Sympathetic responses to exercise in myocardial infarction rats: a role of central command

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EXERCISE ACTIVATES THE SYMPATHETIC nervous system, increases blood pressure, and leads to an increase in blood flow to exercising skeletal muscle. This increase in muscle blood flow is associated with reduced renal blood flow (23). Two principal neural mechanisms are proposed to increase sympathetic nerve activity (SNA) and regulate the cardiovascular system during exercise. These are termed the exercise pressor reflex and central command. The exercise pressor reflex is a neural reflex that arises from receptors sensitive to mechanical and metabolic stimuli in exercising skeletal muscles and stimulates the medulla through the muscle thin afferent fibers (18). Central command is a feed-forward neural mechanism that induces parallel activation of motor and cardiovascular systems (9, 50).

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Moreover, the changes in renal and muscle vascular conductance were linearly correlated with the changes in RSNA and LSNA, respectively. These data suggested that sympathetic outflows to each peripheral organ elicited by central command induced neurally dependent vasoconstriction (21). If the central command-elicited sympathetic activations are exaggerated in CHF, this could serve as an important contributing mechanism to the excessive peripheral vasoconstrictor responses seen during exercise.

The present study was designed to identify the possible role played by central command in regulating the sympathetic nervous system during exercise in CHF. We measured RSNA and LSNA during fictive locomotion evoked by electrical stimulation of the mesencephalic locomotor region (MLR) in decerebrated and paralysed rat and compared the responses in healthy control and MI animals. The MLR, involved in an initiation of locomotion by directly activating the locomotor reticulospinal cells, has been found in the periaqueductal gray, the cuneiform nucleus, the pedondunculopontine nucleus, and the locus corruleus (11, 17, 43). It has also been reported that the MLR is activated during treadmill exercise in conscious rats by using immunocytochemical labeling of the c-Fos protein (16). Moreover, electrophysiological (14, 21) and neuroanatomic (19, 22) studies have found that activation of the MLR also stimulates sympathetic neurons. Thus stimulating the MLR in paralyzed animals allows us to study the role of central command. This study provides evidence demonstrating that increases in SNA evoked by stimulation of the MLR are augmented in heart failure.

**MATERIALS AND METHODS**

All procedures of this study were approved by the Animal Care Committee of this institution.

**Coronary artery ligation.** Coronary artery ligation surgery was performed as described in our previous study (26). Male Sprague-Dawley rats (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.** More than 6 wk after the ligation surgery, transthoracic echocardiography (Sequoia C256 from Acuson/Siemens) was performed to assess the cardiac structure and function (26). The echocardiographic data are shown in Table 1. On the basis of the fractional shortening (FS) determined by echocardiography, the animals were divided into three groups: 1) control with FS > 40% (control group, n = 9), 2) 30% < FS < 40% (small MI group, n = 9), and 3) FS < 30% (large MI group, n = 8). In the controls, echocardiography was performed in five animals, four of which were controls and one with postcoronary ligation but with a FS > 40%.

**Experimental preparation.** Experiments were performed in 26 age (13–17 wk)- and body weight (450–620 g)-matched Sprague-Dawley rats. The animal was anesthetized with a mixture of isoflurane (<4%) and oxygen. The trachea was cannulated, and then the lungs were artificially ventilated with a respirator (model 683, Harvard) (2 ml tidal volume and 60 min⁻¹ frequency). 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).

**Table 1. Echocardiography measurements**

<table>
<thead>
<tr>
<th>Control with FS &gt; 40%</th>
<th>30% &lt; FS &lt; 40%</th>
<th>FS &lt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVDD, mm</td>
<td>8.0±0.4</td>
<td>8.5±0.3</td>
</tr>
<tr>
<td>LVSD, mm</td>
<td>3.9±0.5</td>
<td>5.3±0.2*</td>
</tr>
<tr>
<td>FS, %</td>
<td>51.9±4.1</td>
<td>37.1±1.0*</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVDD, left ventricular diastolic dimension; LVSD, left ventricular systolic dimension. *P < 0.05 vs. control with fractional shortening (FS) > 40%. †P < 0.05 vs. control with FS > 40% and 30% < FS < 40%.

