Sympathetic Neural Adjustments to Stress in Physically Trained and Untrained Humans

Douglas R. Seals

The purpose of this study was to determine if the state of physical training influences sympathetic neural activation during acute stress in humans. We recorded muscle sympathetic nerve activity (microneurography of the peroneal nerve), arterial blood pressure, and heart rate in 12 highly trained, endurance athletes (25±1 years, mean±SEM) and 12 untrained subjects (27±1 years) before (supine rest control) and during: 1) lower body negative pressure at -5, -10, -15, and -20 mm Hg (orthostatic stress); 2) isometric handgrip at 30% of maximum (exercise stress); and 3) hand immersion in ice water, that is, the cold pressor test (thermal stress). Body weight was not different in the two groups, but the athletes had a lower body fat content (8.9±1.3% versus 16.1±2.0%, p<0.05). During supine rest, muscle sympathetic nerve burst frequency (24±3 versus 24±2 bursts/min, athletes versus untrained subjects) and burst incidence (36±3 versus 44±4 bursts/100 heart beats) and arterial blood pressure were not different in the two groups, but heart rate was lower in the athletes (54±2 versus 67±3 beats/min, p<0.05). During graded lower body negative pressure, mean arterial pressure and heart rate did not change from control levels in either group, but muscle sympathetic nerve activity increased in a stimulus-dependent manner in both groups; the changes in total minute activity (% control) in the athletes (113±8, 136±11, 174±12, and 209±20) and the untrained subjects (132±6, 163±8, 210±19, and 262±30) were not different. The magnitudes of increases in total minute muscle sympathetic nerve activity in response to isometric handgrip (161±15 versus 204±34% control) and the cold pressor test (300±29 versus 255±39% control) was not different in the two groups nor were the associated changes in arterial pressure and heart rate. The results indicate that the sympathetic neural and cardiovascular adjustments to these common laboratory stimuli are not significantly influenced by the individual's level of aerobic conditioning. In addition, the data confirm the previous finding that the state of physical training does not affect muscle sympathetic nerve activity at rest. Thus, this factor does not appear to be a primary contributor to the marked intersubject variability observed in sympathetic nerve discharge at rest and in response to acute physical stress in humans. (Hypertension 1991;17:36-43)
Exercise are attenuated in the aerobically trained state, and it has recently been reported that handgrip training blunt the MSNA response to this form of exercise. If these differences are due to non-specific sympathetic nervous system adaptations evoked by physical conditioning, the MSNA responses to other sympathoexcitatory stimuli could be altered and therefore contribute to the intersubject variation.

The primary purpose of the present study was to determine if sympathetic neural reactivity to standard laboratory stressors in humans is influenced by the state of physical training. A secondary aim was to confirm that sympathetic nervous system activity at rest is not affected by differences in chronic physical activity. To address these aims, we made microneurographic measurements of MSNA and recorded heart rate and arterial blood pressure in highly trained endurance athletes and untrained subjects during supine rest and in response to three different types of acute physical stress: graded lower body negative pressure (simulated orthostatic stress), isometric handgrip (exercise stress), and hand immersion in ice water (i.e., cold pressor test-thermal stress). The stressors were applied at levels and for durations commonly used in laboratory investigations of autonomic function in humans.

Methods

Subjects

Twenty-four healthy subjects aged 19–35 years participated in this study after their written, informed consent was obtained. Subjects were normotensive, were free of known cardiopulmonary disease, and were not taking medications that could influence the results of the study. Twelve subjects (11 men, one woman) were highly trained endurance athletes who had performed intensive, aerobic exercise on a daily basis (more than 1 hour) for at least 2 years. Thus, by their maximal O2 uptake obtained during treadmill running or cycle ergometry ranged from 60 to 75 ml·kg−1·min−1. The other 12 subjects (10 men, two women) had not performed aerobic exercise on a regular basis for at least 2 years. Thus, by examining groups as diverse as possible in aerobic conditioning we hoped to provide an optimal degree of resolution from which to observe training-induced differences in sympathetic nervous system behavior. All experimental procedures and protocols performed by these subjects had received prior approval from the Institutional Committee for Research on Human Subjects.

