Stimulation of Skin Sympathetic Nerve Discharge by Central Command

Differential Control of Sympathetic Outflow to Skin and Skeletal Muscle During Static Exercise

Susanne F. Vissing, Urs Scherrer, and Ronald G. Victor

Microneurographic measurements of muscle sympathetic nerve activity (SNA) have suggested that, during static exercise, central command is much less important than skeletal muscle afferents in causing sympathetic neural activation. The possibility remains, however, that the sympathetic discharge produced by central command is targeted mainly to tissues other than skeletal muscle. To examine this possibility, we recorded SNA with microelectrodes placed selectively in skin, as well as in muscle, nerve fascicles of the peroneal nerve during static handgrip maneuvers designed to separate the effects of central command from those of muscle afferents. To study the relative effects of cutaneous sympathetic activation on sudomotor versus vasomotor function, we simultaneously estimated changes in skin blood flow (laser Doppler velocimetry) and sudomotor (electrodermal) activity in the region of skin innervated by the impaired nerve fascicle. Two minutes of static handgrip at 10%, 20%, and 30% of maximal voluntary contraction caused large and intensity-dependent increases in skin SNA. These increases in SNA immediately preceded the onset of muscle tension, accelerated progressively during sustained handgrip, and resolved promptly with the cessation of motor effort. The handgrip-induced increases in skin SNA were not maintained when handgrip was followed by arrest of the forearm circulation, a maneuver that maintains the stimulation of chemically sensitive muscle afferents while eliminating the influences of central command and mechanically sensitive muscle afferents. During normothermia, static handgrip at 30% maximal voluntary contraction caused sustained increases in skin SNA (+400±83%, mean±SEM, p<0.05) and in electrodermal activity (+276±56%, p<0.05) but only transient increases in estimated skin vascular resistance (+11±2%, p<0.05). When skin temperature was increased or decreased to a new stable baseline level, subsequent increases in skin SNA during handgrip were accompanied by sustained but directionally opposite changes in estimated skin vascular resistance, with exercise-induced vasodilation during hyperthermia but exercise-induced vasoconstriction during hypothermia. From these observations, we conclude the following: 1) static exercise markedly increases sympathetic outflow to skin as well as to skeletal muscle; 2) the increases in skin SNA, unlike muscle SNA, appear to be caused mainly by central command rather than by muscle afferent reflexes; and 3) this cutaneous sympathetic activation appears to be targeted both to sweat glands and to vascular smooth muscle, with the relative targeting being temperature dependent. These findings provide neurophysiological evidence in humans to support the hypothesis that central command can be a potent stimulus to sympathetic outflow, and they emphasize the marked heterogeneity in the regulation of regional sympathetic discharge during exercise by central neural and peripheral reflex mechanisms. (Circulation Research 1991;69:228–238)

Activation of the sympathetic nervous system produces many of the circulatory adjustments during exercise. However, the underlying mechanisms that activate sympathetic outflow during exercise still are incompletely understood. Two principal theories have been proposed. The first
is that sympathetic activation is caused by a contraction-induced reflex arising in chemically and mechanically sensitive muscle afferents.1–5 The second theory is that during exercise, the central motor command signal emanating from the rostral brain irradiates to autonomic circuits in the brain stem, causing parallel activation of motor and sympathetic neurons.6,7 In conscious humans, central command is related to voluntary motor effort.8–10 Although neurophysiological studies in anesthetized or decerebrate animals have provided experimental support for both theories, the relative importance of muscle afferent reflexes and central command in causing sympathetic activation during exercise in conscious humans remains an unsolved problem in cardiovascular physiology.11,12

Recent neurophysiological studies in humans have provided considerable evidence that during static exercise, muscle afferent activation is a potent stimulus to sympathetic outflow.13–17 In contrast, these studies have indicated that central command is at most a weak stimulus to sympathetic outflow.17 This conclusion, however, is based solely on the measurement of sympathetic discharge to skeletal muscle, which may not be representative of sympathetic discharge to other tissues or vascular beds.

Skin sympathetic activity, for example, characteristically is much more responsive than muscle sympathetic activity to cognitive processes, such as those involved in mathematical calculation.18–20 We therefore hypothesized that skin sympathetic activity might also be more responsive than muscle sympathetic activity to the central neural drive that accompanies voluntary motor effort. To test this hypothesis, we performed microelectrode recordings of sympathetic discharge selectively from both skin and muscle nerve fascicles of the peroneal nerve during static handgrip maneuvers designed to isolate the autonomic effects of central command from those of chemically and mechanically sensitive muscle afferents. To study the relative effects of cutaneous sympathetic activation on sudomotor versus vasomotor function, we simultaneously estimated changes in skin blood flow (laser Doppler velocimetry) and in sudomotor (electrodermal) activation within the region of skin innervated by the impaled nerve fascicle.

