and normal subjects (●). Pre, pre-HG; HG1 and HG2, first and second minutes, respectively, of HG exercise; PHGI, post-HG ischemia; and Rec, recovery. *P < 0.05 compared with pre-HG in both HF and normal subjects; †P < 0.05 compared with pre-HG in HF patients only.
Fig. 2. Heart rate (HR) response to HG exercise in HF (○) and normal subjects (●). *P < 0.05 compared with pre-HG in both HF and normal subjects; †P < 0.05 compared with pre-HG in HF patients only; and #P < 0.05 compared with pre-HG in normal subjects only.

Fig. 3. Muscle sympathetic nerve activity (MSNA) response to HG exercise in heart failure (○) and normal subjects (●). Stated P values refer to the significance level of the main effect of group; *P < 0.05 compared with pre-HG in both HF and normal subjects; †P < 0.05 compared with pre-HG in HF patients only.
FBF at rest in the $\text{VO}_2 \text{peak} < 56\%$ group. MSNA burst frequency at rest was significantly higher in the low-$\text{VO}_2 \text{peak}$ group ($P = 0.007$) whereas burst incidence was not.

In contrast to healthy subjects, MSNA rose significantly above baseline values during 30% isometric and 50% rhythmic handgrip exercise in both HF patient groups, with burst frequency significantly higher in the low $\text{VO}_2 \text{peak}$ group. When compared with both high $\text{VO}_2 \text{peak}$ patients and normal subjects, MSNA burst frequency was significantly higher in low $\text{VO}_2 \text{peak}$ patients at baseline, during handgrip at all intensities, PHGI, and recovery ($P = 0.0001$; Fig. 4). Results were similar for integrated MSNA except for 50% isotonic handgrip, which showed only a nonsignificant trend toward higher values in the low $\text{VO}_2 \text{peak}$ group.

Despite the profound reduction in ejection fraction in the high $\text{VO}_2 \text{peak}$ patients, with one exception there was no significant difference in sympathetic activity between this HF group and age-matched normal subjects. Burst frequency during the second minute of 30% isometric exercise was significantly lower in control subjects (Fig. 4). The lowest intensity of exercise (10% of rhythmic exercise) elicited a significant increase in MSNA from baseline in patients with high $\text{VO}_2 \text{peak}$, but not low $\text{VO}_2 \text{peak}$ or control subjects (Fig. 4).

**DISCUSSION**

The new findings of this study are the following: 1) in HF, significant reflex increases in MSNA can be induced by ischemic and nonischemic handgrip exercise at intensities without effect on MSNA in age-matched subjects with normal left ventricular function, even at intensities of rhythmic handgrip as low as 10% MVC; 2) HF patients with low $\text{VO}_2 \text{peak}$ have consistently higher MSNA during and after exercise, whereas patients with left ventricular systolic dysfunction and high $\text{VO}_2 \text{peak}$ display responses to handgrip that are either intermediate with respect to the other two groups or virtually indistinguishable from normal subjects; and 3) MSNA and heart rate remain elevated during PHGI after both isometric exercise at 30% MVC and isotonic exercise at 50% MVC in HF but not normal subjects. Taken together, these observations indicate that sympthoexcitatory reflexes arising from ex-
ercising muscle are stimulated at a lower threshold in advanced HF patients than in subjects with normal ventricular function and are triggered by local ischemia during isometric and intense rhythmic handgrip exercise.

**Hemodynamic and sympathoneural responses to handgrip exercise.** In healthy young (age <30 yr) volunteers, sustained handgrip at 30% MVC causes immediate increases in heart rate and blood pressure, whereas MSNA does not increase until the second minute of exercise (13). During forearm PHGI, heart rate returns to baseline whereas blood pressure and MSNA remain elevated. This sustained elevation in MSNA and blood pressure has been attributed to the muscle metaboreflex which is mediated via chemosensitive type III and type IV muscle afferents (13). Metabolites such as lactic acid, arachidonic acid products, and adenosine, which are generated by muscle contraction, can stimulate these nerve endings (2, 22). Infusion of adenosine into the brachial artery at a concentration without systemic effect causes a marked reflex increase in the rate of total body norepinephrine appearance into plasma (21). However, the role of endogenous adenosine in triggering the sympathetic pressor response to static exercise remains controversial (12).

