

Forearm elevation augments sympathetic activation during handgrip exercise in humans

Daisaku MICHIKAMI*, Atsunori KAMIYA*, Qi FU*, Yuki NIIMI*, Satoshi IWASE*, Tadaaki MANO† and Akio SUZUMURA*

*Department of Autonomic Neuroscience, Research Institute of Environmental Medicine, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan, and †Tokai Central Hospital, Kakamigahara, Sohara-Higashijima-cho, 6-2,4-chome, 504-8601, Japan

A B S T R A C T

Although angina pectoris in patients with coronary heart disease often occurs when their forearms are in an elevated position for a prolonged period, and sympathetic activation is a major cause of this condition, little is known about the physiological effects of forearm elevation on sympathetic activity during forearm exercise. We hypothesized that forearm elevation augments sympathetic activation during the static handgrip exercise in humans. A total of 10 healthy male volunteers performed 2 min of static handgrip exercise at 30% of maximal voluntary contraction followed by 2 min of post-exercise muscle ischaemia (PEMI; specific activation of the muscle metaboreflex) with two forearm positions: the exercising forearm was elevated 50 cm above the heart (forearm-elevated trial) or fixed at the level of the heart (heart-level trial). Muscle sympathetic nerve activity (MSNA), blood pressure and heart rate were monitored. MSNA increased during handgrip exercise in both forearm positions ($P < 0.001$); the increase was 51% greater in the forearm-elevated trial (516 ± 99 arbitrary units) than in the heart-level trial (346 ± 44 units; $P < 0.05$). The increase in mean blood pressure was 8.4 mmHg greater during exercise in the forearm-elevated trial ($P < 0.05$), while changes in heart rate were similar in both forearm positions. The increase in MSNA during PEMI was 71% greater in the forearm-elevated trial (393 ± 71 arbitrary units/min) than in the heart-level trial (229 ± 29 units/min; $P < 0.05$). These results support the hypothesis that forearm elevation augments sympathetic activation during handgrip exercise. The excitatory effect of forearm elevation on exercising MSNA may be mediated primarily by increased activation of the muscle metaboreflex.

INTRODUCTION

Angina pectoris in patients with coronary heart disease often occurs when they work with their forearms in an elevated position [1]. Since a major cause of the disease is sympathetic activation [2,3], the clinical finding suggests a potential excitatory effect of forearm elevation on sympathetic activation during forearm exercise. However, although several studies have addressed the effects of forearm elevation on cardiovascular responses to forearm exercises (handgrip, finger twitch), mixed results

have been reported, including augmented [1,4] and attenuated [5] responses. Moreover, these studies investigated only responses of arterial pressure and heart rate; accordingly, the physiological effect of forearm elevation on sympathetic neural activity during forearm exercise remains unknown.

The hypothesis that we examined in the present study is that forearm elevation augments sympathetic activation during static handgrip exercise in humans. We measured muscle sympathetic nerve activity (MSNA) during 2 min of static handgrip exercise in 10 healthy male volunteers.

Key words: cardiovascular system, microneurography, muscle reflex, muscle sympathetic nerve activity, static exercise, sympathetic nervous system.

Abbreviations: MSNA, muscle sympathetic nerve activity; PEMI, post-exercise muscle ischaemia.

Correspondence: Dr Atsunori Kamiya (e-mail kamiya@ri.ncvc.go.jp or dmichi@ri.ncvc.go.jp).

Two forearm positions were used: the exercising forearm was elevated 50 cm above the heart (forearm-elevated trial) or was fixed at heart level (heart-level trial).

METHODS

Subjects

We studied a total of 16 healthy male subjects with a mean \pm S.E.M. age of 24.8 ± 1.9 years (range 19–46 years). None of the subjects had a habit of smoking, experience of recreational drug use or any chronic medical problem. All subjects were evaluated as healthy by detailed medical history, physical examination, resting ECG, blood chemistry and psychological testing. All subjects gave their informed consent to participate in the study, which was approved by the Committee on Human Research, Research Institute of Environmental Medicine, Nagoya University. Ten subjects [age 22.1 ± 1.0 (19–30) years] participated in experiment 1, while six other subjects [age 29.8 ± 4.4 (20–46) years] participated in experiment 2.

