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INFLUENCE OF FORCE ON MUSCLE AND SKIN SYMPATHETIC NERVE ACTIVITY DURING SUSTAINED ISOMETRIC CONTRACTIONS IN HUMANS

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SUMMARY

1. Our purpose was to test the hypothesis that efferent sympathetic nerve activity to non-active skeletal muscle (MSNA) and skin (SSNA) is independent of the level of force during sustained submaximal isometric contractions in humans.

2. In twelve healthy subjects, arterial blood pressure, heart rate, and MSNA ($n = 6$) or SSNA ($n = 6$) (peroneal microneurography) were recorded before and during isometric handgrip contractions sustained to exhaustion at 20, 40 and 60% of maximal force. Responses were examined at similar percentages of endurance time at each level of force.

3. Contraction duration decreased progressively with increasing force (495 ± 54, 140 ± 13, 73 ± 8 s, respectively), but peak ratings of perceived effort were similar for the three force levels.

4. The peak increases in systolic pressure were not different among the three levels of force. The increases in diastolic and mean pressure were similar at 40 and 60% of maximal force, but were smaller at the end of 20% of maximal force. The contraction-induced rise in heart rate was directly related to the level of force.

5. The contraction-evoked stimulation of both MSNA and SSNA was similar during handgrip at 40 and 60% of maximal force, but was much less during handgrip at 20% of maximal force. The increases in SSNA were associated with increases in both skin blood flow and skin electrical conductance suggesting primarily sudomotor fibre activation.

6. These findings indicate that there is a minimum force necessary to elicit peak levels of MSNA and SSNA during sustained isometric contractions in humans. When normalized to endurance time, however, the regulation of these sympathetic outflows appears to be independent of force above this minimum level. The results also indicate that during this type of muscle activity the relationship between force and heart rate is different to that between force and peripheral sympathetic discharge.

INTRODUCTION

In humans, sustained submaximal isometric contractions stimulate sympathetic nerve activity to both non-active skeletal muscle (MSNA) (Mark, Victor, Nerhed & Wallin, 1985; Seals & Victor, 1991) and skin (SSNA) (Saito, Naito & Mano, 1990;

Vissing, Scherrer & Victor, 1991). An important determinant governing the contraction-induced activation of sympathetic outflow to these regions may be the level of force. It has been shown that the magnitude of increase in MSNA or SSNA at a particular absolute point in time after the onset of contraction (e.g. 90, 120 s, etc.) is directly related to the force (Saito, Mano, Abe, & Iwase, 1986; Seals, Chase & Taylor, 1988; Vissing *et al.* 1991). It is also well documented, however, that, once stimulated, MSNA and SSNA increase throughout the duration of a contraction (Saito, Mano & Iwase, 1989; Seals & Enoka, 1989; Vissing *et al.* 1991), and that the endurance time for isometric contractions is inversely proportional to the level of force (Petrofsky, 1982; Lind, 1983). Thus, it is possible that the level of MSNA and/or SSNA produced during an isometric contraction is not affected by the level of force when examined at end-contraction or at similar points relative to endurance time.

Accordingly, the purpose of this investigation was to test the hypothesis that the regulation of MSNA and SSNA during submaximal isometric contractions in humans is independent of the level of force. To accomplish this, peroneal MSNA or SSNA was recorded in healthy human subjects during three levels of isometric handgrip. Each level of contraction was sustained to the same perceptual and performance endpoint (i.e. exhaustion), and the responses were compared at similar percentages of the respective endurance times. Preliminary results from the present study have been published in abstract form (Seals, Reiling & Johnson, 1990; Reiling & Seals, 1991).

METHODS

Subjects

Twelve healthy men and women aged 22–29 years served as subjects after providing written, informed consent. They were normotensive (brachial artery blood pressure $< 140/90$ mmHg) and were taking no medications. All experimental procedures and protocols in which they participated were approved by the Institutional Committee for Research on Human Subjects.

