

Skeletal Muscle Metaboreceptor Exercise Responses Are Attenuated in Heart Failure

David A. Sterns, MD; Steven M. Ettinger, MD; Kristen S. Gray, MS; Sandra K. Whisler; Timothy J. Mosher, MD; Michael B. Smith, PhD; and Lawrence I. Sinoway, MD

Background. Resting sympathetic nervous system activity is increased in heart failure. Whether sympathetic nervous system responses during exercise are increased is controversial. Furthermore, the role of muscle metaboreceptors and central command in regulating sympathetic outflow has been largely unexplored.

Methods and Results. Muscle sympathetic nerve activity (MSNA, peroneal nerve) was measured in nine heart failure subjects and eight age-matched control subjects during static exercise (30% maximal voluntary contraction) for 2 minutes and during a period of posthandgrip regional circulatory arrest. This maneuver isolates the metaboreceptor contribution to sympathetic nervous system responses. MSNA responses were similar during static exercise in the two groups. During posthandgrip regional circulatory arrest we observed a marked attenuation in MSNA responses in the heart failure subjects (15% increase in heart failure versus 57% increase in control subjects). A cold pressor test demonstrated a normal MSNA response to a potent nonspecific stimulus in the heart failure subjects (heart failure subjects, 141% increase; control subjects, 215% increase; NS). Nuclear magnetic resonance spectroscopy studies in five separate heart failure subjects and five control subjects suggested that the attenuated metaboreceptor response in heart failure was not due to reduced H⁺ production.

Conclusions. Skeletal muscle metaboreceptor responses are impaired in heart failure. Because MSNA responses during static exercise are similar in the two groups, mechanisms aside from metaboreceptor stimulation must be important in increasing sympathetic nervous system activity. (*Circulation* 1991;84:2034–2039)

During exercise, sympathetic nervous system activity increases.¹ This enhanced activity is important in increasing cardiac output and in regulating blood flow delivery to both metabolically active and inactive vascular beds.² Two separate reflex systems are thought to be predominantly responsible for this increase in sympathetic outflow.

First, a central neural system termed central command appears to be activated in parallel with α -motor neuron unit recruitment.^{3,4} This system plays an important role in heart rate control and appears to have less of an impact on sympathetic constrictor activity to peripheral vascular beds.⁵ In fact, some have suggested that central command can act to reduce sympathetic outflow to the periphery.^{6,7}

The second important reflex system is termed the skeletal muscle metaboreflex.⁸ The afferent component of this system is composed of finely myelinated and unmyelinated group III and IV fibers.⁹ The endings of these fibers reside in the interstitium of the skeletal muscle and are thought to be responsive to changes in metabolite concentrations. The precise stimulants of this system are unclear, although a number of studies suggest a prominent role for lactic acid and/or reductions in muscle pH.^{10–13,27} Activation of this system in humans increases sympathetic outflow to skeletal muscle and has less of an influence on heart rate.^{6,12,13}

In heart failure, sympathetic nervous system activity is increased at rest.^{14–16} However, it is unclear if sympathetic neural responses to exercise in this disease are attenuated,¹⁷ normal,¹⁸ or exaggerated.¹⁹ Moreover, the relative contributions of central command and skeletal muscle metaboreceptor stimulation to overall sympathoexcitation have been largely unexplored. This would seem to be an important area of investigation because the level and distribution of sympathetic outflow may contribute to exercise intolerance, a hallmark of heart failure.

From the Departments of Medicine and Radiology, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pa.

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Address for correspondence: Lawrence I. Sinoway, MD, Milton S. Hershey Medical Center, Pennsylvania State University, Division of Cardiology, PO Box 850, Hershey, PA 17033.

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In the present report, we examined direct intraneural recordings of muscle sympathetic nerve activity (MSNA) from the peroneal nerve during static forearm exercise in a group of subjects with severe heart failure and in age-matched controls. We also compared MSNA in these groups during a period of posthandgrip regional circulatory arrest. This postexercise maneuver isolates the MSNA response that is due to skeletal muscle metaboreceptor stimulation.^{6,12,13,27} Our results demonstrated that during static exercise, MSNA rose similarly in the two groups. However, MSNA fell to near baseline values during posthandgrip regional circulatory arrest in the heart failure subjects, whereas it remained elevated in the control group. Separate exercise studies using ³¹P nuclear magnetic resonance (NMR) techniques demonstrated that acid production was not attenuated in the heart failure subjects. These results suggest that muscle metaboreceptor responsiveness to released muscle acid is impaired in heart failure. Moreover, for MSNA responses to be the same during static exercise in the presence of attenuated metaboreceptor responsiveness, it is suggested that there is a greater reliance on central command in heart failure.

