Exaggerated muscle mechanoreflex control of reflex renal vasoconstriction in heart failure

HOLLY R. MIDDLEKAUFF,1 EGBERT U. NITZSCHE,2 CARL K. HOH,1 MICHELE A. HAMILTON,1 GREGG C. FONAROW,1 ANTOINE HAGE,1 AND JAIME D. MORIGUCHI

1Division of Cardiology, Department of Medicine, University of California, Los Angeles, California 90095; and 2Division of Nuclear Medicine, Department of Radiology, University of Basel, School of Medicine and Medical Center, CH-4031 Basel, Switzerland

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Middlekauff, Holly R., Egbert U. Nitzsche, Carl K. Hoh, Michele A. Hamilton, Gregg C. Fonarow, Antoine Hage, and Jaime D. Moriguchi. Exaggerated muscle mechanoreflex control of reflex renal vasoconstriction in heart failure. J Appl Physiol 90: 1714–1719, 2001.—In heart failure (HF) patients, reflex renal vasoconstriction during exercise is exaggerated. We hypothesized that muscle mechanoreceptor control of renal vasoconstriction is exaggerated in HF. Nineteen HF patients and nineteen controls were enrolled in two exercise protocols: 1) low-level rhythmic handgrip (mechanoreceptors and central command) and 2) involuntary bicep contractions (mechanoreceptors). Renal cortical blood flow was measured by positron emission tomography, and renal cortical vascular resistance (RCVR) was calculated. During rhythmic handgrip, peak RCVR was greater in HF patients compared with controls (37 ± 1 vs. 27 ± 1 units; P < 0.01). Change in (Δ) RCVR tended to be greater as well but did not reach statistical significance (10 ± 1 vs. 7 ± 0.9 units; P = 0.13). RCVR was returned to baseline at 2–3 min postexercise in controls but remained significantly elevated in HF patients. During involuntary muscle contractions, peak RCVR was greater in HF patients compared with controls (36 ± 0.7 vs. 24 ± 0.5 units; P < 0.0001). The Δ RCVR was also significantly greater in HF patients compared with controls (6 ± 1 vs. 4 ± 0.6 units; P = 0.05). The data suggest that reflex renal vasoconstriction is exaggerated in both magnitude and duration during dynamic exercise in HF patients. Given that the exaggerated response was elicited in both the presence and absence of central command, it is clear that intact muscle mechanoreceptor sensitivity contributes to this augmented reflex renal vasoconstriction.

DURING STATIC HANDGRIp in normal volunteers, there is reflex renal vasoconstriction (12). The principal afferent nerve fibers mediating this reflex vasoconstriction are the muscle metaboreceptors, nerve endings located in skeletal muscle that are sensitive to ischemic metabolites generated during exercise (12). But renal vasoconstriction begins at the onset of exercise, before ischemic metabolites have been generated; therefore, it is likely that muscle mechanoreceptors, sensitive to muscle contraction, and/or central command, which is related to voluntary motor effort, contribute to reflex renal vasoconstriction in normal humans during static exercise.

In heart failure (HF) patients, the situation is very different. First, reflex renal vasoconstriction during exercise is exaggerated, in both magnitude and duration, compared with normal volunteers (11). Second, it is not mediated by the muscle metaboreceptors. We have recently reported that muscle metaboreceptor control of reflex renal vasoconstriction during exercise is blunted in patients with HF (11). It is likely then that muscle mechanoreceptor and central command control of renal vasoconstriction during exercise is exaggerated in HF. In this investigation, we have focused on the muscle mechanoreceptors.

To begin to study the muscle mechanoreceptor contribution to reflex renal vasoconstriction during exercise, we measured renal cortical vascular resistance (RCVR) during mild rhythmic handgrip (RHG). RHG is a form of dynamic exercise that is performed many times a day during activities of daily living and therefore has direct clinical relevance. Evidence in normal humans suggests that reflexes activated during mild RHG are principally mediated by muscle mechanoreceptors, not metaboreceptors (2). There is likely some overlap, because direct afferent nerve recording in cats during moderate muscle stimulation demonstrates that both mechanoreceptors and metaboreceptors are activated (7, 8). RHG does not isolate the muscle mechanoreceptors from central command. To eliminate central command, we performed a second series of experiments using rhythmic, involuntary biceps muscle contraction, thereby isolating the muscle mechanoreceptors from central command and largely from muscle metaboreceptors.
METHODS

Study Population for RHG

After informed written consent with Internal Review Board-approved consent forms was obtained, 10 patients with advanced HF (New York Heart Association functional class II-III, 9 men), mean age of 53 ± 3 yr, and mean left ventricular ejection fraction 22 ± 4% were enrolled in the RHG study. Etiology of HF was coronary disease in four patients and idiopathic in six patients. Nine age-matched [mean age 42 ± 5 yr; P = not significant (NS); 5 men] normal volunteers with normal history and physical examinations were enrolled in the study.