Fig. 1. A: arterial pressure (AP), EMG generated within the left triceps surae muscles, and the integrated EMG (iEMG) over 100 ms before and during stimulation of the mesencephalic locomotor region (MLR) at 30 µA in a nonparalyzed rat, whose motor threshold was 14 µA. According to the procedure described in the text, a brain site was determined as the MLR. This stimulation induced rhythmic muscle activity. au, Arbitrary units. B: effect of the MLR stimulation at 30 µA after muscle paralysis on the left and right tibial nerve discharges (TND) in the same rat shown in A. The stimulating duration is indicated by the thick bar. This stimulation resulted in both left and right TND. *Recording artifact.
Needle electrodes were placed on the back of the animal to record the ECG. The ECG signal was amplified with an AC preamplifier (P55, Grass Instruments). Heart rate (HR) was calculated beat to beat with the detection of the time between successive R waves in the ECG. Body temperature was adequately maintained with a heating pad. Ear temperature was monitored, and the core temperature was maintained with an insulated heating blanket. 

Basal MAP, HR, ratio of RSNA and LSNA to maximal values, and motor threshold for evoking locomotion

<table>
<thead>
<tr>
<th>Control with FS &gt; 40%</th>
<th>30% &lt; FS &lt; 40%</th>
<th>FS &lt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>376 ± 16</td>
<td>397 ± 9</td>
</tr>
<tr>
<td>RSNA, % of maximum</td>
<td>29 ± 5</td>
<td>35 ± 3</td>
</tr>
<tr>
<td>LSNA, % of maximum</td>
<td>47 ± 4</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>Motor threshold, µA</td>
<td>25 ± 3</td>
<td>25 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. RSNA, renal sympathetic nerve activity; LSNA, lumbar sympathetic nerve activity; MAP, mean arterial pressure; HR, heart rate. There were no significant differences in those values between the groups (P > 0.05).

Animals were kept in a stereotactic apparatus (900LS, David Kopf Instruments). Decerebration at precollicular level was performed as previously described (21). Immediately before the decerebration, the right carotid artery was occluded to reduce brain bleeding. The upper skull and dura matter were removed, and then cortical tissue was removed with aspiration. The brain was then sectioned coronally with a blade at the precollicular level. All neural tissue rostral to the section and the cortical tissues covering the cerebellum were aspirated. Small pieces of cotton gauze were set in the cranial vault to arrest bleeding, and then the isoflurane anesthesia was withdrawn. The cranial vault was filled with mineral oil. To replace the blood lost during decerebration, saline was given intravenously in an amount sufficient to maintain basal AP if necessary. A recovery period >60 min was allowed before beginning the experimental protocols.

**Experimental design.** After the recovery period, the junction of the superior and inferior colliculus was searched to find the site of the MLR with electrical stimulation at 30- to 40-µA current intensity (60 Hz, 1-ms duration) with a needle-type bipolar microelectrode (CBBPE75, FHC) connected to an electronic stimulator (S88, Grass Instruments). The detailed procedure is described in the previous studies (5, 21). The determination of the site of the MLR was affirmed from the physiological criteria as follows: 1) threshold of locomotion with reciprocal limb movement <40 µA, 2) stimulus-bound locomotion, and 3) graded activity of locomotion and gait changes with increased stimulation current (5, 21).

![Fig. 2. Typical recordings of the changes in mean arterial pressure (MAP), renal sympathetic nerve activity (RSNA), lumbar sympathetic nerve activity (LSNA), and heart rate (HR; bpm = beats/min) during 30-s stimulation of the MLR at 20 µA in a control rat [A; fractional shortening (FS) = 56%, motor threshold = 27 µA] and a large myocardial infarction (MI) rat (B; FS = 21%, motor threshold = 28 µA). The stimulating duration is indicated by the thick bars. Stimulation of the MLR increased MAP, RSNA, and LSNA. The increases appeared not to be different between the rats. *Recording artifact. The magnified data of RSNA and LSNA for 1 s before (a) and during (b) stimulation of the MLR of the control and large MI animals are shown in C and D, respectively. Recording durations are indicated by arrows in A and B.](http://ajpheart.physiology.org/)

**Table 2. Basal MAP, HR, ratio of RSNA and LSNA to maximal values, and motor threshold for evoking locomotion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>MAP (mmHg)</th>
<th>HR (beats/min)</th>
<th>RSNA (µV)</th>
<th>LSNA (µV)</th>
<th>Motor threshold, µA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control with FS &gt; 40%</td>
<td>94 ± 6</td>
<td>376 ± 16</td>
<td>37 ± 5</td>
<td>47 ± 4</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>30% &lt; FS &lt; 40%</td>
<td>98 ± 9</td>
<td>397 ± 9</td>
<td>35 ± 3</td>
<td>45 ± 3</td>
<td>25 ± 2</td>
</tr>
<tr>
<td>FS &lt; 30%</td>
<td>95 ± 8</td>
<td>385 ± 11</td>
<td>29 ± 3</td>
<td>44 ± 6</td>
<td>26 ± 3</td>
</tr>
</tbody>
</table>