Rhythmic handgrip, in contrast, whether at 10, 30, or 50% MVC, does not increase MSNA in healthy young volunteers, presumably because the intermittent muscle relaxation permits rapid washout of any ischemic metabolites that are generated (32). However, if washout is interrupted by occlusion of forearm venous return, 30% rhythmic handgrip does elicit a significant increase in MSNA (32).

The MSNA response to isometric exercise is attenuated with age (15). This has been attributed in part to the higher baseline levels of MSNA that are characteristic of older subjects and are present in the middle-aged control group in the current study (see Ref. 8 for comparison). In young subjects with normal ventricular function, 30% isometric handgrip increases MSNA during the second minute of exercise (13). In the present study there was a trend toward higher MSNA during the second minute of 30% isometric handgrip, a finding that is consistent with that obtained by Stearns and colleagues (30) in a similar older but healthy group of subjects. Of the several tasks performed in the present series, only rhythmic exercise at 50% MVC increased integrated MSNA significantly in control subjects.

In advanced HF, skeletal muscle metabolism is altered (14) and blood flow to small and large muscle groups is reduced at rest and during dynamic exercise (1, 10, 20, 33). Patients with the lowest VO\textsubscript{2}\text{peak} have the greatest impairment in blood flow (33). As a consequence, low levels of rhythmic handgrip exercise that are insufficient to elicit sympathetic excitation in healthy subjects might induce ischemia and trigger the muscle metaboreflex in patients with HF due to systolic dysfunction. Indeed, in experimental canine HF, the muscle metaboreflex is tonically active during moderate exercise, is stimulated at a lower threshold, and raises blood pressure primarily by means of reflex neurogenic vasoconstriction rather than through an increase in cardiac output (6). However, there is disagreement as to whether this reflex contributes to the increase in resting adrenergic tone in human HF or becomes active and functionally important during exercise (18, 19, 27, 29, 30).

Sterns and co-workers (30) observed similar increases in MSNA (which was expressed as the percent change in total amplitude) in response to static handgrip at 30% MVC in HF and control subjects. MSNA rose further during PHGI in controls but diminished in HF subjects. These authors concluded that the metaboreceptor reflex is impaired in HF. In contrast, in a subsequent report from the same laboratory, rhythmic handgrip (25% MVC) produced greater percentage increases in integrated MSNA in HF than control subjects. These were sustained during PHGI after fatiguing exercise in the HF group only (29). Although the pressor response to handgrip exercise in HF could be augmented further under ischemic conditions, this did not improve limb perfusion or muscle metabolism, two determinants of exercise capacity (27).

In another study, the effects of 50% rhythmic handgrip exercise on diastolic blood pressure, heart rate, and leg vascular resistance were greater in HF than control subjects. Forearm training attenuated these responses (18). There was a direct relation between the muscle ergoreflex (metaboreflex) contribution to the ventilatory response to handgrip and New York Heart Association class and an inverse relationship with VO\textsubscript{2}\text{peak} (19), suggesting a neural link among impaired exercise capacity, exertional dyspnea, and an augmented ergoreceptor reflex in HF.

Differences in patient characteristics or experimental protocols may be responsible for these discordant results. The present experiments were undertaken to resolve these ambiguities by recording MSNA directly in patients with HF due to left ventricular systolic dysfunction and in age-matched healthy subjects during both isometric and rhythmic handgrip exercise according to a similar timed protocol, including a broad range of intensities of isotonic handgrip and the application of PHGI. We hypothesized that compared with normal subjects, sympathetic traffic to muscle in HF would be augmented during both isometric handgrip and rhythmic handgrip exercises, and that this increase would be maintained during PHGI after those exercise tasks that induced sympathoexcitation.