Experimental measurements

Multiunit recordings of either MSNA ($n = 6$) or SSNA ($n = 6$) were obtained from the right peroneal nerve at the fibular head using the microneurographic method as described in detail previously (Seals *et al.* 1988; Wallin & Fagius, 1988). The neural activity was amplified, filtered (bandwidth, 700–2000 Hz), full-wave rectified, and integrated (time constant, 100 ms). The criteria for MSNA included elicitation of a muscle contraction with weak intraneural electrical stimulation, elicitation of afferent discharge upon tapping or stretching the muscle in the innervated area, and spontaneous, pulse-synchronous bursting activity that was stimulated by blood pressure-lowering manoeuvres and end-expiratory apnoea, but not by arousal (unexpected loud noise) or a deep inspiration (Wallin, 1983; Wallin & Fagius, 1988). The criteria for SSNA included elicitation of paraesthesias with weak intraneural electrical stimulation, elicitation of afferent discharge with light stroking of the skin in the innervated area, and erratic, relatively non-pulse-synchronous activity increased by arousal and a deep inspiration, but not by stimuli for MSNA (Wallin, 1983; Wallin & Fagius, 1988). Because multiunit recordings of SSNA consist of activity from both vasoconstrictor and sudomotor neurons (Jänig, Sundlöf & Wallin, 1983), skin blood flow (Laserflow Blood Perfusion Monitor, model 403-A, TSI, St Paul, MN, USA) and electrical skin conductance (Bioderm model 2701, UFI, Morro Bay, CA, USA) also were measured in the innervated regions.

A continuous recording of arterial blood pressure was obtained using finger photoplethysmography (Finapres monitor no. 2300, Ohmeda, USA). The cuff was positioned on the second phalanx of the middle finger of the left hand. Arterial blood pressure measured with this method correlates well with direct radial artery recordings both at rest and during contralateral isometric

handgrip exercise (Parati, Casadei, Groppelli, Di Rienzo & Mancia, 1989). Heart rate was determined from a standard electrocardiogram. Breathing was monitored using a pneumobelt positioned at mid-abdomen in order to detect abnormal respiratory manoeuvres which could affect sympathetic activity. Ratings of perceived effort (Borg, 1970) were obtained to ensure that the same peak level of voluntary effort was attained during each trial of a particular subject.

Experimental protocol

In orientation sessions, all subjects were trained to perform isometric handgrip contractions to exhaustion at the same relative levels of force and under the same laboratory conditions as in the actual experiment. During the experimental session, maximal voluntary handgrip force was determined prior to microneurography as described previously (Seals *et al.* 1988). After an adequate nerve recording was obtained subjects rested quietly in the supine position for 10–15 min to ensure that sympathetic activity and the cardiorespiratory variables were stable. This was followed by an additional 3–5 min period of rest used to establish baseline (control) levels of all variables. Isometric handgrip exercise was then performed at 20, 40 or 60% of maximal force until exhaustion, defined as both an inability to maintain target force and the attainment of a peak level of perceived effort. This sequence was repeated at the other two levels of force in randomized order; 20–25 min of rest was allowed between the end of a contraction and the start of the subsequent control period. Both the target force and the actual handgrip force were shown on an oscilloscope to assist the subject in maintaining the appropriate, constant level. Sympathetic activity, arterial pressure, heart rate, and breathing were measured continuously during the control and contraction periods. During the contraction periods, force was measured continuously, whereas ratings of perceived effort were obtained every 15 s. No abnormal respiratory manoeuvres were noted during any of the protocols.

Data analysis

Bursts of MSNA were determined by visual inspection of the neurogram and the area under each burst was calculated by computer. Because individual bursts of SSNA can be difficult to identify, a cursor was set just above the noise level by the investigator and the area above this level was determined by computer. Total minute activity for both MSNA and SSNA was taken as the total burst area per minute.

For each control period, sympathetic activity, heart rate and arterial pressure were averaged over 30 s intervals, and a grand mean determined. For each isometric contraction period of each subject, averages for these variables were determined in 20% intervals (i.e. 0–20, 20–40, 40–60, 60–80 and 80–100% of endurance time).

Differences between the control and contraction periods within a trial and among the three trials were assessed by analysis of variance with repeated measures; specific comparisons were made using planned contrasts (SUPERANOVA Software, Abacus Concepts, Inc., Berkeley, CA, USA). P values $< 0{\cdot}05$ were considered significant. All data are presented as means $\pm$ S.E.M.

RESULTS

The average endurance times at 20, 40 and 60% of maximal force were 495 ± 54, 140 ± 13, and 73 ± 8 s, respectively (all $P < 0{\cdot}05$ *vs.* each other). At all three levels of force, ratings of perceived effort rose continuously from the onset of contraction to the point of exhaustion (Fig. 1). Perceived effort was directly related to force during the initial phase of the contractions, but thereafter ratings were similar among the three contraction intensities, reaching identical peak levels at exhaustion.