Experimental Measurements

*Muscle sympathetic nerve activity.* Multunit recordings of MSNA were obtained from the right peroneal nerve at the fibular head using microneurography as described in detail previously. The neural activity was amplified, filtered (band width=700–2,000 Hz), full-wave rectified, and integrated (time constant=100 msec). Only neurograms of efferent MSNA were accepted based on previously described criteria.

*Arterial blood pressure and heart rate.* Arterial blood pressure was obtained by conventional sphygmomanometry in the right arm (brachial artery). Heart rate was determined from an electrocardiographic tracing.

*Transathoracic impedance.* Transthoracic impedance was determined by impedance cardiography (Minnesota Impedance Cardiograph model 304B, Surcom Inc., Minneapolis, Minn.). The change in transthoracic impedance, produced by lower body negative pressure, was used as a noninvasive index of the shift in thoracic blood volume and therefore cardiac filling pressure. Ebert et al. reported a strong relation between increases in transthoracic impedance and decreases in central venous pressure during lower body negative pressure in humans.

*Breathing.* Qualitative measurements of the rate and depth of breathing were obtained from a pneumobelt positioned around the abdomen. These measurements were made to ensure that abnormal breathing maneuvers (e.g., Valsalva) that could influence MSNA were not performed by the subjects during the experimental protocols.

*Body fat content.* Body fat content was estimated from skinfold thickness measured at six sites. Body density and the percentage of the body that was fat were determined using the equations of Jackson and Pollock and Siri, respectively.

*Lower body negative pressure.* Subjects were sealed at the waist in a metal tank designed to apply suction to the lower body. The tank was modified to allow microneurographic measurements of right peroneal nerve activity. Suction was produced by a commercial vacuum cleaner with the exact level adjusted by altering input voltage via a rheostat. The level of negative pressure in the tank was measured with a pressure transducer.

*Isometric handgrip exercise.* Isometric handgrip exercise was performed with the left arm using a Stoelting Dynamometer (Stoelting Co., Chicago, Ill.). During exercise the target force and the dynamometer force were displayed on an oscilloscope to provide visual feedback to the subject.

*Cold pressor test.* A cold pressor test was performed by immersing the subject’s left hand to the wrist in ice water (1°C).

Experimental Protocol

Subjects were positioned supine in the lower body negative pressure tank in a quiet, semidarkened room (22°C). After instrumentation, the maximal handgrip
TABLE 1. Baseline (Control) Values Before the Three Interventions in the Untrained Subjects and the Endurance Athletes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group</th>
<th>Frequency (bursts/min)</th>
<th>Incidence (bursts/100 beats)</th>
<th>Heart rate (beats/min)</th>
<th>Arterial blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
</tr>
<tr>
<td>Isometric handgrip</td>
<td>UT</td>
<td>22±3</td>
<td>34±5</td>
<td>66±3</td>
<td>128±4</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>21±2</td>
<td>37±4</td>
<td>56±2*</td>
<td>126±2</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td>UT</td>
<td>22±3</td>
<td>35±5</td>
<td>65±2</td>
<td>126±4</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>21±3</td>
<td>37±4</td>
<td>56±2*</td>
<td>126±2</td>
</tr>
<tr>
<td>Lower body negative pressure</td>
<td>UT</td>
<td>24±2</td>
<td>36±3</td>
<td>67±3</td>
<td>126±4</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>24±3</td>
<td>44±4</td>
<td>54±2*</td>
<td>123±2</td>
</tr>
<tr>
<td>Range</td>
<td>UT</td>
<td>16–37</td>
<td>22–56</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>12–42</td>
<td>27–68</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Range is based on control measurements before lower body negative pressure was applied. UT, untrained subjects (n=12); ATH, endurance athletes (n=12).

*p≤0.05 vs. untrained subjects value.

Data Analysis

Bursts of MSNA were determined from the integrated neurogram by D.R.S.; the investigator was unaware of the identity of the subjects. MSNA was expressed as burst frequency (bursts/min), burst incidence (bursts/100 heart beats), and as total minute activity (calculated as the product of bursts/min and average burst amplitude/min and presented in arbitrary units). Because burst amplitude is influenced by factors such as the proximity of the recording electrode to the sympathetic neurons and the gain of the amplifier, total minute activity cannot be used for intersubject (or intergroup) comparisons of absolute MSNA. However, it can be used to quantitate changes in MSNA in response to some perturbation within a subject. Because average burst amplitude usually increases during sympathetic stimulation, examination of changes in total activity should provide a more precise means of determining alterations in overall minute MSNA during stress than burst frequency alone.

