Central motor command activates sympathetic outflow to the cutaneous circulation in humans

Susanne F. Vissing and Else M. Hjortsø

The Copenhagen Muscle Research Centre and Department of Anaesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

1. The aim of this study was to provide direct evidence that sympathetic outflow to the skin in humans is governed by central neural mechanisms.

2. Microneurographic measurements of skin sympathetic nerve activity (SNA) from the peroneal nerve was performed in nine subjects during: (1) static hand grip at 10, 20 and 30% maximal voluntary contraction (MVC); and (2) attempted static hand grip during partial neuromuscular blockade produced by injection of vecuronium.

3. Two minutes of static hand grip at 20 and 30% MVC (force output, 9·6 ± 0·2 and 14·4 ± 0·3 kg, respectively) evoked significant increases in skin SNA that were graded to the intensity of the exercise. Static hand grip at 10% MVC (force output, 4·8 ± 0·1 kg) caused a small but insignificant increase in skin SNA.

4. During vecuronium-induced neuromuscular blockade, subjects failed to maintain a force output equivalent to the output produced during 10% MVC before vecuronium (force output: 1st min, 4·4 ± 0·6 kg; 2nd min, 2·1 ± 0·4 kg), in spite of maximal effort being applied. This attempted hand grip exercise consistently evoked considerable increases in skin SNA that did not significantly differ from the responses produced by hand grip at 30% MVC; total skin SNA increased by 246 ± 93% during 2 min of attempted hand grip and increased by 243 ± 77% during 2 min of static hand grip at 30% MVC (means ± S.E.M., $P < 0·05$). These increases in skin SNA were not due to activation of resting muscles because measurements of surface electromyography showed no activity in resting forearm muscles during static or attempted hand grip exercise.

5. This study provides direct neurophysiological evidence that central motor command can activate sympathetic outflow. During static hand grip, central motor command is the primary mechanism that stimulates sympathetic outflow to skin.

Two main theories have been proposed to explain the underlying mechanisms that activate sympathetic outflow in humans during exercise. The first is that sympathetic activation is caused by a contraction-induced reflex arising in chemically and mechanically sensitive muscle afferents (Volkmann, 1841; Alam & Smirk, 1937; McCloskey & Mitchell, 1972; Kaufmann, Longhurst, Rybicki, Wallach & Mitchell, 1983; Victor, Rotto, Pryor & Kaufmann, 1989). The other is that during exercise, the central motor command signal emanating from the rostral brain radiates to autonomic circuits in the brainstem, causing parallel activation of motor and sympathetic neurons (Krogh & Lindhard, 1913; Eldridge, Millhorn & Waldrop, 1981). In conscious humans, central command is related to voluntary motor effort.

Obviously, a demonstration of an important role for one mechanism does not exclude the importance of the other mechanism. There is now some evidence to suggest that the relative contributions of central command and muscle-afferent reflexes in causing the sympathetic activation during exercise can vary, depending on the specific sympathetic outflow under study. For example, several neurophysiological studies both isolating the effects of muscle afferents (Mark, Victor, Nerhed & Wallin, 1985; Victor, Bertocci, Pryor & Nunnally, 1988; Wallin, Victor & Mark, 1989; Pryor, Lewis, Haller & Victor, 1990; Vissing, Scherrer & Victor, 1991) and isolating effects of central command (Victor, Pryor, Secher & Mitchell, 1989) have shown that during static exercise in humans, muscle afferent activation is the primary mechanism that triggers sympathetic discharge to muscle. In contrast, a recent study comparing effects of static exercise on muscle *versus* skin nerve fascicles suggested that during exercise in humans, central motor command is the primary mechanism that triggers sympathetic activation to skin

(Vissing *et al.* 1991). In that study no single finding definitely proved that central command caused the increases in skin sympathetic nerve activity (SNA) during hand grip exercise. However, based on the time course of the sympathetic activation and on interventions designed to increase central command while decreasing effects of muscle afferents, that hypothesis was strongly supported.