Arterial blood pressure rose progressively from onset to end-contraction at all three levels of force (Fig. 2). There were no differences in the systolic pressure responses during the three contraction intensities. Diastolic and mean pressures increased similarly during handgrip at the 40 and 60% of maximal force levels attaining identical peak levels; however, the increases at 20% of maximal force were

smaller during the latter phase (final 20%) of contraction ($P < 0{\cdot}05$ *vs.* 40 and 60% of maximal force). Heart rate also rose continuously throughout handgrip at each level of force (Fig. 2). The initial rapid rates of rise, the more gradual increases thereafter, and peak levels of heart rate all were directly related to the contraction force (all $P < 0{\cdot}05$ *vs.* each other).

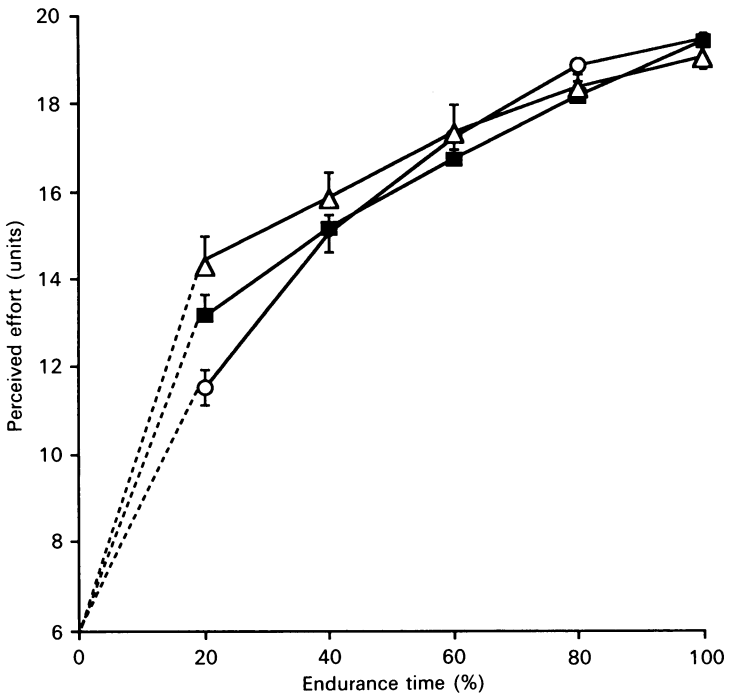

Fig. 1. Average ratings of perceived effort in twelve subjects who performed isometric handgrip at 20 (○), 40 (■) and 60% (△) of maximal force to exhaustion. Ratings were similar among the three levels of force over the latter portion of the contraction periods. Data are means ± S.E.M.

MSNA remained at control levels during the initial phase of the contractions, and then rose progressively until exhaustion (Fig. 3). The responses were similar during contractions at 40 and 60% of maximal force (peak increases in total activity above control = 435–442 units min^{-1}). However, both the rate of rise and the peak levels attained (left side of Fig. 4) were smaller during handgrip at 20% of maximal force (peak increase in total activity above control = 195 units min^{-1}; $P < 0{\cdot}05$ *vs.* 40 and 60% of maximal force). When the circulation to and from the active forearm was arrested by the inflation of an upper-arm cuff to suprasystolic levels just prior to stopping contraction in one of the subjects, the end-contraction differences in MSNA were maintained during a subsequent 90 s period of postcontraction forearm blood flow occlusion (right side of Fig. 4).

