

Static handgrip exercise modifies arterial baroreflex control of vascular sympathetic outflow in humans

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Kamiya, Atsunori, Daisaku Michikami, Qi Fu, Yuki Niimi, Satoshi Iwase, Tadaaki Mano, and Akio Suzumura. Static handgrip exercise modifies arterial baroreflex control of vascular sympathetic outflow in humans. *Am J Physiol Regulatory Integrative Comp Physiol* 281: R1134–R1139, 2001.—To examine effects of static exercise on the arterial baroreflex control of vascular sympathetic nerve activity, 22 healthy male volunteers performed 2 min of static handgrip exercise at 30% of maximal voluntary force, followed by postexercise circulatory arrest (PE-CA). Microneurographic recording of muscle sympathetic nerve activity (MSNA) was made with simultaneous recording of arterial pressure (Portapres). The relationship between MSNA and diastolic arterial pressure was calculated for each condition and was defined as the arterial baroreflex function. There was a close relationship between MSNA and diastolic arterial pressure in each subject at rest and during static exercise and PE-CA. The slope of the relationship significantly increased by >300% during static exercise ($P < 0.001$), and the x -axis intercept (diastolic arterial pressure level) increased by 13 mmHg during exercise ($P < 0.001$). These alterations in the baroreflex relationship were completely maintained during PE-CA. It is concluded that static handgrip exercise is associated with a resetting of the operating range and an increase in the reflex gain of the arterial baroreflex control of MSNA.

arterial pressure; microneurography; muscle sympathetic nerve activity; pressor response

ARTERIAL BAROREFLEXES are important mechanisms for the overall regulation of circulation (1, 5, 27). Under resting conditions, an increase in arterial pressure stimulates arterial baroreceptors and decreases the heart rate and the peripheral vascular resistance in resting skeletal muscles. Handgrip exercise induces an increase in arterial pressure, and although the increase in pressure should stimulate the arterial baroreceptors, it is accompanied by increases in heart rate and peripheral vascular resistance in resting skeletal muscles. This phenomenon indicates that arterial baroreflex functions are modified during exercise and that this modification may include changes in the gain and/or operating range of the reflex (11, 12, 15, 18, 24,

25). There are a number of studies addressing changes in arterial baroreflex function during exercise. However, most of them have focused on the reflex control of heart rate (11, 12, 18, 21, 25) or arterial pressure (21, 25). In contrast, little is known about the effect of exercise on the arterial baroreflex control of vascular sympathetic nerve activity in humans.

A previous study (29) showed that partial pharmacological suppression of the exercise-induced increase in arterial pressure during static handgrip (nitroprusside infusion) augmented the exercise-induced increase in vascular sympathetic activity by >300%, while pharmacological accentuation of the exercise-induced increase in arterial pressure (phenylephrine infusion) attenuated the reflex increase in sympathetic activity by >50%. That study clearly indicated that the arterial baroreflex is effective in buffering the sympathetic activation induced by static muscle contraction. However, the detailed baroreflex relationship between vascular sympathetic activity and arterial pressure during static exercise remains unknown.

Accordingly, the purpose of this study was to examine the arterial baroreflex control of vascular sympathetic outflow during static handgrip exercise in humans. We performed microneurographic recording of vascular sympathetic nerve discharge to resting skeletal muscles (muscle sympathetic nerve activity; MSNA) in exercising volunteers and assessed the stimulus-response relation between diastolic arterial pressure and vascular sympathetic nerve activity during static exercise.

SUBJECTS AND METHODS

Subjects. After being informed of all procedures and risks, 22 healthy male volunteers with a mean age of 22 ± 2 (SE) yr, mean height of 171 ± 2 cm, and mean weight of 65 ± 2 kg gave written consent to serve as subjects for this investigation. All experimental procedures and protocols were approved by the Ethical Committee of the National Space Development Agency of Japan. All subjects were evaluated as being normally physically fit from a detailed medical history, physical examination, complete blood count, resting electrocardiogram, a panel of blood chemistry analyses, and a

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psychological test. No subjects were smokers, used recreational drugs, or had chronic medical problems. Each subject signed informed consent after a complete explanation of the testing procedures.