Therefore, the aim of this study was to provide direct evidence that central motor command stimulates sympathetic outflow to skin. To isolate the effects of central motor command and eliminate or minimize input from muscle afferents, microelectrode recordings of sympathetic discharge from skin nerve fascicles of the peroneal nerve were performed during partial neuromuscular blockade. The rationale was that the neuromuscular blockade would decrease or abolish force development during attempted exercise. This would eliminate or minimize feedback from metabo- and mechanoreceptor afferents, but increase the contribution of central command because maximal effort would be needed in an attempt to sustain contraction in the weakened muscles.

METHODS

Subjects

Fourteen males aged 20–30 years participated in this study. All subjects were normotensive, had no history of cardiopulmonary disease or evidence of it during physical examination and were taking no medication at the time of the study. The studies were approved by the Ethics Committee of Copenhagen, and each subject gave written informed consent to participate.

Measurements

Subjects were studied in the supine position. Heart rate was measured continuously by an electrocardiogram. Intra-arterial pressure was measured with a catheter in the radial artery.

Respiratory movements were monitored with pneumographs around the abdomen and chest to detect the inadvertent performance of Valsalva's manoeuvre, held expiration, or a sudden deep breath, because such respiratory manoeuvres can have pronounced effects on skin SNA (Delius, Hagbarth, Hongell & Wallin, 1972).

Multiunit recordings of postganglionic SNA were obtained using unipolar tungsten microelectrodes inserted selectively into skin nerve fascicles of the peroneal nerve using the microneurographic technique (Vallbo, Hagbarth, Torebjörk & Wallin, 1979). The neural signals were amplified, filtered (bandwith, 700–2000 Hz), rectified, and integrated to obtain a mean voltage display of SNA. A recording of skin SNA was considered acceptable when: (1) weak electrical stimulation through the microelectrode elicited paraesthesias without muscle contraction; (2) the mean voltage neurogram revealed bursts of neural activity (with a signal-to-noise ratio greater than 3 : 1); and (3) the neural activity increased during arousal stimuli (loud noise, skin pinch). Neurograms revealing simultaneous skin and muscle sympathetic activity were not accepted.

Sympathetic bursts were identified by inspection of the filtered and mean voltage neurograms. The number of bursts per minute was used as an index of the frequency of sympathetic discharge. The filtered neurogram also was routed to a window discriminator that counted nerve spikes exceeding a threshold voltage set just above the noise level. The number of nerve spikes per minute was counted using an integrator circuit that resets after each 100 spikes. The output of the integrator was expressed as a percentage of the control value to provide an estimate of relative changes in integrated activity. Nine records obtained in this study were played back and systematically evaluated to estimate intra-observer variability in identifying bursts. The intra-observer variability had a mean of 3·4% (range, 0–11%). All records were analysed by the same investigator.

Inadvertent contraction of the leg muscles, adjacent to the recording electrode, produces electromyographic artifacts that are easily distinguished from sympathetic bursts; neurograms containing such artifacts were excluded from analysis.

Sympathetic activity, electrocardiogram, respiratory excursions, intra-arterial blood pressure and force of muscle contraction were recorded continuously on a Gould TA 2000 thermal array recorder (Gould Corp., Oxnard, CA, USA) and on a DTR 1800 digital audio recorder (Bio Logic, France).

In protocol 4 (see below), rectified smoothed surface electromyographical activity (EMG) was recorded with skin electrodes (5 mm diameter) (Blue sensor type N-10-A, Medicotest, Copenhagen, Denmark) over the exercising and resting forearm muscles (right and left flexor carpi radialis) connected to a DISA-EMG amplifier (Copenhagen, Denmark) with a built-in mean voltage unit kit (type 15C01).

In protocol 4, oxygen uptake and ventilation was monitored using open-circuit spirometry (Medical Graphics Corp., Spiroharma, Denmark).

