Comparison of skin sympathetic nerve responses to isometric arm and leg exercise

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Ray, Chester A., and Thad E. Wilson. Comparison of skin sympathetic nerve responses to isometric arm and leg exercise. J Appl Physiol 97: 160–164, 2004. First published March 19, 2004; 10.1152/japplphysiol.00699.2003.—Measurement of skin sympathetic nerve activity (SSNA) during isometric exercise has been previously limited to handgrip. We hypothesized that isometric leg exercise due to the greater muscle mass of the leg would elicit greater SSNA responses than arm exercise because of presumably greater central command and muscle mechanoreceptor activation. To compare the effect of isometric arm and leg exercise on SSNA and cutaneous end-organ responses, 10 subjects performed 2 min of isometric knee extension (IKE) and handgrip (IHG) at 30% of maximal voluntary contraction followed by 2 min of postexercise muscle ischemia (PEMI) in a normothermic environment. SSNA was recorded from the peroneal nerve. Cutaneous vascular conductance (laser-Doppler flux/mean arterial pressure) and electrodermal activity were measured within the field of cutaneous afferent discharge. Heart rate and mean arterial pressure significantly increased by 16±3 and 23±3 beats/min and by 22±2 and 27±3 mmHg from baseline during IHG and IKE, respectively. Heart rate and mean arterial pressure responses were significantly greater during IKE compared with IHG. SSNA increased significantly and comparably during IHG and IKE (52±20 and 50±13%, respectively). During PEMI, SSNA and heart rate returned to baseline, whereas mean arterial pressure remained significantly elevated (Δ12±2 and Δ13±2 mmHg from baseline for IHG and IKE, respectively). Neither cutaneous vascular conductance nor electrodermal activity was significantly altered by either exercise or PEMI. These results indicate that, despite cardiovascular differences in response to IHG and IKE, SSNA responses are similar at the same exercise intensity. Therefore, the findings suggest that relative effort and not muscle mass is the main determinant of exercise-induced SSNA responses in humans.

 skin blood flow; electrodermal activity; microneurography

IT IS WELL ESTABLISHED THAT sympathetic activation to different vascular beds is nonuniform during exercise. This is clearly evident when comparing muscle and skin sympathetic nerve activity (MSNA and SSNA, respectively) at the onset of isometric handgrip (IHG). SSNA is activated immediately (14, 16, 26), whereas sympathetic outflow to nonactive skeletal muscle is delayed (i.e., 45–60 s) (9, 17). Studies have indicated that SSNA responses may vary depending on the exercising posture (12), exercising limb (leg vs. arm) (11), amount of muscle mass involved (15), and mode of exercise (17, 24). Ray et al. (11) reported contrasting MSNA responses during isometric arm and leg exercise. In their study, MSNA increased during IHG but did not increase during isometric knee extension (IKE). Most notably, MSNA decreased during the first minute of IKE (11).

Studies of SSNA of the peroneal nerve innervating nonglabrous skin during exercise have been limited to isometric (16, 26) and rhythmic handgrip (6, 21). Moreover, investigations of SSNA innervating glabrous skin have focused solely on IHG (14). These studies have demonstrated immediate increases in SSNA during handgrip. Increases in SSNA have been observed with attempted (partial neuromuscular blockade) and virtual (visualization) handgrip, suggesting a central command component (6, 25). Additionally, increases in SSNA have been observed with external compression, suggesting involvement of muscle mechanoreceptors (6). The contributions of muscle metaboreceptors on SSNA have been examined with the use of postexercise muscle ischemia (PEMI) after handgrip. However, these studies have produced contrasting findings because some indicate SSNA returns to baseline, whereas others report SSNA remains elevated during PEMI (6, 14, 25, 26). Thus the contribution of muscle metaboreceptors to SSNA responses remains unclear.

SSNA responses to isometric leg exercise and subsequent PEMI have not been reported. Therefore, the purpose of this study was to compare SSNA and cutaneous end-organ responses between IHG and IKE. We hypothesized that greater increases in SSNA would be observed during IKE than IHG when performed at the same exercise intensity because of greater activation of central command and muscle mechanoreceptors due to greater muscle mass in the leg compared with the arm. Additionally, we hypothesized that SSNA would be the same during PEMI after each isometric exercise bout.

METHODS

Subjects. We studied 10 healthy volunteers, age 18–25 yr. The study was verbally explained, and written, informed consent was obtained from all subjects for this institutionally approved study.