Measurements. MSNA was recorded by microneurography from the tibial nerve of the leg. An electrocardiogram was monitored from chest lead II, and respiration was measured with a thermistor. Finger arterial pressure was measured using a volume-clamp method (Portapres, TNO Institute of Applied Physics Biomedical Instrumentation) (35). Arterial pressure values were confirmed every minute by an automated upper arm sphygmomanometer (BP203MII, Nippon Colin, Komaki, Japan). The finger cuff of the Portapres was attached to two digits of the left hand at the height of the heart level and inflated alternately to prevent pain due to continuous air pressure load.

Microneurography. A tungsten microelectrode with a shaft diameter of 120 μm and an electrode impedance of 2–5 M Ω (model 26–05–1, Frederick Haer, Bowdoinham, ME) was inserted percutaneously into the muscle nerve fascicles of the tibial nerve at the popliteal fossa without anesthesia. Nerve signals were fed into a high-input impedance preamplifier (Kohno Instruments, Nagoya, Japan; input impedance 100 M Ω ; gain 40,000) with two active band pass filters set between 500 and 5,000 Hz and monitored with a loudspeaker. MSNA was identified according to the following discharge characteristics: 1) pulse synchronous spontaneous efferent discharges, 2) afferent activity evoked by tapping of the soleus muscle but not in response to a gentle skin touch, and 3) enhancement during phase II of Valsalva's maneuver.

Experimental protocol. The subjects lay in the supine position. Each subject performed two brief (<5 s) maximal contractions using a handgrip dynamometer (Digital Grip Dynamometer, Takei Kiki Kogyo, Japan), and the average of these two contractions was determined as the maximal voluntary contraction (MVC). After this MVC determination, the subjects were permitted to rest quietly in the supine position for over 30 min. At least 10 min after a satisfactory recording site for MSNA was obtained, preexercise baseline recordings of MSNA, finger arterial pressure, upper arm arterial pressure, and heart rate were performed for 2 min. Static handgrip exercise was performed at 30% of MVC with the dominant arm for 2 min. Subjects were breathing spontaneously throughout experimental periods, but they were required not to breathe deeply, hold their breath, or do Valsalva maneuvers. Furthermore, subjects were prohibited from contracting other limbs. The absolute force output from a handgrip dynamometer was displayed to the subjects on an oscilloscope with the target force.

Next, postexercise circulatory arrest (PE-CA) was done to estimate the effect of muscle metaboreflex (14, 26, 34). PE-CA was performed for 2 min as follows: 5 s before the release of isometric handgrip, the upper arm cuff was inflated to suprasystolic arterial pressure (>230 mmHg), and the subjects then released their grip. After PE-CA, the upper arm cuff was deflated, and 2 min of recovery recording was done.

MSNA, electrocardiogram, and finger arterial pressure were continuously recorded during preexercise rest, handgrip, PE-CA, and recovery and stored on a DAT recorder (PC-216Ax, Sony Magnescale, Japan).

Data analysis. MSNA was full-wave rectified and fed through a resistance-capacitance integrating circuit with a time constant of 0.1 s to obtain the mean voltage neurogram, which was displayed along with the electrocardiograms, arterial pressure, and respiration on a pen recorder (RECTI-HORIZ, NEC San-Ei, Tokyo, Japan). MSNA was

expressed as 1) MSNA burst rate, i.e., the mean number of sympathetic bursts per minute; 2) MSNA burst amplitude; and 3) total MSNA, i.e., the sum of the MSNA burst amplitudes of all bursts for each analyzed period per minute. To calculate the MSNA burst amplitude in the mean voltage neurogram, all burst amplitudes were measured using a paper sheet. The mean MSNA burst amplitude during 2 min of preexercise rest was given the arbitrary value of 100 (arbitrary units), and all other MSNA burst amplitudes during handgrip, PE-CA, and recovery were expressed in relation to this value. The beat-to-beat data for R-R interval and systolic and diastolic arterial pressure were obtained by detecting R-wave peaks and identifying peaks and troughs on the arterial pressure wave, respectively. The analyzed periods included preexercise rest (2 min) and the last minute of each exercise, PE-CA, and recovery.

