Dissociation of Sympathetic Nerve Activity in Arm and Leg Muscle During Mental Stress

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SUMMARY Mental stress, which increases blood pressure and heart rate, increases forearm blood flow but does not change calf blood flow. The purpose of this study was to determine if mental stress 1) increases muscle sympathetic nerve activity in the leg and 2) causes a dissociation of muscle sympathetic nerve activity in the arm and the leg. We recorded heart rate, blood pressure, and efferent sympathetic nerve activity during mental stress (4 minutes of mental arithmetic) in 13 healthy men. Microelectrodes were inserted percutaneously into a fascicle of the peroneal nerve (leg) and radial nerve (arm) to measure sympathetic discharge to muscle. In Study 1, leg muscle sympathetic nerve activity was recorded in seven subjects. Mental stress significantly increased heart rate and blood pressure. Despite the increased blood pressure (which would be expected reflexly to inhibit sympathetic nerve activity), leg muscle sympathetic nerve activity (in total integrated activity, bursts per 100 heart beats or bursts per minute) increased significantly during stress. Further, whereas heart rate and blood pressure returned to normal during recovery, leg muscle sympathetic nerve activity remained elevated during recovery. In Study 2, simultaneous recordings were made of arm and leg muscle sympathetic nerve activity in six subjects. Mental stress increased heart rate and arterial pressure. Leg muscle sympathetic nerve activity again increased significantly during stress and remained elevated during recovery. In contrast, arm muscle sympathetic nerve activity did not change during stress. However, arm muscle sympathetic nerve activity increased significantly during recovery after stress. These studies indicate that 1) a sympathoexcitatory influence of mental stress over-rides or inhibits baroreceptor control of leg sympathetic nerve activity and 2) stress causes a dissociation of arm and leg muscle sympathetic nerve activity with increased outflow to the leg but not to the arm. These observations may contribute to differences in blood flow to arm and leg during mental stress. (Hypertension 9 [Suppl III]: III-114-III-119, 1987)

KEY WORDS • sympathetic nervous system • humans • microneurography

MENTAL stress elicits a complex pattern of cardiovascular changes that include tachycardia, increased blood pressure, and increased blood flow to skeletal muscle. In addition, there may be regional differences in stress-induced vasomotor reactions in skeletal muscle. Rusch et al. reported that mental arithmetic and an echo (delayed auditory feedback) stress test increased forearm blood flow but did not change calf blood flow.

Blood flow to skeletal muscle is controlled, in part, by changes in sympathetic vasoconstrictor outflow to resistance vessels. It is, therefore, possible that altered sympathetic outflow to the arm and leg during stress could be involved in the differing blood flow responses in the arm and leg.

There are several brief reports of effects of mental stress on muscle sympathetic nerve activity (MSNA), but the effects have not been studied systematically. Delius et al. reported a reduction in MSNA in the arm during brief (less than 1 minute) periods of mental stress in four normotensive subjects. Wallin et al. reported that mental stress increased MSNA in two hypertensive subjects, decreased activity in three subjects, and had no effect on sympathetic activity in four subjects. However, blood pressure in-
creased markedly during only four of 13 stress periods in the hypertensive subjects. This suggests that the stimulus was not very stressful in this study, since increases in blood pressure characterize the response to mental stress. Wallin\textsuperscript{2} concluded that mental stress has variable effects on MSNA. Some of this variability may result from the fact that sympathetic activity has been measured in both the arm and the leg.\textsuperscript{3,4} The observations on arm and leg blood flow\textsuperscript{5} suggest that mental stress may differentially affect sympathetic outflow to arm and leg.

The current study was designed to assess systematically the effects of mental stress on MSNA with two specific goals. The first was to determine whether mental stress changes MSNA in the leg. The second was to determine whether mental stress differentially alters sympathetic outflow to the arm and leg. This was accomplished by simultaneously recording sympathetic activity in the arm and the leg during stress.