The RSNA and LSNA were recorded as previously described (21, 32, 33). Briefly, either a bundle of the renal nerves or the lumbar sympathetic trunk at L3 to L4 or L4 to L5 segment was carefully dissected from other connective tissues. A piece of laboratory film electrode to record neural activity were placed between the nerves and the film. These were embedded in a silicone gel. Once the gel was hardened, the silicone rubber was fixed to the surrounding tissue with a glue containing α-cyanoacrylate. LSNA at the L3 to L5 segment mainly reflects the component regulating hindlimb muscle circulation (21, 33). The RSNA and LSNA signals were amplified with a differential amplifier (P511, Grass Instruments) with a band-pass filter of 100 Hz in low-cut frequency and of 3 kHz in high-cut frequency and made audible.

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In a subset of four control rats, we confirmed that the MLR stimulation evokes fictive locomotion in the paralyzed animal. As shown in Fig. 1, it was observed that electrical stimulation of the site determined as the MLR induced rhythmic muscle activity in the triceps surae muscles before muscle paralysis. This stimulation also evoked both left and right tibial nerve discharges supplying triceps surae muscles after muscle paralysis. These data were consistent with previous studies by others (5, 9, 28, 43, 50).

After determination of the site of the MLR, we paralyzed the animal with an intravenous infusion of pancuronium bromide (0.5 mg/kg body wt). After 30 s of baseline data collection, we electrically stimulated the MLR for 30 s at 20, 30, 40, and 50 μA current intensity. The order of the current intensity was random.

At the conclusion of the experiments, the MLR was stimulated for 10 s at 100, 125, or 150 μA to obtain maximal values of RSNA and LSNA. The animal was then killed with an overdose of potassium chloride, and the background noise signals of RSNA and LSNA were recorded.

Data acquisition and statistical analysis. All measured variables were displayed continuously on a computer monitor and stored on a hard disk thorough analog-digital conversion (Powerlab/8s, AD Instruments) at a 1-kHz sampling rate. Mean AP (MAP) was calculated beat by beat. Signals of the SNAs were transformed into absolute values, integrated over every 1 s, and subtracted by the 1-s integrated background noise. The absolute values of the SNAs varied between rats. To quantify the sympathetic responses to stimulation of the MLR, basal values were obtained by taking mean values for 30 s immediately before stimulation and by evaluating the mean as 100%, and then relative changes from baseline during and after stimulation were evaluated. In addition, basal RSNA and LSNA values were also expressed as the absolute value by calculating the ratio to maximal sympathetic activation obtained by stimulating the MLR at 150 μA. This current intensity was considered to be sufficient to evoke maximal sympathetic activation because either RSNA or LSNA response during stimulation at 150 μA was almost the same compared with the response at a lower current intensity (<115% and <135%, compared with the responses at 125 and 100 μA, respectively).

The data are expressed as means ± SE. Baseline data were obtained from the averaged values for 30 s immediately before stimulation of the MLR. The baseline data were compared with paired $t$-tests between trials in the same group and with unpaired $t$-tests between groups. Two-way ANOVA was used to assess the effects of stimulation of the MLR on the cardiovascular responses from baseline and to assess differences in the responses between groups. When significant $F$ ratios were found with the ANOVA procedure, post hoc analysis was performed with Tukey’s procedure to detect significant differences. Linear regression analysis was used to examine the correlation between FS and RSNA or LSNA responses. The level of the statistical significance was set at $P < 0.05$.

RESULTS

Basal MAP, HR, ratios of RSNA and LSNA to maximal activation, and motor threshold for evoking locomotion are presented in Table 2. There were no significant differences for the values between the groups ($P > 0.05$). In each group, there were also no significant differences in the resting values between the trials ($P > 0.05$).
Typical recordings of MAP, RSNA, LSNA, and HR of control and large MI animals when the MLR was electrically stimulated at 20 and 50 μA are presented in Figs. 2 and 3, respectively. The FS values of the control and large MI animals were 56% and 21%, and motor thresholds were 27 and 28 μA, respectively. Low stimulation of the MLR at 20 μA increased AP, RSNA, and LSNA in both groups, and the increases were similar. Intense stimulation of the MLR at 50 μA also elicited increases in AP, RSNA, and LSNA, and responses were larger in the MI animals. HR was not altered significantly during stimulation of the MLR at each current intensity in both groups.