Experiment 1

Experiment 1 was conducted to determine the effects of forearm elevation on MSNA activation during static handgrip exercise in humans.

Measurements

MSNA was recorded using microneurography from the right tibial nerve. A tungsten microelectrode with an uninsulated tip diameter of $\sim 1 \mu\text{m}$ and an impedance of 3–5 M Ω (model 26-05-1; Federick Haer and Co., Bowdoinham, ME, U.S.A.) was inserted manually at the popliteal fossa. A reference electrode was placed near the recording electrode. Identification of MSNA was performed according to previous studies [6–8]. Nerve signals were amplified (Kohno Instruments, Nagoya, Japan; input impedance, 100 M Ω ; gain, $\times 40000$), and filtered with a bandwidth of 500–5000 Hz to improve the signal/noise ratio. MSNA neurograms were full-wave rectified and integrated with a time constant of 0.1 s and displayed on a pen recorder (Recti-Horiz, NEC-San-ei, Japan). MSNA was expressed as (1) MSNA burst rate, i.e. the mean number of sympathetic bursts per min, and (2) total MSNA, i.e. the sum of the MSNA burst amplitudes of all bursts during each period analysed. To calculate the MSNA burst amplitude in the mean voltage neurogram, all burst amplitudes were measured using a digitizing tablet. The mean value per min of total MSNA (the sum of all MSNA burst amplitudes) during 2 min of pre-exercise baseline without forearm elevation (Baseline I) was given the arbitrary value of 100 arbitrary units/min, and all total MSNA values following the Baseline I period were expressed relative to this arbitrary value.

Blood pressure was measured with a Portapres (model BP-508S; TNO Institute of Applied Physics Biomedical

Instrumentation) [9]. The finger cuffs of the Portapres were attached to the index or middle finger of the left hand. Mean blood pressure was calculated as the sum of the diastolic blood pressure plus one-third of the pulse pressure. Heart rate was monitored continuously using a bipolar chest ECG (model MEG-1251; Nihon Kohden, Tokyo, Japan).

At the end of each trial, the ratings of perceived effort were assessed using the 15-point (6–20 point) Borg scale [10] and used as an index of central command activation.

Blood sampling was carried out from the antecubital vein of the exercising limb at rest and during the final 30 s of post-exercise muscle ischaemia (PEMI) to determine the plasma lactate concentration, since lactate is the best studied stimulant of the muscle metaboreflex [11,12].

Protocol

We aimed to determine the effect of forearm elevation on MSNA activation during static handgrip exercise in humans. Before the experiment, subjects were required to lie in the supine position with their right forearms extended. The right arm was dominant for all subjects. Maximal voluntary handgrip forces were determined using a dynamometer (model 5701A; Takei Instrumentation, Nagoya, Japan) at two positions of the right forearm: the exercising forearm was elevated 50 cm above the heart, or fixed at heart level. During handgrip with the elevated forearm, a stable supporting board was used, so that the contracting muscle mass was equivalent for the forearm-elevated and heart-level handgrip exercises.

At least 60 min after the determination of maximal voluntary forces, static handgrip exercises followed by PEMI were performed at two positions of the right forearm, i.e. elevated 50 cm above the heart (forearm-elevated trial) and fixed at heart level (heart-level trial). These two trials were separated by more than 45 min of rest. Since Seals and Enoka [13] showed a link between the development of fatigue and the proportional increase in MSNA during handgrip exercise in repeated exercises, the order of these trials was randomized in order to eliminate any effect of the former trial.

In the forearm-elevated trial, baseline measurements of MSNA, blood pressure and heart rate were taken for 2 min with the right wrist joint fixed at heart level (Baseline I). Then the right forearm was elevated passively for 4 min at 50 cm above heart level with an extended elbow joint using a stable supporting board (Baseline II). Subjects then performed static handgrip exercise at 30% of maximal voluntary contraction for 2 min. An occlusion cuff placed on the right upper arm was then inflated to a suprasystolic pressure (250 mmHg) for 2 min to block the blood supply to the contracting muscle (PEMI; specific activation of the muscle metaboreflex). The forearm was kept elevated during the first 2 min of recovery (Recovery I) and was then returned to heart level during the final 2 min of recovery (Recovery II).