Experimental design. All subjects were tested in the sitting position. IHG and IKE were performed on the right side of the body with the arm extended laterally (60–90°) from the body and knee flexed at ~90°, respectively. Maximal voluntary contraction was determined from the peak forces of 3 maximal isometric efforts, and both IHG and IKE were performed at 30% of maximal voluntary contraction. After a 2-min baseline period, isometric exercise was performed for 2 min. The target force and isometric force produced by the subject were displayed on an oscilloscope for visual feedback. Just before the end of exercise (5 s), the circulation to the exercising limb was occluded by inflation of a pneumatic cuff. This cuff was placed on the upper portion of the arm or thigh and inflated to suprasystolic tension (IKE). Most notably, MSNA decreased during the first minute of IKE (11).

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levels (280 mmHg). During PEMI, no pulse distal to the cuff was detected in the wrist (radial) or lower leg (posterior tibial or dorsalis pedis). Occlusion was maintained for 2 min. IHG and IKE trials were randomized and performed during the same laboratory visit. The second exercise trial did not commence until heart rate and arterial blood pressure returned to baseline (minimum of 15 min). All experiments were performed in a dimly lit, quiet, normothermic (21–23°C) laboratory to minimize environmental influences on SSNA.

Measurements. Multifiber recordings of SSNA were made with a tungsten microelectrode inserted in the peroneal nerve at the head of the fibula of a resting leg. A reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The criteria for acceptable recordings of SSNA included paresthesias with weak intraneural electrical stimulation, stimulation of afferent discharge with light stroking of the skin in the innervated region, and non-pulse-synchronous activity augmented by deep inspirations and arousal (10). The nerve signal was amplified (40,000–80,000 times), fed through a band-pass filter with a bandwidth of 700–2,000 Hz, and passed through a resistance-capacitance integrating network with a time constant of 0.1 s to obtain a mean voltage display of the nerve activity (Iowa Bioengineering, Iowa City, IA). Additionally, the filtered neurogram was routed through a nerve spike counter (Iowa Bioengineering). The mean voltage neurogram and nerve spikes counter were displayed together with the electrocardiogram, respiratory pattern, and force output from isometric exercise on a chart recorder (model ES2000, Gould, Valley View, OH) at a paper speed of 5 mm/s and on an online computer. The mean voltage neurogram was routed to a storage oscilloscope and a loudspeaker for monitoring during the study.

The number of nerve spikes per minute was counted with the use of an integrator circuit that reset after 1,000 spikes. The output of this nerve spike counter was expressed as a percentage of the control value to provide an index of relative change in total SSNA. Records of SSNA were divided into 1-min periods for statistical analysis. Sym pathetic recordings that demonstrated possible electrode site shifts, altered respiratory patterns, or electromyography artifact during the experimental interventions were excluded from analysis.

Skin blood flow was indexed via laser-Doppler flowmetry (Laserflow blood perfusion monitor, TSI, St. Paul, MN). Cutaneous vascular conductance (laser-Doppler signal/mean arterial pressure) and cutaneous vascular resistance (mean arterial pressure/laser-Doppler signal) were calculated and expressed as a percentage of baseline values. To provide relative index of sweating, changes in electrodermal activity were measured with a skin conductance meter between Ag-AgCl electrodes and expressed as a percentage of baseline values. Cutaneous measures (i.e., skin blood flow and electrodermal activity) were placed so that the area sampled was within the area of cutaneous mechanoreceptor afferent fiber discharge. This area was composed of nonglabrous skin located either on the lower lateral aspect of the leg or top of the foot (i.e., dorsal aspect). No systematic differences in skin blood flow and sweating were noted between recording sites.

Heart rate was derived from an electrocardiogram, and arterial pressure was measured continuously by a finger cuff (Finapres, Ohmeda, Englewood, CO). To ensure that subjects avoided respiratory maneuvers that may affect sympathetic activity during interventions, respiratory patterns were monitored with the aid of a strain gauge strapped around the chest. If an altered respiratory (e.g., apnea) pattern was observed, these data were excluded from analysis.

Statistical analysis. To identify possible differences between the arm and leg during isometric exercise and PEMI, a one-between (limb), one-within (time) repeated-measures ANOVA was used to determine differences between trials. A significance level of $P < 0.05$ was used for all tests. Values are presented in the text, the figures, and the table as means ± SE.

RESULTS

SSNA increased significantly and progressively throughout both IHG and IKE (Fig. 1). At the onset of isometric exercise, most subjects had an immediate increase in SSNA (8 of 10 and 9 of 10 for IHG and IKE, respectively). During PEMI, SSNA returned to baseline levels after IHG and IKE. There were no significant differences observed in SSNA responses between exercising limbs (Fig. 1).