Study Population for Involuntary Biceps Muscle Contractions

After written, informed consent with Internal Review Board-approved consent forms was obtained, a different group of nine advanced HF patients (mean age 54 ± 2 yr, mean left ventricular ejection fraction 21 ± 3%, 8 men) were enrolled in the involuntary biceps muscle contraction study. Etiology of HF was coronary disease in five patients and idiopathic in four patients. Ten age-matched (mean age 44 ± 5 yr; P = NS; 5 men) normal volunteers with normal history and physical examinations were enrolled in the study. In both studies, medications, including vasodilators, diuretics, and β-blockers, were withheld for 24 h before the study. All subjects abstained from caffeine for 18–24 h before the study and were studied in the postabsorptive state.

Renal Cortical Blood Flow

Renal cortical blood flow (RCBF) was quantified based on dynamic positron emission tomography (PET) imaging by using the blood flow agent oxygen-15-labeled water. This technique has previously been described in detail (11, 12, 14). Briefly, after a 20-min transmission image for photon attenuation, correction was obtained, and study participants were injected with 30 mCi oxygen-15-labeled water over 30 s into a peripheral vein while acquisition of the serial transaxial tomographic images was started. Twelve 10-s frames, four 30-s frames, and one 60-s frame were acquired. Cross-sectional images were reconstructed employing a Shepp-Logan filter with a cutoff frequency of 30% of the Nyquist frequency of the system, yielding an in-plane spatial resolution of ~10.8-mm full-width half-maximum. To minimize invasiveness, the arterial tracer input function was determined from dynamic PET measurements of the abdominal aortic activity. This technique has been validated by comparing PET measurements of abdominal aortic activity with well-counter measurements of arterial blood samples (5).

The time-activity curves of the renal cortex were generated by region of interest analysis and corrected for dead time of the scanner and partial volume effects (14). RCBF was then estimated by fitting the PET measured time-activity curves to a validated one-compartment model for oxygen-15-labeled water. The RCBF value (ml·min⁻¹·g⁻¹) for one kidney was calculated as the average value for all analyzed regions of interest per kidney. All analyses were performed by a single investigator (E. U. Nitzsche) blinded to the experimental conditions. RCVR (units) was estimated by dividing mean arterial pressure (one-third of pulse pressure plus diastolic pressure) by RCBF.

RHG

Before the start of the study, maximum voluntary contraction (MVC) was determined in the nondominant arm. RHG was performed at 20% MVC for 3 min at a rate of approximately one contraction per 2 s. Immediately after exercise, subjects were asked to estimate perceived effort using the Borg scale (3).

Rhythmic Involuntary Muscle Contractions

Before the study, subjects were familiarized with the muscle stimulating device (Respond Select, Medtronic Nortech, San Diego, CA). Two 3.5 × 4.5-cm electrodes were placed over the biceps muscle of the nondominant arm. Within the manufacturer’s specified “low range” (<20 mA) of muscle stimulation, the maximum level of stimulation producing visible biceps muscle contraction, without causing discomfort, was determined. The rhythmic stimulation sequence and stimulating device are depicted in Fig. 1.

To isolate the muscle metaboreceptor contribution to renal vasoconstriction during involuntary muscle contractions, poststimulation circulatory arrest was performed in normal volunteers. A blood pressure cuff was placed on the upper arm and inflated to suprasystolic levels (240 mmHg) at the termination of rhythmic muscle stimulation for 4 min.

Blood Pressure and Heart Rate

Blood pressure and heart rate were monitored noninvasively by using an automatic blood pressure cuff on the dominant arm (Press-Mate 8800, Colin Medical Instrument, San Antonio, TX). Systolic, diastolic, and mean blood pressure and heart rate were monitored every 20 s at baseline during exercise. The accuracy of the Colin 8800 is within ±5 mmHg and ±2 beats/min required by the Association for Advanced Medical Instruments and was found to be ±2.81, ±0.04, and ±0.96 mmHg for systolic, diastolic, and mean blood pressure, respectively, compared with auscultatory methods (9).

