

Altered mechanisms of sympathetic activation during rhythmic forearm exercise in heart failure

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Silber, David H., Greg Sutliff, Qing X. Yang, Michael B. Smith, Lawrence I. Sinoway, and Urs A. Leuenberger. Altered mechanisms of sympathetic activation during rhythmic forearm exercise in heart failure. *J. Appl. Physiol.* 84(5): 1551–1559, 1998.—In congestive heart failure (CHF), the mechanisms of exercise-induced sympathoexcitation are poorly defined. We compared the responses of sympathetic nerve activity directed to muscle (MSNA) and to skin (SSNA, peroneal microneurography) during rhythmic handgrip (RHG) at 25% of maximal voluntary contraction and during posthandgrip circulatory arrest (PHG-CA) in CHF patients with those of an age-matched control group. During RHG, the CHF patients fatigued prematurely. At end exercise, the increase in MSNA was similar in both groups (CHF patients, $n = 12$; controls, $n = 10$). However, during PHG-CA, in the controls MSNA returned to baseline, whereas it remained elevated in CHF patients ($P < 0.05$). Similarly, at end exercise, the increase in SSNA was comparable in both groups (CHF patients, $n = 11$; controls, $n = 12$), whereas SSNA remained elevated during PHG-CA in CHF patients but not in the controls ($P < 0.05$). In a separate control group ($n = 6$), even high-intensity static handgrip was not accompanied by sustained elevation of SSNA during PHG-CA. ³¹P-nuclear magnetic resonance spectroscopy during RHG demonstrated significant muscle acidosis and accumulation of inorganic phosphate in CHF patients ($n = 7$) but not in controls ($n = 9$). We conclude that in CHF patients rhythmic forearm exercise leads to premature fatigue and accumulation of muscle metabolites. The prominent PHG-CA response of MSNA and SSNA in CHF patients suggests activation of the muscle metaboreflex. Because, in contrast to controls, in CHF patients both MSNA and SSNA appear to be under muscle metaboreflex control, the mechanisms and distribution of sympathetic outflow during exercise appear to be different from normal.

muscle sympathetic nerve activity; skin sympathetic nerve activity; muscle metaboreceptors; nuclear magnetic resonance spectroscopy

IN HUMAN CONGESTIVE HEART FAILURE (CHF), sympathetic activity is increased at rest (6, 11, 30). Less is known about sympathetic nervous system function during exercise in CHF patients. Depending on the type of exercise and the method by which neural activity was measured, prior investigations have found augmented (4), attenuated (8), or normal (28) sympathetic responses to exercise. Two important modulators of the sympathetic response to exercise are the muscle metaboreflex and central command (18, 21).

In a prior report (28) we demonstrated an increase in directly measured muscle sympathetic nerve activity (MSNA) during static handgrip in CHF patients. Dur-

ing this type of exercise, the magnitude of the rise in MSNA and the metabolic changes in skeletal muscle determined by ³¹P-nuclear magnetic resonance (NMR) spectroscopy were similar to normal (28). However, during posthandgrip circulatory arrest (PHG-CA), MSNA and arterial pressure remained elevated in normal subjects while these responses were attenuated in CHF patients (28). Because the PHG-CA maneuver isolates the effects of stimulation of metabolite-sensitive afferents, these findings suggest that the muscle metaboreflex is attenuated in CHF patients.

The mechanisms of sympathetic activation during rhythmic, nonfatiguing exercise may be different from those observed during fatiguing static exercise. We have shown in normal subjects that prolonged (30-min) bouts of rhythmic handgrip can lead to a progressive rise in MSNA without significant muscle acidosis (1). Because, during PHG-CA, MSNA returned to baseline, no clear role for metaboreceptor activation was apparent during this type of exercise (1). Thus, in healthy humans, some other neural system must be operative in evoking the MSNA response seen during rhythmic handgrip exercise.

For several reasons, in CHF the neural responses to rhythmic exercise may be altered. On the one hand, the production and/or accumulation of by-products of high-energy phosphate metabolism may be accelerated during rhythmic exercise in CHF patients (14, 34). This would be expected to increase stimulation of metabolite-sensitive muscle afferents. On the other hand, the desensitization of muscle metaboreceptors observed during static exercise (28) may counteract metaboreflex-mediated sympathoexcitation in CHF patients.

In the present report our goal was to examine the response of the sympathetic nervous system to rhythmic exercise in CHF patients. Because in healthy humans the muscle metaboreflex did not appear to be an important determinant of the sympathetic responses to rhythmic exercise and because in CHF patients this reflex appeared to be attenuated, we postulated that mechanisms aside from the muscle metaboreflex would be important in the sympathoexcitation associated with rhythmic handgrip exercise. Because in normal humans sympathetic nerve activity directed to skin (SSNA) is thought to be independent of input from muscle metaboreceptors and may reflect central command (33), we speculated that this neural index would provide further insight into the mechanisms of neural control during exercise in CHF patients.

Our data suggest that, in contrast to healthy control subjects, patients with CHF fatigued rapidly with

exercise, muscle metaboreceptor stimulants were produced in far larger quantities and metaboreflex activation contributed to increases in both SSNA and MSNA. On the basis of these findings, we propose that in CHF patients the mechanism of activation and the distribution of sympathetic outflow are distinctly different from normal.

METHODS

The studies were performed in a quiet, temperature-controlled (70–72°F) human research laboratory. To assess the subjects' suitability and to ensure patient safety for the trials of rhythmic handgrip exercise, a brief evaluation and a physical examination were performed before the study. The studies were approved by the Hershey Medical Center's Clinical Investigation Committee. All subjects signed written informed consent before participating.

