Sympathetic nerve responses to muscle contraction and stretch in ischemic heart failure

Satoshi Koba, Jihong Xing, Lawrence I. Sinoway, and Jianhua Li

Penn State Heart and Vascular Institute, Pennsylvania State University College of Medicine, Milton S. Hershey Medical Center, Hershey, Pennsylvania

Submitted 17 July 2007; accepted in final form 23 October 2007

Koba S, Xing J, Sinoway LI, Li J. Sympathetic nerve responses to muscle contraction and stretch in ischemic heart failure. Am J Physiol Heart Circ Physiol 294: H311–H321, 2008.—Congestive heart failure (CHF) induces abnormal regulation of peripheral blood flow during exercise. Previous studies have suggested that a reflex from contracting muscle is disordered in this disease. However, there has been very little investigation of the muscle reflex regulating sympathetic outflows in CHF. Myocardial infarction (MI) was induced by the coronary artery ligation in rats. Echocardiography was performed to determine fractional shortening (FS), an index of the left ventricular function. We examined renal and lumbar sympathetic nerve activities (RSNA and LSNA, respectively) during 1-min repetitive (1-to 4-s stimulation to relaxation) contraction or stretch of the triceps surae muscles. During these interventions, the RSNA and LSNA responded synchronously as tension was developed. The RSNA and LSNA responses to contraction were significantly greater in MI rats (n = 13) with FS <30% than in control animals (n = 13) with FS >40% (RSNA: +49 ± 7 vs. +19 ± 4 a.u., P < 0.01; LSNA: +28 ± 7 vs. +8 ± 2 a.u., P < 0.01) at the same tension development. Stretch also increased the RSNA and LSNA to a larger degree in MI (n = 13) than in control animals (n = 13) (RSNA: +36 ± 6 vs. +19 ± 3 a.u., P < 0.05; LSNA: +24 ± 3 vs. +9 ± 2 a.u., P < 0.01). The data demonstrate that CHF exaggerates sympathetic nerve responses to muscle contraction as well as stretch. We suggest that muscle afferent-mediated sympathetic outflows contribute to the abnormal regulation of peripheral blood flow seen during exercise in CHF.

First published October 26, 2007; doi:10.1152/ajpheart.00835.2007.

© 2008 the American Physiological Society

Address for reprint requests and other correspondence: J. Li, Penn State Heart and Vascular Institute, H047, Pennsylvania State Univ. College of Medicine, Milton S. Hershey Medical Center, 500 Univ. Drive, Hershey, PA 17033 (e-mail: jz110@psu.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://ajpheart.physiology.org by 10.220.33.3 on May 1, 2017

Downloaded from http://ajpheart.physiology.org/ by 10.220.33.3 on May 1, 2017
The RSNA and LSNA on the left side were recorded as previously described (12–15, 23, 40). The nerves were kept intact during the recording. Briefly, a bundle of the renal nerves and the lumbar sympathetic trunk at the L3–L4 or L4–L5 segment were carefully dissected from other connective tissues. A piece of laboratory film was placed under the isolated nerves, and two tips of a bipolar electrode to record neural activity were placed between the nerves and the film. They were embedded in a silicon gel. Once the gel was hardened, the silicon rubber was fixed to the surrounding tissue with a glue containing α-cyanacrylate. Changes in the LSNA at the L3–L5 segment, a major component projecting hindlimb in rats (1), have been reported to be linearly related with the changes in vascular conduction at the hindlimb (14, 23). This suggests that the recording of LSNA at the L3–L5 segment should be a valid index of SNA of the hindlimb. The RSNA and LSNA signal were amplified with a differential amplifier (P511; Grass Instruments) with a band-pass filter of 100 Hz in low-cut frequency and 3 kHz in high-cut frequency and made audible. The left Achilles tendon was isolated by cutting the calcaneus bone, and the left triceps surae muscles were isolated. The hindlimb was fixed in space with a patellar precision clamp to prevent limb movement. All visible branches of the left sciatic nerve except for those innervating the triceps surae muscles were cut. The common tibial nerve was carefully dissected and then placed on a shielded bipolar electrode for electrically evoking contraction of the triceps surae muscles. The electrode was stabilized and connected to a stimulator (S88; Grass Instruments). The tension generated by the triceps surae muscles was recorded with a force transducer (FT03; Grass Instruments) connected to the Achilles tendon.