Values for all variables were averaged for each of the 3-minute control periods. For lower body negative pressure, the 2-minute period at each level was averaged and used to calculate individual changes from control because there was no difference in the values for minutes 1 and 2 at any level of suction. The last 30 seconds of the cold pressor test and isometric handgrip exercise were used to calculate changes from control since MSNA and arterial pressure increased throughout these interventions on average; however, using the last 60 seconds did not change the results.

To determine differences 1) within a subject group among the three control periods or from control to intervention, 2) at rest (control) between the two subject groups, and 3) in the changes from control to each intervention between the two subject groups, an analysis of variance for repeated measures was performed. Scheffe’s test was used for post hoc analysis of specific comparisons. Values of p<0.05 were considered to be statistically significant. All values are expressed as mean±SEM.

Results

Baseline Characteristics

Age and body weight were not different in the two groups (25±1 versus 27±1 years and 69.3±2.3 versus 67.0±3.0 kg, athletes versus untrained subjects), but the athletes had a lower body fat content (8.9±1.3% versus 16.1±2.0%, p<0.05). Group data during supine rest (control period) before each of the interventions are shown in Table 1; there were no differences within a group for any variable among the three control
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Figure 1. Bar graphs showing average increases in muscle sympathetic nerve activity from control (baseline) during graded lower body negative pressure in endurance athletes (ATH) and untrained (UT) subjects. Changes are expressed in terms of minute burst frequency (top panel), burst incidence (middle panel), and total minute activity (bottom panel). Increases in burst frequency and incidence were less in the athletes at the —10 mm Hg level, but the changes in total minute activity were not different in the two groups at any level of negative pressure. *Denotes significant change from control; p<0.05 denotes significant difference between groups.

Lower Body Negative Pressure

MSNA increased to a progressively greater extent with increasing levels of lower body negative pressure in both groups of subjects (Figure 1). The magnitude of changes in burst frequency and burst incidence tended to be less in the athletes at the two lowest levels of suction (p<0.05 at -10 mm Hg only) but were not different in the two groups during higher levels of suction. The increases in total MSNA were not different in the athletes and untrained subjects at any level of suction. The magnitudes of the changes in total minute activity (% control) were 113±8 (range 72–176), 136±11 (87–221), 174±12 (113–237), and 209±20 (100–331) for the athletes, and 132±6 (97–164), 163±8 (133–206), 210±19 (140–313), and 262±30 (134–457) in the untrained subjects.

Mean arterial blood pressure did not change from control levels during any level of suction in either group (Table 2). Heart rate did not change from control levels during any level of suction in either group (Table 2).

Transthoracic impedance was not different in the athletes (23.1±0.8 Ω) and the untrained subjects (25.4±1.1 Ω) during supine rest. Transthoracic impedance increased progressively with increasing levels of lower body negative pressure in both groups; the magnitudes of the changes during graded suction were not different in the athletes (0.22±0.03, 0.44±0.06, 0.66±0.07, and 0.93±0.10 Ω) and untrained subjects (0.33±0.04, 0.62±0.09, 0.90±0.12, and 1.14±0.16 Ω).

Isometric Handgrip Exercise

Maximal voluntary contraction force was not different in the athletes (39.9±1.7 kg) and the untrained subjects (37.0±2.9 kg). Isometric handgrip exercise evoked increases in the burst frequency, burst incidence, and total minute activity of MSNA in both groups (Figure 2); the magnitudes of the changes were not different in the two groups. For example, the increases in total minute activity were 161±15% of control (62–250) for the athletes and 204±34% of control (80–357) in the untrained subjects. Systolic, diastolic, and mean arterial blood pressure and heart rate increased above control levels in both groups during exercise (Figure 3); the magnitudes of the changes were not different in the athletes and the untrained subjects.
TABLE 2. Average Changes in Heart Rate and Arterial Blood Pressure From Control During Graded Lower Body Negative Pressure in Athletes and Untrained Subjects