MSNA burst frequency was significantly higher in HF patients under all experimental conditions, and in contrast to normal subjects, each of these exercise protocols evoked a significant increase in MSNA above baseline. This novel finding is consistent with the concept that HF lowers the threshold to muscle ischemia and metaboreflex stimulation during handgrip exercise. This concept is supported by experimental evidence from a canine model of HF (6). It is also concordant with the observation in human HF that the metaboreflex-induced pressor response can be enhanced during low-intensity prolonged rhythmic hand-
grip exercise if muscle blood flow is constrained by the application of external positive pressure (27). In the present study, MSNA in HF patients remained elevated during PHGI after both 30% isometric and the highest intensity (50% MVC) of isotonic handgrip exercise and during the recovery period after sustained handgrip. This suggests that these tasks reduced oxygen delivery to muscle to the point where the threshold for activation of the muscle metaboreflex was exceeded, resulting in the generation of sufficient ischemic metabolites to sustain this sympathetic activation even after the termination of exercise. The return of MSNA to baseline values immediately after lower intensities of rhythmic handgrip exercise would be anticipated if the local concentration of ischemic metabolites generated by these two tasks was less but still greater than in the control subjects with normal ventricular function.

Heart rate responses to handgrip exercise. O’Leary (17) noted an increase in heart rate that was maintained in dogs given atropine during muscle ischemia after whole body exercise. Thus in the present study, decreased vagal tone in the HF group (3) might unmask underlying sympathetically induced increases in heart rate. Consistent with this concept and in contrast to control subjects, the heart rate of HF patients remained elevated during PHGI after both isometric exercise and isotonic exercise at 50% MVC. This additional novel finding suggests that the muscle metaboreflex has an important role in determining the heart rate response to exercise in human HF.

Impact of exercise capacity. Controversy in the literature with respect to effects of handgrip exercise and PHGI on MSNA may arise from differences in patient characteristics. When compared with both high VO$_2$ peak patients and normal subjects, patients with low VO$_2$ peak had consistently higher MSNA during and after exercise. This observation is consistent with our recent demonstration of an inverse relationship between MSNA at rest and VO$_2$ peak in HF (16).

Despite their marked reduction in ejection fraction, MSNA at rest in the high VO$_2$ peak group was remarkably similar to that in control subjects. However, MSNA increased significantly from baseline during 30% isometric and 10% and 50% rhythmic handgrip exercise. Thus an exaggerated sympathetic response to exercise is present in HF even in patients without activation of MSNA at rest and relatively preserved VO$_2$ peak. Interestingly, the significant increase in MSNA in response to 10% handgrip was confined to the high VO$_2$ peak group, suggesting that activation of the metaboreflex at very low levels of exercise might be a characteristic of the early stages of HF, which is attenuated with disease progression.

In subjects with normal ventricular function, physical conditioning has no effect on MSNA at rest or in the response to handgrip exercise (25). Furthermore, all subjects were exercised at a workload relative to their own maximum voluntary contraction. Therefore it is unlikely that the observed differences between high VO$_2$ peak and low VO$_2$ peak patients are simply a result of physical deconditioning.

The limitations of this study are the following. The present experiments do not address the question as to whether an activated muscle metaboreflex at rest contributes to the marked increase in adrenergic drive observed in patients with advanced HF. Because previous experiments in normal subjects demonstrated that the muscle metaboreflex evokes parallel sympathetic activation to exercising and nonexercising muscle (7), it was assumed that MSNA measured in the peroneal nerve supplying calf muscle reflects sympathetic activation in the exercising forearm. These patients were receiving medications that might affect baseline values and heart rate responses to exercise. However, the present observations in treated subjects avoid the adverse effects of drug withdrawal and are directly relevant to the effect of exercise in optimally managed HF patients.

In conclusion, this study shows that the sympathetic response to both isometric and rhythmic handgrip exercise of various intensities is exaggerated in patients with HF compared with normal subjects. Sympathetic activation is greatest in patients with low VO$_2$ peak who have higher resting, exercise, and recovery MSNA compared with patients with higher VO$_2$ peak and normal subjects. However, patients with higher VO$_2$ peak also show a significant increase in MSNA in response to ischemic and nonischemic handgrip exercise. Stimulation of the muscle metaboreflex elicits an augmented MSNA and heart rate response to ischemic or intense nonischemic exercise in HF, which could further limit exercise capacity and accelerate disease progression in such patients.

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