The animals were held in a stereotaxic apparatus (900LS; David Kopf Instruments) and decerebrated. The procedure for decerebration was previously described in detail (13, 15). This procedure allowed us to observe the sympathetic nervous responses to muscle contraction/stretch without the potential confounding influences of anesthesia. In decerebrated rats, but not in anesthetized rats, static contraction evoking activation of the muscle reflex induces a pressor response (15, 33), which is consistent with observation obtained from cat and dog preparations, commonly used to study the muscle reflex. After cerebral tissue was removed in the skull cavity and covering the cerebellum, a recovery period of >75 min was allowed before the experimental protocols were begun.

**Experimental Design**

The triceps surae muscles were lightly stretched to create a baseline tension of 50–100 g.

Muscle contraction. The motor threshold (MT), the minimum current intensity necessary to evoke twitching of the triceps surae muscles, was determined by electrical stimulation of the tibial nerve with 0.1-ms pulse duration. After 30 s of baseline data were collected, 1 min of repetitive contraction of the triceps surae muscles was induced. The duty cycle was 1- to 4-s stimulation to relaxation so that the muscle was stimulated 12 times for 1 min. Contraction was evoked by electrical stimulation of the tibial nerve [40 Hz of frequency, 0.1 ms of pulse duration, >2× MT of intensity (<0.1 mA)] (13, 27).

The RSNA and LSNA were recorded from the left side on the left side of the rats by integrating the changes in muscle activity as previously described (12–15, 23, 40). The nerves were kept intact during the recording. Briefly, a bundle of the renal nerves and the lumbar sympathetic trunk at the L3–L4 or L4–L5 segment were carefully dissected from other connective tissues. A piece of laboratory film was placed under the isolated nerves, and two tips of a bipolar electrode to record neural activity were placed between the nerves and the film. They were embedded in a silicon gel. Once the gel was hardened, the silicon rubber was fixed to the surrounding tissue with a glue containing α-cyanacrylate. Changes in the LSNA at the L3–L5 segment, a major component projecting hindlimb in rats (1), have been reported to be linearly related with the changes in vascular conduction at the hindlimb (14, 23). This suggests that the recording of LSNA at the L3–L5 segment should be a valid index of SNA of the hindlimb. The RSNA and LSNA signal were amplified with a differential amplifier (P511; Grass Instruments) with a band-pass filter of 100 Hz in low-cut frequency and 3 kHz in high-cut frequency and made audible. The left Achilles tendon was isolated by cutting the calcaneus bone, and the left triceps surae muscles were isolated. The hindlimb was fixed in space with a patellar precision clamp to prevent limb movement. All visible branches of the left sciatic nerve except for those innervating the triceps surae muscles were cut. The common tibial nerve was carefully dissected and then placed on a shielded bipolar electrode for electrically evoking contraction of the triceps surae muscles. The electrode was stabilized and connected to a stimulator (S88; Grass Instruments). The tension generated by the triceps surae muscles was recorded with a force transducer (FT03; Grass Instruments) connected to the Achilles tendon.

The animals were held in a stereotaxic apparatus (900LS; David Kopf Instruments) and decerebrated. The procedure for decerebration was previously described in detail (13, 15). This procedure allowed us to observe the sympathetic nervous responses to muscle contraction/stretch without the potential confounding influences of anesthesia. In decerebrated rats, but not in anesthetized rats, static contraction evoking activation of the muscle reflex induces a pressor response (15, 33), which is consistent with observation obtained from cat and dog preparations, commonly used to study the muscle reflex. After cerebral tissue was removed in the skull cavity and covering the cerebellum, a recovery period of >75 min was allowed before the experimental protocols were begun.

**Experimental Design**

The triceps surae muscles were lightly stretched to create a baseline tension of 50–100 g.

Muscle contraction. The motor threshold (MT), the minimum current intensity necessary to evoke twitching of the triceps surae muscles, was determined by electrical stimulation of the tibial nerve with 0.1-ms pulse duration. After 30 s of baseline data were collected, 1 min of repetitive contraction of the triceps surae muscles was induced. The duty cycle was 1- to 4-s stimulation to relaxation so that the muscle was stimulated 12 times for 1 min. Contraction was evoked by electrical stimulation of the tibial nerve [40 Hz of frequency, 0.1 ms of pulse duration, >2× MT of intensity (<0.1 mA)] (13, 27).