Subjects

We examined 24 men [age 58 ± 2 (SE) yr, range 27–85 yr] with moderate to severe CHF (New York Heart Association classes II–IV) during a rhythmic handgrip exercise protocol. All patients had cardiomegaly, and the estimated left-ventricular ejection fraction (by 2-dimensional echocardiography) was $19 \pm 1\%$ (range 10–30%). The etiology of CHF was ischemic heart disease in 14 patients, idiopathic dilated cardiomyopathy in 6 patients, and acquired valvular disease in 4 patients (2 patients had undergone aortic valve replacement for aortic regurgitation, 1 patient had advanced uncorrected aortic regurgitation, and 1 patient had a mitral valve prosthesis with a paraprosthetic leak). Many of the CHF patients were under evaluation for orthotopic heart transplantation. Twenty-three patients were taking oral furosemide, 22 were treated with an angiotensin-converting-enzyme inhibitor, 18 were on digoxin, and 1 was taking hydralazine. In addition, seven patients were on various nitrate preparations, and four were receiving antiarrhythmic agents (2 amiodarone, 1 quinidine, 1 mexiletine). These medications were not withheld before the studies because many of the patients were judged to be too ill to tolerate interruption of drug therapy. Twenty healthy subjects who were matched for age (64 ± 2 yr, range 47–71 yr), had a normal resting electrocardiogram, and were not taking any medications served as a control group. Responses to high-intensity static handgrip were examined in a separate group of six normal subjects (age 25 ± 1 yr, range 23–29 yr).

Measurements

In these studies we measured heart rate (HR; beats/min) via electrocardiogram, mean arterial pressure (MAP; mmHg) by utilizing an automated photoplethysmographic device (Finapres, Ohmeda, Fort Lee, NJ) (19), respiratory move-

ments (pneumograph), and MSNA or SSNA (31). In some subjects we performed ^{31}P -NMR spectroscopy on the exercising forearm (1, 26, 28).

Microneurography

This technique allows the direct recording of efferent sympathetic nerve activity targeted to skeletal muscle (MSNA) or skin (SSNA) (31). The general method used in our laboratory has been described previously (1, 28).

Briefly, with the subject in the supine position, the peroneal nerve at the level of the fibular head was stimulated transcutaneously to determine its precise location. A 5- μm -tip tungsten microelectrode was then inserted within a nerve fascicle subserving muscle or skin, and a reference electrode was placed in the adjacent subcutaneous tissue. The signal was then amplified ($\times 50,000$ – $90,000$), filtered (700–2,000 Hz), rectified, and integrated (Nerve Traffic Analyzer, University of Iowa, Iowa City, IA) to obtain a mean-voltage neurogram. A signal was felt to be MSNA when it bore a fixed relationship to the QRS complex (electrocardiogram), was not influenced by arousal stimuli, and was stimulated by a fall in blood pressure, a Valsalva maneuver, or voluntary apnea. A signal was believed to be SSNA when it was not linked to the QRS complex, was not stimulated by maneuvers that elicit MSNA, but was provoked by arousal stimuli (loud noise or questions). Recording sites with mixed MSNA and SSNA characteristics were rejected. Each MSNA and SSNA recording was reviewed by two separate investigators, and the incidence and height of individual bursts were determined. MSNA and SSNA were expressed in bursts per minute and in arbitrary units (units: bursts/min \times average burst height in mm) (15, 28). In the case of complex multiphased bursts of SSNA, peaks that were separated by a decrease in voltage to less than one-half of the smaller peak were counted as separate bursts (15).

HR, MAP, respirations and the MSNA or SSNA signals were recorded on a multichannel recorder (Gould TA4000, Valley View, OH).

NMR Spectroscopy

^{31}P -NMR spectroscopy allows an assessment of intracellular phosphate metabolism (3). The ^{31}P -NMR spectra were obtained with a 1.9-T, 26-cm-bore superconducting magnet (Oxford Instruments, Abingdon, UK) interfaced to a radio-frequency transmitter and receiver (Nicolet Instrument, Madison, WI), with a Tecmag Taurus upgrade (TecMag, Houston, TX). With use of transcutaneous electrical stimulation, the flexor digitorum superficialis muscle was located in the forearm, and a 2.5-cm coil was placed precisely over the area where optimal stimulation of this muscle was achieved. The proton homogeneity was maximized by adjusting the room-temperature gradients. The ^{31}P spectra were collected at 32.5 MHz with a 1.9-s delay between radio-frequency pulses. The

Table 1. Effects of rhythmic handgrip exercise on muscle sympathetic nerve activity

	Baseline	G1	G2	EG	PHG-CA	Recovery	Statistics
MSNA, units							
CHF patients	415 ± 50	$483 \pm 53^*$	$529 \pm 58^*$	$581 \pm 68^*$	$565 \pm 71^*$	464 ± 67	$F=8.1; P<0.001$
Controls	275 ± 45	297 ± 41	280 ± 39	$394 \pm 78^*$	306 ± 53	311 ± 58	$F=3.3; P=0.014$
MSNA, bursts/min							
CHF patients	52 ± 5	$57 \pm 5^*$	$60 \pm 5^*$	$61 \pm 6^*$	$58 \pm 5^*$	52 ± 5	$F=5.1; P<0.001$
Controls	31 ± 5	30 ± 4	29 ± 4	34 ± 6	32 ± 5	33 ± 5	$F=0.9; P=NS$

Values are means \pm SE for 12 congestive heart failure (CHF) patients and 10 controls. MSNA, muscle sympathetic nerve activity; G1, first minute of handgrip; G2, second minute of handgrip; EG, last minute of handgrip; PHG-CA, posthandgrip circulatory arrest; NS, not significant. Baseline and recovery are average of 5 min. * $P < 0.05$ compared with baseline.