Materials and Methods

Subjects

Twenty-two subjects (20 men and two women) aged 24–45 years participated in this study after providing written informed consent. The protocol was approved by the Institutional Review Board on human investigation. All subjects were normotensive (supine blood pressures <140/90 mm Hg), were taking no medications, and had no evidence of cardiopulmonary disease on history or physical examination at the time of the study.

Measurements

Subjects in the supine position were studied with most of their torso and extremities enclosed in a water-perfused thermal suit. Heart rate was measured continuously from the electrocardiogram. Arterial pressure was measured either in the arm with sphygmomanometry using an automated system (Dinamap, Criticon Corp., Tampa, Fla.) that recorded arterial pressure once every 60 seconds or in the finger using a Finapres continuous blood pressure monitor (Ohmeda Corp., Madison, Wis.).

Multiunit recordings of postganglionic sympathetic nerve activity (SNA) were obtained using unipolar tungsten microelectrodes inserted selectively into skin or muscle nerve fascicles of the peroneal nerve using the microneurographic technique of Valbo et al.18 The neural signals were amplified, filtered (bandwidth, 700–2,000 Hz), rectified, and integrated to obtain a mean voltage display of SNA. A recording of skin SNA was considered acceptable when 1) weak electrical stimulation through the microelectrode elicited paresthesias without muscle contraction, 2) the mean voltage neurogram revealed bursts of neural activity (with a signal-to-noise ratio of greater than 3:1), and 3) the neural activity increased during arousal stimuli (loud noise, skin pinch). A recording of muscle SNA was considered acceptable when 1) weak electrical stimulation through the microelectrode elicited twitch contractions without paresthesias, and 2) the mean voltage neurogram revealed spontaneous, pulse-synchronous bursts that increased during the Valsalva maneuver (phases II and III) but not during the arousal stimuli.

Respiratory excursions were monitored with pneumographs around the abdomen and chest to detect inadvertent performance of Valsalva’s maneuver, held expiration, or a sudden deep breath, because such respiratory maneuvers can have pronounced effects on both skin and muscle SNA.19,20 Neurograms revealing simultaneous skin and muscle sympathetic activity were not accepted. Inadvertent contraction of the leg muscles adjacent to the recording electrode produces electromyographic artifacts that are easily distinguished from sympathetic bursts; neurograms containing such artifacts were excluded from analysis. Before beginning the protocol, subjects rested quietly for 10 minutes to ensure a stable baseline.

Sympathetic bursts were identified by inspection of the filtered and mean voltage neurograms. The number of bursts per minute was used as an index of the frequency of sympathetic discharge. The filtered neurogram also was routed to a window discriminator that counted nerve spikes exceeding a threshold voltage set just above the noise level. The number of nerve spikes per minute was counted using an integrator circuit that reset after each 100 spikes. The output of the integrator was expressed as a percentage of the control value to provide an estimate of relative changes in integrated activity.
Once a stable recording of skin SNA had been obtained, the region of skin innervated by the impaled nerve fascicle was determined with light stroking of the skin to obtain cutaneous mechanoreceptor discharge. The laser Doppler probe and electrodermal electrodes were placed on the surface of the skin within this region.

Changes in phasic and mean skin blood flow were estimated continuously using laser Doppler velocimetry (ALF 2100, Advance Company, Ltd., Ithaca, N.Y.). Values of estimated mean skin blood flow are reported in milliliters per minute per 100 ml skin, which represents voltage output (in volts) multiplied by a conversion factor of 10. Relative changes in skin blood flow are expressed as a percentage of the control value during normothermia. Skin vascular resistance was estimated by dividing mean arterial pressure (diastolic pressure plus one third pulse pressure) in millimeters of mercury by estimated skin blood flow in milliliters per minute per 100 ml.