### Table 1. Morphometric and echocardiographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>564±14</td>
<td>604±16</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>1.53±0.05</td>
<td>2.03±0.08*</td>
</tr>
<tr>
<td>Heart weight/body weight, mg/g</td>
<td>2.72±0.07</td>
<td>3.55±0.12*</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>3.3±1.9</td>
<td>11.6±2.4*</td>
</tr>
<tr>
<td>LVSD, mm</td>
<td>0.82±0.02</td>
<td>1.14±0.02*</td>
</tr>
<tr>
<td>FS, %</td>
<td>0.43±0.02</td>
<td>0.95±0.02*</td>
</tr>
<tr>
<td>TTI</td>
<td>48±2</td>
<td>17±1*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 16 control and 17 myocardial infarction (MI) rats. *P < 0.05 vs. control with the unpaired t-test. LVEDP, left ventricular end-diastolic pressure; LVDD, left ventricular end-diastolic diameter; LVSD, left ventricular end-systolic diameter; FS, fractional shortening (=LVDD − LVSD)/LVDD × 100.

**Coronary Artery Ligation**

Coronary artery ligation surgery was performed as described in our previous studies (7, 12, 18, 39). Male Sprague-Dawley rats (6–7 wk, 160–200 g) were anesthetized by inhalation of an isoflurane–oxygen mixture (2–5% isoflurane in oxygen), intubated, and artificially ventilated. An incision between the fourth and fifth ribs was made, and the left ventricular wall was exposed through a thoracotomy. The left coronary artery was then ligated.

**Echocardiography**

A transthoracic echocardiography (Sequoia C256; Acuson/ Siemens) was performed to assess the left ventricular function more than 9 wk after the ligation surgery (7, 12, 18, 39). The echocardiographic data are shown in Table 1. On the basis of the fractional shortening (FS) determined by echocardiography, the control animals with FS >40% and animals with heart failure of FS <30% induced by MI were used in the experiment.

**Experimental Preparation**

MI (n = 17) and control rats (n = 16) were used in the experiments 14–22 wk after the ligation surgery. The animals were anesthetized with a mixture of isoflurane (<4%) and oxygen. The trachea was cannulated, and then the lungs were artificially ventilated with a respirator (Harvard model 683; tidal volume 2.0–2.5 ml and frequency 70 min⁻¹). The left jugular vein and common carotid artery were cannulated to administer drugs and to record arterial pressure (AP), respectively. The arterial catheter was attached to a pressure transducer (MLT0380/D; AD Instruments). Needle electrodes were placed on the back of the animal to record the electrocardiogram (ECG). The ECG signal was amplified with an AC Preamplifier (P55; Grass Instruments). HR was calculated beat to beat with detection of the time between successive R waves in the ECG. Arterial pH was measured with a pH meter (B-212; Horiba) and was maintained within normal limits (pH 7.5) by administering sodium bicarbonate solution (8.4%) intravenously during the experiment. Body temperature was adequately maintained with a heating pad.

**Fig. 1.** A: typical recordings of muscle tension developed within the triceps surae muscles, renal sympathetic nerve activity (RSNA), lumbar sympathetic nerve activity (LSNA), arterial pressure (AP), and heart rate (HR; bpm, beats/min) before and during 1 min of repetitive muscle contraction in a control rat [fractional shortening (FS) = 53%] and a myocardial infarction (MI) rat (FS = 15%). B: magnified data of tension, RSNA, and LSNA and the relative changes in RSNA (ΔRSNA) and LSNA (ΔLSNA) from baseline for 5 s including 5th muscle contraction of the control and MI animals. Recording durations are indicated by arrows in A. The relative changes in the SNAs were evaluated with each basal value averaged for 30 s just before the first contraction. C: superimposed plots of changes in tension (Δtension), ΔRSNA, and ΔLSNA and averaged ΔRSNA (ΔRSNAmean) and ΔLSNA (ΔLSNAmean) during a cycle averaged over 12 interventions of repeated muscle contraction. Of note, both the RSNA and LSNA responded synchronously as tension was developed, and the responses of the RSNA and LSNA appeared larger in the MI rat than in the control rat. D: changes from baseline in tension (Δtensionmean), and SNA (ΔSNAmean) after the normalization. Time 0 indicates the onset of tension development. These data were sampled from the MI rat shown in A–C, and the SNA was sampled from the RSNA. Tension-time index (TTI) was obtained by integrating the developed tension and time, as shown by the shaded area (top). The integrated change in the SNA (Int ΔSNA) was obtained by integrating the changes in the SNA and time, as shown with the shaded area (bottom), a.u., Arbitrary unit.
**RESULTS**

