Determinants of skin sympathetic nerve responses to isometric exercise

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Wilson, Thad E., Damian J. Dyckman, and Chester A. Ray. Determinants of skin sympathetic nerve responses to isometric exercise. J Appl Physiol 100: 1043–1048, 2006. First published November 10, 2005; doi:10.1152/japplphysiol.00579.2005.—Exercise-induced increases in skin sympathetic nerve activity (SSNA) are similar between isometric handgrip (IHG) and leg extension (IKE) performed at 30% of maximal voluntary contraction (MVC). However, the precise effect of exercise intensity and level of fatigue on this relationship is unclear. This study tested the following hypotheses: 1) exercise intensity and fatigue level would not affect the magnitude of exercise-induced increase in SSNA between IHG and IKE, and 2) altering IHG muscle mass would also not affect the magnitude of exercise-induced increase in SSNA. In protocol 1, SSNA (peroneal microneurography) was measured during baseline and during the initial and last 30 s of isometric exercise to volitional fatigue in 12 subjects who randomly performed IHG and IKE bouts at 15, 30, and 45% MVC. In protocol 2, SSNA was measured in eight subjects who performed one-arm IHG at 30% MVC with the addition of IHG of the contralateral arm in 10-s intervals for 1 min. Exercise intensity significantly increased SSNA responses during the first 30 s of IHG (34 ± 13, 70 ± 11, and 92 ± 13% change from baseline) and IKE (30 ± 17, 69 ± 12, and 76 ± 13% change from baseline) for 15, 30, and 45% MVC. During the last 30 s of exercise to volitional fatigue, there were no significant differences in SSNA between exercise intensities or limb. SSNA did not significantly change between one-arm and two-arm IHG. Combined, these data indicate that exercise-induced increases in SSNA are intensity dependent in the initial portion of isometric exercise, but these differences are eliminated with the development of fatigue. Moreover, the magnitude of exercise-induced increase in SSNA responses is not dependent on either muscle mass involved or exercising limb.

SYMPATHETIC OUTFLOW TO THE SKIN is increased during isometric and rhythmic exercise (7, 12, 26). This exercise-induced increase in skin sympathetic nerve activity (SSNA) is controlled by the engagement of central command and activation of muscle mechanoreceptors, and it may be controlled, under very specific conditions, by activation of muscle metaboreceptors (11). Unlike muscle sympathetic nerve activity, the precise determinants of exercise-induced increases in SSNA are equivocal.

Previous studies indicate that the exercise-induced increases in SSNA are intensity dependent to ~45% of maximal voluntary contraction (MVC) and that level of effort modulates SSNA responses to isometric exercise (27, 28). Seals (20) observed another determinant to exercise-induced increases in SSNA by demonstrating that the level of fatigue may be a prime factor regardless of exercise intensity. In these experiments, he observed no difference in SSNA responses between higher exercise intensities (i.e., 45 and 60% MVC) during isometric handgrip (IHG) at and near volitional fatigue (20). Despite these key findings, observations were limited to handgripping, and other important issues such as the amount of muscle mass involved were not addressed.

To begin to address these issues, Ray and Wilson (16) compared IHG and isometric knee extension (IKE) at a moderate intensity (30% MVC) for a fixed time duration (2 min). They determined that exercise-induced increases in SSNA were similar between IHG and IKE, indicating that relative effort, as opposed to muscle mass or exercising limb, appears to be a primary determinant of SSNA responses (16). Their study left open the possibility that altering exercise intensity or level of fatigue may alter the relationship between IHG and IKE. Also, it did not completely answer the question of the effect of muscle mass involved on exercise-induced increase in SSNA, because it may be possible that there are muscle mass differences but not limb differences in SSNA responses to exercise. Accordingly, the following hypotheses will be tested: 1) intensity will modulate exercise-induced increases in SSNA during the beginning portion of exercise but not at fatigue; 2) alteration in muscle mass by engaging either the forearm or leg will not modulate exercise-induced increases in SSNA; and 3) alterations in muscle mass by the addition of forearm exercise of the contralateral limb, but not altering intensity, also will not modulate forearm exercise-induced increases in SSNA.