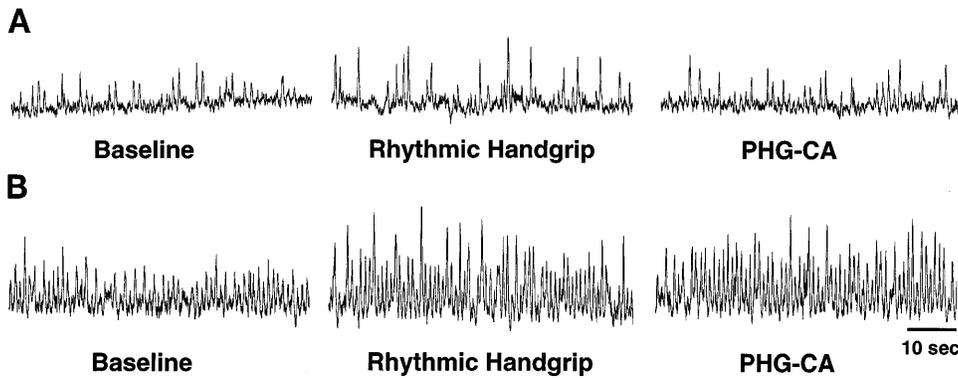


Fig. 1. Recordings of muscle sympathetic nerve activity (MSNA) from a control subject (A) and a patient with heart failure (B) at baseline, during rhythmic handgrip exercise, and during posthandgrip circulatory arrest (PHG-CA). Baseline MSNA was higher in the heart failure patient, but during exercise MSNA increased similarly in both subjects. In contrast to the control subject, in the heart failure patient MSNA remained elevated during PHG-CA.

spectra obtained represented the Fourier transformation of 32 transients that were averaged over 60 s.

Intracellular pH and H^+ concentration were calculated from the chemical shift of P_i relative to the fixed position of the phosphocreatine (PCr) peak (3). The relative concentrations of P_i and PCr were determined by calculating the area under their respective resonance and were expressed in arbitrary units. The relative concentration of diprotonated phosphate ($H_2PO_4^-$) was derived from the pH, the relative concentration of P_i , and the negative logarithm of acidic dissociation constant (pK_a) for the conversion of HPO_4^{2-} to $H_2PO_4^-$.

Maximal Voluntary Contraction (MVC)

To normalize the exercise workload for muscle strength in each individual, the subjects performed three separate MVCs ~ 1 min apart by using a handgrip dynamometer (Stoelting, Wood Dove, IL). The average MVC in the CHF patients was insignificantly lower than that of the controls [39 ± 2 kg vs. 43 ± 2 kg; $P =$ not significant (NS)].

Exercise Protocols

Most subjects participated in a single protocol; four control and four CHF subjects participated in two protocols. If a subject participated more than once, the experiments were separated by a period of several weeks. For the rhythmic handgrip studies, the workload was chosen as 25% of MVC (12 contractions/min) because prior studies in normal subjects demonstrated that this workload evoked an increase in MSNA, could be maintained for an extended period (>30 min), and did not evoke a metaboreceptor response (1).

The studies were conducted with the subjects in the supine position, and handgrip exercise was performed with the nondominant arm. The Finapres cuff was placed on a finger of the nonexercising arm. An occlusion cuff was placed above the elbow of the exercising arm. The cuff was connected to a compressed-air tank preset to deliver a pressure of 250 mmHg and thereby arrest the circulation to the forearm at the end of exercise (PHG-CA). A microelectrode was then positioned in the peroneal nerve to measure MSNA or SSNA.

Protocol 1: Effects of rhythmic handgrip and PHG-CA on MSNA. After a MSNA site was obtained, baseline data were collected over 5 min. The subjects then performed rhythmic handgrip with the nondominant arm at 25% MVC. The exercise rhythm was given by an audiotape recording and consisted of a 2-s contraction followed by a 3-s rest (12 contractions/min). Exercise was continued for 20 min or until the subjects were unable to repeat contractions at 25% MVC. During the last contraction, the upper arm cuff was inflated to produce PHG-CA for 1 min. After release of PHG-CA, recovery data were collected over 5 min. At 2-min intervals during exercise, the subjects rated the perceived level of effort according to the Borg scale (2).

Protocol 2: Effects of rhythmic handgrip and PHG-CA on SSNA. The SSNA studies were identical to the MSNA experiments except for the nerve recording site. To minimize arousal stimuli, the audiotape, which provided the cues for the exercise rhythm, was begun before baseline measurements and was continued throughout the recovery period. Brief verbal instructions were given to prepare for the onset of exercise.

Protocol 3: Effects of rhythmic handgrip on forearm muscle metabolism. In the NMR laboratory the subject's nondominant forearm was positioned in the magnet. MVC was then determined, and an occlusion cuff was placed above the elbow. HR and MAP were determined with an automated blood pressure device (Dynamap, Tampa, FL). After calibration of the magnet, the subjects completed the rhythmic handgrip protocol as described in *Protocol 1: Effects of rhythmic handgrip and PHG-CA on MSNA*. Care was taken to maintain constant the coil's position relative to the underlying muscle.