Experimental Protocols

Protocol 1: RHG exercise. Subjects were positioned in the PET scanner. The blood pressure cuff was positioned. After the 20-min transmission scan, baseline RCBF, blood press-

Fig. 1. Involuntary biceps muscle contractions. Two electrodes were placed over the biceps muscle and attached to a neuromuscular stimulator. Every 5 s the biceps muscle was stimulated at <20 mA for 10 s for a total of 3 min.
ure, and heart rate were determined. Three minutes of RHG (20% MVC) were performed. RCBF, blood pressure, and heart rate were measured at peak exercise, 2–3 min of recovery, and 20 min of recovery.

Protocol 2: Involuntary biceps muscle contractions. Subjects were positioned in the PET scanner. The blood pressure cuff and biceps muscle electrodes were positioned. After the 20-min transmission scan, baseline RCBF, blood pressure, and heart rate were determined. Three minutes of rhythmic, involuntary muscle contractions were performed. RCBF, blood pressure, and heart rate were measured at peak biceps muscle contraction.

To determine whether muscle metaboreceptors were engaged, the stimulation paradigm was performed as above, but this time an upper arm blood pressure cuff was inflated to 240 mmHg just before termination of muscle stimulation. RCBF, blood pressure, and heart rate were measured during the 4-min poststimulation circulatory arrest period in normal volunteers.

**Data Analysis**

Statistical analysis was performed by using two-sample t-tests and paired t-tests. Fisher-Tukey least significant difference criterion was used to judge statistical significance to control for artifacts due to multiple significance testing. Probability values $\leq 0.05$ were considered statistically significant. Values are presented as means $\pm$ SE.

**RESULTS**

**RHG at 20% MVC**

**Baseline hemodynamics.** Baseline hemodynamic measurements are shown in Table 1. Patients with HF had higher heart rates and RCVR, and lower RCBF, at rest compared with normal volunteers.

**Hemodynamics during rhythmic handgrip.** Exercise hemodynamic measurements are shown on Table 1. Heart rate and blood pressure increased significantly in both groups during RHG, but the increases were not different between the groups. In both patients with HF and normal volunteers, RCVR significantly increased, and RCBF significantly decreased. Peak RCVR was significantly greater in HF patients than in normal volunteers. The $\Delta$ increase in RCVR tended to be greater in HF patients compared with normal volunteers (10 $\pm$ 1 vs. 7 $\pm$ 0.9 units; $P = 0.13$), but it did not reach statistical significance. The percent change in RCVR was similar in HF patients compared with normal volunteers (37 $\pm$ 1 vs. 35 $\pm$ 1%; $P = NS$). RCVR returned to normal at 2–3 min of recovery in normal volunteers, but it remained significantly elevated in HF patients (Fig. 2). At 20 min recovery, RCVR was back to baseline levels in HF patients.

**Borg scores.** Borg scores serve as a self-reported estimate of perceived exertional effort and therefore may be used as an estimate of central command (1, 4). Borg scores were not greater in HF patients compared with normal volunteers during RHG (Fig. 3).

**Hemodynamics during rhythmic, involuntary biceps muscle contraction.** To separate the contribution of muscle mechanoreceptors from central command, rhythmic, involuntary biceps muscle contraction was used. During rhythmic, involuntary biceps muscle contraction, heart rate did not increase in either normal volunteers or HF patients, suggesting that this maneuver did not stimulate an arousal or defense response (Table 2). In patients with HF and normal volunteers, RCVR significantly increased, and RCBF significantly decreased during rhythmic, involuntary biceps muscle contraction (Table 2). Peak RCVR was significantly greater in HF patients than in normal volunteers. The $\Delta$ increase in RCVR was significantly greater in HF patients compared with normal controls (Fig. 4). The

![Fig. 2. Renal cortical vascular resistance (RCVR) during recovery from rhythmic handgrip.](image)

**Table 1. Hemodynamics at rest and during rhythmic handgrip exercise**

<table>
<thead>
<tr>
<th></th>
<th>Normal Volunteers ($n = 9$)</th>
<th>Heart Failure Patients ($n = 10$)</th>
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<tbody>
<tr>
<td></td>
<td>Rest RHG</td>
<td>Rest RHG</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>$67 \pm 1^*$</td>
<td>$74 \pm 1^*$</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>$83 \pm 1^*$</td>
<td>$94 \pm 2$</td>
</tr>
<tr>
<td>RCBF, ml min$^{-1}$ g$^{-1}$</td>
<td>$4.2 \pm 0.05^*$</td>
<td>$3.7 \pm 0.1^*$</td>
</tr>
<tr>
<td>RCVR, units</td>
<td>$20 \pm 0.5^*$</td>
<td>$27 \pm 1^*$</td>
</tr>
<tr>
<td>$20%$ MVC, kg</td>
<td>$7.4 \pm 0.9$</td>
<td>$6.2 \pm 0.7$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE; $n$, no. of subjects. HR, heart rate; MAP, mean arterial pressure; MVC, maximum voluntary contraction; RCBF, renal cortical blood flow; RCVR, renal cortical vascular resistance; RHG, rhythmic handgrip exercise. $^*P < 0.05$ between-group comparison. $^+P < 0.05$ within-group comparison, rest vs. peak RHG.
DISCUSSION