METHODS

Subjects

Twelve healthy young volunteers (7 men and 5 women; age: 25 ± 1 yr; height: 176 ± 3 cm; weight: 76 ± 4 kg) participated in the study. All subjects were nonsmokers, nonobese, normotensive, and not taking any medications that would influence the results of the study. The experiments were approved by the Institutional Review Board of the Pennsylvania State University College of Medicine and verbally explained to all subjects with written, informed consent obtained.

Experimental Design

All subjects were tested in the supine position. IHG was performed with the right arm straight but abducted 30–45° from the torso. IKE was performed with the right leg flexed 90° at the hip and the lower leg positioned in a manner that during IKE the lower leg would be parallel to the floor (i.e., 90° of knee flexion). Thus IKE was performed in an upward kicking direction. Neutral skin temperature was maintained by perfusing 35°C water through a tube-lined suit. After a 2-min baseline period, isometric exercise was performed until fatigue. A target force for isometric exercise was displayed on a computer monitor, and minimal feedback was provided to the subject when necessary to maintain force output. No external cues were given to the

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subject to begin exercise (i.e., the subjects started on their own accord), nor was the subject externally engaged during exercise. The subsequent exercise trials did not commence until heart rate and mean arterial blood pressure (MAP) returned to baseline (minimum of 10 min). All experiments were performed in a dimly lit, quiet laboratory maintained at 21–23°C to minimize environmental influences on SSNA. MVC was determined for IHG and IKE via three separate isometric bouts.

**Protocol 1.** Subjects then performed alternating bouts of IHG and IKE at 15, 30, and 45% of MVC, with each limb’s three exercise bouts randomized with respect to exercise intensity. The subject maintained all exercise bouts until fatigue, which was defined when force output decreased by 5% in voluntary contraction for more than 2 s.

**Protocol 2.** Each subject then performed one-arm IHG at 30% MVC with the addition of IHG of the contralateral arm in 10-s intervals for 1 min (Fig. 1). Contralateral IHG was also performed at 30% MVC.

**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 paraesthesia 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 (3, 4). The nerve signal was amplified, fed through a band-pass filter with a bandwidth of 700–2,000 Hz, and integrated using a 0.1-s time constant (University of Iowa Bioengineering, Iowa City, IA), and then it was recorded electronically (16SP Powerlab, ADInstruments, New Castle, Australia). The mean voltage neurogram was routed to a computer screen and a loudspeaker for monitoring during the study.

Local skin blood flow was measured via laser-Doppler flowmetry using two integrating flow probes (Moor Instruments, Wilmington, DE) attached to nonglabrous skin on the dorsal portion of the foot within the area of innervation of the nerve fascicle being recorded (i.e., dorsal aspect of foot). Heart rate was derived from an electrocardiogram. Arterial pressure was measured continuously by a finger cuff (Finapres, Ohmeda, Englewood, CO) during protocol 1, but no measures of MAP were obtained during protocol 2 because both forearms were engaged in isometric exercise.

**Data Analysis**

Sympathetic recordings that demonstrated possible electrode site shifts, altered respiratory patterns (e.g., breath holding, inspiratory gasp, and hyperventilation), or electromyographic artifact during an experimental intervention were excluded from analysis. To assess total SSNA, the area of the mean voltage neurogram was calculated, as previously described (30), for each segment via computer software (Chart 5, ADInstruments) for a 30-s (protocol 1) or a 10-s (protocol 2) time period and normalized as percent of baseline before each exercise bout. Baseline SSNA measures were taken for a minimum of 60 s before the voluntary initiation of exercise. During protocol 1, we define “initial” portion of exercise as the first 30 s after the achievement of the steady-state force and “fatigue” as the last 30 s of exercise before volitional fatigue or test end point.