Protocol 4: Effects of high-intensity static exercise and PHG-CA on SSNA. To assess the effect of intense muscle discomfort on SSNA, in six additional control subjects SSNA was measured during three different workloads of static handgrip. The subjects were instrumented as described in *Exercise Protocols*. The workloads selected were 35, 45, and 60% of MVC. Once an adequate SSNA site was obtained, care was taken to prevent arousal stimuli. After collection of

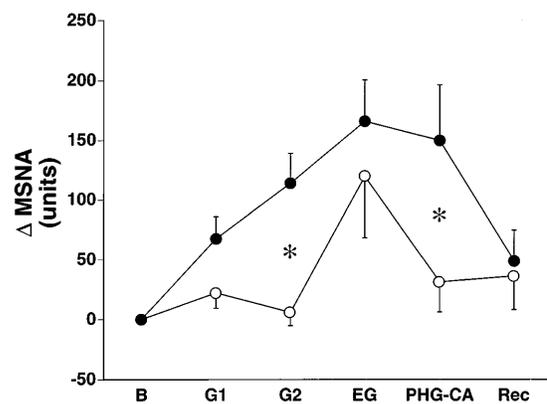


Fig. 2. Responses of MSNA to rhythmic handgrip exercise and PHG-CA in congestive heart failure (CHF) patients ($n = 12$; ●) and in controls ($n = 10$; ○). Muscle sympathetic responses are expressed as a change from baseline (Δ MSNA; units). During early exercise, MSNA increased in CHF patients and remained unchanged in controls, whereas, during the last minute of exercise, MSNA was elevated in both groups. During PHG-CA, MSNA returned toward baseline in the controls but remained elevated in CHF patients. (For within-group comparisons, see Table 1.) B, baseline; G1 and G2, minutes 1 and 2 of handgrip exercise, respectively; EG, last minute of exercise; Rec, recovery. * $P < 0.05$, CHF patients vs. controls.

Table 2. Effects of rhythmic handgrip exercise on skin sympathetic nerve activity

	Baseline	G1	G2	EG	PHG-CA	Recovery	Statistics
SSNA, units							
CHF patients	90 ± 25	146 ± 36*	130 ± 33*	128 ± 29*	152 ± 32*	80 ± 19	$F=5.9; P<0.001$
Controls	69 ± 13	144 ± 31*	131 ± 21*	128 ± 24*	81 ± 13	58 ± 10	$F=7.9; P<0.001$
SSNA, bursts/min							
CHF patients	13 ± 3	17 ± 3	15 ± 3	15 ± 2	18 ± 3*	12 ± 2	$F=3.1; P=0.017$
Controls	11 ± 2	17 ± 2*	16 ± 2*	15 ± 2*	12 ± 2	12 ± 1	$F=6.0; P<0.001$

Values are means ± SE for 11 CHF patients and 12 controls. SSNA, skin sympathetic nerve activity. Baseline and recovery are average of 4–5 min. * $P < 0.05$ compared with baseline.

baseline data (5 min), the subjects performed static handgrip to fatigue, i.e., until they were unable to maintain the contraction. The arm cuff was then inflated, and PHG-CA was maintained for 2 min. Recovery data were obtained over 3 min. The protocol was then repeated by using the second and third workloads, each separated by at least 15 min of rest. The order of the workloads was 35, 45, and 60% in three subjects and the reverse in the other three subjects.

Statistics

Group characteristics and resting discharge frequency of MSNA and SSNA were compared between CHF patients and controls with the two-tailed t -test for unpaired samples. Within each group, the exercise and PHG-CA responses of HR, MAP, MSNA, and SSNA were analyzed by one-way analysis of variance for repeated measures. Post hoc comparisons were performed with Fisher's least squares method. Comparisons between CHF patients and controls were made by two-way analysis of variance. Point-wise comparisons were made by the simple-effects method. $P < 0.05$ was considered statistically significant. All data are reported as means ± SE.

RESULTS

Resting Sympathetic Nerve Activity

At rest, the discharge rate of muscle sympathetic nerves (MSNA) was higher in the CHF patients than in the controls (CHF patients vs. controls: 52 ± 5 vs. 31 ± 5 bursts/min; $P < 0.01$) (CHF patients, $n = 12$; controls, $n = 10$). In contrast, the discharge rate of skin sympathetic nerves (SSNA) was similar in CHF patients and controls (CHF patients vs. controls: 13 ± 3 vs. 11 ± 2 bursts/min; $P = \text{NS}$) (CHF patients, $n = 11$; controls, $n = 12$).

Exercise Time and Perceived Effort

Sixteen of 20 control subjects but only 4 of 24 CHF patients were able to complete 20 min of rhythmic handgrip (CHF patients vs. controls: 9.0 ± 1.0 vs.

18.6 ± 0.7 min; $P < 0.001$). At end exercise and during PHG-CA, the Borg score for the CHF patients was higher than in the controls (18 ± 0.3 vs. 15 ± 1 and 19 ± 1 vs. 14 ± 1 respectively; $P < 0.01$ for both).

Protocol 1: Effects of Rhythmic Handgrip and PHG-CA on MSNA (CHF Patients, $n = 12$; Controls, $n = 10$)

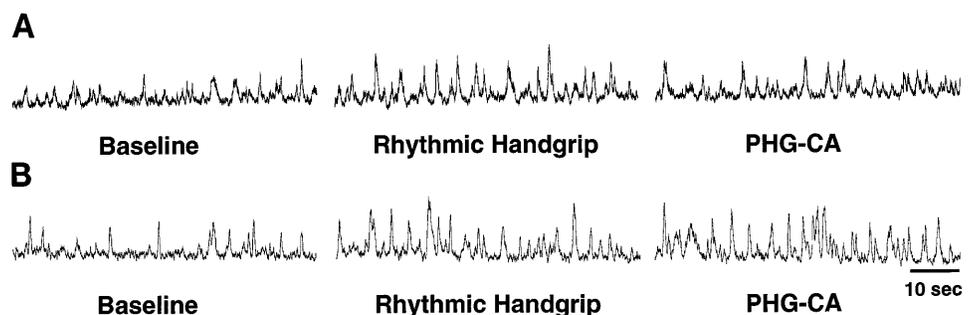
MSNA during the rhythmic handgrip protocol in CHF patients and in controls is presented in Table 1, and representative neurographic recordings are shown in Fig. 1. In the controls, rhythmic handgrip did not lead to a rise of MSNA until late during the handgrip protocol. During PHG-CA, MSNA returned toward baseline. In contrast, in CHF patients, a significant rise in MSNA was evident in the first 2 min of handgrip with a further increase by the last minute of exercise (end grip). During PHG-CA, MSNA remained elevated.