Partial neuromuscular blockade

Vecuronium (Norcuron, Organon Teknika, Turnhout, Belgium) was injected into a forearm vein at an initial dose of 15 μg (kg body wt)$^{-1}$. Small supplemental doses of 5 μg (kg body wt)$^{-1}$ were administered until the subject's maximal voluntary hand grip contraction was decreased to a value less than 50% of the initial maximal contraction force before vecuronium. The neuromuscular blockade was maintained throughout the study by injections of supplemental doses of vecuronium of 5 μg (kg body wt)$^{-1}$. To ensure normal respiratory function during the experiments, arterial gases were monitored repeatedly and respiratory movement was registered continuously as previously described.

Interventions

At the beginning of each experiment, maximal voluntary contraction (MVC) was determined using a hand grip dynamometer. During hand grip, subjects were given visual feedback of force output on an oscilloscope. Subjects were instructed to avoid performance of a Valsalva manoeuvre and to avoid inadvertent contraction of non-exercising muscles during hand grip. At the end of each exercise period, subjects were asked to rate their perceived effort on a scale of 6 (minimal effort) to 20 (maximal effort) as a subjective index of central command (Borg, 1970).

Before beginning the protocol, subjects rested quietly for 10 min to ensure a stable baseline.

Table 1. Skin sympathetic responses to static hand grip at 30% maximal voluntary contraction and attempted hand grip exercise during neuromuscular blockade

	Mean arterial pressure (mmHg)	Heart rate (beats min^{-1})	Skin sympathetic activity (bursts min^{-1})	Skin sympathetic activity Integrated activity (%)
Static hand grip				
Control	89 ± 2	54 ± 3	20 ± 2	100
30 s	96 ± 3	65 ± 2	44 ± 3*	254 ± 33*
60 s	103 ± 4	70 ± 4*	45 ± 3*	264 ± 41*
90 s	112 ± 4*	71 ± 4*	49 ± 3*	338 ± 82*
120 s	120 ± 4*	73 ± 4*	46 ± 3*	343 ± 77*
Recovery	91 ± 3	52 ± 2	21 ± 2	116 ± 30
Attempted hand grip				
Control	96 ± 3	56 ± 2	28 ± 3	100
30 s	101 ± 4	66 ± 3	51 ± 3*	274 ± 43*
60 s	108 ± 5*	68 ± 4*	50 ± 3*	267 ± 49*
90 s	110 ± 4*	70 ± 4*	52 ± 3*	287 ± 94*
120 s	112 ± 4*	73 ± 4*	55 ± 3*	346 ± 93*
Recovery	95 ± 2	56 ± 2	30 ± 2	114 ± 11

Data are means ± S.E.M. for nine subjects. *$P < 0.05$ *vs.* control.

Specific protocols

Protocol 1. Graded levels of static hand grip before partial neuromuscular blockade (29 experiments on 9 different subjects).

Effects of 2 min of static hand grip at 10, 20 and 30% of maximal voluntary contraction (MVC) was studied to examine responses to three levels of effort before vecuronium injection. To minimize muscular fatigue, the order of the exercise bouts were from least to most difficult with 10 min rest periods between bouts.

Protocol 2. Attempted hand grip during partial neuromuscular blockade (15 experiments on 9 different subjects).

By injecting vecuronium the subjects' maximal hand grip force was decreased to a level below 50% of the initial MVC. During this partial neuromuscular blockade subjects attempted to sustain a hand grip contraction for 2 min at a tension equivalent to 10% of the maximum force before partial neuromuscular blockade.

Protocol 3. Mental arithmetic (14 experiments on 7 different subjects).

The mental stress was used as an internal control, that is a non-exercise stimulus to skin sympathetic nerve activity. Responses to mental stress were compared before and during partial neuromuscular blockade produced by vecuronium.

Protocol 4. Recruitment of other muscle groups during attempted hand grip (15 experiments on 3 different subjects).

To examine if attempted static hand grip exercise during neuromuscular blockade was accompanied by activity in other muscle groups, protocols 1 and 2 were repeated during simultaneous measurements of muscular activity estimated by EMG and changes in metabolism estimated by oxygen uptake.