To identify possible differences between the arm and leg during exercise, a two-way (one between factor, limb; and one within factor, exercise intensity for protocol 1 and time for protocol 2) 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 text, figures, and table as means ± SE.

**RESULTS**

**Protocol 1**

SSNA increased significantly during the initial portion of exercise as a function of exercise intensity in both IHG and IKE (Fig. 2). During the initial portion of IHG, SSNA increased by 34 ± 13, 70 ± 11, and 92 ± 13% for 15, 30, and 45% MVC, respectively. During the initial portion of IKE, SSNA increased significantly (30 ± 17, 69 ± 12, and 76 ± 13%) for 15, 30, and 45% MVC, respectively. SSNA at fatigue significantly increased compared with baseline in all trials, but this increase was not intensity dependent (Fig. 3). However, no significant difference in SSNA activation between IHG and IKE existed at the initial portion of exercise or at fatigue. Thus exercise intensity affected SSNA activation, whereas the exercising limb had no measurable influence on SSNA.

Baseline heart rate and MAP were not significantly different between the IHG and IKE trials (Table 1). Heart rate and MAP

![Figure 1](image-url)
SSNA AND ISOMETRIC EXERCISE

The major findings regarding determinants of exercise-induced increases in SSNA are the following: 1) SSNA responses increase as a function of intensity during the initial nonfatiguing portion of exercise during IHG and IKE, 2) SSNA responses are similar at or near fatigue during IHG and IKE regardless of intensity, 3) SSNA responses are similar between IHG and IKE at a given relative intensity, and 4) SSNA responses are not augmented by the engagement of muscle mass of the contralateral arm. These data indicate that exercise-induced increases in SSNA are intensity dependent in the early portion of isometric exercise but are eliminated with the development of fatigue. Moreover, the magnitude of exercise-induced increase in SSNA does not seem to be related to either the amount of muscle mass involved or the exercising limb.

Previously, we demonstrated that SSNA responses are similar during nonfatiguing forearm and leg isometric exercise (16). In that study, we concluded that relative effort appears to be the primary modulator of exercise-induced SSNA responses in humans. Our present study confirms and extends these observations across a wide range of exercise intensities. We observed that increasing exercise intensity (i.e., 15, 30, and 45% MVC) caused increasing SSNA responses during the first 30 s of isometric exercise. This intensity-dependent exercise-induced increase in SSNA was observed in both IHG and IKE with no significant differences noted between the two limbs. Thus relative effort must be a primary determinant of nonfatiguing exercise-induced increases in SSNA.

This intensity-dependent exercise-induced increase in SSNA was observed only at the beginning of exercise but not at fatigue. This lack of an effect of relative intensity on SSNA during fatigue could indicate relative effort is a less important modulator after sustained engagement. Seals (20) observed that above a particular intensity and after sustained engagement, SSNA responses were similar during IHG. This raises the question of how much force is necessary to broach this threshold to maximally activate SSNA. Seals used IHG forces of 20, 40, and 60% MVC and found that 40 and 60% MVC responded similarly. In the present study, during the initial portion of exercise, 15, 30, and 45% MVC responded in a graded fashion, but by fatigue SSNA was similar at all intensities (see Figs. 2 and 3). IHG at 15% MVC appeared to experience less of an increase in SSNA response at fatigue, but these values were not statistically different from other IHG or IKE bouts. To further probe this question, one-way repeated-measures ANOVA analysis on IHG by intensity also yielded nonsignificant differences (P = 0.23). Although we cannot ascertain this for certain, one possible explanation for the slight differences between studies involves the higher IHG intensities used by Seals. Nonetheless, these data indicate exercise-induced increases in SSNA after

![Fig. 2. Changes (Δ) in skin sympathetic nerve activity (SSNA) during initial 30 s of IHG and isometric knee extension (IKE) and at fatigue while at 15, 30, and 45% of MVC in protocol 1. Values are means ± SE. SSNA significantly increased during initial portion in both IHG and IKE and was intensity dependent.](http://jap.physiology.org/)

![Fig. 3. ΔSSNA during the last 30 s of IHG and IKE before volitional fatigue at 15, 30, and 45% of MVC in protocol 1. Values are means ± SE. No significant differences were observed between exercising limbs or at fatigue.](http://jap.physiology.org/)
sustained engagement until fatigue are similar regardless of exercising limb or the relative intensities used in this study.