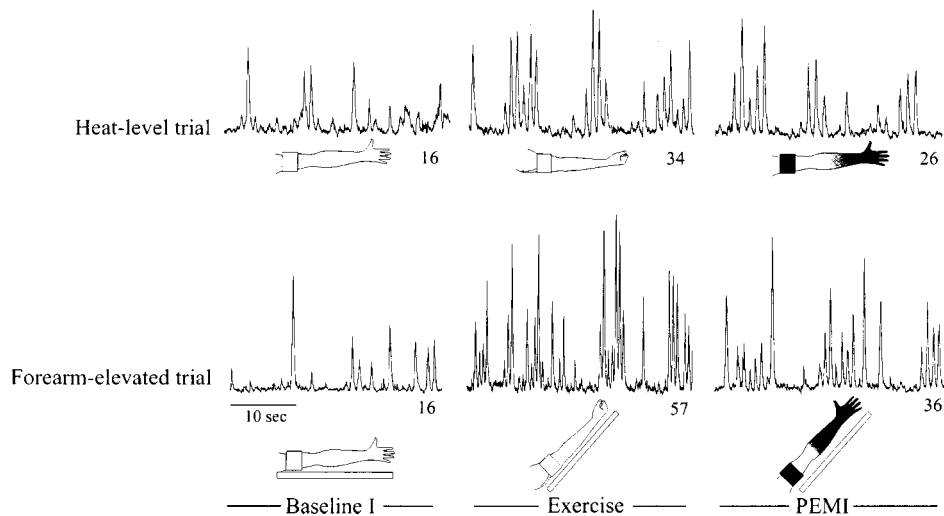


Figure 1 Integrated neurogram during Baseline I, the 2nd min of exercise and PEMI in the heart-level and the forearm-elevated handgrip trials for one typical subject

Elevation and return of the forearm was performed passively by the investigators in order to avoid additional voluntary muscle contraction by the subject.

In the heart-level trial, handgrip exercise and PEMI were carried out in the same way as in the forearm-elevated trial, except for the forearm position: the wrist joint was fixed at heart level throughout the experiment.

Experiment 2

To determine the effect of forearm elevation on forearm perfusion pressure, we performed an additional experiment (experiment 2). Experiment 2 was similar to experiment 1 except that the handgrip exercise and PEMI were not performed.

Measurements

Digital blood pressure was measured with a Portapres attached to the index or middle finger of the right hand. Venous pressure was recorded from the cephalic vein at the wrist using a Teflon catheter connected to a pressure transducer (MP5200; Baxter, Tokyo, Japan). Net forearm perfusion pressure was calculated as the difference between mean blood pressure and venous pressure.

Protocol

Before the experiment, subjects were required to lie in the supine position with their right forearms extended. Digital blood pressure and cephalic venous pressure in the right arm were measured at two positions of the right forearm: elevated 50 cm above the heart (forearm-elevated trial) and fixed at heart level (heart-level trial). These trials were applied randomly, and each was separated from the preceding trial by at least 10 min.

In the forearm-elevated trial, baseline pressure measurements were taken for 2 min with the right wrist joint

fixed at heart level, and then the right forearm was elevated passively for 10 min at 50 cm above heart level with an extended elbow joint using the supporting board. After that, the forearm was returned to heart level and fixed for 2 min. In the heart-level trial, monitoring of pressures was performed in the same manner as the forearm-elevated trial, except that the wrist joint was fixed at the heart level throughout the experiment.

Statistical analysis

The analysed periods consisted of the first 2 min of baseline (Baseline I), the final 2 min of baseline, during which the forearm was elevated in the forearm-elevated trial (Baseline II), the 1st and 2nd min of the exercise period, the 2nd min of PEMI, the first 2 min of recovery, during which the forearm was kept elevated in the forearm-elevated trial (Recovery I), and the final 2 min of recovery (Recovery II).

Values are expressed as means \pm S.E.M. The effects of forearm elevation on variables were evaluated by two-way repeated-measures ANOVA [time and condition (heart-level trial, forearm-elevated trial)]. When the main effect or the interaction term was found to be significant, *post hoc* comparisons were made with Fisher's protected least-squares difference procedure. The effects of forearm elevation on maximal voluntary contraction force and rating of perceived effort were evaluated by paired Student's *t* tests. Differences at the $P < 0.05$ level were considered statistically significant.