Basal MAP and HR are shown in Table 2. There were no significant differences between the experimental groups. Signal-to-noise ratios of the SNAs at baseline before muscle contraction were 3.8 ± 0.6 and 5.3 ± 0.6 in RSNA and LSNA in the controls and 4.8 ± 0.8 and 5.7 ± 0.7 in the MI rats. The ratios before stretch were 3.7 ± 0.5 and 5.2 ± 0.6 in the controls and 5.5 ± 0.9 and 5.4 ± 0.7 in the MI rats. In the comparison of the ratio between the controls and MI rats, only the ratio of the RSNA before stretch was significantly larger in the MI than in the control rats.

**Muscle Contraction**

Original tracings of tension generated within the triceps surae muscles as well as RSNA, LSNA, AP, and HR before and during 1 min of repetitive muscle contraction of a control rat (FS = 53%) and a rat with MI (FS = 15%) are presented in Fig. 1A. During 1 min of repetitive contractions, the RSNA and LSNA responded synchronously as tension was developed. Although AP and HR fluctuated as tension was developed, the relative changes were of small magnitude. The RSNA and LSNA during a stimulation-relaxation cycle and the overlapped SNAs data over 12 cycles of stimulation-relaxation are shown in Fig. 1, B and C, respectively. The responses in the RSNA and LSNA during contraction interventions of the MI rat appeared to be larger than those of the control one. Figure 1D shows the methods to calculate the TTI and the integrated ΔSNA.

Changes in the RSNA, LSNA, MAP, and HR as well as developed tension during a stimulation-relaxation cycle averaged over 12 interventions of muscle contraction of the controls (n = 13) and the MI rats (n = 13) are presented in Fig. 2. In both groups, muscle contraction significantly increased both the RSNA and LSNA. The RSNA and LSNA responses to contraction occurred rapidly. Of note, the increases in the RSNA and LSNA rapidly returned toward baseline level. There were significant differences between the basal value and the overshoot of the decrease in the RSNA followed by muscle contraction in both groups. The repetitive contractions did not significantly change MAP and HR on average, because this muscle stimulation induced both a presser and depressor response or no blood pressure change between individuals. The pattern of differential blood pressure responses during repetitive muscle contraction between individuals is consistent with previous studies (11, 13).

The TTI, integrated ΔRSNA and ΔLSNA, and integrated ΔRSNA and ΔLSNA per TTI were compared between the controls and MI rats, as presented in Fig. 3. There was no significant difference in the TTI between the groups (+341 ± 30 vs. +340 ± 36 g·s, MI vs. control rats). The integrated ΔRSNA [+49 ± 7 vs. +19 ± 4 arbitrary units (a.u.); P < 0.01], as well as the integrated ΔLSNA (+28 ± 7 vs. +8 ± 2 a.u.; P < 0.01), was significantly greater in the MI rats than in the controls. The integrated ΔRSNA per TTI [+15 ± 2 vs. +7 ± 1 a.u. (×10⁻²); P < 0.05], as well as

<table>
<thead>
<tr>
<th>Table 2. Basal MAP and HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>MAP, mmHg</td>
</tr>
<tr>
<td>HR, beats/min</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of rats. There were no significant differences. MAP, mean arterial pressure; HR, heart rate.

Data Acquisition and Statistical Analyses

All measured variables were displayed continuously on a computer monitor and stored on a hard disk through analog-to-digital conversion (Powerlab/8s; AD Instruments) at a 1-kHz sampling rate. RSNA and LSNA responses to muscle stimulation were analyzed using methods reported previously (13).

