Augmentation of exercise-induced muscle sympathetic nerve activity during muscle heating

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Ray, Chester A., and Kathryn H. Gracey. Augmentation of exercise-induced muscle sympathetic nerve activity during muscle heating. J. Appl. Physiol. 82(6): 1719–1725, 1997.—The muscle metabo- and mechanoreflexes have been shown to increase muscle sympathetic nerve activity (MSNA) during exercise. Group III and IV muscle afferents, which are believed to mediate this response, have been shown to be thermosensitive in animals. The purpose of the present study was to evaluate the effect of muscle temperature on MSNA responses during exercise. Eleven subjects performed ischemic isometric handgrip at 30% of maximal voluntary contraction to fatigue, followed by 2 min of postexercise muscle ischemia (PEMI), with and without local heating of the forearm. Local heating of the forearm increased forearm muscle temperature from $34.4 \pm 0.2$ to $38.9 \pm 0.3 ^\circ C$ ($P = 0.001$). Diastolic and mean arterial pressures were augmented during exercise in the heat. MSNA responses were greater during ischemic handgrip with local heating compared with control (no heating) after the first 30 s. MSNA responses at fatigue were greater during local heating. MSNA increased by $16 \pm 2$ and $20 \pm 2$ bursts per 30 s for control and heating, respectively ($P = 0.03$). When expressed as a percent change in total activity (total burst amplitude), MSNA increased $531 \pm 159$ and $941 \pm 237\%$ for control and heating, respectively ($P = 0.001$). However, MSNA was not different during PEMI between trials. This finding suggests that the augmentation of MSNA during exercise with heat was due to the stimulation of mechanically sensitive muscle afferents. These results suggest that heat sensitizes skeletal muscle afferents during muscle contraction in humans and may play a role in the regulation of MSNA during exercise.

exercise pressor reflex; isometric contraction; muscle ischemia; muscle temperature; group III and IV afferents

Since the studies of Alam and Smirk (1, 2), reflexes originating from the exercising muscle have been recognized to play an important role in cardiovascular regulation during exercise in humans. Both chemical and mechanical stimuli of muscle afferents (groups III and IV) have been shown to elicit cardiovascular responses (8, 9, 15, 17). Mark et al. (12) were the first to demonstrate that the muscle metaboreflex was the primary stimulus for augmenting muscle sympathetic nerve activity (MSNA) during isometric handgrip in humans. The importance of the muscle metaboreflex in activating MSNA has also been demonstrated during other forms of exercise (18, 30). Recently, McClain et al. (13, 14) have demonstrated, by using muscle compression and venous congestion, a possible role for the muscle mechanoreflexes in augmenting MSNA during ischemic forearm exercise.

It has been reported that both group III and IV muscle afferents increase their firing rate when exposed to elevated temperatures (6, 11). Hertel et al. (6) reported that $\sim 67\%$ of group III and $\sim 50\%$ of group IV muscle afferents increased their discharge rate when the muscle temperature was increased in the cat. Kumazawa and Mizumura (11) reported that in the dog all group III and two-thirds of group IV muscle afferents increased their discharge rate when muscle temperature was increased. In both of these studies, increased muscle afferent discharge occurred at physiological temperatures.

Dynamic exercise can produce marked increases in muscle temperature (23). This increase in muscle temperature is related to the metabolic activity of the muscle. Because muscle afferents are sensitive to heat and muscle contractions increase muscle temperature, we sought to determine whether changes in muscle temperature during exercise can contribute to increases in MSNA in humans. We hypothesized that raising muscle temperature would augment exercise-induced increases in MSNA by increasing the discharge rate of the group III and group IV muscle afferents. To test this hypothesis, MSNA was recorded during ischemic isometric handgrip before and after local forearm heating that elevated muscle temperature. The results demonstrate greater MSNA during isometric exercise when muscle temperature is elevated.

METHODS

Seventeen healthy subjects (13 men and 4 women) were recruited to participate in the study. All subjects were between the ages of 20 and 27 yr. Each subject signed an informed consent after a complete explanation of the testing procedures. The study was approved by the Institutional Review Board.

Experimental protocol. Before the experimental session, each participant performed three maximal isometric handgrips on 3 separate days to habituate to the exercise and to determine their maximal voluntary contraction. All subjects used the dominant arm in testing. Baseline data were collected for 2 min for MSNA, heart rate, arterial blood pressure, and skin temperature. A pneumatic cuff was then inflated to suprasystolic levels (220 mmHg) to induce forearm muscle ischemia. After 1 min of muscle ischemia, the subject performed ischemic isometric handgrip at 30% of maximum voluntary contraction until fatigue. Fatigue was defined as when the subject could not maintain a predefined force during isometric handgrip. Postexercise muscle ischemia (PEMI) was then continued for 2 min after the termination of exercise. A 2-min recovery period followed PEMI.

