Influence of sex and active muscle mass on renal vascular responses during static exercise

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EXERCISE CAUSES ACTIVATION of the sympathetic nervous system, which leads to increases in heart rate (HR), blood pressure, and peripheral vasconstriction. As part of these processes, renal vasconstriction helps maintain blood pressure and redistribute blood flow to the active skeletal muscle. Two important neural mechanisms are believed to be involved in the sympathoexcitatory responses during exercise: 1) central command, a feedforward system that stems from the higher brain center and causes parallel activation of motor and cardiovascular control centers; and 2) the exercise pressor reflex, a feedback system from exercising muscle. This reflex mechanism is activated when mechanosensitive and metabosensitive afferent nerve endings within the contracting skeletal muscle are stimulated. Activation of these neural mechanisms results in efferent sympathetic outflow to different effector organs. Studies have shown that different neural mechanisms have different onset latencies for increases in muscle sympathetic nerve activity (MSNA), an important index of sympathetic drive directed to skeletal muscle blood flow. Specifically, increases in MSNA during the initial several seconds of exercise are due to central command and/or the muscle mechanoreflex (10, 11), whereas metabosensitive muscle afferent nerves activate the sympathetic system >60 s after initiation of muscle contraction (19, 33–35).

Prior reports examining the effects of sex on sympathoexcitatory responses to exercise have yielded conflicting results. Some reports showed no effect of sex on cardiovascular responses during exercise (13, 27), whereas others showed reduced exercise-induced pressor responses in women compared with men (4–6). Ettinger et al. (6) postulated that the muscle metaboreflex contribution to sympathetic outflow of exercise was reduced in women compared with men. It was also suggested that the sex-related differences in sympathetic outflow are not due to differences in muscle mass.

There has been considerable debate regarding the effects of exercising muscle mass on sympathoexcitatory responses during exercise. A number of reports in healthy human subjects have suggested that the magnitude of the pressor response during static exercise is dependent on the size of the active muscle mass (3, 12, 16, 23, 31). Other studies have suggested that increases in cardiovascular responses are dependent on the relative tension generated by the contracting muscle and not on the size of the active muscle mass (9, 17, 21, 38).

Recently, studies from this laboratory have used Doppler ultrasound technology (duplex ultrasound) to measure renal blood flow in humans during exercise. The excellent time resolution of this method has afforded the opportunity to observe renal vascular responses within the first few seconds after the initiation of exercise. Using this method, we have found that activation and sensitization of mechanosensitive muscle nerve afferents play a crucial role in evoking renal vasoconstriction during static exercise in healthy humans (25) as well as in those with heart failure (24).

However, it is not known whether sex and/or muscle mass influences renal vascular responses to exercise in humans.

Therefore, in this report, we examined renal vasconstrictor responses to static exercise in age- and body mass index (BMI)-matched healthy young men and women to address the following questions: 1) Do men and women exhibit different renal vasconstrictor responses during fatiguing handgrip (HG) and post-HG circulatory arrest (PHG-CA)? 2) Do men and women exhibit differences in renal vascular responses to short...
(15-s) bouts of static exercise? 3) Does the size of the active muscle mass affect renal vascular responses to static exercise during short (15-s) bouts of exercise?

Our studies suggest that renal vasoconstrictor responses are similar in men and women during HG. Our results also reveal that the size of the active muscle mass does not influence the renal vasoconstrictor response during short bouts of exercise.

METHODS

Study Population

A total of 10 healthy young men (age 28 ± 2 yr, mean BMI 24 ± 1 kg/m²) and 10 healthy young women (age 25 ± 2 yr, mean BMI 22 ± 1 kg/m²) were recruited for protocols 1–3 (see below). The same nine men and the same eight women participated in protocols 1 and 2; some of these individuals participated in protocol 3. Each subject signed an informed written consent and had a physical examination before participating in the study protocols, which had been approved by the Institutional Review Board. Volunteers were nonsmokers and nonmedicated and were taking no medication.

Renal Blood Flow Velocity

All subjects were studied in the postabsorptive state. Duplex ultrasound (model HDI 5000, ATL Ultrasound, Bothell, WA) was used to determine renal blood flow dynamics. The renal artery was scanned using the anterior abdominal approach while the subject was supine. A curved-array transducer (2–5 MHz) with a 2.5-MHz pulsed Doppler frequency was used. The probe insonation angle to the renal artery was <60°. The focal zone was set at the depth of the renal artery. To obtain optimum velocity traces, the transducer was held in a constant position; thus the data were obtained in the same phase of the respiratory cycle. Care was taken to ensure that the subject did not perform Valsalva maneuvers during the HG protocols. Each cardiac cycle Doppler trace was analyzed using software provided with the ATL duplex ultrasound equipment to obtain mean renal blood flow velocity (RBV, cm/s).