In Fig. 1, A and B, representative and simultaneous recording of muscle tension, RSNA, LSNA, AP, and HR responses during 1 min of repetitive contraction of the triceps surae muscles are presented for a control and MI animal. An outline of the analytic approach employed in this study is also presented in Fig. 1, C–D. Full-wave rectified signals of the SNAs as well as the background noise signals were obtained. The noise component was subtracted from the rectified signal, and then a moving average over 50 ms was performed. To quantify the sympathetic responses to muscle stimulation, basal values were obtained by taking mean values for 30 s of baseline, and this value was denoted as 100%. Relative changes from baseline were then evaluated. The obtained values were averaged over every 100 ms (Fig. 1, B and C). The SNA responses to 12 muscle stimulations were then superimposed on one another and averaged (Fig. 1C). This was done to remove any effects that might be due to respiration and blood pressure. Mean AP (MAP) and HR from baseline were also analyzed using the same method. For this analysis, MAP and HR, which were calculated beat to beat, were resampled at 1 kHz and averaged over 100 ms. The data obtained from each animal after this normalization process were used to obtain the results reported.

Tension-time index (TTI) (26), the integrated change in SNA (ΔSNA) during tension development, and the integrated ΔSNA per TTI were assessed, as shown in Fig. 1D. The TTI and the integrated ΔSNA values were calculated by integrating the developed tension and the time period during development of muscle tension and by integrating ΔSNAs (≥0) during tension development and its time period, respectively.

The data are means ± SE. Baseline data were obtained from the averaged values for 30 s immediately before first muscle contraction or stretch. The time-series data were analyzed with one-way repeated ANOVA. If appropriate, Dunnett’s post hoc test was used to assess significant changes from baseline. An unpaired t-test was used to assess significant differences in the data between the control and MI animals. The criterion of the significance was set at P < 0.05.
Fig. 2. Changes from baseline in muscle tension, RSNA, LSNA, mean AP (MAP), and HR during a cycle averaged over 12 interventions of muscle contraction in controls (n = 13) and MI rats (n = 13). Time 0 indicates the onset of tension development. Values are means ± SE. The changes in these values were evaluated with each basal value averaged for 30 s just before the first contraction. Horizontal bars indicate significant differences in responses from baseline, detected by the Dunnett post hoc test following one-way repeated ANOVA.
the integrated ΔLSNA per TTI [+/−8 ± 1 vs. +3 ± 1 a.u. (×10^−2); P < 0.05] between controls (n = 13) and MI rats (n = 13) detected by the unpaired t-test. N.S., no significant difference.

After muscle paralysis with pancuronium bromide (0.5 mg/kg), electrical stimulation of the tibial nerve did not change RSNA and LSNA in all rats. This suggests that the observed responses to muscle contraction evoked by this electrical stimulation were due to muscle contraction but not direct stimulation of afferents in the tibial nerve.

**Tendon Stretch**

Characteristics of the responses during stretch appeared similar to those seen during contraction. Original tracings of tension generated within the triceps surae muscles as well as RSNA, LSNA, AP, and HR before and during 1 min of repetitive tendon stretch of a control rat (FS = 42%) and a rat with MI (FS = 18%) are presented in Fig. 4A. The overlapped SNA data over 12 cycles of stimulation-relaxation are shown in Fig. 4B. The responses in the RSNA and LSNA during stretch of the MI rat appeared to be larger than those of the control rat.

Figure 5 shows changes in the RSNA, LSNA, MAP, and HR as well as developed tension during a stimulation-relaxation cycle averaged over 12 interventions of muscle stretch of the controls (n = 13) and the MI rats (n = 13). In both groups, both the RSNA and LSNA were significantly increased by tendon stretch and rapidly returned toward baseline level. There were significant differences between the basal value and the overshoot of the decrease in the RSNA followed by muscle stretch in both groups. The repetitive stretch did not significantly change MAP and HR. As seen in the contraction trial, the differential blood pressure change during repetitive muscle stimulations between individuals was observed.