Because baseline MSNA was higher in CHF patients than in controls and to account for exercise-induced changes in incidence and amplitude of sympathetic bursts, for the between-group comparisons the data were expressed as a change in MSNA compared with baseline (ΔMSNA ; units). Two-way analysis of variance revealed an exercise effect for both groups ($F = 6.2$, $P < 0.001$). Point-wise comparisons revealed greater responses of MSNA in CHF patients at minute 2 of exercise ($P < 0.02$) and during PHG-CA ($P < 0.01$) (Fig. 2).

Protocol 2: Effects of Rhythmic Handgrip and PHG-CA on SSNA (CHF Patients, $n = 11$; Controls, $n = 12$)

Analysis of baseline SSNA in 15-s epochs revealed a consistent rise in SSNA in the 30-s period preceding the onset of exercise. Because this coincided with the brief verbal instructions given in preparation for exercise, the last 30 s before exercise were excluded from the baseline average.

Fig. 3. Recordings of skin sympathetic nerve activity (SSNA) from a control subject (A) and a patient with heart failure (B) at baseline, during rhythmic handgrip exercise, and during PHG-CA. Baseline SSNA was similar in the heart failure and control subjects and increased similarly during rhythmic handgrip exercise. However, during PHG-CA, SSNA returned toward baseline in the control subject, whereas it remained elevated in the patient with heart failure.



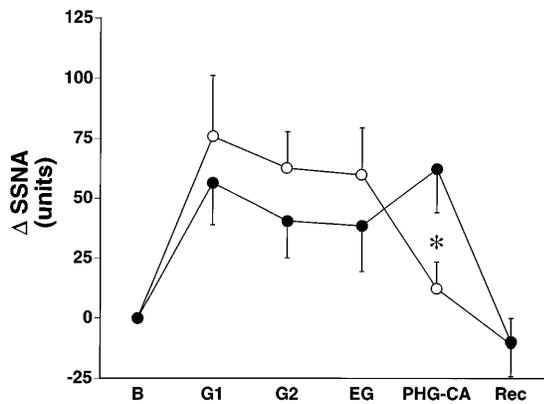


Fig. 4. Responses of SSNA to rhythmic handgrip exercise and PHG-CA in CHF patients ($n = 11$; ●) and in controls ($n = 12$; ○). Skin sympathetic responses are expressed as a change from baseline (Δ SSNA; units). During exercise, SSNA increased in both groups. During PHG-CA, SSNA returned toward baseline in the controls but remained elevated in CHF patients. (For within-group comparisons see Table 2.) * $P < 0.05$, CHF patients vs. controls.

SSNA during the rhythmic handgrip protocol is shown in Table 2, and representative neurographic recordings are shown in Fig. 3. In the controls, SSNA rose within the first minute of exercise and returned toward baseline during PHG-CA. Similarly, in CHF patients, SSNA rose promptly during exercise but remained elevated during PHG-CA.

For between-group comparisons and to account for exercise-induced changes in incidence and amplitude of sympathetic bursts, the SSNA data were expressed as a change in SSNA compared with baseline (Δ SSNA; units). Two-way analysis of variance revealed an exercise effect for both groups ($F = 10.1$, $P < 0.001$). Point-wise comparisons demonstrated similar responses during exercise. However, during PHG-CA, SSNA remained elevated in CHF patients but not in the controls ($P < 0.05$; Fig. 4).

Inflation of the circulatory occlusion cuff alone during a separate resting period (10- to 60-s duration; 10 trials in 3 CHF patients and 8 trials in 2 controls) did not increase SSNA (CHF patients, 96 ± 55 before and 58 ± 46 units during cuff inflation, $P = \text{NS}$; controls, 82 ± 34 before and 49 ± 46 units during cuff inflation, $P = \text{NS}$).

Effects of Rhythmic Handgrip and PHG-CA on HR and MAP (CHF Patients, $n = 19$; Controls, $n = 13$)

HR and MAP data from protocols 1 and 2 are presented in Table 3. In those subjects who performed both

protocols, data from protocol 1 only are included. Results from subjects participating in protocol 3 (NMR studies) were similar and are not presented. Baseline HR was higher ($P < 0.01$) and MAP was lower ($P < 0.02$) in CHF patients. However, the HR and MAP responses to exercise were similar for both CHF patients and control subjects. MAP decreased to a greater extent during PHG-CA in controls; however, it was still higher than baseline.

Protocol 3: Effects of Rhythmic Handgrip and PHG-CA on Forearm Muscle Metabolism (CHF Patients, $n = 7$; Controls, $n = 9$)

^{31}P -NMR spectroscopy data are presented in Table 4 and Fig. 5. Rhythmic handgrip exercise lead to a progressive muscle acidosis in CHF patients but not in controls. In addition, in CHF patients but not controls, there was a prominent accumulation of H_2PO_4^- and an increase of P_i and $\text{P}_i/(\text{P}_i + \text{PCr})$.

Protocol 4: Effects of High-Intensity Static Exercise and PHG-CA on SSNA in Controls ($n = 6$)

The SSNA responses to static handgrip at 35, 45, and 60% of MVC and the effects of PHG-CA are shown in Table 5. The time to fatigue was workload dependent (3.7 ± 0.7 min at 35% MVC, 1.9 ± 0.3 min at 45% MVC, 1.3 ± 0.2 min at 60% MVC). In all subjects, subjective fatigue was maximal at end exercise. At all three workloads, SSNA rose substantially during grip but returned to baseline during PHG-CA. The effects of static handgrip on HR and MAP are shown in Table 6. As expected, at all workloads, MAP and HR rose during static handgrip. Whereas HR returned to baseline during PHG-CA, MAP remained elevated.