During one trial, the exercising forearm was heated for 30 min before and during the experimental session with the application of two heat packs containing silicate gel in a cotton pad. These packs were immersed in water at a temperature of $\sim 75^\circ C$. Each pack was wrapped in a terry-cloth cover to protect the skin from direct contact. Heat was not applied during the second trial. Six subjects performed
the heated trial first, and five subjects performed the control trial first. The two trials were separated by 40 min of rest. This time period has been shown to provide ample recovery for the measured variables (19).

The experimental protocol was repeated in six subjects for determination of muscle temperature. The muscle temperature probe (model 552, Yellow Springs Instruments, Yellow Springs, OH) was inserted into the flexor muscles of the exercising forearm, and temperature was recorded every 30 s. Tympanic temperature was recorded in four subjects as an indicator of body core temperature (Genius model 3000A, Sherwood Medical, St. Louis, MO).

Measurements. Multifiber recordings of MSNA were made with a tungsten microelectrode inserted in the peroneal nerve. A reference electrode was placed subcutaneously ~2 cm from the recording electrode. Adjustments were made in the placement until a satisfactory site was located. The criteria for acceptable recordings of MSNA were 1) weak electrical stimulation through the electrode elicited involuntary contraction of the appropriate muscles but no paresthesia; 2) tapping of muscles or tendons innervated by the nerve evoked afferent mechanoreceptor discharges, but afferent activity was not elicited by stroking the skin; 3) held expiration increased spontaneous pulse-synchronous bursts of sympathetic impulses; and 4) a sudden arousal stimulus (a loud yell or clap) did not elicit an increase in sympathetic nerve activity.

The nerve signal was amplified (×20,000–40,000), fed through a band-pass filter with a bandwidth of 700–2,000 Hz, and passed through a resistance-capacitance integrating network with a time constant of 0.1 s to obtain a mean voltage display of the nerve activity. The mean voltage was then displayed on a chart recorder (Gould ES2000) with a paper speed of 5 mm/s. The nerve signal was also routed through a loudspeaker as well as to an on-line computer for monitoring purposes throughout the study.

Sympathetic bursts were identified by inspection of the mean voltage neurogram. MSNA was expressed as burst frequency (bursts/30 s) and total activity. Total activity was calculated as the sum of the amplitudes of the bursts.

Skin thermistors were used to measure skin surface temperature. Two thermistors were placed between the skin and the moist heat pack (one proximal and one distal) on the heated forearm. A third thermistor was placed on the nonheated forearm to serve as a control. Each skin thermistor was insulated with a small piece of foam.

A Finapres blood pressure monitoring unit was used to measure heart rate and arterial blood pressure. The photoplethysmographic cuff was placed on a finger of the nonexercising arm. Borg’s numerical scale from 6 to 20 was used to monitor the participant’s perception of exertion at fatigue (3).

Data analysis. MSNA, heart rate, arterial pressure, and skin and muscle temperatures were determined for each 30 s
of the experimental protocol. Data were analyzed by using a two-within factor repeated analysis of variance [time and condition (heat, no heat)]. Tests for simple effects were done when the interaction term (time × condition) was found to be significant. Statistical significance was accepted at P < 0.05. All values are expressed as means ± SE.

RESULTS

Time to fatigue was unaffected by local heating (P = 0.16). Fatigue time was 158 ± 9 and 144 ± 11 s for control and heat, respectively. Preexercise values for all variables during the control and heat trials are presented in Table 1. There were no significant differences between preexercise values obtained before and after forearm muscle ischemia.

Heart rate and arterial pressure responses to the experimental protocols are shown in Figs. 1 and 2. Heart rate increased during exercise, but the responses were not significantly affected by local heating (time × condition interaction; P = 0.07). However, there was a main effect (condition) on heart rate (P = 0.008). During PEMI, heart rate returned to baseline for both conditions (control and heat; Fig. 2).

Arterial pressure increased with exercise (Fig. 1). Heating had no effect on systolic arterial pressure responses to exercise (time × condition interaction; P = 0.2), but significant interactions were observed for diastolic and mean pressures (P = 0.001 and P = 0.004, respectively). However, no diastolic or mean pressure differences were observed at fatigue (Fig. 2). Arterial pressure remained significantly elevated during PEMI, but there was no difference between conditions (Fig. 2).