Arterial baroreflex control of MSNA. As described in previous reports (6–8, 16, 32), the baroreflex relationship between MSNA and diastolic arterial pressure was determined from spontaneous changes in diastolic arterial pressure to changes in MSNA for each subject. Beat-by-beat values for MSNA burst amplitudes (arbitrary units) were averaged over 2-mmHg diastolic arterial pressure ranges, and a weighted linear regression between MSNA burst amplitude and diastolic pressure was performed. The relationship was defined as the arterial baroreflex control of MSNA.

Statistical analysis. A one-way repeated-measures analysis of variance (preexercise rest, exercise, PE-CA, and recovery) was performed. Tests for simple effects were done with Scheffé's *F* procedure when the main effect was found to be significant. The baroreflex relation between sympathetic activity and diastolic arterial pressure was determined by least-squares linear regression analysis with repeated measures. To determine baroreflex regressions, the statistical criteria for a significant correlation were that the correlation coefficient *r* was >0.70 with *P* < 0.05 by Fisher's *r* to *z* (*P* value). Data are expressed as means \pm SE. A *P* < 0.05 level of difference was considered significant.

RESULTS

Static handgrip and PE-CA. Figure 1 shows representative data from one subject during static handgrip exercise and PE-CA. Table 1 shows sympathetic and cardiovascular responses from all subjects. MSNA gradually and progressively increased during static handgrip exercise (*P* < 0.0001) and remained elevated above baseline during PE-CA (*P* < 0.0001). Heart rate increased during exercise and returned to the baseline during PE-CA. Systolic and diastolic arterial pressure increased during exercise and remained at higher levels above baseline during PE-CA. Breathing frequency did not change during exercise and PE-CA.

Arterial baroreflex control of MSNA. The relationship between MSNA and diastolic arterial pressure derived from the data in Fig. 1 is shown in Fig. 2. A significant negative correlation was observed between them in each condition, and this relationship was used to assess the arterial baroreflex control of MSNA. Similarly to the subject represented in Figs. 1 and 2, a significantly negative correlation between MSNA and diastolic arterial pressure was observed in each subject. The mean *r* (correlation coefficient) of individual regressions was 0.82 ± 0.02 at rest, 0.89 ± 0.03 during handgrip exercise, 0.91 ± 0.02 during PE-CA, and