The major findings of this study are as follows. 1) In normal humans during RHG, reflex renal vasoconstriction occurs, and 2) in patients with advanced HF, reflex renal vasoconstriction during RHG exercise is exaggerated in both magnitude and duration. 3) Using involuntary biceps muscle stimulation to isolate muscle mechanoreceptors from central command, reflex RCVR increased in normal humans, confirming that muscle mechanoreceptors normally contribute to reflex renal vasoconstriction. Finally, 4) muscle mechanoreceptor control of reflex renal vasoconstriction contributes to the exaggerated reflex renal vasoconstriction during RHG in HF patients. In animal studies, exposure to ischemic metabolites has been shown to sensititize muscle mechanoreceptor response to contraction (7, 16, 18). We speculate that, in HF patients, muscle mechanoreceptors are sensitized by frequent exposure to augmented levels of ischemic metabolites generated during exercise.

We have previously reported that, during static handgrip exercise, reflex renal vasoconstriction in patients with HF is exaggerated in both duration and magnitude compared with normal volunteers (11). The present study extends those findings to dynamic exercise, during which reflex renal vasoconstriction is exaggerated in both magnitude and duration, in HF patients compared with normal volunteers. Activities of daily living, such as walking, shopping, gardening, and housework, often require dynamic exercise. Therefore, it is possible that frequently and repeatedly throughout the day, HF patients experience exaggerated renal vasoconstriction, leading to increased afterload, and sodium and fluid retention, potentially exacerbating exercise intolerance.

During dynamic exercise, muscle mechanoreceptors and central command are both activated, and muscle metaboreceptors may be activated as well. To address the contributions of central command to the exaggerated reflex renal vasoconstriction during RHG exercise in HF, one can compare Borg scores, which are self-reported numerical estimates of voluntary effort, as an index of central command activity (1, 4). During RHG, the Borg scores were not significantly higher in HF patients compared with normal volunteers. This would suggest that central command control of reflex RCVR is not exaggerated in HF patients. Heart rate, too, may be used as an indicator of activation of central command (10). In our study, Δ HR was not greater in HF patients compared with normal controls during RHG exercise. However, the real purpose of our study was to examine the role of muscle mechanoreceptors in the exaggerated renal vasoconstriction. To isolate mechanoreceptor contribution from central command, we used rhythmic, involuntary biceps muscle contraction.

During involuntary biceps muscle contraction, heart rate did not increase in HF patients or normal volunteers, arguing against an inadvertent arousal or stress stimulus. Furthermore, during poststimulation circulatory arrest in normal volunteers, RCVR returned to baseline levels, confirming that the muscle metaboreceptors did not mediate the reflex renal vasoconstriction during rhythmic, involuntary muscle stimulation in normal volunteers. This maneuver would not provide meaningful information in HF patients, in whom reflex renal vasoconstriction is prolonged (12); therefore, it was not performed. During biceps contraction, reflex renal vasoconstriction was exaggerated in patients with HF compared with normal volunteers. Not only was the peak RCVR during involuntary muscle contraction greater in HF patients compared with normal volunteers but the Δ increase in RCVR was significantly greater as well. On the basis of these results, we conclude that muscle mechanoreceptors contribute to the exaggerated reflex renal vasoconstriction during exercise in patients with HF. Why might muscle mechanoreceptors be sensitized in patients with HF?

Muscle mechanoreceptor nerve fibers have been shown to be sensitized to muscle contraction in the presence of ischemic metabolites (7, 16, 18). In cats, arachidonic acid had no effect on baseline mechanoreceptor nerve activity, but it increased mechanoreceptor responsiveness during contraction by 265% (16). Lactic

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**Table 2. Hemodynamics during rhythmic involuntary biceps muscle contraction**