**Methods**

We recorded heart rate, blood pressure, and efferent MSNA in the leg (Study 1) and the leg and arm (Study 2) during mental stress in supine human volunteers. A total of 37 men, aged 21 to 36 years, were studied. All were normotensive when studied, although one subject in Study 2 was later classified as borderline hypertensive. In Study 1, four of 11 subjects were excluded because we were unable to obtain satisfactory recordings of MSNA from a peroneal nerve. In Study 2, satisfactory simultaneous recordings of MSNA from arm and leg were achieved in only six of 26 subjects. This low percentage of technically satisfactory simultaneous recordings from arm and leg is expected since it is technologically more difficult to obtain satisfactory recordings of MSNA from a nerve in the arm than from one in the leg, and obtaining simultaneous arm and leg recordings of MSNA is considerably more difficult than obtaining single nerve recordings. The studies were approved by the institutional committee on human investigation, and each subject gave informed consent to participate.

Heart rate was recorded by an electrocardiograph, respiration by a pneumograph, blood pressure by an automatic sphygmomanometer (Life Stat 200, Physio Control Corp., Redmond, WA, USA), and sympathetic nerve activity by microneurography.

**Microneurography**

Multifiber recordings of sympathetic nerve activity were obtained from a muscle fascicle in the right peroneal nerve posterior to the fibular head (Studies 1 and 2) and in the radial nerve as it courses around the lateral aspect of the humerus in the arm (Study 2). The recordings were made with tungsten microelectrodes 200 \( \mu m \) in diameter in the shaft, tapering to an uninsulated tip of 1 to 5 \( \mu m \). A reference electrode was inserted subcutaneously 1 to 3 cm from the recording electrode. The electrodes were connected to a preamplifier with a gain of 1000 and an amplifier with a variable gain of 50 to 90. The neural activity was then fed through a band-pass filter with a bandwidth of 700 to 2000 Hz. For monitoring during the experiment, the filtered neurogram was routed through an amplitude discriminator to a storage oscilloscope and a loudspeaker. For recording and analysis, the filtered neurogram was fed through a resistance-capacitance integrating network (time constant 0.1 second) to obtain a mean voltage display of the neural activity.

There were three criteria for an acceptable recording of MSNA. The first was that weak electrical stimulation (1–3 V, 0.2 msec, 1 Hz) through the electrode in the peroneal or radial nerve elicited involuntary muscle contraction but not paresthesia. The second criterion was that tapping or stretching the muscles or tendons supplied by the impaled fascicle elicited afferent mechanoreceptor discharges, but that stroking the skin did not elicit discharges. The third criterion was that the neurogram revealed spontaneous, intermittent, pulse-synchronous bursts that increased during held expiration and phases two and three of Valsalva’s maneuver — bursts characteristic of MSNA.\textsuperscript{6,7} Evidence that such activity represented efferent sympathetic nerve activity was derived from earlier studies and included 1) interruption of the activity by local nerve block proximal, but not distal, to the recording site; 2) elimination of the activity by ganglionic blockade; and 3) conduction velocity approximating 1 m/sec.\textsuperscript{6,7} Neurograms that revealed spontaneous activity characteristic of cutaneous sympathetic activity were not accepted. This was assessed from the response to arousal stimuli that elicited single reflex bursts of cutaneous but not muscle sympathetic activity.

In over 450 microneurographic studies at the University of Iowa, we have found a low (i.e., 7\%) frequency of symptoms after microneurography. All symptoms were transient and mild. In the present study, the frequency of symptoms after microneurography was 11\% and consisted of transient and mild paresthesias.

**Mental Stress**

Mental stress was elicited by 4 minutes of a mental arithmetic task.\textsuperscript{8} The stress task was performed over 30 minutes after a satisfactory recording site was obtained and was preceded and followed by 2-minute control and recovery periods. The arithmetic task involved having subjects serially subtract a two-digit from a four-digit number orally (e.g., 17 from 1497). Throughout the task, subjects were pressured to speed their performance. All subjects remained actively engaged in the task. This was accomplished by altering the task difficulty as needed to match a subject’s ability and by frequently presenting new arithmetic problems. All subjects reported the task as aversive and showed other evidence of stress, such as flushing, stammering, and obvious relief at the end of the task.

**Analyses**

The mean voltage neurogram, electrocardiogram, and respiratory movements were displayed on a physiological recorder (Model 2800S, Gould, Cleveland, Ohio).
OH, USA) and recorded at a paper speed of 5 mm/sec. Sympathetic bursts were identified by inspection of the mean voltage neurogram and expressed as bursts per minute and bursts per 100 heart beats. Neurograms were scored by one observer (E. A. A.). Peroneal and radial neurograms in Study 2 were analyzed simultaneously. The amplitude of each burst was also measured by inspection. Integrated MSNA was calculated as bursts per minute times mean burst amplitude and expressed in arbitrary units. Values for sympathetic activity reflect the entire activity for each minute.