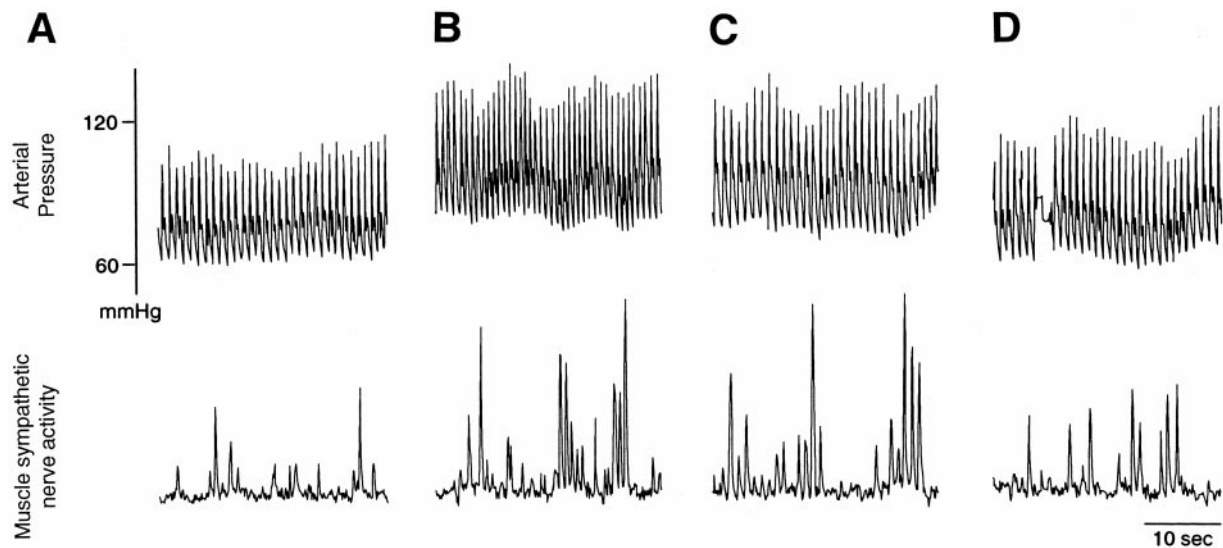


Fig. 1. Simultaneous recordings of the blood pressure wave and integrated muscle sympathetic nerve activity (MSNA) trace from 1 subject at rest (A) and during handgrip exercise (B), postexercise circulatory arrest (PE-CA; C), and recovery (D).

0.87 ± 0.02 during recovery. The mean slope of the relationship from all subjects was 3.2 ± 0.5 arbitrary units/mmHg at rest, and this significantly increased by $>300\%$ during static handgrip exercise (12.1 ± 2.1 arbitrary units/mmHg, $P < 0.001$) (Fig. 3). Moreover, the mean slope remained elevated during PE-CA (12.9 ± 2.7 arbitrary units/mmHg, $P < 0.001$) and then returned to baseline during recovery (Fig. 3). The mean x -axis intercept (threshold diastolic pressure) of the relationship from all subjects was 77.1 ± 1.4 mmHg at rest, and this significantly increased by 13 mmHg during static exercise (89.6 ± 1.9 mmHg, $P < 0.001$) (Fig. 3). The increase in the mean intercept was maintained during PE-CA (89.6 ± 2.4 mmHg, $P < 0.001$), and the intercept returned to baseline during recovery (Fig. 3).

DISCUSSION

Sympathetic vascular contraction plays an important role in regulating the circulation during exercise (5, 27), but little is known about the arterial baroreflex control of vascular sympathetic outflow during static exercise in humans. The present study for the first time examined the arterial baroreceptor-MSNA stimulus-response relationship during static exercise in

humans and showed that the operating range of the arterial baroreflex shifted to a higher pressure (resetting) and that the gain was markedly increased during static exercise.

The results from this study are in general agreement with previous studies that showed resetting of the arterial baroreflex during exercise in animals (3, 24, 33) and humans (12, 25). Walgenbach and Donald (33) first reported that when a sensory input from carotid baroreceptor (carotid sinus pressure) was held constant, exercise-induced increases in heart rate and arterial blood pressure were augmented compared with when carotid sinus pressure was allowed to follow the changes in arterial blood pressure in dogs. This finding was thought to show that the arterial baroreflex was reset to a higher operating pressure range during exercise. This concept was supported by a study from DiCarlo and Bishop (3) showing that partial suppression of exercise-induced increase in blood pressure augmented the reflex increases in renal sympathetic nerve activity and heart rate in rabbits. Recently, Potts et al. (25) and Iellamo et al. (11, 12) assessed the stimulus-response relationship of the carotid baroreflex during exercise in humans and reported that the baroreflex relationship is reset to a higher operating

Table 1. MSNA burst rate, total MSNA, heart rate, systolic and diastolic arterial pressure, and breathing frequency

	Rest	Handgrip	PE-CA	Recovery
MSNA burst rate, bursts/min	14.1 ± 0.9	$36.4 \pm 1.1^*$	$31.8 \pm 0.7^*$	16.0 ± 0.8
Total MSNA, arbitrary units/min	$1,410 \pm 90$	$4,787 \pm 241^*$	$4,353 \pm 225^*$	$1,563 \pm 134$
Heart rate, beats/min	73.4 ± 1.1	$92.6 \pm 1.4^*$	75.7 ± 0.9	74.8 ± 1.0
Systolic pressure, mmHg	120.3 ± 3.7	$139.8 \pm 5.0^*$	$139.9 \pm 3.7^*$	125.5 ± 4.0
Diastolic pressure, mmHg	74.3 ± 2.5	$89.2 \pm 4.3^*$	$86.7 \pm 3.3^*$	76.8 ± 3.4
Breathing frequency, breaths/min	15 ± 1	15 ± 1	15 ± 1	15 ± 1