Changes from baseline in MAP, RSNA, and LSNA averaged for 30 s during stimulation of the MLR were compared at each current intensity between the control, small MI, and large MI groups, as presented in Fig. 4. The responses were not significantly different between the groups when the MLR was stimulated at 20 and 30 μA. Differences between the groups were noted as the current intensity during stimulation was increased. MAP responses in the small and large MI rats were significantly greater than those in the control rats at 40 and 50 μA. RSNA responses in the large MI rats were significantly greater than those in the other groups at 40 and 50 μA. LSNA responses in the large MI group were significantly greater than those in the controls at 50 μA. Interestingly, when the MLR was stimulated at 40 and 50 μA, RSNA responses were similar in the control and small MI rats. On the other hand, LSNA responses tended to be greater in small MI rats than in controls, although the differences did not reach statistical significance. In every trial, stimulation of the MLR did not significantly change HR (from 0 to +2 beats/min in 30 s average).

The time courses of the changes in MAP, RSNA, and LSNA during the MLR stimulation are shown in Fig. 5. Stimulation of the MLR significantly changed the responses in every trial. MLR stimulation at 40 and 50 μA evoked greater MAP responses in the small and large MI rats than in the controls. MLR stimulation at 40 and 50 μA evoked greater RSNA responses in the large MI than in the small MI and control groups. MLR stimulation at 50 μA evoked greater LSNA responses in the large MI rats than in the controls.

We examined whether a linear relationship was present between FS and RSNA or LSNA responses at each level of MLR stimulation using linear regression analyses (Table 3). At 20 μA, neither the RSNA nor LSNA response was correlated with the decrease in FS. At 30 μA, RSNA responses were not correlated, whereas LSNA responses were significantly correlated with the decrease in FS. At 40 and 50 μA, both RSNA and LSNA responses were significantly correlated with the decrease in FS. The linear relationships between FS and RSNA as well as LSNA responses at 50 μA are presented in Fig. 6.

**DISCUSSION**

The present study was undertaken to test whether selective engagement of central command evokes exaggerated sympathetic response in CHF animals. The main findings of this study were 1) the MLR stimulation at intense but not low-current intensity evoked greater increases in RSNA in large MI than in small MI and in control animals, 2) intense MLR stimulation led to greater LSNA responses in the large MI than in the control animals, and 3) the sympathetic responses to intense stimulation of the MLR were linearly correlated with the decrease in FS. These data demonstrate that RSNA and LSNA responses to intense stimulation of the MLR were exaggerated in the MI animals. This suggests that intense activation of central command may play a role in causing the exaggerated sympathetic responses to skeletal muscle and the kidney during exercise in CHF.

One must consider the spread of electrical stimulation around the stimulated site. It has been reported that, as the greater current intensity to stimulate a neural site is delivered, the electrical stimulation would extensively spread more (2). Thus intense stimulation might activate cell bodies and fibers of neural pathways in a wider range around the stimulated site than low stimulation. Although 20 and 50 μA were considered...
as low and intense stimulation in this report, it is unclear whether more numbers of neurons were activated by intense stimulation of the MLR. In MI animals and CHF patients, abnormal cardiac output distribution during exercise, that is, the exaggerated decrease in renal blood flow and the attenuated increase in muscle blood flow, is observed (13, 25, 30, 34, 41). The mechanism reported in the present study, namely greater central command-elicited sympathetic outflows to internal organs and skeletal muscles, may contribute to the greater renal vasoconstriction and the attenuated muscle vasodilatation seen during exercise in CHF.

Factors that help determine peripheral vasomotor tone include 1) the local vasodilator and vasoconstrictor mechanisms independent of neural pathways, 2) vascular sensitivity to sympathetic activation, and 3) the amount of sympathetic activation. Thus all of these mechanisms must be considered as contributing to the excessive peripheral vasoconstriction seen during exercise in CHF. Endogenous nitric oxide-mediated endothelial responses have been reported to be impaired in renal (15) and skeletal muscle vessels (48) of the MI rat. Myogenic vasoconstrictor responses have been reported to be exaggerated in the mesenteric arteries of the MI rat (12), and vascular sensitivity to sympathetic activation has been reported to be exaggerated in the kidney of the MI rat (8) and in the skeletal muscle of the dog with heart failure (1). However, it must be noted that contradicting data, regarding impairment of the sensitivity, have also been reported for the skeletal muscle vasculature (52). The amount of sympathetic activation has been reported to be excessive at rest and during exercise in CHF patients (24, 29, 36, 42, 47). Moreover, the excessive sympathetic activation in exercise has been suggested to be partially due to muscle mechanoreflex sensitization (26, 27, 29, 30, 34, 44, 45). The present study contributes to an understanding of sympathoexcitation in CHF by suggesting for the first time that central command stimulation evokes an exaggerated