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group</th>
<th>Lower body negative pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>UT</td>
<td>-2±1</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>0±1</td>
</tr>
<tr>
<td>Arterial blood pressure (mm Hg)</td>
<td>UT</td>
<td>-2±1</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>0±1</td>
</tr>
<tr>
<td>Systolic</td>
<td>UT</td>
<td>0±1</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>-1±1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>UT</td>
<td>-2±1</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>1±1†</td>
</tr>
<tr>
<td>Pulse</td>
<td>UT</td>
<td>0±1</td>
</tr>
<tr>
<td></td>
<td>ATH</td>
<td>0±1</td>
</tr>
</tbody>
</table>

Values are mean±SEM. UT, untrained subjects (n = 12); ATH, endurance athletes (n = 12).

Cold Pressor Test

Hand immersion in ice water produced increases in the burst frequency, burst incidence, and total minute activity of MSNA in both groups (Figure 2). The magnitudes of the cold-induced changes in MSNA were not different in the athletes and untrained subjects. The increases in total minute activity were 300±29% of control (118–519) for the athletes and 255±39% of control (138–480) for the untrained subjects. Systolic, diastolic, and mean arterial blood pressure and heart rate increased above control levels in response to hand immersion in both groups (Figure 3); the magnitudes of the changes were not different in the athletes and the untrained subjects.

Discussion

The primary new conclusion of this study is that, in general, the direction and magnitude of the sympathetic neural responses to nonactive skeletal muscle in response to lower body suction, isometric exercise, and the cold pressor test are not different in aerobically trained and untrained subjects. The increases in total minute activity were 300±29% of control (118–519) for the athletes and 255±39% of control (138–480) for the untrained subjects. Systolic, diastolic, and mean arterial blood pressure and heart rate increased above control levels in response to hand immersion in both groups (Figure 3); the magnitudes of the changes were not different in the athletes and the untrained subjects.

Sympathetic activation during acute stress. In the present study, the magnitudes of increases in total minute MSNA in response to graded, mild levels of lower body negative pressure were not different in the endurance athletes and the untrained subjects. However, there was a strong tendency for lesser increases in the burst frequency and burst incidence of MSNA during the two lowest levels of suction in the athletes (significant only at the −10 mm Hg level). Although arterial pulse pressure decreased in the untrained subjects at −15 and −20 mm Hg, mean arterial pressure and heart rate did not change from control levels during any stage of suction in either group. This suggests that arterial baroreceptor reflexes probably did not participate in these sympathetic neural adjustments to any significant degree. Instead, our data are consistent with the idea that during mild, simulated orthostasis, withdrawal of cardiopulmonary baroreceptor reflex central sympathoinhibitory tone evokes stimulus-specific increases in MSNA in both aerobically conditioned and untrained, healthy humans. Suction-induced changes in transthoracic impedance were not different in the two groups, suggesting that the changes in thoracic blood volume (and presumably cardiac filling pressure) were not different.

Previous efforts to determine the influence of physical training or fitness on the reflex circulatory adjustments to orthostatic stress have examined the increases in forearm vascular resistance to lower body negative pressure. The findings have been remarkably inconsistent, with augmented, unchanged, and even attenuated vasconstrictor responses reported in aerobically trained versus untrained subjects. Our neurophysiological data would suggest that any pronounced, training-induced changes in the vasoconstrictor responses to orthostasis are not mediated by corresponding changes in
sympathetic nerve discharge but instead by neurotransmitter release or its vascular effects.

We also found that the increases in MSNA in response to isometric exercise and the cold pressor test were not different in the athletes and untrained subjects. These observations are consistent with previous findings of similar increases in antecubital venous norepinephrine concentrations during these stressors in aerobically trained and unconditioned subjects.22-23 In the present study, the increases in arterial blood pressure and heart rate in response to handgrip and local cold also were not different in the two groups; similar results have been reported previously.22-25 Because the tachycardia evoked by isometric exercise of this duration is due primarily to vagal withdrawal,26 whereas the increases in heart rate associated with the cold pressor test are sympathetically mediated,5 these findings indicate that training may not influence the stress-induced adjustments in either of these efferent cardiac autonomic pathways.