Values are means \pm SE. MSNA, muscle sympathetic nerve activity; PE-CA, postexercise circulatory arrest. $*P < 0.05$ vs. preexercise baseline (Rest).

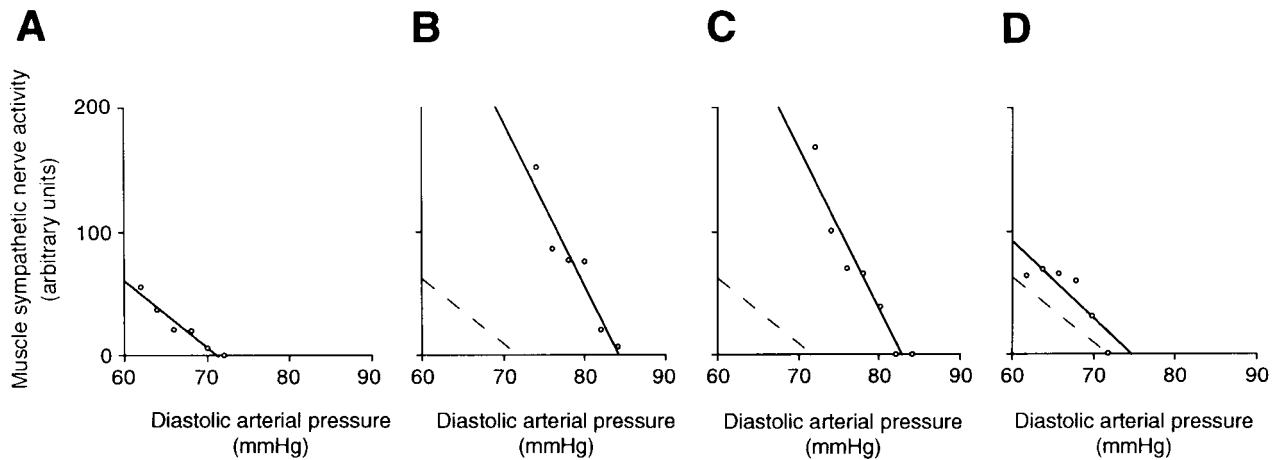


Fig. 2. The relationship between MSNA and diastolic arterial pressure derived from the same subject as in Fig. 1. The abscissa represents diastolic arterial pressure, while the ordinate shows MSNA. The linear equation was $y = -5.3x + 380.1$ ($r = 0.98$) at rest (solid line in A). This equation at rest is shown as a broken line for handgrip exercise (B), PE-CA (C), and recovery (D). The linear equation was $y = -13.2x + 1113.1$ ($r = 0.95$) during handgrip exercise (solid line; B), $y = -13.1x + 1087.4$ ($r = 0.96$) during PE-CA (solid line; C), and $y = -6.2x + 466.2$ ($r = 0.86$) during recovery (solid line; D). The slopes of the regression line were defined as the baroreflex slopes for MSNA.

pressure range when reflex responses are determined by heart rate and mean arterial pressure. Moreover, Martinez-Nieves et al. (15) found a similar exercise-induced resetting of the baroreflex control of hindlimb vascular conductance in hypertensive rats. The present study confirms these previous findings and adds new information to our understanding of the neural mechanism during exercise: static exercise causes resetting of the arterial baroreflex control of vascular sympathetic outflow in humans.