SSNA increased immediately above control levels during each contraction

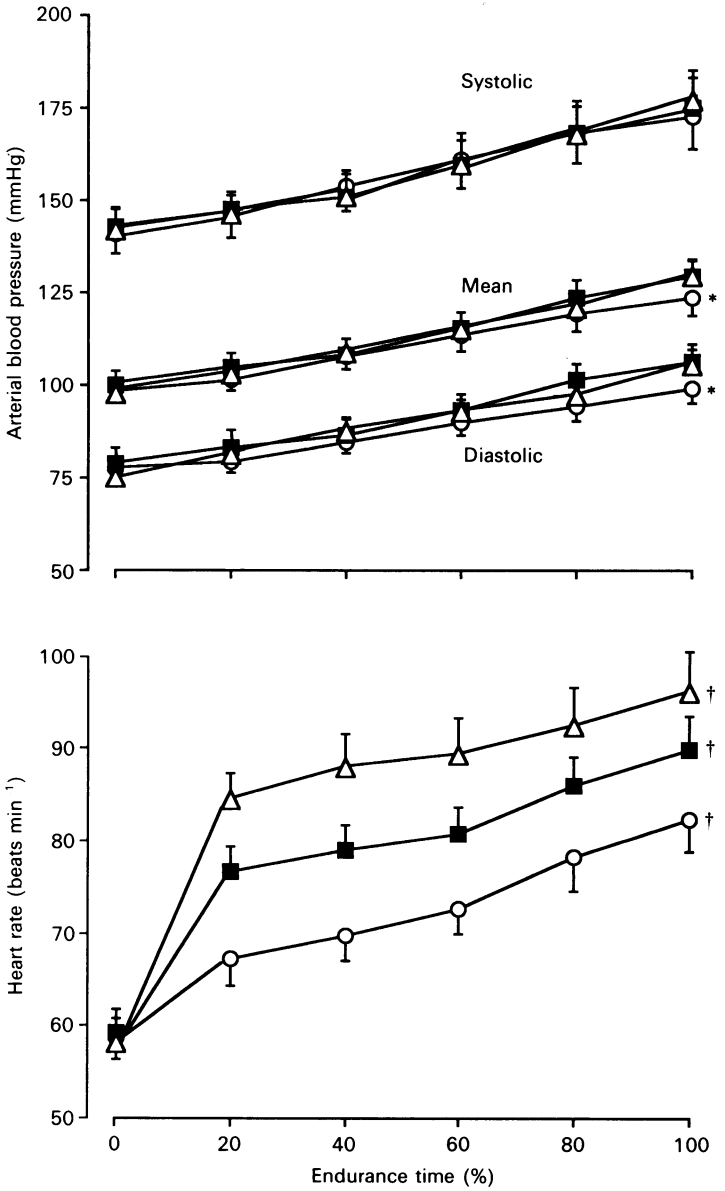

Fig. 2. Average levels of arterial blood pressure and heart rate in twelve subjects before (point 0) and during isometric handgrip. There were no differences in the systolic pressure responses among the three contraction intensities, but the mean and diastolic pressure responses were smaller during contractions at 20% of maximal force. Heart rate increased in direct proportion to the level of force. * $P < 0{\cdot}05$ for 20 *vs.* 40 and 60% levels; † $P < 0{\cdot}05$ *vs.* other two levels. See Fig. 1 for other details. Symbols represent handgrip at: ○, 20; ■, 40; and △, 60% of maximal force.

intensity, and rose gradually thereafter attaining peak levels at exhaustion (Fig. 5). The increases were similar during handgrip at 40 and 60% of maximal force (peak increases in total activity above control levels = 228–230 units min^{-1}), but both the rates of rise and peak levels attained (Fig. 6) were smaller throughout the contraction