Data analysis

Statistical analysis was performed with Page's test for ordered alternatives followed by multiple comparison with a control, or by Wilcoxon ranked sign test (Siegel & Castellan, 1988). Results are expressed as means ± S.E.M. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Responses to static hand grip and attempted static hand grip during neuromuscular blockade

Two minutes of static hand grip at 20 and 30% MVC (force output, 9·6 ± 0·2 and 14·4 ± 0·3 kg, respectively) evoked significant increases in skin SNA that were graded to the intensity of the exercise. Static hand grip at 10% MVC (force output, 4·8 ± 0·1 kg) caused a small but insignificant increase in skin SNA (Table 1 and Figs 1, 2 and 3). During neuromuscular blockade attempted static hand grip (force output: 1st min, 4·4 ± 0·6 kg; 2nd min, 2·1 ± 0·4 kg) consistently evoked considerable increases in skin SNA that did not differ significantly from the responses produced by hand grip at 30% MVC. Total skin SNA increased by 246 ± 93% (*versus* baseline during neuromuscular blockade) during 2 min of attempted hand grip and increased by 243 ± 77% (*versus* baseline before neuromuscular blockade) during 2 min of static hand grip at 30% MVC (means ± S.E.M., $P < 0.05$). The increases in skin SNA preceded the onset of force development, accelerated during sustained and/or attempted hand grip and resolved promptly with the cessation of motor effort (Table 1 and Figs 1, 2 and 3).

Increases in skin SNA were proportional to the subjects' rating of perceived motor effort, which increased from 9 ± 1 to 13 ± 1 to 16 ± 1 ($P < 0.05$) when the level of

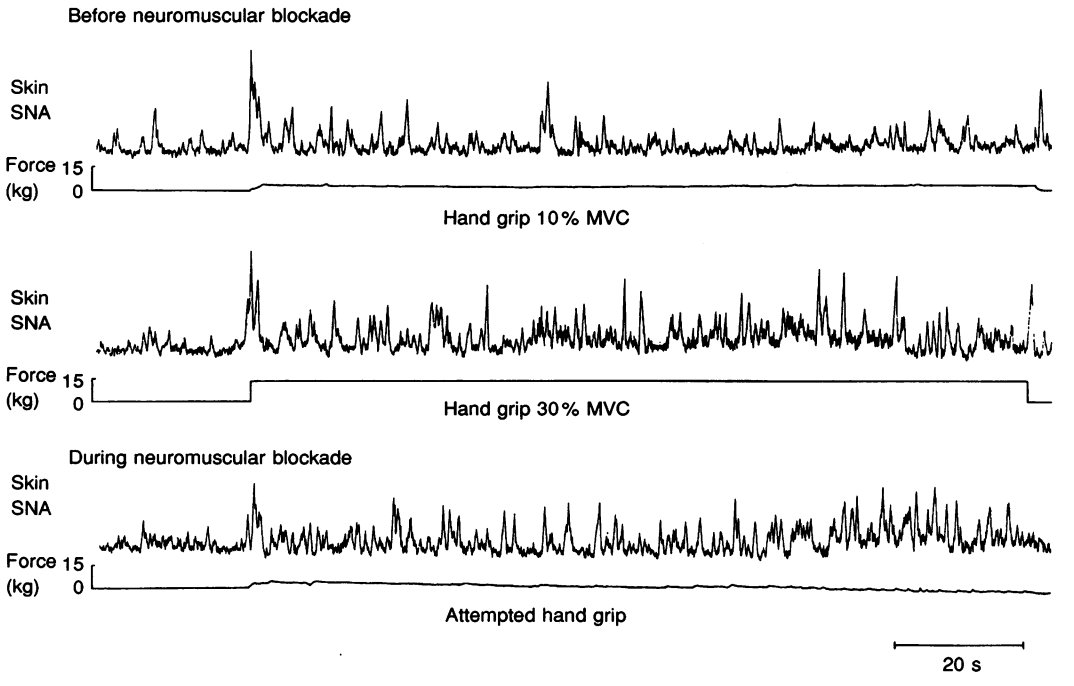

Figure 1. Skin sympathetic responses to static hand grip exercise and to attempted hand grip during neuromuscular blockade

Illustrative record from one subject showing skin sympathetic nerve activity (SNA) and hand grip force during static hand grip at 10 and 30% maximal voluntary contraction (MVC) before neuromuscular blockade, and attempted hand grip during neuromuscular blockade.