Methods

We studied nine heart failure subjects and eight controls. All subjects signed an informed consent form previously approved by our clinical investigation committee. In the heart failure subjects, medications were held for at least 12 hours before the study.

The maximal voluntary contraction (kg) was measured in the nondominant forearm of each subject. The subjects were placed supine and were instrumented with electrocardiogram leads, an automated blood pressure device (Dinamap; Tampa, Fla.), and a pneumograph to record the stage of ventilation.

After instrumentation, baseline heart rate, mean arterial blood pressure (MAP), and MSNA data were obtained for 5 minutes. The subjects then performed static forearm exercise at 30% of maximal voluntary contraction. This stimulus has previously been shown to increase MSNA levels in normal volunteers.^{6,12} Two minutes after the initiation of exercise, the circulation to the forearm was arrested by inflating an upper arm occlusion cuff (250 mm Hg), and forearm exercise was discontinued. Posthandgrip regional circulatory arrest was continued for 3 minutes.

Microneurographic Technique

The right leg was slightly raised and supported for the microneurographic procedure that has been previously described.^{6,20,21} Multiunit recordings of MSNA were obtained using a tungsten electrode placed in a muscle fascicle in the peroneal nerve just below the fibular head. The electrode has a 200- μ m shaft that tapers to a 1–5- μ m tip. A reference electrode was placed 1–3 cm from the active electrode. The neural signal was amplified by a factor of 50,000–100,000. The resultant signal was fed through

a bandpass filter with low- and high-frequency cutoffs of 700 and 2,000 Hz, respectively. The signal was then rectified and integrated. Upon completion of the experiment, the neurogram was analyzed by manually counting the number of bursts per minute as well as the amplitude of each burst for total amplitude per minute. The data are presented as bursts and as percent change in total amplitude (A% MSNA).

In five of these heart failure subjects and eight controls, we performed a cold pressor test by applying ice to the forehead for 90 seconds as we measured MSNA. This was done in an effort to determine if heart failure and control subjects respond similarly to a strong nonspecific neural stimulus.

NMR Studies

In five separate heart failure subjects and five age-matched controls, we measured forearm skeletal muscle pH during two protocols: 30% and 40% of maximal voluntary contraction, both followed by posthandgrip regional circulatory arrest. For these experiments we used ³¹P NMR spectroscopy as previously described in our laboratory.¹³ These additional experiments were performed to determine if differences in muscle acid production between heart failure and control subjects could potentially explain differences in MSNA that were seen during the peroneal nerve recording experiments.

The ³¹P NMR spectra were obtained with a 1.9-T, 27-cm bore superconducting magnet (Oxford Instruments) interfaced to an NMR spectrometer (Nicolet). A 2.5-cm circular two-turn surface coil was placed on the forearm over the flexor digitorum superficialis and held in place by a piston and cylinder coil mount. Field homogeneity was optimized by adjusting the room temperature gradients to maximize the proton signal.²² The ³¹P spectra were collected at 32.5 MHz with a 1.9-second delay between radiofrequency pulses. Spectra were obtained from the Fourier transformation of 32 transients averaged over 60 seconds. The concentrations of inorganic phosphate (P_i) and phosphocreatine (PCr) were determined using the areas under each respective spectral curve. Intracellular pH was calculated from the chemical shift of the P_i resonance in relation to the PCr peak.²³

Statistical Analysis

Heart rate, MAP, and MSNA (burst count and A% MSNA) data were compared using a repeated measures two-way analysis of variance testing for two main effects: subject group (heart failure versus control subjects) and protocol (first and second minute of static exercise and posthandgrip regional circulatory arrest). If significant main effects or a statistical interaction were noted, the simple effects were analyzed. With this method, the effects of each independent variable (subject group) are examined at the various levels of the other independent variable (protocol). Probability values of less than 0.05 were considered statistically significant. Values are presented as mean \pm SEM.