The data from this study clearly demonstrate that the gain in the arterial baroreflex control of vascular sympathetic outflow was greatly increased by $>300\%$ during static exercise. The increase in the gain is consistent with a previous report by Scherrer et al. (29). They showed that the sympathetic excitation caused by static handgrip during infusion of nitroprus-

side was more than two times greater than the simple algebraic sum of the excitation caused by handgrip alone or that caused by infusion of nitroprusside alone. Their finding may in part be explained by the baroreflex relationship with a steeper slope during exercise observed in this study, because a reflex increase in MSNA caused by a certain magnitude of hypotension will be more on a regression line during exercise compared with at rest (Fig. 2). The increased gain of the arterial baroreflex control of vascular sympathetic outflow, however, stands in contrast to previous reports in humans that showed no change (25), or a decrease (21), in the gain of the carotid baroreceptor-systemic arterial pressure relationship during exercise. Moreover, a recent study in rats showed that a spontaneous baroreflex gain in hindlimb vascular conductance was unchanged, or partially attenuated, during exercise (15).

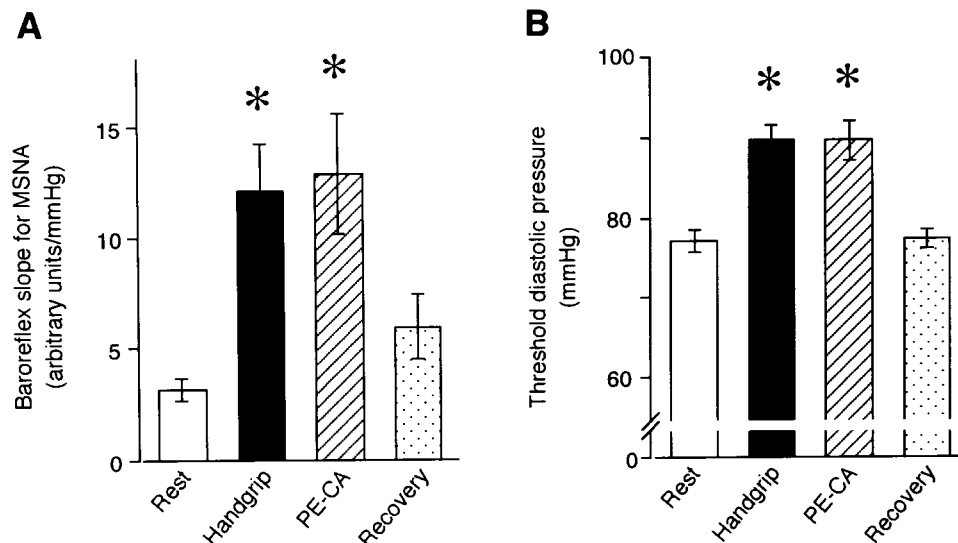


Fig. 3. The mean baroreflex slope (A) and the mean diastolic arterial pressure (B) of the baroreflex relationships derived from all subjects. Values are means \pm SE. $*P < 0.01$ vs. preexercise rest.

This discrepancy may be due to a difference in the experimental approaches that determined the reflex outflow in this (vascular sympathetic nerve activity) and previous studies (systemic arterial pressure and vascular conductance). Because several studies have demonstrated that α -adrenergic receptor-mediated vasoconstrictor responsiveness is attenuated during exercise (2, 4, 9, 10), the decreased constrictor response of vessels can mask the augmented ability of a reflex sympathetic response, resulting in no change or an attenuation, rather than an increase, in the total baroreflex gain involving vascular responses.

The mechanism responsible for the modification of arterial baroreflex control of vascular sympathetic nerve activity during static handgrip exercise was not completely understood in this study. However, the muscle metaboreflex (28) may contribute to the altered baroreflex response. This is based on the finding that during PE-CA, in which chemosensitive muscle afferents are stimulated and the muscle metaboreflex is activated while the muscle mechanoreflex and central command are inoperative (14, 26, 34), exercise-induced modification (including a resetting and an increase in the gain) of the arterial baroreflex was entirely maintained. This finding confirms the concept of a reflex interaction between the muscle reflex and the arterial baroreflex (11, 23). This concept is supported by neurophysiological and electrophysiological evidence showing that afferent fibers from arterial baroreceptor and skeletal muscle receptor synapse in discrete regions of the medulla that are related to cardiovascular regulation, including the nucleus tractus solitarius (13, 17, 20, 22). Therefore, we suggest that some of the modification of the arterial baroreflex during static exercise was caused by the muscle metaboreflex.