To determine whether the amount of muscle mass involved alters exercise-induced increases in SSNA, we employed two separate approaches. First, we compared exercise-induced increases in SSNA between IHG and IKE. The rationale for this comparison is that IHG engages a smaller muscle mass compared with IKE with the ability to maintain the same relative effort or intensity. We observed comparable SSNA responses between IHG and IKE, indicating that muscle mass involved in the activity does not significantly influence SSNA responses to exercise. However, it could be argued that although more muscle mass is recruited in IKE, there may be differences in number and size of motor units engaged and/or differences in the densities of muscle afferents involved in IKE compared with IHG. To account for this potential confounding variable, the second approach was employed. In protocol 2, the muscles involved and relative intensity were similar, but the amount of muscle engagement was altered (see Fig. 1). We did not observe a significant difference in the increase in SSNA between one- and two-arm IHG. This lack of an effect of muscle mass involved is in contrast to observations of muscle sympathetic nerve activity, which is proportional to muscle mass that involved some (19, 21) but not all (15) muscle groups. Combined, these data strongly suggest that muscle mass involved is not a determinant of exercise-induced increases in SSNA.

So what are the mechanisms for eliciting increases in SSNA during isometric exercise? Our data combined with previous research suggest the central command is likely the major stimulant of SSNA responses. A number of approaches such as neuromuscular blockade (27), visualization (11), transcutaneous magnetic stimulation of the motor cortex (23), and electrical stimulation of the mesencephalic locomotor region (5) have suggested the importance of central command in skin sympathetic responses to exercise. These data coupled with SSNA responses occurring early in exercise and the lack during postexercise muscle ischemia indicate that activation of muscle metaboreceptors is less important in this response (18). However, our data, as well as those of others (20), also suggest that this cortical activation can be saturated (i.e., no further increase in SSNA with further increases in central command). This can be observed in our data when motor units are fatiguing, and thus a greater recruitment (more cortical engagement) is necessary to achieve the same amount of force, but no significant differences in SSNA are observed between trials.

SSNA consists of both vasomotor and sudomotor fibers (29). To determine the physiological effect of the increase in SSNA, sweating and CVC were measured within the area innervated by the sympathetic recordings. Our previous study had two limitations to observe sweating responses; first, we used electrodermal activity as an index of sweating but did not directly measure sweat secretions, and second, subjects exercised in ambient conditions, which could have locally inhibited sweating (16). In the present study, we used improved methodology (i.e., capacitance hygrometry) and maintained neutral skin temperature (via a water-perfused suit); however, we still did not observe an alteration in sweating during the exercise bouts. Kondo et al. (9, 10) have nicely demonstrated that as IHG intensity increases, sweat rate increases in both glabrous and nonglabrous skin in warm ambient conditions. It is likely that conditions of our study were not warm enough to elicit non-

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**Table 1. Changes in mean arterial blood pressure, heart rate, and cutaneous vascular conductance during 30-s baseline, initial, and fatigue for both isometric handgrip and isometric knee extension at 15, 30, and 45% of maximal voluntary contraction**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Initial</th>
<th>Fatigue</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>15% MVC</td>
<td>30% MVC</td>
<td>45% MVC</td>
</tr>
<tr>
<td><strong>MAP, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHG</td>
<td>87±5</td>
<td>86±3</td>
<td>89±4</td>
</tr>
<tr>
<td>IKE</td>
<td>92±5</td>
<td>91±6</td>
<td>93±3</td>
</tr>
<tr>
<td><strong>HR, beats/min</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHG</td>
<td>59±5</td>
<td>58±4</td>
<td>61±5</td>
</tr>
<tr>
<td>IKE</td>
<td>61±4</td>
<td>62±4</td>
<td>62±4</td>
</tr>
<tr>
<td><strong>CVC, units</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHG</td>
<td>22±6</td>
<td>21±6</td>
<td>16±3</td>
</tr>
<tr>
<td>IKE</td>
<td>16±2</td>
<td>16±3</td>
<td>19±4</td>
</tr>
</tbody>
</table>