RESULTS

Experiment 1

The maximal voluntary contraction force was similar in the forearm-elevated trial and the heart-level trial ($428 \pm$

17 and 441 ± 17 N respectively). Original recordings of integrated neurograms are shown in Figure 1. Pre-exercise baseline measurements (Baseline I) of MSNA, mean blood pressure and heart rate were similar in these trials, and forearm elevation did not affect these resting variables (Baseline II; Figure 2).

MSNA had increased after 2 min of handgrip exercise in both the forearm-elevated and heart-level trials (both $P < 0.001$; Figures 1 and 2); the increase in total MSNA was 51% greater in the forearm-elevated trial than in the heart-level trial (time \times condition interaction, $P < 0.05$; Figure 2). Total MSNA during the 2nd min of exercise was 516 ± 99 arbitrary units/min in the forearm-elevated trial and 346 ± 44 units/min in the heart-level trial ($P < 0.05$). During PEMI, MSNA remained elevated above Baseline I in both trials (both $P < 0.001$; Figures 1 and 2), and the increase was 71% greater in the forearm-elevated trial than in the heart-level trial (time \times condition interaction, $P < 0.05$; Figure 2).

The increase in mean blood pressure during both handgrip exercise and PEMI was greater in the forearm-elevated trial than the heart-level trial (time \times condition interaction, $P < 0.05$; Figure 2). Mean blood pressure was 8.4 mmHg higher after 2 min of exercise in the forearm-elevated trial ($P < 0.05$; Figure 2). In contrast, the heart rate response was not significantly different between the two trials (Figure 2).

Ratings of perceived effort were higher in the forearm-elevated trial (16.9 ± 0.3 points) than in the heart-level trial (14.7 ± 0.7 points; $P < 0.05$). The increase in plasma lactate with exercise did not differ between the forearm-elevated trial (1.9 ± 0.2 mmol \cdot l $^{-1}$) and the heart-level trial (1.8 ± 0.3 mmol \cdot l $^{-1}$).

Experiment 2

Forearm elevation reduced mean digital blood pressure by 35.0 ± 3.8 mmHg ($P < 0.005$), but venous pressure was unchanged; both pressures were unchanged when the forearm was fixed at heart level (Figure 3). Consequently, forearm perfusion pressure (mean digital blood pressure minus venous pressure) was reduced by 35.9 ± 3.5 mmHg when the forearm was elevated ($P < 0.005$), while this pressure was stable when the forearm was fixed at heart level (Figure 3).

DISCUSSION

Angina pectoris in patients with coronary heart disease often occurs when they work with their forearms in an elevated position [1]. Since a major cause of the disease is sympathetic activation [2,3], we hypothesized that forearm elevation augments sympathetic activation during static handgrip exercise in humans. The present results support this hypothesis, since we found that MSNA activation during static handgrip exercise was 51%