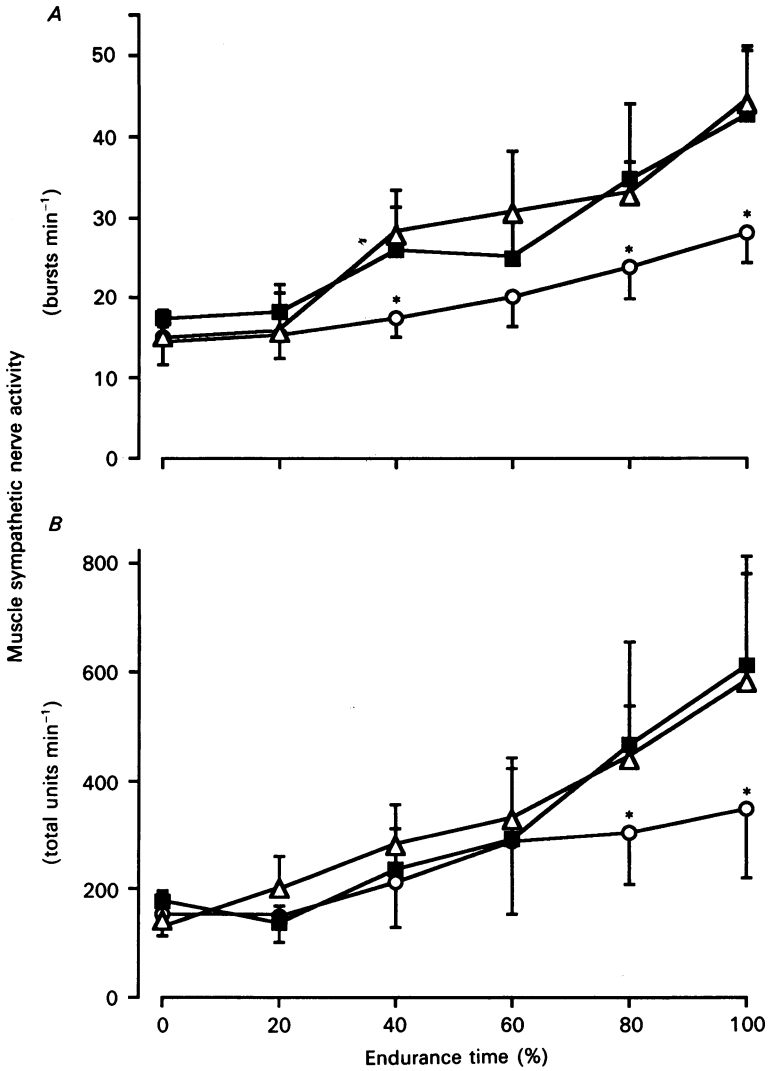

Fig. 3. Muscle sympathetic nerve activity burst frequency (*A*) and total activity (*B*) in six subjects before and during isometric handgrip. Responses were similar during handgrip at 40 and 60% of maximal force, but were smaller at 20% of maximal force. * $P < 0{\cdot}05$ for 20 *vs.* 40 and 60% levels. See Figs 1 and 2 for other details. Symbols represent exercise at: ○, 20; ■, 40; and △, 60% of maximal force.

period at 20% of maximal force (peak increases in total activity above control = 108 units min^{-1}; $P < 0{\cdot}05$ *vs.* 40 and 60% of maximal force).