DISCUSSION

In this report we examined the sympathetic responses to rhythmic forearm exercise directed to skeletal muscle (MSNA) and to skin (SSNA) in patients with CHF and in a healthy control group. In contrast to controls, patients with CHF fatigued prematurely during rhythmic handgrip, and this was associated with a large increase in muscle metaboreceptor stimulants as determined by NMR spectroscopy. The principal new findings of this study are that fatigue and metabolite production in CHF were associated with an increase in sympathetic activity directed to muscle and to skin that was sustained during the subsequent period of PHG-

Table 3. Effects of rhythmic handgrip exercise on mean arterial blood pressure and heart rate

	Baseline	G1	G2	EG	PHG-CA	Recovery	Statistics
HR, beats/min							
CHF patients	83 ± 4	87 ± 5	$91 \pm 6^*$	$96 \pm 5^*$	$91 \pm 4^*$	87 ± 5	$F = 11.0; P < 0.001$
Controls	70 ± 3	$76 \pm 3^*$	$77 \pm 3^*$	$80 \pm 3^*$	71 ± 3	70 ± 2	$F = 16.8; P < 0.001$
MAP, mmHg							
CHF patients	85 ± 4	89 ± 4	91 ± 4	$101 \pm 4^*$	$99 \pm 4^*$	89 ± 3	$F = 15.6; P < 0.001$
Controls	99 ± 4	$107 \pm 5^*$	$110 \pm 5^*$	$115 \pm 5^*$	$108 \pm 4^*$	100 ± 5	$F = 14.8; P < 0.001$

Values are means \pm SE for 19 CHF patients and 13 controls. HR, heart rate; MAP, mean arterial pressure. Baseline and recovery are average of 5 min. * $P < 0.05$ compared with baseline.

Table 4. Effects of rhythmic handgrip exercise on forearm muscle metabolism

Subjects	Baseline	G1	G2	EG	PHG-CA	Recovery	Statistics
pH							
CHF patients	7.13 ± 0.02	7.03 ± 0.02	6.99 ± 0.04	6.79 ± 0.10†	6.80 ± 0.08†	6.84 ± 0.10*	Subjects: $F=4.1$, $P=NS$ Paradigm: $F=9.6$; $P<0.001$ Interaction: $F=5.6$; $P<0.001$
Controls	7.04 ± 0.01	7.06 ± 0.01	7.00 ± 0.02	6.98 ± 0.03	7.02 ± 0.02	7.01 ± 0.01	
Relative $H_2PO_4^-$							
CHF patients	0.30 ± 0.01	0.86 ± 0.15	1.17 ± 0.34	1.30 ± 0.36†	1.45 ± 0.37†	0.90 ± 0.23*	Subjects: $F=5.4$; $P<0.05$ Paradigm: $F=11.4$; $P<0.001$ Interaction: $F=4.2$; $P<0.01$
Controls	0.34 ± 0.01	0.57 ± 0.07	0.82 ± 0.13	0.64 ± 0.08	0.61 ± 0.09	0.36 ± 0.02	
Relative P_i							
CHF patients	1.0	2.51 ± 0.43	2.96 ± 0.60	2.71 ± 0.48*	2.95 ± 0.59†	1.79 ± 0.23	Subjects: $F=4.8$; $P<0.05$ Paradigm: $F=18.7$; $P<0.001$ Interaction: $F=2.7$; $P<0.05$
Controls	1.0	1.72 ± 0.20	2.22 ± 0.29	1.71 ± 0.21	1.69 ± 0.24	1.02 ± 0.04	
$P_i/(P_i + PCr)$							
CHF patients	0.14 ± 0.01	0.33 ± 0.04	0.42 ± 0.07	0.39 ± 0.08†	0.45 ± 0.09†	0.26 ± 0.04	Subjects: $F=4.2$; $P=NS$ Paradigm: $F=18.7$; $P<0.001$ Interaction: $F=3.5$; $P<0.01$
Controls	0.16 ± 0.01	0.26 ± 0.03	0.32 ± 0.04	0.26 ± 0.03	0.25 ± 0.03	0.16 ± 0.01	

Values are means ± SE for 7 CHF patients and 9 controls. PCr, phosphocreatine. Baseline and recovery are average of 5 min. * $P < 0.05$; † $P < 0.01$, CHF vs. controls.

CA. By contrast, in normal subjects, MSNA and SSNA rose during exercise but decreased to baseline during PHG-CA. Because PHG-CA isolates the influence of muscle metaboreflex stimulation from that of other afferent reflex effects and central command, these findings suggest an important role of the muscle metaboreflex in the sympathetic response to rhythmic exercise in CHF.

In agreement with prior reports, we found increased resting discharge rates of sympathetic nerves targeted to skeletal muscle (11, 28) but not to skin (16) in CHF patients compared with controls, suggesting differential effects of CHF on the control of MSNA and SSNA at rest.