There are lots of studies addressing the exercise-induced alteration in arterial baroreflex function, but most (3, 12, 21, 23–25, 33) involved isotonic or isokinetic exercise (e.g., dynamic) rather than isometric (e.g., static) exercise. In contrast, we examined the effect of static exercise on baroreflex function in the present study. It is possible that different mechanisms are involved in altering baroreflex control of vascular sympathetic nerve activity during static vs. dynamic exercise. Further investigations are necessary to clarify this point.

Limitation. We used a nonperturbational spontaneous method to assess the arterial baroreflex function. Compared with perturbational methods, the nonperturbational spontaneous method has several limitations. The nonperturbational spontaneous method assesses a limited range of pressure for the stimulus-response baroreflex relationship, while the perturbational methods allow the examination of a prevailing range of pressure. Furthermore, the nonperturbational baroreflex determination might be more affected by spontaneous changes in central venous pressure and respiratory gating compared with perturbational methods.

Conversely, the perturbational methods also have several limitations. Pharmacological agents and extensive surgical procedures may have indirect effects on,

and somewhat modify, experimental results. Moreover, perturbational methods in which arterial pressure is greatly changed may produce nonphysiological artifacts. Therefore, there is no perfect methodology for evaluating the arterial baroreflex function (15).

We examined a limited range of arterial pressure-to-baroreflex relationships. However, this is a physiological range of pressure. Under physiological conditions, the arterial baroreflex functions within this narrow range, and the baroreceptor-MSNA stimulus-response relationship is linear (32). In addition, although we cannot exclude a possible influence of the cardiopulmonary baroreflex on the sympathetic response, it is thought that the cardiopulmonary baroreflex has little role in the control of MSNA during static handgrip exercise in humans (30, 31). Furthermore, the breathing frequency was held constant during exercise and PE-CA in this study, suggesting that respiration exerted less influence on the alteration of the baroreflex function.

In conclusion, the arterial baroreflex control of vascular sympathetic nerve activity was greatly modified during static handgrip exercise in humans: the baroreceptor-vascular sympathetic response relationship was rightward shifted to a higher pressure, and the gain in the reflex was markedly increased. In addition, the muscle metaboreflex appears to be involved in this modification.

Perspectives

Potts and Li (23) recently suggested the concept that modification of the baroreflex during exercise plays two functional roles: 1) to buffer the degree of sympathoexcitation evoked by the exercise pressor reflex, and 2) to increase sympathoexcitation at the onset of exercise to minimize the fall in arterial blood pressure. The baroreceptor-MSNA stimulus-response relationship during static handgrip exercise observed in this study confirms and partially explains this concept because 1) the negative relationship between MSNA and arterial pressure was entirely preserved with a steeper slope during static exercise, and 2) across all diastolic arterial pressures the MSNA was higher during static exercise. Therefore, it is likely that the modification of the arterial baroreflex is a powerful modulator of sympathoexcitation during exercise (23), having both buffering and excitatory effects on the sympathetic neural activity. The buffering effect is consistent with the results from Scherrer et al. (30) and DiCarlo et al. (3), showing that partial pharmacological suppression/elevation of the exercise-induced rise in arterial pressure augmented/attenuated the reflex sympathetic activation, respectively. The buffering effect may in part be related to data from Potts and Li (23), showing that when carotid sinus pressure was higher, the reflex increase in systemic arterial pressure during muscle contraction was lower, and vice versa. Furthermore, the excitatory effect may be in agreement with the study from Melcher and Donald (19), showing that when no baroreceptor systems were able to participate

in the regulation of circulation, the systemic arterial pressure greatly dropped during exercise in dogs.

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