During handgrip at 40 and 60% of maximal force, skin blood flow increased

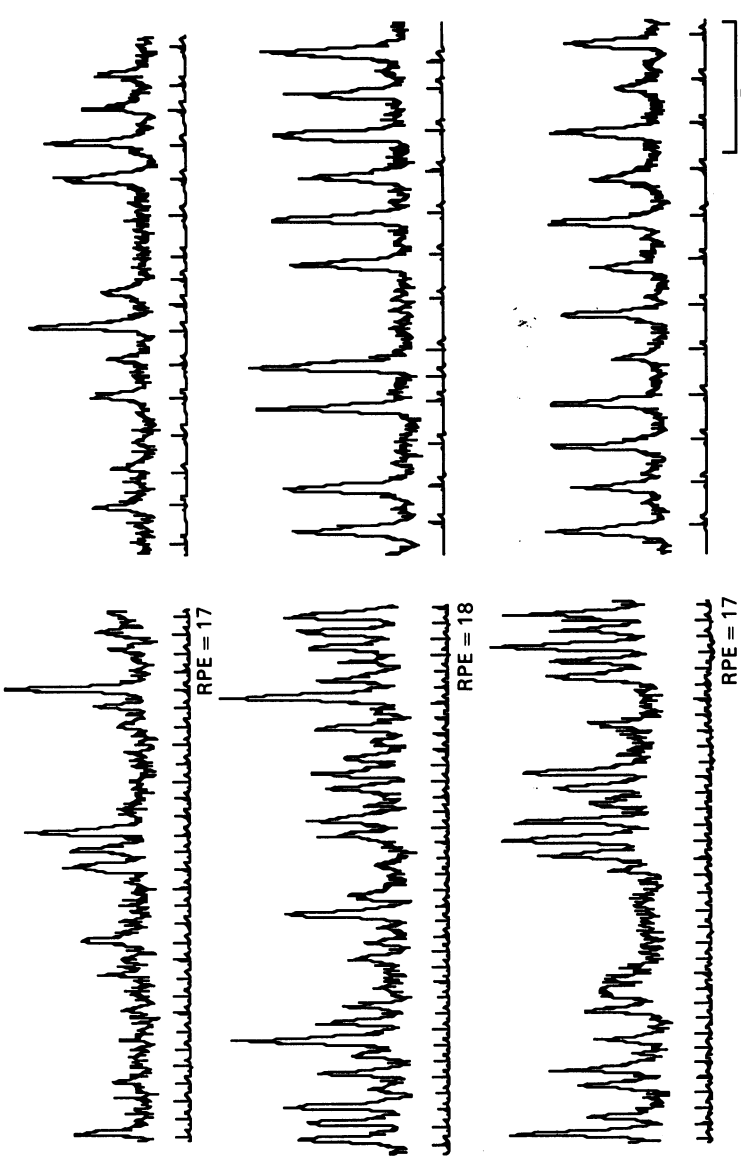

Fig. 4. Peak levels of muscle sympathetic nerve activity (MSNA) during isometric handgrip at three contraction intensities (*A*) and the corresponding levels during post-handgrip forearm circulatory arrest (*B*) in one subject. Note the greater levels of MSNA during both exercise and postcontraction circulatory arrest at 40 and 60% of maximal force *vs.* 20% of maximal force (burst frequency is lower during circulatory arrest than during exercise due to a marked postcontraction fall in heart rate). Ratings of perceived effort (RPE) were similar among the three levels of force. MVC, maximal voluntary contraction.

slightly at the onset of contraction and thereafter rose steadily reaching peak levels of ~ 100% above control at end-contraction. During the 20% of maximal force contractions, the initial rise was less and peak levels of only ~ 50% above control were attained at end-contraction (peak increases above control = 1·6±0·9, 4·3±1·4

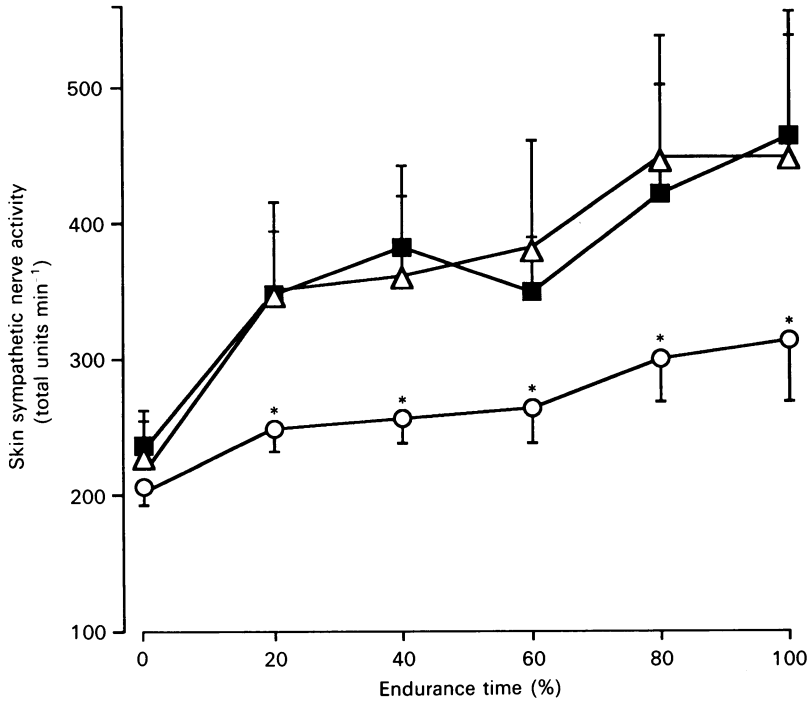

Fig. 5. Total minute skin sympathetic nerve activity in six subjects before and during isometric handgrip. Responses were similar during handgrip at 40 and 60% of maximal force, but were smaller at 20% of maximal force. *$P < 0.05$ for 20 *vs.* 40 and 60% levels. See Figs 1 and 2 for further details. Symbols represent exercise at: ○, 20; ■, 40; and △, 60% of maximal force.

and 4·6±1·4 units for 20, 40 and 60% of maximal force, $P < 0.05$). Skin electrical conductance rose by 20–30% soon after the onset of contraction at all force levels, and then increased more gradually, attaining peak levels of 30–50% above control at end-exercise. The magnitudes of the increases were not consistently related to contraction force (peak increases above control levels = 2·6±1·0, 3·2±0·6 and 2·8±1·0 units for 20, 40 and 60% of maximal force).

There were no differences in the control levels of any variable prior to the three contraction periods (Figs 2, 3 and 5).

DISCUSSION

The primary new conclusion from the present findings is that during sustained submaximal isometric contractions in humans the regulation of both non-active skeletal muscle and skin sympathetic discharge is influenced by the level of force

maintained. At least during isometric handgrip, contractions > 20% of maximum voluntary force are necessary to stimulate peak levels of sympathetic outflow to these regions. Above this minimal level, however, the control of MSNA and SSNA appears to be independent of force.