Table 3. Regression linear analysis between FS and RSNA or LSNA

<table>
<thead>
<tr>
<th>Current Intensity, μA</th>
<th>FS-RSNA</th>
<th>FS-LSNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>30</td>
<td>NS</td>
<td>r = 0.52</td>
</tr>
<tr>
<td>40</td>
<td>r = 0.42</td>
<td>y = 84 - 76 × 10^{-2}x</td>
</tr>
<tr>
<td>50</td>
<td>r = 0.66</td>
<td>y = 156 - 196 × 10^{-2}x</td>
</tr>
</tbody>
</table>

Regression linear analysis was used to test whether there is a linear relationship between FS and RSNA (FS-RSNA) or LSNA (FS-LSNA) at each current intensity for stimulation of the mesencephalic locomotor region (MLR). The FS data were obtained from 22 animals (5: control, 9: small myocardial infarction, and 8: large myocardial infarction), RSNA were obtained from the animals and LSNA were obtained from 20 of them. In the case that regression linear analysis showed significant correlation (P < 0.05), the r values and equations of the regression line [x: FS (%), y: changes in RSNA or LSNA (%)] are presented. NS, not significant (P > 0.05).
sympathetic engagement to both the renal and lumbar beds in this disease.

In this study, we noted that, in small MI animals, LSNA tended to be greater than baseline, whereas RSNA was similar in control and small MI groups. The cause of this difference is not entirely clear, although it would suggest that heightened skeletal muscle sympathetic tone is seen earlier in the course of the disease than is accentuated renal nerve responses. The reason for this is not clear, and additional investigation will be required.

Stimulating the MLR in paralyzed animals has been extensively used to study the physiological roles played by central command (5, 7, 14, 21, 28, 43). However, in this experimental preparation, it is difficult to equate the MLR stimulation with the way that this site is activated as central command during actual exercise. Muscle contraction stimulates the pendopuculopontine nucleus in the MLR in rats (39). Thus the MLR stimulated by muscle contraction may also engage in the exaggerated sympathetic activation during actual exercise in CHF.

The reason why MLR stimulation evoked greater sympathetic activations in MI is not clear. It has been demonstrated that MI can alter the function and structure of neural sites in the rat responsible for cardiovascular regulation, such as hypothalamus and the nucleus of solitary tract (10, 37, 40, 49). These plastic alterations may also occur in the neural sites for cardiovascular regulation associated with central command, such as pontomedullary reticular formation neurons (7, 11, 19, 20, 22). In CHF, it would be anticipated that, when central command is activated, the brain stem excitatory neurons for sympathetic activation may be sensitized and/or that the inhibitory neurons, such as barosensitive neurons, may be desensitized. Moreover the structural characteristics of these excitatory and inhibitory neurons may be altered in CHF. Future studies are necessary for understanding the neural mechanism inducing abnormal cardiovascular regulation during exercise in CHF.

Resting SNA is elevated in CHF patients (24, 29, 36, 42, 47). In the present study, the elevations of basal RSNA and LSNA in MI animals were not observed (Table 2). However, in our report, the hypothalamus of the animal was removed during the decerebration. This area is known to be important for cardiovascular regulation. First, the contribution of the posterior hypothalamus can be pointed out. This area is also considered as a locomotor area (9, 19, 50), and has neural projections to the MLR (4) and to sympathetic neurons responsible for tonic sympathoexcitation (3, 19). Second, the paraventricular nucleus of the hypothalamus, which has direct projections to spinal cord intermediolateral cell columns, has been suggested to contribute to the elevated SNA seen in CHF. The neural activity of the paraventricular nucleus has been reported to be increased after MI (37, 49), possibly because of the attenuated effects of GABA (53) and nitric oxide-mediated neural pathways (38, 54). Thus the removal of the hypothalamus may have resulted in elevation of neither RSNA nor LSNA at baseline in the MI animals.

In conclusion, the data of the present study demonstrate that RSNA and LSNA responses to intense stimulation of the MLR are exaggerated in MI animals. This suggests that intense activation of central command plays a role in excessive peripheral vasoconstriction via sympathetic outflow in CHF.

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