Changes in electrodermal activity were used as an index of sudomotor function and were measured by recording changes in electrical resistance between two Ag/AgCl electrodes when current intensity was held constant at 50 µA. Studies in both animals and humans have established the validity of using electrodermal activity to study effects of sympathetic discharge on sweat gland activity. The changes in electrical resistance were converted to an AC voltage output using a Model 7P1F preamplifier (Grass Instruments, Quincy, Mass.) with a rise time constant of 0.3 second and a decay time constant of 3 seconds. The AC signal was integrated using an RC circuit (Gould Instruments, Cleveland, Ohio) that summed the total positive and negative deflections in voltage that occurred within a 60-second bin. Electrodermal activity was expressed as deflections per minute and as the total integrated voltage deflection (in volts) per minute, with relative changes being expressed as a percentage of the baseline values during normothermia.

Skin temperature was measured using surface probes connected to a Gould temperature amplifier. At the beginning of each experiment, the amplifier output was calibrated against a mercury thermometer between 20° and 40°C. This system can detect differences in temperature of less than 0.1°C.

In each experiment, probes were placed on the lower extremity within the receptive field of the impaled nerve fascicle, chest, back, and thigh. Skin surface temperature was calculated according to the method of Hardy and DuBois.

Sympathetic activity, electrodermal activity, skin blood flow indexes (phasic and mean), electrocardiogram, respiratory excursions, and force of muscle contraction (handgrip dynamometer, Stoelting Co., Chicago) were recorded continuously on a Gould ES1000 electrostatic recorder and on an R 71 tape recorder (TEAC, Tokyo, Japan).

Interventions

At the beginning of each experiment, maximal voluntary contraction (MVC) was determined using a handgrip dynamometer. During handgrip, subjects were given visual feedback of force output on an oscilloscope. Subjects were instructed to avoid performance of a Valsalva maneuver and to avoid inadvertent contraction of nonexercising muscles during handgrip. At the end of each exercise period, subjects were asked to rate their perceived effort on a scale of 6 (minimal effort) to 20 (maximal effort) as a subjective index of central command.

Mild hyperthermia and hypothermia were produced by perfusing a thermal suit with water at 45° or 15°C.

Specific Protocols

Protocol 1: Skin sympathetic, sudomotor, and vasomotor responses to static handgrip (18 experiments on 12 subjects). To determine the time course and magnitude of changes in skin SNA during handgrip and the corresponding end-organ responses, we simultaneously recorded skin SNA, laser Doppler skin blood flow, and electrodermal activity during 2 minutes each of control, static handgrip at 30% MVC, and recovery.

Protocol 2: Comparison of skin and muscle sympathetic responses to static handgrip and to posthandgrip forearm vascular occlusion (10 experiments on nine subjects). We recorded both skin and muscle SNA during 2 minutes of static handgrip at 30% MVC followed immediately by 2 additional minutes of posthandgrip forearm vascular occlusion produced by inflation of a pneumatic cuff on the upper arm to suprasystolic pressure (250 mm Hg). Posthandgrip forearm vascular occlusion maintains the stimulation of metaboreceptor muscle afferents and the reflex activation of muscle SNA, while muscular relaxation eliminates both central command and the stimulation of mechanoreceptor muscle afferents. In one of the nine subjects, skin and muscle SNA were recorded simultaneously; in the remaining eight subjects, skin and muscle SNA were recorded on separate days.

Protocol 3: Responses of skin SNA to graded levels of static handgrip (27 experiments on nine subjects). To determine if the skin sympathetic responses during handgrip were proportional to the intensity of the exercise, we studied responses during 2 minutes of static handgrip at 10%, 20%, and 30% MVC. To minimize muscular fatigue, the order of the exercise bouts was from least to most difficult, with 10-minute rest periods between bouts.

Protocol 4: Effects of muscular fatigue on skin SNA responses to static handgrip (37 experiments on 10 subjects). In 10 subjects, we recorded skin SNA during repeated bouts of static handgrip at 20% MVC followed by posthandgrip forearm vascular occlusion. The exercise bouts were performed in rapid succession, with only 2 minutes of rest between handgrip sequences, to accelerate the development of muscular fatigue. The rationale was that fatigue would increase the degree of motor effort required to maintain a given level of muscle tension and thus augment the contribution of central command.
TABLE 1. Skin Sympathetic, Vasomotor, and Electrodermal Responses to Static Handgrip at 30% Maximal Voluntary Contraction