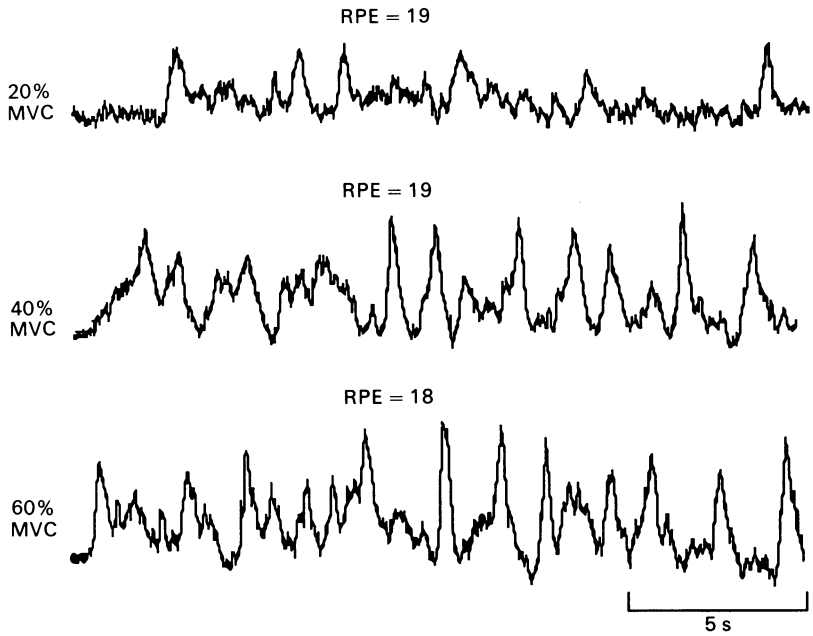

Fig. 6. Peak levels of skin sympathetic nerve activity (SSNA) and corresponding ratings of perceived effort (RPE) before and during isometric handgrip exercise in one subject. Note the greater levels of SSNA evoked during contractions performed at 40 and 60% of maximal force *vs.* 20% of maximal force.

Previous investigations in which isometric handgrip exercise was performed at different levels of force, but for the same durations, have demonstrated that at any particular absolute point in time after the onset of contraction the stimulation of both MSNA (Saito *et al.* 1986; Seals *et al.* 1988) and SSNA (Vissing *et al.* 1991) is directly related to the force maintained. However, because once stimulated, MSNA and SSNA increase throughout the duration of an isometric muscle contraction (Saito *et al.* 1989; Seals & Enoka, 1989; Vissing *et al.* 1991), and at any absolute point during the task subjects are closer to exhaustion as the level of force increases, the responses are being sampled under very different local (i.e. active muscle) conditions. To determine if the control of these sympathetic outflows is dependent on the level of force, we sought to examine MSNA and SSNA at similar perceptual and performance timepoints. This was accomplished by having our subjects sustain each level of force to exhaustion, a standardized performance end-point that was also associated with similar peak ratings of voluntary effort. When examined in this manner, the direct relationship between the stimulation of MSNA and SSNA and the

level of force observed in previous studies is no longer evident. Instead, there seems to be a threshold level above which the regulation of these sympathetic outflows is independent of force.

We found that skin blood flow and skin electrical conductance in the regions innervated by our SSNA recordings both increased progressively with time during the contractions. These responses indicate that the handgrip-evoked increases in multiunit SSNA represented primarily a stimulation of sudomotor fibres innervating sweat glands, in support of previous investigations (Saito *et al.* 1990; Vissing *et al.* 1991). While it is not possible to determine the behaviour of skin vasoconstrictor fibres *per se* under these experimental conditions in the human, their activity appears to be controlled in an antagonistic manner to that of sudomotor fibres in many physiological states in the cat (Gregor & Jänig, 1977; Jänig *et al.* 1984). Thus, it is possible that skin vasoconstrictor activity actually was inhibited during the contractions, which would be consistent with the increases in skin blood flow. In contrast to a previous report (Vissing *et al.* 1991), we did not observe a direct relationship between the increases in SSNA and skin electrical conductance in the group as a whole. This may simply be the result of differences in methodology. Alternatively, there may have been differences in the degree of sudomotor fibre activation between the two studies. Wallin, Blumberg & Hynninen (1983) found that during graded intraneural stimulation of skin fibres, reductions in skin electrical resistance were directly related to the stimulation rate at lower, but not higher, frequencies. Perhaps, the firing frequencies attained during contractions in the present study approached or fell in the latter range.