Values are means ± SE. IHG, isometric handgrip; IKE, isometric knee extension; MVC, maximal voluntary contraction; MAP, mean arterial blood pressure; HR, heart rate; CVC, cutaneous vascular conductance. No differences were noted between limbs. HR and MAP were significantly greater during fatigue compared with baseline and onset. HR and MAP were also significantly greater as a function of exercise intensity during fatigue. *Significant difference from baseline, P < 0.05. †Significant difference from initial portion of exercise, P < 0.05. ‡Significant difference from 15% MVC, P < 0.05.

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Fig. 4. ΔSSNA during 10-s intervals of 1- and 2-arm IHG in protocol 2. Values are means ± SE. SSNA significantly increased from baseline, but no significant differences were noted between 1- and 2-arm IHG.
thermoregulatory sweating. It appears that to elicit sweating during IHG, subjects must exercise in a warm room (i.e., ambient temperature greater than skin temperature) or have already occurred a perturbation that resulted in heat storage (8). CVC was not significantly altered via intensity during IHG or IKE. This observation is in agreement with others who have measured CVC with isometric exercise of the arm and/or leg (1, 17, 25). It is possible that alterations in CVC may occur during isometric exercise in heated conditions (1, 2), but it is unknown whether there would be a difference between IHG and IKE in these conditions.

There is an apparent disconnect between SSNA and cutaneous end-organ responses, because SSNA increases without observable end-organ response. This is not unexpected because many local factors, such as changes in local transmural pressure, local temperature, etc., can affect or override neural signals for sweat secretion and skin blood flow (7, 13, 14, 22). To achieve high end-organ output, there must be a central neural signal (SSNA) as well as peripheral augmentation. In the present study, we tried to optimize conditions (e.g., maintaining neutral skin temperature) to observe end-organ responses but did not pursue perturbations that would increase SSNA (e.g., whole body heating). A second point that should be stressed is that we thoroughly explained the procedures and vehemently stressed the need to exercise until volitional fatigue. But because mental arousal causes increases in SSNA, we kept verbal feedback and encouragement to a minimum. Subjects closely watched force output on a monitor, and all subjects experienced difficulty maintaining force output before reaching fatigue criteria. Although subjective and less quantifiable, all subjects reported exercising to maximum or could not continue isometric exercise during IHG and IKE bouts. Hence, we do not believe that fatigue level was different between exercise bouts or between subjects.

Many disease states have altered SSNA and/or cutaneous end-organ responses during or after stress. For example, individuals with congestive heart failure have altered postexercise SSNA responses compared with controls, suggestive of differing control mechanisms between patients and controls (24). Disease states may also augment or attenuate SSNA responses to stress. Iwase et al. (6) observed augmented stress-induced increases in SSNA and sweating in subjects with palmoplantar hyperhidrosis compared with controls. By furthering our understanding of the determinants of stimulus-induced increases in SSNA and cutaneous end-organ responses, we may be able to gain insight into underlying mechanisms causing these altered responses.

Summary

SSNA responses increase as intensity increases during the initial portion of exercise but are comparable at fatigue during IKE and IHG. Similarly, exercise-induced increases in SSNA are comparable between IKE and IHG, as well as between one- and two-arm IHG. These data indicate that exercise-induced increases in SSNA are intensity dependent in the early portion of isometric exercise, but these differences are eliminated with the development of fatigue. These data also support the hypothesis that muscle mass does not contribute to the magnitude of exercise-induced increase in SSNA in humans.

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