Rhythmic handgrip exercise resulted in a time-dependent increase of MSNA in CHF patients and in the control group. Because in CHF but not in the

controls MSNA remained elevated during PHG-CA, the mechanism of sympathoexcitation was likely different in the two groups. In healthy humans, reflex activation of the muscle metaboreflex can be evoked by static handgrip for 2 min at 30% MVC (1, 26, 28, 32, 33). However, in a prior study from our laboratory, in CHF the muscle metaboreceptor responses to static exercise were attenuated (28). In the present report we wished to determine whether during rhythmic exercise in CHF this apparent "desensitization" of the muscle metaboreflex would be offset by a greater production of metabolic by-products of muscle contraction. Our results suggest that during rhythmic exercise in CHF the attenuation of the metaboreceptor responses is more than counterbalanced by the relatively large metabolic changes in skeletal muscle. Indeed, whereas at rest H^+ and $H_2PO_4^-$ values were similar in the two groups, their peak values were severalfold greater in CHF patients than in the controls, although they did not exceed levels achieved during fatiguing static exercise (28). However, it should be emphasized that in addition to these metabolic by-products, which have been identified as potent stimulants of metabolite-sensitive muscle afferents (26, 27, 32), other factors such as prostaglandins (20), lactic acid (20, 24), K^+ (7), and adenosine (5) may play an equally important role in stimulating these afferents but may escape detection by the NMR technique.

The mechanism underlying the increased metabolic drive observed during rhythmic handgrip exercise in CHF is not clear. Apart from intrinsic structural and biochemical abnormalities of skeletal muscle (29), impaired skeletal muscle blood flow responses to exercise (12) may also have contributed to the more rapid accumulation of metabolic by-products of muscle contraction in heart failure.

It is noteworthy that the time to fatigue was markedly different in the two subject groups. In fact, in those

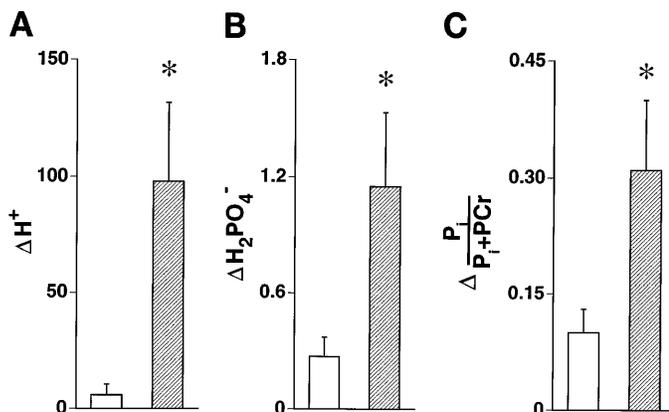


Fig. 5. Changes (Δ) of H^+ (A; nM), $H_2PO_4^-$ (B; relative units), and $P_i/[P_i + \text{phosphocreatine (PCr)}]$ (C) at end of rhythmic handgrip exercise compared with baseline. In contrast to control subjects ($n = 9$; open bars), at end of exercise CHF patients ($n = 7$; hatched bars) demonstrated a marked rise of H^+ , reflecting skeletal muscle acidosis, and increases of $H_2PO_4^-$ and of $P_i/(P_i + PCr)$. * $P < 0.05$, CHF patients vs. controls.

Table 5. Effects of high-intensity static handgrip exercise on SSNA in control subjects at three different workloads

Workload	Baseline	EG	PHG-CA	Recovery	Statistics
SSNA, units					
35% MVC	248 ± 59	415 ± 99*	290 ± 64	187 ± 71	<i>F</i> = 3.7; <i>P</i> < 0.05
45% MVC	222 ± 65	453 ± 134*	293 ± 84	174 ± 71	<i>F</i> = 9.7; <i>P</i> < 0.001
60% MVC	183 ± 39	375 ± 61*	186 ± 51	211 ± 62	<i>F</i> = 15.8; <i>P</i> < 0.001
SSNA, bursts/min					
35% MVC	20 ± 4	26 ± 5	23 ± 4	15 ± 4	<i>F</i> = 2.3; <i>P</i> = NS
45% MVC	18 ± 4	28 ± 6*	22 ± 4	15 ± 5	<i>F</i> = 7.5; <i>P</i> < 0.003
60% MVC	16 ± 4	28 ± 3*	16 ± 4	19 ± 5	<i>F</i> = 9.5; <i>P</i> < 0.01

Values are means ± SE for 6 subjects. MVC, maximal voluntary contraction. Baseline is average of 5 min. Recovery is final (3rd) minute after release of circulatory arrest. * *P* < 0.05 compared with baseline.

subjects who did not fatigue, exercise was discontinued after 20 min. Therefore, the difference in exercise duration in our study probably underestimated the true difference in endurance time between the two groups.

In addition to a metaboreceptor-mediated increase in MSNA, we also observed an increase in SSNA that appeared to result at least in part from activation of this reflex. Vissing et al. (33) have suggested that in normal subjects changes in SSNA during static handgrip are likely due to central command. In our studies we attempted to apply this concept to rhythmic exercise in CHF. We had postulated that SSNA would rise with handgrip exercise and would return to baseline during PHG-CA. Although during exercise SSNA rose in both groups, surprisingly it did not rise in a time-dependent fashion, and during PHG-CA it remained elevated in CHF patients, whereas it returned to baseline in the controls. We considered the possibility that the sustained elevation of SSNA during PHG-CA in CHF patients was due to an engagement of metaboreceptors in CHF patients but not in the controls. For this reason we performed control experiments with high-intensity static handgrip, an exercise paradigm that is known to produce substantial muscle acidosis and engagement of the muscle metaboreflex in normal humans (26, 28, 32). Surprisingly, despite activation of the metaboreflex as evident by the characteristic elevation of blood pressure and despite intense muscle discomfort in these normal subjects, during the period of PHG-CA, SSNA returned to baseline levels. Therefore, metaboreflex activation alone in normal humans did not cause the rise in SSNA during static handgrip. Furthermore,

inflation of the circulatory occlusion cuff alone during rest did not elicit a rise in SSNA in either group, suggesting that a specific effect of arousal in CHF was not the cause of the difference in the PHG-CA responses between the two groups. Thus these additional studies suggest that the increased PHG-CA responses of SSNA in CHF were not due solely to the presence of fatigue and accumulation of metaboreceptor stimulants but may be specific for fatiguing exercise in CHF.