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Static handgrip</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st min</td>
<td>2nd min</td>
<td>Recovery</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>80±2</td>
<td>85±2*</td>
<td>96±3*</td>
<td>80±2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>58±3</td>
<td>67±3*</td>
<td>74±4*</td>
<td>58±2</td>
</tr>
<tr>
<td>Skin sympathetic activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bursts · min⁻¹</td>
<td>18±2</td>
<td>38±3*</td>
<td>46±3*</td>
<td>20±1</td>
</tr>
<tr>
<td>Integrated activity (%)</td>
<td>100</td>
<td>254±52*</td>
<td>357±78*</td>
<td>142±27</td>
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<tr>
<td>Estimated skin blood flow</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Units</td>
<td>2.5±0.5</td>
<td>2.9±0.6</td>
<td>3.3±0.7*</td>
<td>2.7±0.7</td>
</tr>
<tr>
<td>% of control</td>
<td>100</td>
<td>115±9</td>
<td>138±10*</td>
<td>101±5</td>
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<tr>
<td>Estimated skin vascular resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Units</td>
<td>49.1±9.3</td>
<td>49.2±10.4</td>
<td>43.8±7.9</td>
<td>52.9±12.1</td>
</tr>
<tr>
<td>% of control</td>
<td>100</td>
<td>98±6</td>
<td>92±8</td>
<td>102±4</td>
</tr>
<tr>
<td>Electrodermal activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responses · min⁻¹</td>
<td>2±1</td>
<td>8±1*</td>
<td>12±2*</td>
<td>3±1</td>
</tr>
<tr>
<td>V · min⁻¹</td>
<td>1.35±0.25</td>
<td>3.39±0.74*</td>
<td>2.74±0.39*</td>
<td>1.58±0.29*</td>
</tr>
<tr>
<td>% of control</td>
<td>100</td>
<td>270±65*</td>
<td>239±35*</td>
<td>139±22</td>
</tr>
</tbody>
</table>

Data are mean±SEM for 12 subjects.
p<0.05 vs. control.

Protocol 5: Time course of cutaneous vasomotor responses during static handgrip (12 experiments on nine subjects). To examine more closely the time course of cutaneous vasomotor responses during handgrip (normothermia), we measured laser Doppler skin blood flow velocity (dorsum of the foot) and simultaneously obtained continuous measurements of arterial pressure (Finapres monitor) during 2 minutes of static handgrip at 30% MVC. The aim of this protocol was to determine if cutaneous vasomotor tone increases transiently at the onset of static handgrip.

Protocol 6: Effects of hypothermia and hyperthermia on skin sympathetic, vasomotor, and sudomotor responses to handgrip (33 experiments on 10 subjects). The aim of this protocol was to alter the baseline level of sudomotor activation and examine the effects of such alterations on the cutaneous vasomotor response to static handgrip. The rationale was that the ratio of cutaneous sympathetic vasoconstrictor to sudomotor outflow is dependent on skin temperature, with hypothermia favoring vasoconstrictor outflow and hyperthermia favoring sudomotor outflow.30–32 We studied effects of 2 minutes of static handgrip at 30% MVC on skin SNA, laser Doppler skin blood flow velocity, and electrodermal activity under three conditions: normothermia, mild hypothermia, and mild hyperthermia. Normothermic responses always were studied first; the order of hypothermia and hyperthermia was random.

Data Analysis
Statistical analysis was performed by repeated measures analysis of variance in conjunction with Bonferroni post hoc adjustments for multiple comparisons. Ratings of perceived effort also were analyzed using Page’s nonparametric test; because the interpretation of the parametric and nonparametric tests were identical, all results are expressed as mean±SEM. A value of p<0.05 was considered statistically significant.

TABLE 2. Comparison of Skin and Muscle Sympathetic Nerve Responses During Static Handgrip at 30% Maximal Voluntary Contraction and During Posthandgrip Forearm Vascular Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>5 sec Before start of handgrip</th>
<th>Handgrip</th>
<th>Posthandgrip forearm vascular occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st 5 sec</td>
<td>1st min</td>
<td>2nd min</td>
</tr>
<tr>
<td>Skin sympathetic activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bursts · min⁻¹</td>
<td>23±3</td>
<td>40±3*</td>
<td>37±5*</td>
<td>39±4*</td>
</tr>
<tr>
<td>Integrated activity (%)</td>
<td>100</td>
<td>207±30*</td>
<td>215±15*</td>
<td>232±52*</td>
</tr>
<tr>
<td>Muscle sympathetic activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bursts · min⁻¹</td>
<td>18±3</td>
<td>11±5</td>
<td>11±6</td>
<td>18±4</td>
</tr>
<tr>
<td>Integrated activity (%)</td>
<td>100</td>
<td>91±16</td>
<td>72±19</td>
<td>93±13</td>
</tr>
</tbody>
</table>