TABLE 1. Heart Rate, Blood Pressure, and Burst (Muscle Sympathetic Nerve Activity) Data

	Baseline	Grip (min 1)	Grip (min 2)	PHG-RCA
Heart rate (beats/min)				
Heart failure subjects	87±7	90±8	92±8	90±7
Control subjects	65±2*	70±2*	71±3*	66±2*
Mean arterial pressure (mm Hg)				
Heart failure subjects	92±5	94±5	99±6	95±5
Control subjects	97±3	102±2	107±3	103±3
Bursts (units/min)				
Heart failure subjects	50±4	55±5	59±6	54±6
Control subjects	29±5*	32±5*	34±5*	37±6*

Grip (min 1), first minute of static exercise; Grip (min 2), second minute of static exercise; PHG-RCA, posthandgrip regional circulatory arrest. Significant protocol effects noted for each variable and a subject effect was noted for heart rate and bursts.

*Significant simple effect (heart failure vs. control subjects). Values are mean±SEM (heart failure subjects, $n=9$; control subjects, $n=8$). Blood pressure data not obtained during 1 minute of grip for one heart failure subject, therefore his data is not included in mean arterial pressure.

Results

Subject Characteristics

Heart failure and control subjects had similar ages (heart failure, 53 ± 5 years; control subjects, 55 ± 4 years; NS) and weight (heart failure, 176 ± 10 lb; control subjects, 177 ± 12 lb; NS). Heart failure subjects had lower maximal voluntary contraction values than control subjects (heart failure, 38 ± 3 kg; control subjects, 45 ± 2 kg; $p<0.05$).

Eight of the nine heart failure subjects had underlying coronary artery disease as the etiology of their heart failure. Four subjects were New York Heart Association class II, four were NYHA class III, and one was NYHA class IV. The mean left ventricular end-diastolic dimension determined by M-mode echocardiography was 77.4 ± 4.4 mm (normal, less than 57 mm). Estimated ejection fractions (echocardiography in eight subjects and nuclear in one) were less than 20% in eight of nine subjects. Angina was not the limiting symptom in any subject tested.

Microneurographic Studies

Heart rate, MAP, and MSNA (bursts per minute) data for the two subject groups are shown in Table 1. Heart failure subjects had higher resting heart rates and lower resting blood pressures, but the responses to the exercise paradigm were similar in the two subject groups.

The resting burst counts for MSNA were higher in heart failure subjects compared with control subjects (heart failure, 50 ± 4 bursts/min; control subjects, 29 ± 5 bursts/min; $p<0.05$). Heart failure subjects had greater nerve activity throughout the protocol (Table 1). Of note, six of nine heart failure subjects had a drop in burst count between the second minute of static exercise and during posthandgrip regional circulatory arrest. This is contrasted with the control subjects, in which seven of eight subjects had an increase in burst count over the same period.

The A% MSNA during the 2 minutes of static exercise was not statistically different in the two

groups (Figure 1). However, during posthandgrip regional circulatory arrest, MSNA responses were much less in heart failure subjects than in control subjects (heart failure subjects, $14.6\pm 9.7\%$ increase; control subjects, $56.7\pm 22.2\%$ increase; $p<0.05$). Representative neurograms from a heart failure and a control subject are shown in Figure 2.

Similar studies were performed during 40% maximal voluntary contraction in three heart failure subjects and in six control subjects. The A% MSNA values during posthandgrip regional circulatory arrest in the three heart failure subjects were 22%, 25%, and 53%, respectively. The posthandgrip re-

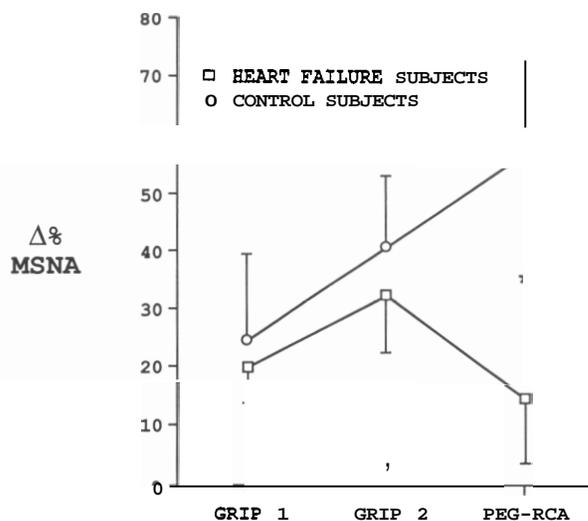


FIGURE 1. Graph shows comparison of percent change in MSNA (muscle sympathetic nerve activity) (A% MSNA) in heart failure subjects ($n=9$) and in control subjects ($n=8$). Grip 1, first minute of static exercise; Grip 2, second minute of static exercise; PHG-RCA, posthandgrip regional circulatory arrest. *Denotes significant difference between two subject groups during posthandgrip regional circulatory arrest ($p<0.05$). A statistical interaction was noted. Error bars represent mean±SEM.