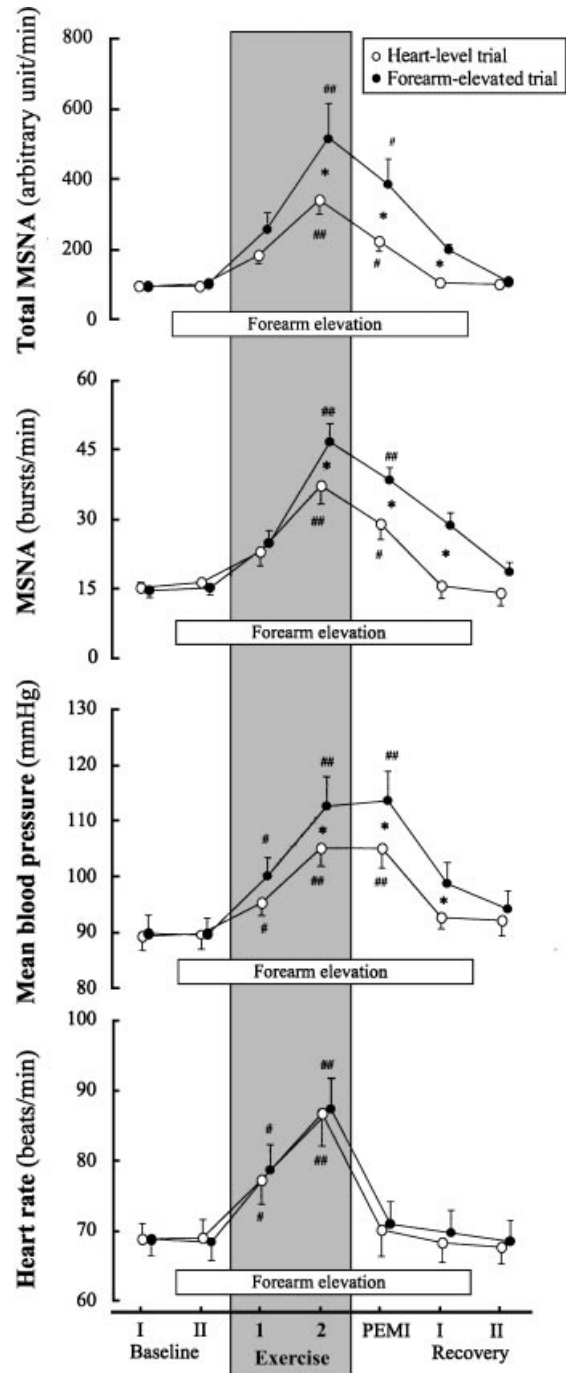


Figure 2 MSNA, mean blood pressure and heart rate during heart-level and forearm-elevated handgrip exercise

In the forearm-elevated trial, the forearm was elevated 50 cm above heart level from Baseline II to Recovery I, while in the heart-level trial the forearm was fixed at heart level throughout the experiment. Error bars denote S.E.M. Significance of differences: * $P < 0.05$ compared with heart-level trial; # $P < 0.05$, ## $P < 0.01$ compared with Baseline I.

greater when the exercising forearm was elevated 50 cm above the heart compared with when it was fixed at heart level.

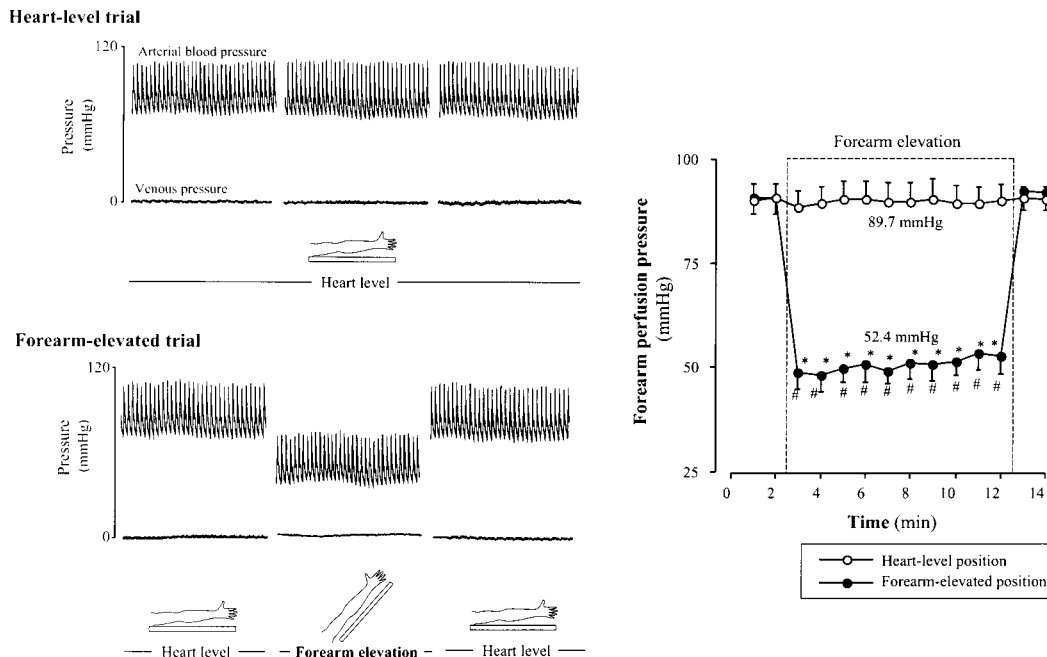


Figure 3 Digital blood pressure and venous pressure measured at the right hand (left panels), and perfusion pressure to forearm muscles (right panel), with the forearm at heart level and in the elevated position

The muscle perfusion pressure is calculated as the difference between the mean arterial and venous blood pressure. Significance of differences: * $P < 0.0005$ compared with heart-level position; # $P < 0.0001$ compared with value during the 1st min.