Because blood flow (BF) is a function of mean blood flow velocity (MBV) and vessel cross-sectional area (BF = MBV · πr², where r is vessel radius), accurate measurements of vessel diameter are required to determine renal blood flow. Because of the limited spatial resolution of the technique, accurate measurements of renal artery diameter are difficult to perform in humans. However, using renal angiography, Marraccini et al. (20) reported no significant changes in renal artery diameter, despite large changes in flow velocity as pharmacological compounds were infused. Thus RBV reflected the real-time renal hemodynamic responses. Therefore, in our report, RBV is used as an index of renal blood flow, and the renal vascular resistance (RVR) index (arbitrary units) was, in turn, calculated by dividing mean arterial pressure (MAP) by RBV.

Beat-by-beat changes in RBV were recorded during different paradigms. Continuous recordings of HR (ECG) and blood pressure (Finapres, Ohmeda, Madison, WI) were also obtained during each protocol. Subjects rested for ~15 min between protocols. An automated sphygmomanometer (Dinamap, Critikon, Tampa, FL) was used to determine resting blood pressure. Each subject performed HG with an HG dynamometer (Stoelting, Wood Dove, IL) that is adjustable for different hand spans.

Study Protocols

Protocol 1: fatiguing static exercise followed by PHG-CA. We examined the effects of sex differences on renal vasoconstrictor mechanisms during fatiguing exercise in 17 subjects (9 men and 8 women). The effect of muscle metaboreflex engagement on renal vasoconstrictor responses was examined during PHG-CA. Maximum voluntary contraction (MVC) of the nondominant arm was determined in each subject before the HG paradigm. Baseline HR, MAP, and RBV data were obtained over a 5-min period at rest before each protocol. Each subject began HG exercise at 40% MVC and continued until fatigue. At the end of exercise, all the subjects graded their perceived level of exertion as 20 (maximum effort) on the Borg scale (2). Immediately before termination of exercise, PHG-CA was initiated by inflation of a blood pressure cuff that had been previously placed around the arm. The cuff was inflated to ~250 mmHg, and the inflation was maintained for 2 min.

Protocol 2: static HG exercise at graded intensity. The influence of sex on renal vascular responses within the initial several seconds of the onset of HG exercise was studied in 17 subjects (9 men and 8 women).

Baseline HR, MAP, and RBV data were collected for 5 min. Each subject completed 15-s bouts of static HG exercise at 10, 30, 50, and 70% of the respective subject’s MVC. The same sequence was maintained in all subjects. Each bout of exercise was preceded by ~1 min of rest. Our attempt to perform quadriceps contraction (QC) until fatigue was unsuccessful because of technical limitations. To obtain optimum renal artery velocity traces, the Doppler probe must be placed in a constant position. During the sustained and fatiguing QC, the abdominal wall contracted, and the transducer was no longer in the same position relative to the renal artery. Moreover, even if we could obtain a signal, the contracting abdominal muscles would likely make a varied and unquantifiable contribution to the reflex. This would make “QC reflex responses” impossible to quantify during a bout of fatiguing QC. Therefore, we performed only short bouts of QC in the subjects.

Protocol 3: static QC at graded intensity. After protocols 1 and 2 were completed, protocol 3 was performed on a separate day in 15 subjects (8 men and 7 women). This protocol was designed to compare the renal vasoconstrictor responses during muscle contraction trials of a small muscle with those of a large muscle mass. HG was used as the small muscle mass paradigm and QC as the large muscle mass paradigm. A custom-made device for quadriceps exercise was utilized for this paradigm. Subjects were placed in a supine position. The thigh was supported at an angle of 45° by an adjustable, padded, triangular wooden support. A recalibrated, universal, flat load cell (Strainert, West Conshohocken, PA) was mounted directly beneath and attached to the left ankle with nylon strapping. The device was calibrated before each study with 22.7- and 45.5-kg weights.

Before the studies were initiated, the MVC was determined for quadriceps muscle contractions.

Baseline HR, MAP, and RBV data were collected for 5 min. Each subject completed 15-s bouts of static QC at 10, 30, 50, and 70% of the respective subject’s MVC. The subjects received visual feedback, via an analog meter, of the amount of tension generated. The same sequence was maintained in all subjects. Each bout of exercise was preceded by ~1 min of rest.

Data Analysis and Statistics

Beat-by-beat sequential analysis of HR, MAP, RBV, and RVR was performed for all subjects. Baseline values for each parameter were considered the average values obtained during the 5-min rest period before the beginning of each paradigm.