Baseline heart rate (65 ± 4 and 61 ± 3 beats/min) and mean arterial blood pressure (95 ± 4 and 97 ± 3 mmHg) were not significantly different between IHG and IKE, respectively. Heart rate significantly increased during both IHG and IKE. IKE elicited a significantly greater heart rate response (7 beats/min) compared with IHG (Fig. 2). During PEMI, heart rate returned to baseline after IHG and IKE. Similar to heart rate, mean arterial pressure significantly increased during IHG and IKE. IKE resulted in a significantly higher mean arterial pressures (~5 mmHg) compared with IHG (Fig. 2). However, during PEMI mean arterial pressure remained elevated after IHG and IKE ($\Delta 12 ± 2$ and $\Delta 13 ± 2$ mmHg from baseline for IHG and IKE, respectively). The increase in mean arterial pressure during PEMI provides evidence that muscle metaboreceptors were engaged during PEMI during both trials.

Neither calculated cutaneous vascular conductance nor resistance significantly changed during IHG, IKE, or PEMI (Table 1). Electrodermal activity was also not significantly altered by either exercise or PEMI in experimental trials (Table 1). Thus no differences were observed between cutaneous end-organ responses between exercising limbs.

DISCUSSION

The new findings from this study are the following: 1) SSNA responses are comparable between isometric arm and leg exercise performed at the same relative intensity and during PEMI; 2) the magnitude of increase in SSNA with IKE was similar to IHG, despite IKE resulting in greater increases in heart rate and mean arterial pressure; and 3) increases in SSNA during IHG and IKE exercise were not associated with increases in nonglabrous cutaneous end-organ responses (i.e., cutaneous vascular conductance, cu-

![Fig. 1. Changes (Δ) in skin sympathetic nerve activity (SSNA; peroneal microneurography) during 2 min (′) of isometric handgrip (IHG) and knee extension (IKE) at 30% of maximal voluntary contraction followed by 2 min of postexercise muscle ischemia (PEMI). Values are means ± SE. SSNA increased during IHG and IKE but returned to baseline during PEMI. No differences were observed between exercising limbs. Repeated-measures ANOVA: limb, $F_{(1,19)} = 0.01, P = 0.898$; time, $F_{(4,76)} = 7.09, P < 0.001$; interaction (limb × time), $F_{(4,3,60)} = 0.41, P = 0.799$.](http://jap.physiology.org/DownloadedFrom/10.1152/jappl.00904.2004)
suggest that SSNA responses are critically dependent on relative exercise intensity rather than muscle mass.

Our findings of SSNA increases within the first minute in both IHG and IKE, and the cessation of increases in SSNA during PEMI, support the concept that SSNA during exercise is governed by either central command and/or the muscle mechanoreflexes but not by muscle metaboreflexes. Using neuro-muscular blockade, Vissing and Hjortso (25) provide strong evidence that the increase in SSNA is more likely related to central command rather than muscle mechanoreceptors’ stimulation during exercise. Novel approaches, such as using transcortical magnetic stimulation of the motor cortex in humans (20) and electrical stimulation of the mesencephalic locomotor region in animals (2), have suggested the importance of central command in skin sympathetic responses to exercise. Recently, Leuenberger et al. (6) identified small increases in SSNA with mechanoreceptor stimulation independent of central command and increases with central command stimulation independent of mechanoreceptors. PEMI did not affect SSNA responses after either IHG or IKE. Thus our data support the concept that muscle metaboreceptors do not contribute to exercise-induced SSNA. Although the exact mechanism of action is still unknown, our data suggest that a similar pattern of SSNA response during isometric exercise regardless of the exercising limb.

SSNA consists of both vasomotor and sudomotor fibers (27, 28). To determine the physiological effect of the increase in SSNA, skin blood flow and electrophysiological activity were measured within the area innervated by the sympathetic recordings. Previous studies are in disagreement as to whether sweating occurs in normothermia during isometric exercise in nonglabrous skin (16, 26). We did not find a consistent increase in electrophysiological activity with isometric exercise and PEMI. In the present study, electrophysiological activity of the skin was used to provide a relative index of sweating; although less quantitative, in an absolute sense, than capacitance hygrometry or auto-

Table 1. Effect of 2 min of isometric hand grip and knee extension at 30% of maximal voluntary contraction followed by 2 min of postexercise muscle ischemia on cutaneous vascular and electrodermal responses of nonglabrous skin

<table>
<thead>
<tr>
<th>Mode</th>
<th>Exercise 1 min</th>
<th>Exercise 2 min</th>
<th>PEMI 1 min</th>
<th>PEMI 2 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>114 ± 12</td>
<td>116 ± 10</td>
<td>96 ± 8</td>
<td>93 ± 8</td>
</tr>
<tr>
<td>IKE</td>
<td>143 ± 31</td>
<td>137 ± 28</td>
<td>102 ± 10</td>
<td>104 ± 7</td>
</tr>
<tr>
<td>Cutaneous conductance IHG</td>
<td>96 ± 9</td>
<td>92 ± 8</td>
<td>110 ± 8</td>
<td>116 ± 11</td>
</tr>
<tr>
<td>Cutaneous conductance IKE</td>
<td>90 ± 11</td>
<td>98 ± 16</td>
<td>106 ± 13</td>
<td>98 ± 7</td>
</tr>
<tr>
<td>Resistance IHG</td>
<td>112 ± 10</td>
<td>138 ± 25</td>
<td>128 ± 17</td>
<td>127 ± 18</td>
</tr>
<tr>
<td>Resistance IKE</td>
<td>103 ± 6</td>
<td>145 ± 40</td>
<td>121 ± 25</td>
<td>94 ± 15</td>
</tr>
</tbody>
</table>