The present findings have clinical implications for patients with ischaemic coronary heart disease. Although we generally use our forearms not only at heart level but also overhead in our daily lives, little attention has been paid to differences in contraction-induced sympathetic activation between forearm positions in healthy humans or in patients with these diseases. The present finding clearly demonstrates that overhead forearm exercise induces greater MSNA activation than heart-level forearm exercise. These findings imply that overhead forearm exercise could involve more potential risk for patients with ischaemic coronary heart diseases compared with heart-level forearm exercise.

The most likely mechanism responsible for the greater activation of MSNA during handgrip exercise with the forearm in the elevated position is forearm hypoperfusion. Theoretically, elevation of the forearm by 50 cm above heart level is expected to decrease arterial perfusion pressure by 38 mmHg. This was verified by additional experiments (experiment 2). We measured finger arterial pressure and cephalic venous pressures of the right forearm in the absence of muscle contraction when the forearm was elevated above and fixed at heart level, and observed that forearm perfusion pressure (mean arterial pressure minus venous pressure) was decreased by 35.9 ± 3.5 mmHg when the forearm was elevated. Given the reduced forearm perfusion pressure, it is likely that the mildly greater increase (8.4 mmHg) in mean

blood pressure during forearm-elevated exercise is insufficient to achieve similar forearm perfusion during exercise. This inadequate blood pressure response to elevated forearm exercise is likely to account for increased local forearm ischaemia and the greater MSNA activation during forearm-elevated exercise, although, unfortunately, no direct information on true arterial, venous and perfusion pressures in the exercising forearm can be obtained because of technical limitations.

Forearm hypoperfusion due to forearm elevation is likely to induce greater activation of the muscle metaboreflex, resulting in greater augmentation of MSNA during handgrip exercise with the forearm in an elevated position than at heart level. The muscle metaboreflex has a key role in the activation of MSNA during exercise [14–16], and during PEMI the reflex is kept activated while other mechanisms, including the central command and the muscle mechanoreflex, are absent [14–17]. Since in the present study MSNA during PEMI was 71% greater in the forearm-elevated trial than in the heart-level trial, it is likely that the muscle metaboreflex is activated to a greater extent during handgrip exercise with the elevated forearm compared with the heart-level forearm. Although we failed to find a significant difference in the increase in plasma lactate in the forearm-elevated and heart-level trials, it is possible that metabolites other than lactate (e.g. adenosine, potassium, prostaglandin and H^+) which trigger sympathetic ac-

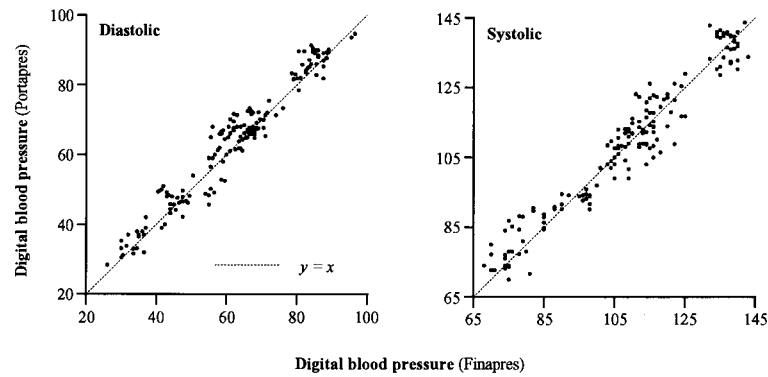


Figure 4 Relationship between systolic and diastolic digital blood pressure values measured by simultaneous Finapres and Portapres recording during experiment 2 ($n = 148$)

Each point represents the average value over 1 min.

tivation [18–21] achieve greater local concentrations in exercising forearm muscles under conditions of forearm hypoperfusion produced by forearm elevation.