The significance of the increase of SSNA during PHG-CA is not clear. Because we did not attempt to differentiate sudomotor activity from skin vasoconstrictor activity and because in CHF the SSNA response to exercise was not greater than in the controls, it is uncertain whether the metaboreflex-induced rise in SSNA relates to the profound exercise-induced skin vasoconstriction in CHF described by Zelis et al. (36). On the basis of animal data, the patterns of sympathetic discharge in response to stress are highly differentiated (23). Our findings raise the possibility that this differentiated pattern of sympathetic nerve discharge may be altered in disease. Whether this reflects altered input from afferent regulatory systems or an intrinsic change in neural regulation in the brain stem remains to be determined.

In CHF patients an increase in MSNA was evident in the first few minutes of rhythmic exercise, whereas in the controls it was delayed. Our data do not clarify the mechanism responsible for this difference. Although during the first 2 min of exercise H₂PO₄⁻ was not statistically higher in CHF patients than in the controls, a trend for increased concentrations of muscle

Table 6. Effects of high-intensity static handgrip exercise on heart rate and mean arterial pressure in control subjects at three different workloads

	Baseline	EG	PHG-CA	Recovery	Statistics
HR, beats/min					
35% MVC	66 ± 4	74 ± 4*	67 ± 3	65 ± 4	<i>F</i> = 11.8; <i>P</i> < 0.001
45% MVC	64 ± 2	73 ± 4*	62 ± 3	61 ± 2	<i>F</i> = 13.4; <i>P</i> < 0.001
60% MVC	63 ± 2	73 ± 6*	59 ± 3	63 ± 2	<i>F</i> = 8.5; <i>P</i> < 0.01
MAP, mmHg					
35% MVC	94 ± 3	115 ± 8*	112 ± 5*	96 ± 3	<i>F</i> = 13.2; <i>P</i> < 0.001
45% MVC	94 ± 5	122 ± 10*	113 ± 6*	97 ± 4	<i>F</i> = 13.9; <i>P</i> < 0.001
60% MVC	99 ± 6	128 ± 13*	117 ± 7*	102 ± 7	<i>F</i> = 10.4; <i>P</i> < 0.001

Values are means ± SE for 6 subjects. Baseline is average of 5 min. Recovery is final (3rd) minute after release of circulatory arrest. * *P* < 0.05 compared with baseline.

metabolites was evident. It is therefore possible that even at this stage of exercise metabolite-sensitive afferents were engaged.

Could differences in central command or activity of muscle mechanoreceptors explain differences in the pattern of exercise-induced sympathoexcitation between the two groups? The exercise response of SSNA, a potential index of central command (33), was not greater in CHF patients than in the controls. Unfortunately, the lack of a progressive rise of SSNA during exercise and the prominent PHG-CA response of SSNA in CHF patients suggests that, during rhythmic handgrip and in CHF, this measure may not be useful as an index of central command. Because of the difficulty in assessing central command, it is also difficult to speculate on the contribution of muscle mechanoreceptor reflexes to the sympathetic response to exercise. In addition, because mechanically sensitive muscle afferents may also be sensitive to muscle metabolites, mechanoreflex responses may increase over time (10), making it difficult to determine the relative contribution of each of these effects in our study. Alternate approaches will be necessary to definitively evaluate the role of central command and muscle mechanoreflexes in CHF.

We cannot exclude the possibility that baroreflex mechanisms may play a role in the differences of sympathoexcitation during early exercise between the two groups. In normal humans, the exercise-induced rise of arterial pressure appears to attenuate the rise of MSNA (22). In addition, in CHF baroreflex-mediated inhibition of sympathetic outflow is impaired (9). Thus the blunted rise of blood pressure we observed in CHF patients and impaired baroreflex function may have contributed to the greater increase of MSNA during early exercise in CHF.

We did not discontinue drug therapy before the studies because many of our CHF patients were judged too ill to tolerate withholding these agents even for a limited time period. However, it should be pointed out that baseline MSNA and SSNA in our patients was very similar to that in CHF patients in whom medical therapy was temporarily withheld (11, 16, 28). Although we cannot be certain in what way the exercise responses may have been altered by the drugs, we believe that withholding therapy might also affect the responses in an unpredictable manner.

Our findings may have clinical implications. In CHF patients, fatigue even at low levels of activity is a major clinical problem (13). Recent studies in normal humans suggest a mechanistic link between the accumulation of by-products of muscle contraction and fatigue (17, 35). In CHF patients, fatigue occurs early and is associated with accumulation of muscle metabolites (14, 34). Our findings extend these observations and suggest that, in CHF patients, rhythmic exercise even at low workloads results in increased sympathetic outflow directed to skeletal muscle and to skin through engagement of the muscle metaboreflex. On the basis of studies from our laboratory and others, we believe that intense metaboreceptor activation may oppose meta-

bolic vasodilation (25). Such a vasoconstrictor influence may be even more important when blood flow in an exercising bed is low such as in CHF patients (36). However, our data do not allow us to comment on sympathetic outflow directed to other vascular beds, e.g., the coronary or renal circulations. The functional consequences of early engagement of the muscle metaboreflex during exercise in CHF patients deserve further investigation.

In conclusion, we demonstrated that in CHF patients rhythmic handgrip exercise is associated with premature fatigue and accumulation of muscle metabolites and results in prominent engagement of the muscle metaboreflex. Activation of this reflex in CHF patients resulted in increased discharge rates of sympathetic nerves directed to skeletal muscle and also to skin. On the basis of these data, we propose that in CHF patients the mechanism and the distribution of exercise-induced sympathoexcitation are distinctly different from normal.

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