It is somewhat surprising that force had the same effects on MSNA and SSNA in that the regulation of these two sympathetic outflows during isometric exercise are thought to be mediated by different mechanisms. MSNA is believed to be primarily stimulated by the contraction-induced activation of muscle chemoreflexes (metaboreflexes) (Mark *et al.* 1985; Victor, Bertocci, Pryor & Nunnally, 1988; Pryor, Lewis, Haller, Bertocci & Victor, 1990), whereas SSNA appears to be stimulated by central command or, possibly, muscle mechanoreflexes (Saito *et al.* 1990; Vissing *et al.* 1991). If so, our findings suggest that the contraction-induced elevations in these excitatory central nervous system inputs were similar at 40 and 60% of maximal force, but less at 20% of maximal force.

With regard to muscle chemoreflexes, whose activation during isometric contractions is facilitated by ischaemia (Kaufman, Longhurst, Rybicki, Wallach & Mitchell, 1983), the higher forces probably resulted in greater mechanical compression of feed arteries and, consequently, greater suppression of active muscle blood flow than the lowest force (Donald, Lind, McNicol, Humphreys, Taylor & Staunton, 1967). Moreover, the fact that end-contraction differences in MSNA were sustained in a subject who underwent postcontraction arrest of the active forearm circulation (Fig. 4), thus maintaining muscle chemoreflex activation without central command or muscle mechanoreflex feedback, supports the likelihood of greater muscle chemoreflex stimulation of MSNA during handgrip at the two highest levels of force.

With respect to muscle mechanoreflexes, during electrically evoked contractions in anaesthetized animals, the response of these afferents appears to be in proportion to

the absolute level of isometric force generated (Kaufman *et al.* 1983). Thus, it is likely that this type of afferent input was greater at the two higher contraction forces than at the lowest of force in the present study.

Central motor command, on the other hand, cannot be measured. In the present study, subject ratings of perceived effort were similar among the three levels of force during all but the initial phase of the contraction periods. These subjective ratings of effort have been used in the past to estimate changes in central command during exercise (Gandevia & Hobbs, 1990; Vissing *et al.* 1991). However, such a quantitative relationship remains to be established experimentally. Therefore, while it is theoretically possible that in the present study central command was greater during the contractions at the two highest levels of force and produced proportionately greater increases in SSNA, our data can neither support nor refute this postulate.

In support of an earlier study by Funderburk, Hipskind, Welston & Lind (1974), we found a direct relationship between the handgrip-evoked tachycardia and the level of force. The increase in heart rate during isometric handgrip contractions appears to be primarily mediated by central command and/or active muscle mechanoreflex inhibition of cardiac vagal nerve activity (Mark *et al.* 1985; Victor, Pryor, Secher & Mitchell, 1989). There is, however, evidence that sympathetic adrenergic mechanisms (i.e. rise in circulating catecholamine levels and/or an increase in cardiac sympathetic nerve activity) contribute to tachycardia during the latter phase of a sustained handgrip contraction (Martin, Shaver, Leon, Thompson, Reddy & Leonard, 1974), possibly as a consequence of active muscle chemoreflex activation (Scherrer, Pryor, Bertocci & Victor, 1991). Thus, the exact mechanism(s) by which force exerts its influence on the tachycardia attendant to sustained isometric muscle contraction in the human is, at present, unknown. The present findings do demonstrate, however, that the relationship between force and heart rate is different from that between force and both sympathetic vasoconstrictor activity to skeletal muscle and skin sudomotor fibre activity.

Finally, our findings indicate the level of force maintained has relatively little influence on the regulation of arterial blood pressure during sustained isometric handgrip. This is generally consistent with the prior study by Funderburk *et al.* (1974) who reported that their three subjects demonstrated similar arterial pressure responses during handgrip performed to exhaustion at the same three relative levels of force used in the present investigation. We did, however, find that the increases in diastolic and mean arterial pressure were slightly, but significantly smaller during the latter portion of the contraction period at 20 *vs.* 40 and 60% of maximal force. This is consistent with the smaller rise in MSNA observed during this period in that we have previously demonstrated a strong relationship between arterial pressure and MSNA under these conditions (Seals *et al.* 1988).

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