Blood pressure was recorded during the last half of each minute. Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure. For technical reasons it was not possible to measure blood pressure during simultaneous arm and leg recording. Therefore, blood pressure was recorded for subjects in Study 2 during a separate session within 2 weeks of the nerve recording session.

Statistical analyses for Study 1 were performed using a repeated-measures analysis of variance with two planned contrasts (control vs stress and control vs recovery periods). Study 2 was analyzed by a mixed model, repeated-measures analysis of variance (effects: subjects, time, limb, limb by time, and subjects by time). An alpha level of 0.05 was used for judging statistical significance. Only analyses with a $p$ of 0.05 or less are referred to as significant. Post hoc comparisons were made by the Bonferroni method. Results are expressed as means ± SE.

**Results**

**Study 1**

In Study 1, MSNA was recorded from the peroneal nerve in seven subjects (Figures 1 and 2). Heart rate, systolic blood pressure, and diastolic blood pressure increased significantly during mental stress and returned to control levels during the 2-minute recovery period (see Figure 2). Mental stress significantly increased MSNA in the leg, whether expressed as integrated MSNA, bursts per 100 heart beats (see Figure 2) or bursts per minute. MSNA expressed as bursts per minute increased from 16.3 ± 3.8 during control to 24.4 ± 6.0 during the last minute of stress. There was some variability among subjects. In five subjects, integrated MSNA increased from 45 to 367%, in one subject.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Neurogram of leg muscle sympathetic nerve activity (MSNA; peroneal nerve) in one subject during control, stress, and recovery periods. Leg MSNA increased markedly during stress and remained elevated during recovery. Heart rate (HR) and blood pressure (BP) also increased during mental stress but returned promptly to control levels during recovery.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Muscle sympathetic nerve activity (MSNA) measured in the leg (peroneal nerve), heart rate, and blood pressure responses to mental stress. As shown on the left, MSNA increased during stress and remained elevated during recovery. As shown on the right, heart rate and blood pressure increased significantly during stress and returned promptly to control levels during recovery. SBP, MBP, and DBP = systolic, mean, and diastolic blood pressures, respectively.
ject MSNA did not change, and in one subject MSNA decreased by 49% during the last minute of stress. Heart rate and blood pressure returned to control levels during recovery (see Figure 2). In contrast, leg MSNA remained significantly elevated above control levels during the recovery period (see Figure 2).

Study 2

In Study 2, simultaneous recordings of MSNA in both the arm (radial nerve) and the leg (peroneal nerve) were made in six subjects during mental stress (Figures 3 and 4). As in Study 1, mental stress significantly increased heart rate, systolic blood pressure, and diastolic blood pressure. Furthermore, as in Study 1, heart rate and blood pressure returned to control levels during recovery (see Figure 2).

In the control state, arm and leg MSNA did not differ significantly (see Figure 4). However, there was a dissociation of arm and leg MSNA during stress. Arm MSNA did not change during stress, while leg MSNA increased to above control levels (see Figure 4). A significant limb (arm/leg)-by-time interaction indicates that the changes in MSNA in the arm and leg differed over time. As shown in Figure 4, post hoc comparisons indicated that leg MSNA was significantly greater than arm MSNA during each minute of stress. This was true for MSNA expressed as integrated activity, bursts per 100 heart beats (see Figure 4) or as bursts per minute. As in Study 1, there was some variability among individuals as indicated by a significant subjects-by-time interaction. For example, in two subjects, MSNA increased in the arm during stress. However, even in these subjects the increases in leg MSNA were greater than the increases in arm MSNA. Leg MSNA declined but remained significantly above control levels during recovery whereas, interestingly, arm MSNA increased to significantly above control levels after the stress period (see Figure 4). Arm and leg MSNA did not differ significantly during the recovery period.

Discussion

The distinctive feature of this study was the simultaneous direct recording of muscle sympathetic activity in arm and leg during stress. There were three principal findings. First, mental stress caused an increase in
muscle sympathetic outflow to the leg. This increase continued into the recovery period. Second, mental stress caused a dissociation of muscle sympathetic activity in the arm and the leg: arm sympathetic activity remained unchanged while leg sympathetic activity increased. Third, arm sympathetic activity increased significantly after stress.