MSNA responses are shown in Fig. 3. MSNA, expressed as burst frequency and total MSNA, increased during exercise. MSNA responses were augmented during heating (time × condition interaction; P = 0.0001 for both expressions of MSNA). Total MSNA at fatigue increased by 531 ± 159% for the control trial and by 941 ± 237% for the heated trial (Fig. 3). There was no difference in MSNA during PEMI (Fig. 3). Original recordings of MSNA during the two trials are shown in Fig. 4.

Skin temperature was augmented by local heating during the first set of experiments (31.3 ± 0.6 to 40.7 ± 0.4°C). These responses were replicated in the second set of experiments (Fig. 5) when forearm muscle temperature was measured. Resting muscle temperature was increased by heating from 34.4 ± 0.2 to 38.9 ± 0.3°C. Muscle temperature during exercise slightly increased during the heating trial but not during the control trial. Tympanic temperature was unchanged by local forearm heating. Baseline tympanic temperature was 37.4 ± 0.2 and 37.3 ± 0.2°C for the control and heat trials, respectively. Tympanic temperature was unchanged by exercise (37.3 ± 0.2 and 37.4 ± 0.2°C for the control and heat trials, respectively).

Ratings of perceived exertion at fatigue were not altered by heating. Perceived exertion was 18 ± 1 units for both conditions.
DISCUSSION

The purpose of the present study was to evaluate the effect of muscle temperature on MSNA responses to isometric exercise. The main findings of this study were 1) local forearm heating, which was shown to elevate muscle temperature, had no effect on resting MSNA; 2) elevated muscle temperature augmented exercise-induced increases in MSNA; and 3) elevated muscle temperature did not affect MSNA responses during PEMI. The discussion focuses on these findings and examines the possible mechanisms by which increased muscle temperature augments MSNA responses to isometric exercise.

Heat and MSNA responses. Few data exist regarding the relationship of muscle temperature and resting MSNA in humans. Kregel et al. (10) found a dissociation between MSNA and hand muscle temperature during and after a cold pressor test. The present study demonstrates that a 4.5°C increase in forearm muscle temperature fails to increase resting MSNA. It should be recognized that our findings and those of Kregel et al. are the result of changing muscle temperature to only a small muscle mass (i.e., forearm or hand). Therefore, changes in MSNA by altering muscle temperature in a larger muscle mass remain a possibility.

After the first 30 s of exercise, MSNA was augmented by local heating. This result clearly indicates that heating the exercising muscle can augment exercise-induced increases in MSNA. Thus, when the muscle temperature rises during exercise, the observed increase in MSNA is determined in part by heat sensitization of muscle afferents.

What was the mechanism for the augmentation of MSNA during exercise with heating? First, central command did not appear to contribute to the observed increase in MSNA during exercise. Central command has been shown to increase MSNA only during intense bouts of exercise (29, 31). In our study, heating caused increases in MSNA during the first minute of exercise before fatigue or intense volitional effort had occurred. Also, ratings of perceived effort, an index of central command, were similar at fatigue in the two trials when differences in MSNA were present. Second, baroreflexes would not be expected to cause the increase in MSNA. During the heating trial, arterial pressure was greater than during the control trial. The higher arterial pressure would be expected to engage the arterial baroreflex and attenuate MSNA responses during exercise (24). However, MSNA was greater during exercise with heating, despite a greater arterial pressure response. Similarly, the cardiopulmonary baroreflexes would not be expected to be changed by heating of only the forearm. If heating did have an effect on the cardiopulmonary baroreflexes, MSNA should have been greater at rest. This did not occur.
The data indicate that heating altered afferent activity from the exercising muscle. We speculate that the effect of muscle heating during exercise was related to increased activity of mechanosensitive muscle afferents but not metabosensitive muscle afferents. We base this conclusion on the result that MSNA responses were similar during PEMI. This finding suggests two points. First, the activation of the muscle metaboreflex during exercise was similar during both trials. Therefore, stimulation of chemically sensitive muscle afferents would be expected to be the same during exercise. Second, the failure of MSNA to be elevated more during PEMI with heat suggests that chemically sensitive muscle afferents were not sensitized by the heat. Hence, we speculate that muscle mechanoreceptors were responsible for the increase in MSNA with heating.