It is likely that the forearm hypoperfusion produced by forearm elevation induces more activation of the central command, contributing to part of the greater augmentation of MSNA during handgrip exercise with the elevated forearm compared with the heart-level forearm. Since muscle fatigue is increased due to the forearm hypoperfusion produced by elevating the forearm [4], increased motor drive may be required to maintain constant force output in the forearm-elevated than in the heart-level handgrip exercise. Indeed, we observed that the ratings of perceived effort, an index of central command, were higher in the forearm-elevated trial than in the heart-level trial. Although the central command is generally considered to have less influence on MSNA during heart-level handgrip exercise [22], the effect of the central command on MSNA has not been examined during exercise with an elevated forearm, and fatigue has an influence upon exercising MSNA [23].

The greater activation of MSNA during handgrip exercise with the elevated forearm is not due to a potential effect of fatigue accompanying repeated exercise bouts. Since Seals and Enoka [13] showed a link between the development of fatigue and the proportional increase in MSNA during handgrip exercise in three repeated trials, we performed the two exercise trials in a random order. Furthermore, in five subjects who performed the forearm-elevated exercise and then the heart-level exercise, activation of MSNA was greater with the forearm-elevated exercise than with the heart-level exercise.

A potential effect of additional contracting muscles accompanying forearm elevation is unlikely to explain the greater activation of MSNA during handgrip exercise with the elevated forearm. In the present study we used a stable board to support the exercising forearm, and thus attempted to prevent additional muscle contraction. Although some previous studies [1] have reported an

augmented heart rate response to handgrip exercise with an elevated forearm when a supporting board was not used, a larger muscle mass might have contracted to elevate and support the forearm in that study, and this additional muscle contraction might have affected the results.

In the present study, the blood pressure response to exercise with an elevated forearm was consistent with the MSNA response, since the increase in mean blood pressure was greater in the forearm-elevated than in the heart-level trial. The augmented blood pressure response was also consistent with the findings of Wright et al. [4], who showed that forearm elevation augmented an increase in mean blood pressure in response to twitch contraction of the adductor pollicis (unfortunately they did not measure heart rate). In contrast, the augmented blood pressure response in the present study was inconsistent with the findings of Kahn et al. [5], who showed that forearm elevation did not affect the increase in mean blood pressure during handgrip exercise. Furthermore, the present finding that the heart rate response to handgrip exercise was unchanged by forearm elevation is also inconsistent with the observation of Kahn et al. [5] that an increase in heart rate during exercise was attenuated by forearm elevation. A likely reason for the smaller cardiovascular responses observed in the study of Kahn et al. [5] is that the maximal voluntary contraction force and experimental exercise intensity were reduced when the forearm was elevated in their study, while the maximal voluntary handgrip contraction was unchanged with forearm elevation in the present study.

It is likely that the Portapres device measured digital blood pressure accurately under the experimental conditions of the present study. This was verified by an additional experiment (Figure 4). We measured digital finger blood pressures in six subjects at the index finger using the Portapres device and at the middle finger using a Finapres device (Finapres 2300; Ohmeda, Englewood, CO, U.S.A.) simultaneously, both when the forearm was

elevated 50 cm above the heart and when it was fixed at heart level, in a similar manner as in experiment 2. When these blood pressure values were expressed as an average per min, Portapres blood pressure values were highly correlated with Finapres blood pressure values (the correlation coefficients were 0.96 and 0.99 for systolic and diastolic blood pressure values respectively), and these Portapres and Finapres blood pressure values showed a narrow scattering around the identity line ($y = x$) (Figure 4). Therefore it is concluded that the Portapres measured digital blood pressure accurately in the present study.

In summary, we found that MSNA activation during static handgrip exercise was 51% greater when the exercising forearm was elevated 50 cm above the heart compared with when it was fixed at heart level. The present findings suggest that forearm elevation augments sympathetic activation during handgrip exercise. In addition, the stimulatory effect of forearm elevation on exercising MSNA may be mediated primarily by reduced forearm perfusion pressure and increased activation of the muscle metaboreflex.

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