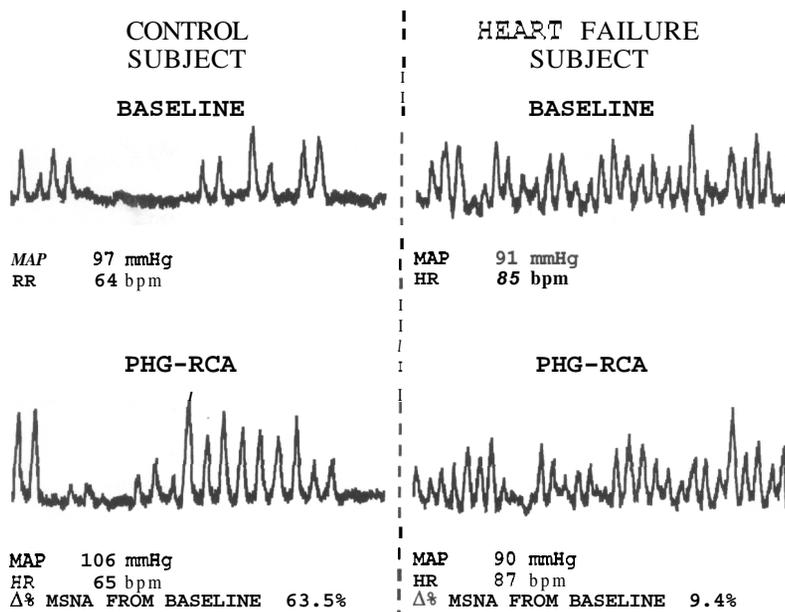


FIGURE 2. Representative neurograms in a control subject and a heart failure subject. PHG-RCA, posthandgrip regional Circulatory arrest; MAP, mean arterial blood pressure; HR, heart rate; bpm, beats per minute; MSNA, muscle sympathetic nerve activity.

gional circulatory arrest values in the six control subjects were 33%, 43%, 62%, 120%, 209%, and 236%, respectively.

Cold pressor responses were not different in the two subject groups (heart failure subjects, $140.9 \pm 37.4\%$ increase; control subjects, $214.5 \pm 82.7\%$ increase in $\Delta\%$ MSNA, NS). One control subject had a 761% increase in MSNA in response to the cold pressor maneuver. If his data were removed from the analysis, then the percent increase in the two groups would be virtually identical (heart failure subjects, $140.9 \pm 37.4\%$ increase; control subjects, $136.5 \pm 31.8\%$ increase in $\Delta\%$ MSNA).

NMR Studies

Age, maximal voluntary contraction values, and NYHA class of the five heart failure subjects were similar to those of the subjects in the microneurography studies. None of these subjects had coronary artery disease as the cause of their heart failure. Control subjects were also similar to their microneurography counterparts. Forearm pH during posthandgrip regional circulatory arrest was similar in the two groups for the 30% protocol (heart failure, 6.78 ± 0.07 ; controls, 6.88 ± 0.07 ; NS) and 40% protocol (heart failure, 6.45 ± 0.10 ; controls, 6.49 ± 0.11 ; NS). One of the heart failure subjects did not perform the 40% protocol because of fatigue.

Discussion

The major finding in this report was that MSNA responses during isolated metaboreceptor stimulation were markedly attenuated in heart failure subjects compared with age-matched controls. Despite this attenuated response, heart failure subjects were able to normally increase MSNA during static exercise. This suggests that during static exercise, heart failure subjects must use different means to augment sympathetic outflow. The two main postulated mech-

anisms by which sympathetic outflow increases during exercise are by increases in skeletal muscle metaboreceptor stimulation and by increments in central command. Thus, by inference, we propose that central volitional neural influences are enhanced in heart failure during static exercise.

A potential confounding factor in these studies is the preponderance of heart failure subjects with coronary artery disease. Significant coronary ischemia could conceivably modify the sympathetic response to exercise. However, because none of the subjects experienced angina during the studies, we think this possibility is unlikely.