Data are mean±SEM for nine subjects.
p<0.05 vs. control.
Results

Two minutes of static handgrip at 30% MVC consistently evoked increases in skin SNA that were graded to the intensity of the exercise. These increases in SNA immediately preceded the onset of muscle tension, accelerated progressively during sustained handgrip, and resolved promptly with the cessation of motor effort (Tables 1 and 2 and Figures 1 and 2). In contrast, muscle SNA did not increase before the onset of handgrip but rather increased slowly, with a latency of approximately 60 seconds from the onset of handgrip to the onset of sympathetic activation. When handgrip was followed by forearm vascular occlusion, skin SNA rapidly decreased toward control, whereas muscle SNA remained elevated (Table 2 and Figures 1 and 2).
Increases in skin SNA were proportional to the subjects’ rating of perceived motor effort, which increased 1) from 11±1 to 15±1 units (p<0.05) from the first to the second minute of static handgrip at 30% MVC; 2) from 11±2 to 13±1 to 15±1 units (p<0.05) with three consecutive bouts of handgrip at 20% MVC (Figure 3); and 3) from 7±2 to 10±1 to 15±1 units (p<0.05) when the level of handgrip was increased from 10% to 20% to 30% MVC. These intensity-dependent increases in skin SNA were accompanied by proportional increases in electrodermal activity (Figure 4 and Table 3).

Handgrip at 30% MVC had no detectable effects on skin temperature (33.1±0.3°C versus 33.1±0.3°C). In nine of 12 subjects, handgrip at 30% MVC had no detectable effects on the rate or depth of breathing. In three subjects, however, handgrip was accompanied by a 35% increase in the depth of breathing. Without handgrip, this small increase in depth of breathing alone had no effect on skin SNA.

Figure 5 depicts the time course of cutaneous vasomotor responses during static handgrip at 30% MVC during normothermia. During the first 20 seconds of static handgrip, estimated skin blood flow did not increase despite a significant increase in mean arterial pressure, indicating a small but statistically significant (p<0.05) increase in vasomotor tone. During the remaining 100 seconds of handgrip, estimated skin vascular resistance returned to baseline, as further increases in arterial pressure were accompanied by proportional increases in estimated skin blood flow.

Alterations in skin temperature produced significant alterations both in baseline values (Table 4) and in the cutaneous vasomotor responses to static handgrip (Table 4 and Figure 6). Hypothermia (decrease in mean skin temperature from 34.0°C to 30.6°C) approximately doubled control values of skin SNA and of estimated skin vascular resistance and greatly attenuated the increase in electrodermal activity evoked by handgrip (Table 4). Hyperthermia (increase in skin temperature from 34.0°C to 36.1°C) increased baseline skin SNA by 164% and baseline electrodermal activity by 185% and de-

![Figure 2](image.png)

**Figure 2.** Differential temporal patterns of skin and muscle sympathetic nerve responses to 2 minutes of static handgrip at 30% maximal voluntary contraction followed by 2 minutes of forearm vascular occlusion. Sympathetic nerve activity (SNA) is expressed as a percentage of the baseline value. Muscle SNA increased during the second, but not during the first, minute of handgrip and remained elevated during posthandgrip forearm vascular occlusion. In contrast, skin SNA increased immediately before the onset of handgrip, rose progressively from the first through the second minute of handgrip, and returned rapidly to baseline during posthandgrip forearm vascular occlusion. Data are mean±SEM for nine subjects. *Significantly different (p<0.05) from baseline.

TABLE 3. Comparison of Skin Sympathetic and Electrodermal Responses to Static Handgrip at 10%, 20%, and 30% Maximal Voluntary Contraction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Skin sympathetic nerve activity (bursts/min)</th>
<th>Electrodermal activity (V/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>16±2</td>
<td>0.98±0.15</td>
</tr>
<tr>
<td>Handgrip at 10% MVC</td>
<td>26±2</td>
<td>1.33±0.23</td>
</tr>
<tr>
<td>Δ</td>
<td>+10±1*</td>
<td>+0.35±0.12*</td>
</tr>
<tr>
<td>Control</td>
<td>18±2</td>
<td>1.16±0.29</td>
</tr>
<tr>
<td>Handgrip at 20% MVC</td>
<td>33±3*</td>
<td>2.14±0.53*</td>
</tr>
<tr>
<td>Δ</td>
<td>+16±2*†</td>
<td>+0.98±0.29†</td>
</tr>
<tr>
<td>Control</td>
<td>18±3</td>
<td>1.14±0.29</td>
</tr>
<tr>
<td>Handgrip at 30% MVC</td>
<td>45±3*</td>
<td>3.29±0.81*</td>
</tr>
<tr>
<td>Δ</td>
<td>+26±4*††</td>
<td>+2.14±0.64††</td>
</tr>
</tbody>
</table>

Responses to handgrip were measured during the last 30 seconds of a 2-minute exercise period. MVC, maximal voluntary contraction.