The TTI, integrated ΔRSNA and ΔLSNA, and integrated ΔRSNA and ΔLSNA per TTI were compared between the controls and MI rats, as presented in Fig. 6. There was no significant difference in the TTI between the two groups (+252 ± 26 vs. +282 ± 39 g·s, MI vs. control rats). The integrated ΔRSNA (+36 ± 6 vs. +19 ± 3 a.u.; P < 0.05), as well as the integrated ΔLSNA (+24 ± 3 vs. +9 ± 2 a.u.; P < 0.01), was significantly greater in the MI rats than in the controls.
controls. The integrated $\Delta$RSNA per TTI [$+17 \pm 4$ vs. $+8 \pm 2$ a.u. ($\times 10^{-2}$); $P < 0.05$], as well as the integrated $\Delta$LSNA per TTI [$+11 \pm 2$ vs. $+3 \pm 1$ a.u. ($\times 10^{-2}$); $P < 0.01$], was also significantly greater in the MI rats than in the controls.

**DISCUSSION**

Using a rat model, we examined the responses in RSNA and LSNA simultaneously in this study. The data demonstrate that the increases in the RSNA and LSNA during repetitive muscle contraction were larger in the MI rats than in the controls. This finding supports our hypothesis that sympathoexcitation elicited by the muscle reflex is exaggerated in CHF. The data further demonstrate that the increases in the RSNA and LSNA during repetitive muscle stretch were also larger in the MI rats, suggesting that the effect of the muscle mechanoreceptor activation on sympathoexcitation was enhanced in the MI rats.

It is noted that muscle paralysis eliminated effects of electrical stimulation of the tibial nerve on the sympathetic nerve responses in all rats. This suggests that the method of electrical stimulation was valid to be used to elicit muscle contraction without directly activatingafferent fibers, and to observe reflex responses to contraction.

Peripheral blood flow responses to exercise in CHF patients (17, 21, 22, 24, 30, 41) and in animal models with heart failure (5, 8) are disordered, including the exaggerated decrease in renal blood flow and the attenuated increase in muscle blood flow. The peripheral vasomotor tone is regulated by sympathetic discharges. Two key mechanisms via sympathetic discharges can contribute to the exaggerated peripheral vasoconstriction in CHF, which are 1) increased vasoconstriction at a given level of sympathetic discharge and 2) exaggerated increases in sympathetic nerve responses to exercise. Supporting the first mechanism, previous studies have reported excessive vasoconstriction in kidney (4) and an excessive increase in norepinephrine release in skeletal muscles (39) at a given sympathetic stimulation in rats with MI. Furthermore, Thomas et al. (37) reported that a role of muscle metabolites in countering sympathetic vasoconstriction in contracting skeletal muscle is blunted in the MI rats. Supporting the second mechanism, a recent study (12) showed that increased RSNA and LSNA by central command, that is, a neural drive originating in cortical brain centers responsible for sympathetic activation during exercise, were larger in the MI rats. Reductions of renal and hindlimb vascular conductance are linearly correlated with increases in RSNA and LSNA, respectively (14, 23, 40). The mechanism found in this study, namely, greater muscle reflex-elicited sympathetic outflows to internal organs and skeletal muscles, may also contribute to the greater renal vasoconstriction and the attenuated muscle vasodilatation seen during exercise in this disease.
Fig. 5. Changes from baseline in muscle tension, RSNA, LSNA, MAP, and HR during a cycle averaged over 12 interventions of tendon stretch in controls ($n = 13$) and MI rats ($n = 13$). Time 0 indicates the onset of tension development. Values are means ± SE. The changes in these values were evaluated with each basal value averaged for 30 s just before the first contraction. Horizontal bars indicate significant differences from baseline, detected by the Dunnett post hoc test following one-way repeated ANOVA.
The muscle reflex activated by contraction comprises the muscle mechanoreflex and metaboreflex (10). In CHF, roles of the muscle mechanoreceptors in activation of the muscle reflex have recently attracted considerable attention. A previous study in humans reported that passive muscle stretch increases muscle SNA in CHF patients but not in healthy controls (20). Tendon stretch induces an exaggerated pressor response in MI rats compared with that observed in control rats (18, 32). Gadolinium, a mechanosensitive receptor blocker, has further been reported to attenuate the pressor response to muscle contraction to a greater degree in MI rats than in control animals (34). These observations have suggested that muscle mechanoreceptors are sensitized in CHF. The repetitive muscle contraction technique employed in the present experiment supports this idea. This fashion of contraction has been considered to mainly activate mechanosensitive components of this reflex. This statement is based on the following considerations: 1) SNA responses observed in this study were synchronized with tension during the bouts of contraction; 2) both the RSNA and LSNA responded rapidly at the onset of muscle tension development; and 3) the characteristic of the dynamics of the SNA during contraction was closely similar to the one seen during stretch that purely stimulates muscle mechanoreceptors (9, 10). Our results show that the repetitive muscle contraction resulted in enhanced sympathetic nerve responses in the MI rats. Thus stimulation of muscle mechanoreceptors during contraction was likely to play a role in the exaggerated sympathoexcitation during contraction of the MI rats observed in this study. Similar to contraction, it was observed that greater sympathetic nerve responses were induced by muscle stretch in CHF in this study.