The mechanisms responsible for the attenuated metaboreceptor response in heart failure are not entirely clear. Skeletal muscle acidosis is thought to be a major stimulant of this reflex system.^{10-13,27} Accordingly, one explanation for our findings is that skeletal muscle acid production is less in heart failure subjects than in control subjects. Our ³¹P NMR experiments, which evaluated forearm skeletal muscle pH during two levels of static exercise, would suggest this possibility is unlikely because forearm pH values during static exercise and posthandgrip regional circulatory arrest were not different in the two groups. A second potential explanation is that the reduced metaboreceptor response seen in heart failure was a manifestation of a generalized impairment in neural responsiveness. This is unlikely because the MSNA responses during static exercise itself were not less in the heart failure group compared with the control group. Moreover, the increases in MSNA observed during the cold pressor maneuver were similar in the two groups. This suggests that neural responsiveness to a nonspecific potent stimulus is not impaired in heart failure subjects.

It is also possible that the attenuated metaboreceptor response seen in heart failure was due to the greater

level of resting activity seen in these subjects. However, if this were the case, we would have also expected to see attenuated MSNA responses during static exercise and during the cold pressor maneuvers.

Another potential explanation for these findings is that the release of other neural-activating metabolites is reduced in heart failure. For example, it has been suggested that prostaglandins and/or thromboxane production are necessary to evoke maximal group IV afferent responses.²⁴ Group IV afferents appear to be the predominant fibers that mediate metaboreceptor responses.²⁴ It is possible that in heart failure the release of prostaglandins from skeletal muscle during exercise is reduced.

It is also possible that a greater percentage of the work during static exercise was performed under ischemic conditions in heart failure subjects. Thus, when regional circulatory arrest was initiated, muscle metaboreceptors in heart failure subjects had fatigued and stopped firing. We cannot exclude this possibility, but we think it is unlikely for two reasons. First, if this were the case, we would have expected earlier and greater increases in A% MSNA during static exercise in the heart failure subjects. This was not the case. Second, recent preliminary studies by Bertocci et al²⁵ suggest that in normal humans, the forearm metabolic responses to static forearm exercise at 30% maximal voluntary contraction are independent of changes in forearm blood flow (i.e., static exercise at this work load is an ischemic maneuver in normal subjects). Based on these findings, it would be unlikely that the exercise performed in heart failure subjects would cause a greater degree of ischemia than that seen in control subjects.

A final possibility is that the heart failure subjects' group IV fibers have become desensitized by the chronic intermittent release of lactic acid by skeletal muscle. In this study, the maximal voluntary contraction values in heart failure subjects were less than in control subjects. Thus, for a given amount of external static exercise, the skeletal muscle of heart failure subjects would tend to be more acidic than the skeletal muscle of age-matched control subjects. We are aware of no prior data demonstrating metaboreceptor desensitization in heart failure, although it has recently been demonstrated that this phenomenon may occur in body builders.²⁶ Presumably, in this setting, the repeated bouts of heavy exercise and the associated lactic acid production attenuate metaboreceptor stimulation.

Clinical Implications

It is known that in normal humans, skeletal muscle metaboreceptor stimulation leads to a potent peripheral vasoconstriction.⁷ Moreover, activation of the metaboreceptor system may prevent vascular conductance from exceeding left ventricular pumping capacity during intense exercise.⁷ We suspect that the absence of an intact metaboreceptor system in heart failure leads to a less effective use of cardiac output during exercise. Whether this contributes to the

prominent exercise intolerance seen in this disease remains to be determined.

A second important issue is that central command appears to be increased during static exercise in heart failure. This may be clinically relevant for two reasons. First, central command is thought to increase in parallel with a-motor neuron recruitment during exercise.³ Second, the level of motor unit recruitment appears to be related to the level of perceived activity.^{3,4} The crucial issue raised by these statements is whether this dependence on central command in heart failure is associated with a greater level of a-motor neuron recruitment and the earlier onset of fatigue. In other words, is fatigue in heart failure in part mediated by central neural mechanisms? However, we must caution that based on our data we can only infer a greater reliance on central command in heart failure. Further studies will be necessary to confirm this hypothesis.

Conclusion

MSNA responses to isolated skeletal muscle metaboreceptor stimulation are impaired in humans with heart failure. Despite this, the magnitude of MSNA responses during static exercise is normal. This suggests that central command is activated to a greater degree in subjects with heart failure than in age-matched control subjects.

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