*p<0.05 vs. control.

†p<0.05 vs. response during next lower level of handgrip.
creased baseline estimated skin vascular resistance by 26%. When skin temperature was increased or decreased to a new stable baseline level, subsequent increases in skin SNA were accompanied by directionally opposite changes in estimated skin vascular resistance, with exercise-induced vasodilation during hyperthermia but exercise-induced vasoconstriction during hypothermia (Table 4 and Figure 6). Handgrip, however, caused comparable increases in mean arterial pressure during normothermia, hypothermia, and hyperthermia.

Discussion

Microneurographic measurements of muscle SNA have suggested that during static exercise, central command is much less important than skeletal muscle afferents in causing sympathetic neural activation.13-17 The possibility remains, however, that the sympathetic discharge produced by central command is targeted mainly to tissues other than skeletal muscle. To examine this possibility, we compared effects of static exercise on sympathetic outflow recorded from both muscle and skin fascicles of the peroneal nerve. The principal new conclusions are threefold: 1) Static exercise markedly increases sympathetic outflow to skin as well as to skeletal muscle; 2) the increases in skin SNA always preceded the onset of muscle tension by 1-2 seconds, were proportional to the subjects' rating of perceived motor effort, and were not maintained during posthandgrip forearm vascular occlusion, suggesting that the exercise-induced increases in skin SNA, unlike muscle SNA, are caused mainly by central command rather than by muscle afferent reflexes; and 3) this cutaneous sympathetic activation is accompanied by increases in both electrodermal activity and in vasomotor tone, with the relative targeting of sympathetic outflow to sweat glands and vascular smooth muscle being temperature dependent. These findings provide neurophysiological evidence in humans to support the hypothesis that central command can be a potent stimulus to sympathetic outflow and empha-

Figure 3. Correlation between peak increases in skin sympathetic nerve activity (SNA) and the subjects' ratings of perceived effort (RPE) during three sequential bouts of static handgrip at constant force. During repeated sequences of handgrip, the increase in skin SNA became progressively larger as the handgrip became progressively more difficult to perform. Data are mean±SEM for nine subjects. *Significantly different (p<0.05) from previous handgrip sequence.

Figure 4. Original record from one subject showing effects of static handgrip at 30% maximal voluntary contraction (MVC) on skin sympathetic nerve activity (SNA), electrodermal activity, and laser Doppler skin blood flow. At the onset of handgrip, increased skin SNA was accompanied by a sharp decrease in the electrical resistance of the skin and a slight decrease in laser Doppler skin blood flow.
Despite a resistance increased, the mean arterial pressure increases after 30% maximal voluntary contraction. At the onset of exercise, estimated skin vascular resistance increased, because skin blood flow did not increase despite a sharp rise in mean arterial pressure. During the remainder of the exercise period, vascular resistance returned to baseline as further increases in arterial pressure were accompanied by proportional increases in skin blood flow. Data are mean ± SEM for nine subjects. *Significantly different (p<0.05) from baseline.

**FIGURE 5.** Time course of cutaneous vasomotor responses during 2 minutes of static handgrip at 30% maximal voluntary contraction. At the onset of exercise, estimated skin vascular resistance increased, because skin blood flow did not increase despite a sharp rise in mean arterial pressure. During the remainder of the exercise period, vascular resistance returned to baseline as further increases in arterial pressure were accompanied by proportional increases in skin blood flow. Data are mean ± SEM for nine subjects. *Significantly different (p<0.05) from baseline.

The principal new observation in this report is the striking temporal dissociation between the skin and muscle SNA responses to static handgrip. Whereas muscle SNA increases slowly with a latency of almost 60 seconds from the onset of tension development to the onset of sympathetic activation, skin SNA increases abruptly at the onset of static exercise, with the first burst of activity immediately preceding the onset of muscle tension. The ensuing discussion outlines the evidence that these dissociated patterns of sympathetic response are caused by differential control of sympathetic outflow to skin and muscle by central command and muscle afferents.