The underlying mechanisms for the exaggerated muscle mechanoreflex in CHF are unclear. CHF includes alteration in skeletal muscle morphology and metabolism (6, 19). Muscle metabolites can enhance muscle reflex-elicited sympathetic nerve responses (13). Abnormal metabolic function in active muscle may sensitize stimulation of mechanoreceptors in CHF during exercise (31). A finding supporting this hypothesis was that an enhancement of the muscle mechanoreflex pressor responses following injection of ATP within the muscle circulation was greater in MI rats (18). Abnormality in receptors of sensory muscle afferents nerves may also induce the exagger-
ated cardioacceleration in CHF (7, 35). In addition, central cardiovascular pathways are also likely to be involved in the abnormal muscle reflex in CHF. For example, central baroreflex pathways are plastically changed, and the role of the baroreflex in inhibiting sympathetic activation is attenuated in heart failure (42). The inhibitory effect of the baroreflex on sympathoexcitation elicited by the muscle reflex (28) may be attenuated in CHF.

We observed the overshoot of the decrease in the RSNA following muscle stimulation. This overshooting response may be caused by an action of central sympathoinhibitory pathways following peripheral reflex-induced sympathoexcitation (29). Consistent with previous reports (11, 13), repetitive muscle contraction and stretch did not significantly increase blood pressure in the present study. However, static muscle contraction has been shown to induce a pressor response (15, 32–35). The discrepancy is likely due to the different modality of muscle contraction. In contraction with muscle relaxation periods, blood flow going to active muscle is increased to a very large degree, whereas in continuous static contraction, it is disturbed due to mechanical compression. Muscle contraction rapidly triggers actions of local vasodilator mechanisms (2). The local vasodilation might play a role to buffer the blood pressure increase in the present study, as Kaufman et al. (11) suggested. Moreover, the short periods of the sympathoexcitation followed by sympathoinhibition might not be enough to increase blood pressure. In addition, the developed tension in the present study was relatively lower than the one in previous studies using static contraction and stretch (32–35), possibly eliciting less sympathoexcitation. These factors can be considered to buffer the effect of sympathoexcitation on the blood pressure during repetitive muscle contraction and stretch. Finally, the attenuated cardiac contractility in the MI rats might buffer effects of the enhanced sympathoexcitation on blood pressure, possibly resulting in no difference in the blood pressure response between the control and MI rats.

In conclusion, we observed that the muscle reflex activated by contraction resulted in greater sympathetic nerve responses innervating both renal and hindlimb beds in the MI rats. Tendon stretch also resulted in the exaggerated sympathoexcitation in the MI rats. These findings demonstrate that heart failure exaggerates the muscle reflex-elicited sympathoexcitation and suggest that the muscle mechanoreceptor activation due to contraction may play a dominant role in the exaggerated sympathoexcitation. This mechanism may be a contributor to limiting blood supply to peripheral organs including kidney and active skeletal muscle observed during exercise in patients with CHF (17, 21, 22, 24, 30, 41).

ACKNOWLEDGMENTS

We thank Valarie Kehoe for technical assistance with coronary artery ligations and Jennie Stoner for outstanding secretarial skills.

GRANTS

This study was supported by National Heart, Lung, and Blood Institute Grants R01 HL075533 and HL078866 (to J. Li) and HL060800 (to L. I. Sinoway).

REFERENCES