FIGURE 2. Bar graphs showing average increases in muscle sympathetic nerve activity (MSNA) from control during isometric handgrip exercise (left) and the cold pressor test (right) in the athletes (ATH) and untrained (UT) subjects. Sympathetic activity increased in response to both forms of stress, but the magnitudes of the changes were in general not different in the two groups. *Denotes significant change from control; p<0.05 denotes significant difference between groups.

Both stress-specific and nonspecific factors probably contribute to the intersubject variability observed in the MSNA responses to these stimuli. Nonspecific factors may include age,27 gender,28 body fat content,29 family history,30 and autonomic-cardiovascular disease.31 Stress-specific influences could include factors such as the rate of fatigue or endurance time (isometric exercise), pain sensitivity (cold pressor test), and venous compliance (lower body negative pressure). The direction and magnitude of the sympathetic neural adjustments would likely depend on the interactions among some or all of these factors.

It is also important to emphasize that, in the present study, we examined the activation of sympathetic nerves to the skeletal muscle vasculature during three specific types of acute, physical stress. Thus, we cannot discount the possibility that aerobic training influences the MSNA responses to other physical stressors (e.g., hypoxia or heat) or to mental stress. It is also possible that this form of training could influence the stress-evoked adjustments in sympathetic nerves innervating other tissues such as skin or the viscera. Finally, it is possible that other types of physical conditioning (e.g., strength training), which evoke cardiovascular adaptations different from
those elicited by chronic endurance exercise, could influence sympathetic responsiveness to acute stress.

**Sympathetic activity at rest.** We found that the burst frequency and burst incidence of MSNA during quiet, supine rest was not different in the athletes and untrained subjects. These observations confirm the previous findings of Svedenhag et al, who reported that MSNA burst frequency and burst incidence was not different in groups of endurance-trained athletes and untrained subjects or before compared with after training in previously untrained subjects. They concluded that differences in physical conditioning did not contribute significantly to the marked intersubject variability in MSNA at rest. These neurophysiological data are also consistent with the results of investigations using antecubital venous norepinephrine concentrations to examine the effects of aerobic training on sympathetic nervous system activity at rest in healthy, normotensive subjects. However, because peripheral venous norepinephrine concentrations are thought to be determined primarily by norepinephrine release from skeletal muscle, and indeed, correlate well with levels of MSNA, it is possible that under resting conditions, sympathetic discharge in tissues other than skeletal muscle could be influenced by physical training. Recent findings of organ-specific changes in norepinephrine spillover at rest after aerobic training support this concept.

In the present study, heart rate was lower in the athletes at rest, but the levels of arterial blood pressure were similar in the two groups. This bradycardia at rest is a common characteristic of the aerobically trained state. The similar levels of arterial blood pressure observed agree with the findings of previous studies comparing endurance athletes with nonobese, normotensive controls. Clinical significance. Chronic elevations in sympathetic nervous system activity at rest and exaggerated sympathetic responsiveness to acute stress are thought to be linked to the etiology of certain types of cardiovascular disease. In contrast, there is a well-established inverse relation between physical activity levels and cardiovascular disease. The observation that plasma norepinephrine concentrations are lower in aerobically conditioned compared with untrained subjects during the same submaximal level of large muscle, dynamic exercise, has led to the hypothesis that chronic physical activity may exert its "protective" effect via the sympathetic nervous system. The assumption is that physical training evokes adaptations within the autonomic nervous system, which result in reduced sympathetic outflow at rest and in a nonspecific blunting of sympathetic responsiveness during stress. The present results and those of others fail to provide experimental support for this postulate, at least in healthy, young humans. Instead, these findings indicate that regular aerobic exercise does not attenuate the sympathetic neural activation attendant to acute physical or mental stress and that the observations of lower plasma norepinephrine levels during exercise in aerobically trained subjects are likely due to the fact that the same work load represents a lesser physiological perturbation (stimulus) compared with untrained subjects. This idea is further supported by findings of similar increases in plasma norepinephrine during the same relative exercise level (i.e., % of maximum) in the physically trained and untrained states. However, regularly performed exercise may modulate sympathetic nervous system behavior at rest or in response to acute stress in certain pathophysiologic states associated with chronic elevations in central sympathetic outflow, as recent findings suggest.

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**References**

Composition. Washington, DC, National Academy of Science, 1961, pp 223–244


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