Although no single finding definitively proves that central command causes the increases in skin SNA during handgrip, our study provides multiple lines of evidence that, taken together, strongly support this hypothesis. The finding that cutaneous sympathetic activation always preceded the onset of muscle tension can only be explained by a central neural, rather than a peripheral reflex, mechanism. The data suggest that this central sympathetic activation is a specific response to the motor effort that accompanies static exercise rather than a nonspecific response to cortical arousal (i.e., simply attending to any task). An arousal or orienting response, such as the increase in skin SNA evoked by a loud noise, is transient (usually measured in seconds) and habituates with repeated presentations of the stimulus. During handgrip, however, the increases in skin SNA were maintained for the entire duration of the exercise and became progressively larger, not smaller, over the 2 minutes of sustained handgrip. With repeated bouts of handgrip, this sympathetic response showed no evidence of habituation, but rather became progressively larger in magnitude. We suggest that the progressive increase in skin SNA during sustained handgrip and the augmentation of this increase with repeated handgrip are explained by an augmentation in central command. Sustained contraction produced muscular fatigue and made the exercise progressively more difficult to perform.

We considered the alternative possibility that the progressive increase in skin SNA during 2 minutes of static handgrip, and the augmentation of this increase with repeated sequences of exercise, might be a reflex response caused by metaboreceptor muscle afferents. When stimulated by static contraction in anesthetized animals, these afferents show a slow and progressive increase in activity that corresponds to the progressive accumulation of intramuscular metabolites within the vicinity of these afferent endings. In humans, this slow pattern of afferent neural activation is reflected in the effluent muscle sympathetic nerve response to static handgrip. However, metaboreceptor muscle afferents are unlikely to have caused the increases in skin SNA during repeated bouts of static handgrip, because these increases were not maintained during post-handgrip forearm vascular occlusion, a maneuver that maintains the stimulation of metaboreceptor muscle afferents and the reflex activation of muscle SNA.

Mechanoreceptor muscle afferents also are unlikely to explain our findings. During static contraction in experimental animals, these afferents, and their resultant reflex increases in SNA, display an initial burst of activity beginning approximately 1 second after the onset of tension development, fol-
TABLE 4. Effects of Hypothermia and Hyperthermia on Responses to Static Handgrip at 30% Maximal Voluntary Contraction

<table>
<thead>
<tr>
<th></th>
<th>Normothermia</th>
<th>Hypothermia</th>
<th>Hyperthermia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Handgrip</td>
<td>Control</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>78±2</td>
<td>90±3</td>
<td>88±3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>58±3</td>
<td>72±4*</td>
<td>55±3</td>
</tr>
<tr>
<td>Skin sympathetic activity</td>
<td>Burst/min^-1</td>
<td>20±7</td>
<td>41±2</td>
</tr>
<tr>
<td></td>
<td>Integrated activity (% of control at normothermia)</td>
<td>100</td>
<td>400±83*</td>
</tr>
<tr>
<td>Estimated skin blood flow</td>
<td>ml/min^-1·100 ml^-1</td>
<td>2.7±0.6</td>
<td>3.6±0.9*</td>
</tr>
<tr>
<td>% of control at normothermia</td>
<td>100</td>
<td>132±8*</td>
<td>85±1</td>
</tr>
<tr>
<td>Estimated skin vascular resistance</td>
<td>Units</td>
<td>44.5±9.7</td>
<td>43.2±10.3</td>
</tr>
<tr>
<td>% of control at normothermia</td>
<td>100</td>
<td>95±6</td>
<td>174±38</td>
</tr>
<tr>
<td>Electrodermal activity</td>
<td>Deflections/min^-1</td>
<td>3±1</td>
<td>10±2*</td>
</tr>
<tr>
<td></td>
<td>V/min^-1</td>
<td>1.3±0.28</td>
<td>3.08±0.61*</td>
</tr>
<tr>
<td>% of control at normothermia</td>
<td>100</td>
<td>276±56*</td>
<td>93±22</td>
</tr>
<tr>
<td>Skin temperature (°C)</td>
<td>34.0±0.2</td>
<td>34.0±0.3</td>
<td>30.6±0.5</td>
</tr>
</tbody>
</table>

Data are mean±SEM for 10 subjects. Responses to handgrip were measured during the last 30 seconds of a 2-minute exercise period. *p<0.05 vs. control.

lowed by rapid adaptation. In our human experiments, however, the increases in skin SNA began before, rather than after, the onset of muscle tension and then increased, rather than decreased, during sustained contraction.