In the fatiguing static HG protocol, each variable was measured around the time that represented 10, 20, 40, 60, 80, and 100% (peak) of the respective subject’s time to exhaustion. Data from the last 15-s period during circulatory arrest were used in the statistical analysis. In protocols 2 and 3, data were analyzed in 5-s time periods. Statistical analyses were performed separately on each 5-s period (i.e., 1–5, 6–10, and 11–15 s).

Values are means ± SE. Resting values were compared using paired t-tests. Repeated-measures two-way ANOVA was applied to the data for each response variable (changes from the respective baseline) to assess the two main effects: sex (male vs. female) and
type of muscle contraction (HG vs. QC). The possible interaction of these two factors was also assessed as a function of time (percent time to fatigue in protocol 1 and each 5 s in protocols 2 and 3 during static exercise). Similarly, comparisons of each response during smaller (HG) and larger (QC) muscle contractions were made by two-way ANOVA, with muscle mass and exercise paradigms as the two main effects. Respective time periods during contraction were compared using simple effects and Bonferroni’s corrections. \( P < 0.05 \) was considered significant.

**RESULTS**

At rest, the average of all baseline hemodynamic variables was similar in the two sex groups. No significant group differences were found with respect to age and BMI. HG and quadriceps muscle MVC were greater in the male than in the female subjects \( (P < 0.0001) \).

### Table 1. Cardiovascular, including renal hemodynamic changes during fatiguing static HG (smaller muscle mass): protocol 1

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>20%</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>HR</td>
<td>16.9 ± 22.9</td>
<td>32.3</td>
<td>38.9</td>
<td>42.0</td>
</tr>
<tr>
<td>MAP</td>
<td>±4.8 ± 2.4</td>
<td>±7.2</td>
<td>±7.4</td>
<td>±8.2</td>
</tr>
<tr>
<td></td>
<td>±4.7 ± 4.4</td>
<td>±5.4</td>
<td>±4.3</td>
<td>±5.6</td>
</tr>
<tr>
<td></td>
<td>9.2 ± 1.1</td>
<td>14.6</td>
<td>20.7</td>
<td>29.6</td>
</tr>
<tr>
<td></td>
<td>±1.5 ± 2.6</td>
<td>±4.2</td>
<td>±5.0</td>
<td>±5.5</td>
</tr>
<tr>
<td>RBV</td>
<td>±9.9 ± 3.1</td>
<td>±13.0</td>
<td>±15.7</td>
<td>±13.7</td>
</tr>
<tr>
<td></td>
<td>±2.4 ± 2.6</td>
<td>±4.9</td>
<td>±8.7</td>
<td>±7.8</td>
</tr>
</tbody>
</table>

Values are means ± SE expressed as percent change from baseline for heart rate (HR, beats/min), mean arterial pressure (MAP, mmHg), and renal blood flow velocity (RBV, cm/s). HG, handgrip. Values for HR, MAP, and RBV are presented at the various percentages of time to fatigue (i.e., 10%, 20%, 40%, 60%, 80%, and 100%). \( P \) values were determined by 2-way ANOVA. NS, not significant.

**Fatiguing Static Exercise Followed by PHG-CA**

The time to fatigue was not significantly different in male and female subjects: 128 ± 21 and 90 ± 19 s, respectively \( (P = 0.19) \). Comparable changes in RVR and RBV from baseline to fatigue were noted in male and female subjects: RVR was 1.79 ± 0.09 and 1.67 ± 0.13 units, respectively, at baseline and 2.73 ± 0.26 and 2.48 ± 0.21 units, respectively, at fatigue, and RBV was 55.7 ± 3.8 and 55.4 ± 4.8 cm/s, respectively, at baseline and 50.5 ± 5.8 and 45.8 ± 3.7 cm/s, respectively, at fatigue. No sex effect was seen during PHG-CA (Fig. 1, Tables 1 and 2).

**Static HG Exercise at Graded Intensity**

RVR responses were similar in men and women (Fig. 2). RBV, HR, and MAP were also similar in men and women during this protocol (not shown).

**Static QC at Graded Intensity**

RVR rose with static QC (Fig. 3), and the pattern of rise in RVR, RBV, and HR was similar in the two groups. However, MAP rose more in men than in women during 11–15 s of quadriceps exercise \( (P < 0.05) \; \text{Table 3}\).
HR, MAP, RBV, and RVR responses were similar during short bouts of quadriceps and HG contractions in 13 subjects (Table 4).

During 11–15 s of static contraction at 70% MVC for HG and QC, HR was 76 ± 4 and 79 ± 4 beats/min, respectively, MAP was 103 ± 7 and 101 ± 7 mmHg, respectively, RBV was 52.2 ± 3.6 and 52.2 ± 3.0 cm/s, respectively, and RVR was 2.03 ± 0.13 and 1.97 ± 0.14 units, respectively.