Values are means ± SE. IHG, isometric hand grip; IKE, isometric knee extension; PEMI, postexercise muscle ischemia. Baseline period before isometric exercise = 100%; and values are expressed as percent change from baseline. No significant differences were observed from baseline at any time point. Repeated-measures ANOVA for cutaneous vascular conductance: limb, $F_{(1,9)} = 3.22$, $P = 0.106$; time, $F_{(4,36)} = 1.90$, $P = 0.131$; interaction (limb × time), $F_{(4,36)} = 0.58$, $P = 0.681$. Repeated-measures ANOVA for cutaneous vascular resistance: limb, $F_{(1,9)} = 0.71$, $P = 0.422$; time, $F_{(4,36)} = 0.82$, $P = 0.520$; interaction (limb × time), $F_{(4,36)} = 0.61$, $P = 0.660$. Repeated-measures ANOVA for electrodermal activity: limb, $F_{(1,9)} = 0.78$, $P = 0.400$; time, $F_{(4,36)} = 1.59$, $P = 0.197$; interaction (limb × time), $F_{(4,36)} = 1.14$, $P = 0.354$.
mated dew-point systems, it does provide an indirect representation of sweat responses (7, 8). It is possible that our method for measuring changes in sweating was not sufficiently sensitive to detect small changes in this parameter. However, increases in electrodermal activity were detected during intraneural stimulation of cutaneous fibers in all subjects. Therefore, we conclude that either the increase in SSNA did not involve sudomotor pathways or the increases in sudomotor fiber activity were not sufficient to reach threshold for sweating. There is some recent evidence to support this latter assertion, because a locally administered acetylcholinesterase inhibitor infused in the dermal layer of nonglabrous skin promoted sweating during isometric handgrip perturbations (18, 19).

Neither cutaneous vascular conductance nor resistance significantly changed during isometric exercise or PEMI of the arm or leg. This observation is in agreement with others who have measured cutaneous vascular conductance with isometric exercise of the arm and/or leg (13). Taylor et al. (22) observed no change in cutaneous vascular conductance during 3 min of either one- or two-legged IKE at 30% of maximal voluntary contraction. These results are in contrast to those observed during dynamic leg exercise, which elicits marked cutaneous vasoconstriction (3, 23). Thus our results and previous findings suggest that brief submaximal isometric exercise in a normothermic environment does not elicit prominent cutaneous vasoconstriction in nonglabrous skin located below the level of the heart.

Although not the focus of this study, an additional modulator of SSNA and cutaneous end-organ responses during rest and isometric exercise is ambient temperature. In this study all testing was done in a normothermic environment (21–23°C). It is likely that responses might be different in cooler or warmer environments. Evidence from Kondo et al. (4) suggests that level of thermal input strongly affects cutaneous end-organ responses to IHG. Additional evidence reveals that, in the heated state, IHG and PEMI modulate sweating (5) and skin blood flow (1). Nonetheless, we observed no consistent changes in cutaneous vascular conductance, cutaneous vascular resistance, or electrodermal activity during isometric arm or leg exercise during normothermia.

We observed greater mean arterial pressure during IKE than during IHG. Could this greater increase in arterial blood pressure mask a greater exercise-induced SSNA response to IKE? We believe that this is unlikely because neither blood pressure modulation nor carotid stimulation has been observed to alter SSNA responses (29, 30). However, the role of the baroreceptor loading and unloading in SSNA responses during exercise remains to be directly tested.

Summary. The present study identifies significant and comparable increases in SSNA during IHG and IKE. The increases in SSNA dissipated during PEMI after IHG and IKE. These similar SSNA findings between IHG and IKE performed at the same relative exercise intensity were elicited despite cardiovascular differences during exercise. These findings support the concept that, regardless of limb, SSNA responses to nonfatiguing isometric exercise is mediated by central command and muscle mechanoreceptors. Moreover, in this experimental paradigm, increased SSNA elicited by IHG or IKE was not associated with nonglabrous cutaneous vascular conductance, cutaneous vascular resistance, or electrodermal activity. Finally, relative effort as opposed to muscle mass appears to be the major determinant of SSNA responses to isometric exercise.

GRANTS

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