Potential Limitations of the Study
While our recording techniques could have provided a less sensitive measure of arm MSNA than of leg MSNA, we think this is unlikely. First, detection of sympathetic bursts depends on the signal-to-noise ratio of a recording. In all studies, we were able to obtain comparable signal-to-noise ratios in arm and leg recordings both in the resting state and during a reflex increase in MSNA produced by a brief period of apnea. Second, there was a remarkable parallelism in arm and leg MSNA during control and recovery periods.

Spoken performance of arithmetic problems is associated with a change in respiratory pattern. However, we doubt that altered respiration could account for the results. First, brief periods of apnea produce comparable increases in arm and leg MSNA. Second, we have not observed that casual conversation changes MSNA or causes the dissociation of arm and leg MSNA found with mental stress. However, we cannot exclude the possibility that intermittent, deep inspirations associated with rapid speech may alter MSNA.

Some subjects inadvertently tense muscles during mental arithmetic. We considered the possibility that mental stress produced greater muscle tension in the arm than in the leg, thereby obscuring increases in MSNA in the arm during mental stress. We believe this unlikely since muscle contraction causes artifacts that are easily recognized and distinguished from MSNA. Such major artifacts were not a frequent problem, and records in which they occurred were eliminated from analysis. It is more difficult to exclude slight, unnoticed electrode movement during mental stress. Minor changes of electrode position may change burst amplitude significantly but usually do not impair detection of a burst. Therefore, burst frequency is less sensitive to such artifacts. Since the number of bursts per minute increased significantly during mental stress, it is unlikely that the increase in MSNA was due to minor changes in electrode position. This is also supported by the finding that the number of bursts in the arm increased after stress, when there is less risk of electrode movement.

Physiological Mechanisms and Significance
Muscle sympathetic activity is normally inhibited by baroreceptor stimulation produced by an increase in blood pressure. The observation that leg MSNA and heart rate increased despite the elevation in blood pressure suggests that during mental stress there is a sympathoexcitatory influence that either inhibits or overrides baroreceptor control of leg MSNA and heart rate. The finding that arm MSNA remained unchanged while leg MSNA increased during stress suggests that differences in sympathetic outflow to the arm and the leg may be one mechanism involved in the differing vascular responses in the arm and leg observed by Rusch et al. Other mechanisms underlying the vascular responses could include differences in arm and calf sensitivity to circulating catecholamines or differences in active vasodilator systems in the arm and leg.

It is not clear what physiological role would be served by the contrasting MSNA (and blood flow) responses in the arm and leg during mental stress. Whatever the physiological role, this finding is, to our knowledge, the first reported demonstration of dissociation of MSNA in different nerves and different extremities. Previous studies comparing MSNA in two nerves and in arm and leg at rest have shown a remarkable parallelism; the finding of similar levels of resting MSNA in arm and leg was confirmed in the present study. In addition, there is evidence that simulated orthostatic stress (lower body negative pressure) increases MSNA in both the leg and the arm. In contrast, our observations reveal a dissociation of MSNA in the arm and leg during mental stress. Post hoc analysis indicated that the increases in leg MSNA were greater in the later minutes of stress. This may explain the varying results of others who have measured sympathetic activity during shorter periods of stress. Interestingly, heart rate and blood pressure increased during the first minutes of stress, which contrasted with the more gradual increase in muscle sympathetic activity. This suggests both a regional specificity and altered time course for sympathetic activation in different cardiovascular regions.

The mechanism of the dissociation of arm and leg MSNA during mental stress is not clear, but presumably involves central neural mechanisms. Moreover, it is not clear why arm and leg MSNA were similarly elevated during the first minute of recovery, whereas during mental stress the increases in MSNA were greater in the leg.

In conclusion, the present study demonstrates that mental stress causes a dissociation of sympathetic outflow to the arm and leg, with leg MSNA increasing and arm MSNA remaining unchanged. Arm MSNA increases after stress and leg MSNA remains elevated. This dissociation of arm and leg MSNA may be involved in the differing arm and leg blood flow responses to mental stress. Although the current study involved a relatively small number of subjects, the results suggest a unique impact of mental stress on MSNA.

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