DISCUSSION

The objectives of this report were to evaluate the effects of sex and muscle mass on renal vascular responses to muscle contraction. The major new findings in this report are as follows: 1) Renal vasoconstrictor responses to HG are similar in men and women. 2) Renal vasoconstrictor responses during short bouts of exercise do not depend on the size of the contracting muscle mass.

Baseline RBV and RVR were similar in men and women. These findings are consistent with several previous animal and human studies (8, 22, 29). Resting MAP and HR were also not different in the groups. Some previous reports have suggested that MAP may be higher in men than in women (13, 22), whereas other reports have noted similar resting blood pressure in men and women (6, 8, 28). The exact reason for this inconsistency in resting blood pressure among men and women is not clear. However, fitness level, family history, or environmental factors could play a role (15, 18, 26, 30).

Fatiguing Static HG Followed by PHG-CA

In this study, no sex differences for RVR were observed during fatiguing HG. Ettlinger et al. (6) observed reduced MSNA responses in women compared with men during the 2nd min of HG. In addition, they noted an attenuated rise in MAP in women, suggesting attenuated engagement of the muscle metaboreflex in women (6). Jones et al. (13) also observed reduced responses in blood pressure and MSNA during HG in women compared with men when absolute values were examined. However, percent increases from baseline were similar in the two groups (13).

The RVR responses in women and men were similar during fatiguing HG, even though the rise in blood pressure tended to be less in women than in men (Table 1). This suggests that sympathetic drive to the kidney during static exercise is similar in men and women. Moreover, similar RVR responses were also found between the groups during PHG-CA (which isolates the muscle metaboreflex), despite a tendency to reduced blood pressure responses in women. These findings suggest that muscle metaboreflex-mediated renal vasoconstriction was similar in men and women.

Static HG and Quadriceps Exercise at Graded Intensities

The data in the present report also suggest that differences in muscle mass do not contribute to RVR responses, because the curves for RVR vs. percent MVC for HG and QC were superimposable. Sympathoexcitatory responses during 15 s of exercise could be due to central command (36) and/or the muscle mechanoreflex (10). Engagement of muscle metaboreflexes is very unlikely, because accumulation of metabolites is not sufficient in the contracting skeletal muscle during 15 s of exercise. An earlier report from this laboratory using involuntary biceps contractions suggested that central volitional influences are not necessary to evoke renal vasoconstriction (25). Thus we would argue that the similar renal vasoconstriction response for HG and QC in the present report suggests that the muscle mechanoreflex control of the renal bed is not influenced by sex.
by muscle mass. It is unlikely that the lack of difference observed between men and women was due to a lack of statistical power. Specifically, to detect the differences in the changes in RVR index that are observed in our study, a sample size of 200 subjects (100 men and 100 women) would yield 80% statistical power to detect a standardized effect size of 0.4 between men and women at any MVC level with use of a two-sided test with a significance level of 0.05.

A number of studies have been performed to examine the effect of muscle mass on cardiovascular responses. Consistent with our findings, a number of reports have demonstrated that exercise-induced cardiovascular responses were not dependent on the size of the exercising muscle mass (17, 21, 33, 38). Contrary to these previous reports, pressor (23, 31) and MSNA (31, 32) responses to muscle contraction have been found to be muscle mass dependent. Interestingly, detailed analysis of these studies showed that the magnitude of increases in pressor responses or MSNA did not vary among different muscle groups within the initial 30 or 40 s of contraction. The observation of McCloskey and Stryatfeld (21) and Mitchell et al. (23) that muscle size affects responses during postexercise circulatory occlusion (which isolates the muscle metaboreflex) suggests that muscle mass influences muscle metaboreflex-mediated responses. Similarly, Iellamo and colleagues (12) observed larger increases in HR and MAP responses with the larger than with the smaller muscle mass contraction and suggested that these greater responses are due to enhanced engagement of muscle metaboreflexes. Franke et al. (7) documented greater sympathoexcitatory responses with quadriiceps than with HG. Using 5-min bouts of supine isometric exercise, they found that sympathoexcitatory responses were dependent on exercising muscle mass. They argued that the greater responses with leg contraction were due to greater engagement of central command.

When these data are viewed collectively with the data from our report, we would conclude that muscle mass may contrib-
ute to blood pressure control, but not to renal vascular control, and that muscle mechanoreflex-mediated control of the renal vascular bed is not influenced by muscle mass. The present report does not allow us to draw inferences regarding the effect of muscle mass on central command and metaboreflex-mediated control of the renal vascular bed. We can also conclude that mechanoreflex control of the renal vascular bed is similar in men and women.

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