Previous investigations have found that both group III and IV muscle afferents increase their rate of firing in response to increases in heat (6, 11, 17). However, these studies did not examine responses of group III and IV muscle afferents to changes in muscle temperature.

Fig. 4. Original MSNA recordings from 2 subjects during baseline, fatiguing isometric handgrip (IHG), and PEMI, with and without heat applied to the exercising forearm.

Fig. 5. Skin and muscle temperature responses during baseline (BL), 2 min of exercise, fatigue (Fat), PEMI, and recovery (Rec). ○, Heat applied; ●, control (no heat).
ture during muscle contractions. We believe the findings of this study represent the first description of the interaction between heat and muscle contractions on skeletal muscle afferents and the resultant effect of the interaction on cardiovascular and sympathetic responses.

It is likely that during muscular contractions, heat produces the same type of effect on group III muscle afferents as altering the chemical milieu of the interstitial space. Studies using drugs to manipulate metabolite concentrations of the interstitial space have reported changes in group III and IV afferent responses to muscular contractions (21, 22, 26). Also, it has been demonstrated that intra-arterial injections of bradykinin increase the discharge of both group III and IV afferents during intermittent tetanic contractions (16). Similarly, intra-arterial injections of arachidonic acid increase the firing of group III but not group IV afferents during static contraction (21, 22). This latter finding illustrates that group III and IV afferents can be selectively sensitized. We speculate that this occurred in the present study. Moreover, it has been demonstrated that heat stimulates the release of arachidonic acid and prostaglandins from human cells (4). Further support for the possibility that group IV muscle afferents were not sensitized by the heat comes from the work of Mense and Stahnke (17). They found that the majority of the contraction-sensitive group IV muscle afferents had a response pattern that was unrelated to muscle temperature.

The results suggest that some change in the chemical milieu of the interstitial space may be necessary for heat to increase group III muscle afferent discharge and MSNA. During the first 30 s of isometric exercise, MSNA failed to change with heating. Chemical changes in the interstitial space may not have been significantly altered at the onset of isometric handgrip. Therefore, both heat and the chemical milieu of the interstitial space may interact to determine the sensitivity of the group III muscle afferents.

Because skin temperature was unchanged during exercise with heat, it is unlikely that stimulation of cutaneous warm receptors was responsible for the increase in MSNA during exercise. Additionally, because subjects did not perceive any discomfort by the heating, it is unlikely that cutaneous nociceptive afferents mediated the augmentation in exercise-induced MSNA. Furthermore, the lack of change in resting MSNA when skin temperature was elevated argues against a role of cutaneous receptors.

We chose to use ischemic forearm exercise for two reasons. First, we wanted to produce the same metabolic stimulus for both trials. An increase in muscle temperature increases the temperature coefficient and, hence, the metabolic rate of skeletal muscle (20). It has been reported that heat increases the rate of glycolysis and lactate production during isometric contraction of the human quadriceps muscle (5). However, it has been demonstrated that differences in the metabolic profile, especially pH, are eliminated by using ischemic forearm exercise (27). Second, occluding blood flow to the working arm eliminated possible changes in blood flow to the forearm induced by heat. Johnson et al. (7) found no effect of arm heating on forearm blood flow at rest. However, the effect that local heating of a small muscle mass, as in this study, would have on muscle blood flow during exercise is unknown. Blocking blood flow to the forearm prevents the delivery of cooler blood to and the removal of heat from the forearm muscle. The latter eliminated any possible contribution that other thermal receptors throughout the body could have made to our results.

Limitations. In the present study, we assume that MSNA responses during PEMI represent the contribution of the chemically sensitive muscle afferents during the end of exercise. We cannot provide definitive data to support this claim. However, in normal subjects, MSNA and calf vascular resistance responses at the end of exercise and during PEMI correspond to decreases in muscle pH (25, 28). Thus we would postulate that the contribution of the chemically sensitive muscle afferents would also be comparable.

Although the results suggest that mechanosensitive muscle afferents mediated the augmented MSNA response to isometric exercise with heat, it is possible that heat may increase contraction-related discharge of chemically sensitive afferents at higher muscle temperatures or during other modes of exercise (i.e., dynamic exercise). Temperature needed to activate group IV muscle afferents has been reported to be slightly higher than temperature needed to activate group III muscle afferents (11).

In conclusion, the present study indicates that elevations in muscle temperature can contribute to increases in MSNA during isometric exercise. The data suggest that this effect is mediated by an interaction of heat and muscle contraction on mechanically sensitive muscle afferents.

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