<table>
<thead>
<tr>
<th></th>
<th>Normal Volunteers (n = 10)</th>
<th>Heart Failure Patients (n = 9)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Involuntary contraction</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>70 ± 1</td>
<td>70 ± 1</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>82 ± 1†</td>
<td>87 ± 2</td>
</tr>
<tr>
<td>RCBF, ml·min⁻¹·g⁻¹</td>
<td>4.2 ± 0.1§</td>
<td>3.7 ± 0.1*</td>
</tr>
<tr>
<td>RCVR, units</td>
<td>20 ± 0.3±</td>
<td>24 ± 0.5*</td>
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Values are means ± SE; n, no. of subjects. *P < 0.05 between-group comparison; †P < 0.05 within-group comparison; rest vs. peak involuntary contractions.
acid increased resting muscle mechanoreceptor nerve activity and significantly increased mechanoreceptor responsiveness during contraction (18). In humans, forearm training, which reduces ischemic metabolite formation during nonfatiguing RHG, also decreases mechanoreceptor-mediated sympathetic activation during forearm exercise (19). Similarly, during a constant workload of repetitive static quadriceps contraction, reflex muscle sympathetic nerve responses during early contraction are increased, consistent with a contraction-induced sensitization of muscle mechanoreceptors attributable to ischemic metabolite production (6). In HF patients, ischemic metabolite production is augmented at a given workload compared with normal volunteers (17). It is unclear whether increased muscle mechanoreceptor sensitivity in HF is transient, attributable to acute exposure to higher levels of ischemic metabolites during exercise, or long lasting, mediated by frequent and repeated exposures to ischemic metabolites, which produce chronic changes in mechanoreceptor responsiveness to contraction.

Sensitization of muscle mechanoreceptors in HF cannot explain the prolonged duration of increased RCVR after RHG in HF. Prolonged reflex renal vasoconstriction is also unlikely to be mediated by muscle metaboreceptors, because we (11) and others (20) have found that the muscle metaboreceptors are blunted in HF. We speculate that, in patients with HF, in whom the renin-angiotensin system has enhanced activity and sensitivity, reflex increases in efferent renal sympathetic nerve activity during exercise are amplified locally by the exquisite sensitivity of the renal renin-angiotensin system, resulting in the persistent increase in RCVR after exercise.

A limitation of this study is that we did not measure ischemic metabolites during RHG or, for that matter, during involuntary biceps muscle stimulation. This study was purposefully designed to eliminate muscle metaboreceptor contribution to reflex renal vasoconstriction. Batman and colleagues (2), using posthand-grip circulatory arrest following RHG at 25% MCV in humans as well as 31P nuclear magnetic resonance, convincingly demonstrated that muscle metaboreceptors were not engaged during low-level (≤25% MCV) RHG. Similarly, activation of muscle metaboreceptors was not detectable during low-level rhythmic, involuntary biceps muscle contraction, because RCVR returned to basal levels during isolation of the muscle metaboreceptors with poststimulation circulatory arrest. Nonetheless, even if very low levels of ischemic metabolites were generated during these exercise paradigms, it is unlikely that they contributed significantly to reflex renal vasoconstriction in HF patients, because we previously found that metaboreceptor control of renal vasoconstriction is blunted (11). It would have strengthened this study to be able to quantify and individualize involuntary biceps muscle contraction to a specific percentile of each subject’s MCV. Because this was technically not feasible, our approach was to stimulate at the maximum, painless level within the manufacturer’s specified low-level range of stimulation. This low-level, painless stimulation fulfilled our goals of inducing muscle contractions while avoiding muscle metaboreceptor stimulation and avoiding an arousal response.

Resting RCVR is increased in HF patients compared with normal volunteers, necessitating comparisons of changes in vascular tone in the setting of unequal baselines. In animals and humans, an increase in basal resistance will amplify responses to vasodilatory, but not vasoconstrictor, stimuli (10). RHG is a vasoconstrictor stimulus to the renal circulation, therefore avoiding this potentially confounding factor. However, the problem of unequal baseline values persists. The percent change in RCVR during involuntary muscle stimulation in HF patients with normal volunteers was not different, despite a significant difference in peak and Δ RCVR values. Comparing the percentage change obscures the marked increase in RCVR in HF patients, and the biological and clinical significance of this elevated RCVR. To preserve and actually highlight the marked renal vasoconstriction in HF, we chose to compare the peak and Δ values rather than percent change values. The clinical relevance of these data is more apparent.

In summary, reflex renal vasoconstriction is exaggerated in both magnitude and duration during exercise, including dynamic exercise, in HF patients. The muscle mechanoreceptors contribute to this heightened reflex renal vasoconstriction in HF failure. Central command contribution, if any, to this exaggerated reflex vasoconstriction requires further investigation.

We are grateful to the PET technologists for performing the PET studies and to the nurses and staff of the UCLA General Clinical Research Center for providing excellent patient care.

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