Thermal and respiratory stimuli are known to exert large effects on sympathetic outflow to skin. To minimize these potentially confounding effects in our experiments, we studied brief periods of static contraction of a small muscle mass rather than prolonged periods of dynamic exercise of a large muscle mass. The highest level of static handgrip used in these experiments had no detectable effect on skin temperature.

Respiratory maneuvers also are unlikely to have had important effects on skin SNA during static handgrip because in most subjects, this form of exercise caused no detectable change in the rate or depth of breathing. In the few subjects who showed small increases in the depth of breathing during handgrip, this change in breathing alone, without handgrip, had no effect on skin SNA.

Previous studies using laser Doppler velocimetry to estimate skin blood flow have supported the view that static exercise does not cause sympathetic activation in skin. That view was initially suggested by preliminary microneurographic data indicating rather inconsistent skin SNA responses to static handgrip. In contrast, in the present study we found that static handgrip consistently evoked large and intensity-dependent increases in skin SNA in 125 experiments performed on 13 different subjects. Our neurophysiological data are consistent with previous hemodynamic data suggesting that static handgrip evokes rapid, and thus presumably neurogenic, increases in cutaneous venous tone.

Microneurographic recordings of skin SNA contain both vasoconstrictor and sudomotor fibers, the latter being thought to promote local cutaneous vasodilation by stimulating the release of vasoactive substances from sweat glands. With such multunit recordings of skin SNA, simultaneous measurements of electrodermal activity and of skin blood flow velocity provided some important clues about
the relative contributions of sudomotor versus vasomotor discharge to the aggregate increase in multunit skin sympathetic outflow elicited by static handgrip. Our initial experiments readily demonstrated that during static exercise, increased skin SNA is accompanied by increased electrodermal activity, suggesting that one function of such sympathetic excitation is the activation of sweat glands.

In contrast, our initial experiments in which arterial pressure and skin vascular resistance during handgrip were measured intermittently failed to demonstrate that increased skin SNA is accompanied by increased cutaneous vasomotor tone. However, our subsequent experiments in which arterial pressure was measured continuously indicate that cutaneous vasomotor tone increases transiently during the first 20 seconds of static handgrip and then gradually returns to baseline during continued handgrip. The gradual decline in vasomotor tone probably was not caused by a decline in the neural stimulus causing this response, because skin SNA increased rather than decreased throughout the duration of the exercise period. On the other hand, neurogenic vasconstrictor drive may have been maintained throughout the exercise but its effect obscured by progressive neurohumoral vasodilation resulting from the gradual release of vasoactive substances from sweat glands. This possibility is further suggested by the additional finding that during attenuated sudomotor activation (hypothermia), increases in estimated skin vascular resistance were maintained throughout the entire 2 minutes of static exercise.

Because sympathetic nerves innervating different regions of skin may vary in the relative densities of vasconstrictor and sudomotor fibers that they contain,30-32 our present data obtained from skin nerve fascicles of the peroneal nerve should not be extrapolated to make general statements regarding the neural control of all cutaneous beds. However, we found no detectable differences in the pattern of skin SNA responses, or in the accompanying indexes of end-organ responses, between deep as compared with superficial fascicles of the peroneal nerve, which together innervate the hairy skin of the dorsal surface of the foot and entire lateral surface of the lower leg from the lateral malleolus to the fibular head.

In summary, the present neurophysiological data strongly suggest that the relative contributions of central command and of muscle afferent reflexes in causing sympathetic activation during exercise can vary greatly depending on the specific sympathetic outflow under study. During static exercise in humans, central command is thought to contribute very little to the activation of sympathetic outflow in skeletal muscle but appears to be the primary mechanism that triggers sympathetic activation in skin.

Acknowledgments

The authors are indebted to Dr. Jere H. Mitchell for his continued support and thoughtful review of this work; to Eric Clough and Troy Obregon for superb research assistance; to Ms. Patricia Powell and Ms. Cindy Lawson for expert secretarial assistance; and to Trans Sonic Systems for the generous loan of the ALF 2100 Laser Doppler flowmeter.

References


23. Lloyd DPC: Average behavior of sweat glands as indicated by impedence changes. *Proc Natl Acad Sci USA* 1959;45:410–413


**KEY WORDS** • sympathetic nervous system • static exercise • central command • skeletal muscle receptors
Stimulation of skin sympathetic nerve discharge by central command. Differential control of sympathetic outflow to skin and skeletal muscle during static exercise.
S F Visking, U Scherrer and R G Victor

Circ Res. 1991;69:228-238
doi: 10.1161/01.RES.69.1.228

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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