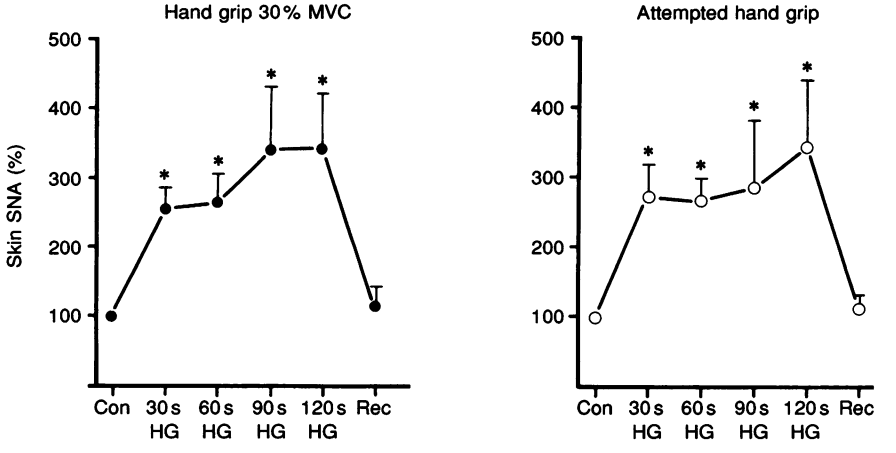

Figure 2. Skin sympathetic responses to static and attempted hand grip exercise during neuromuscular blockade

Temporal patterns of skin sympathetic nerve activity (SNA) during 120 s of static hand grip (HG) at 30% maximal voluntary effort (MVC) (●) and during attempted hand grip with neuromuscular blockade (○). Values are expressed as a percentage of the control baseline value. Data represent means ± S.E.M. for 9 subjects. * Significantly different from the control value at $P < 0.05$.

hand grip was increased from 10 to 20 to 30% MVC. During attempted hand grip the rate of perceived motor effort was 17 ± 1 ($P < 0.05$).

The changes in heart rate evoked by the static hand grip showed a pattern similar to the exercise-induced changes in skin SNA.

Two minutes of static hand grip at 20 and 30% evoked increases in heart rate that were graded to the intensity of the exercise. Static hand grip at 10% MVC caused a small but insignificant increase in heart rate. During neuromuscular blockade, attempted hand grip evoked increases in heart rate that did not significantly differ from the responses evoked by hand grip at 30% MVC (Table 1 and Fig. 3).

Static hand grip at 10, 20 and 30% MVC evoked significant and graded increases in mean arterial pressure. Attempted hand grip during neuromuscular blockade caused a significant increase in mean arterial pressure, but the increase was smaller than the response evoked by hand grip at 30% MVC (Table 1 and Fig. 3).

Effects of neuromuscular blockade on baseline variables

Injection of vecuronium produced an increase in skin SNA; the number of sympathetic bursts per minute increased significantly, by 11 ± 2 bursts min^{-1} ($P < 0.05$), and total integrated skin SNA increased insignificantly by 180 ± 47% *versus* baseline before neuromuscular blockade. Mean arterial pressure increased by 7 ± 2 mmHg, $P < 0.05$.

Resting values before and during vecuronium-induced partial neuromuscular blockade of arterial pH (7·40 ± 0·003 *vs.* 7·40 ± 0·007), P_{CO_2} (38·2 ± 1·1 *vs.* 35·8 ± 1·1 mmHg), and P_{O_2} (106·0 ± 1·9 *vs.* 109·0 ± 1·7 mmHg) were comparable. None of the subjects showed any evidence of respiratory difficulty during neuromuscular blockade.

Effects of vecuronium on responses to mental arithmetic

Performance of mental stress produced comparable increases in skin SNA before and during neuromuscular blockade, and the increases were comparable to the responses evoked by hand grip at 30% MVC and by the attempted hand grip exercise (Table 2).

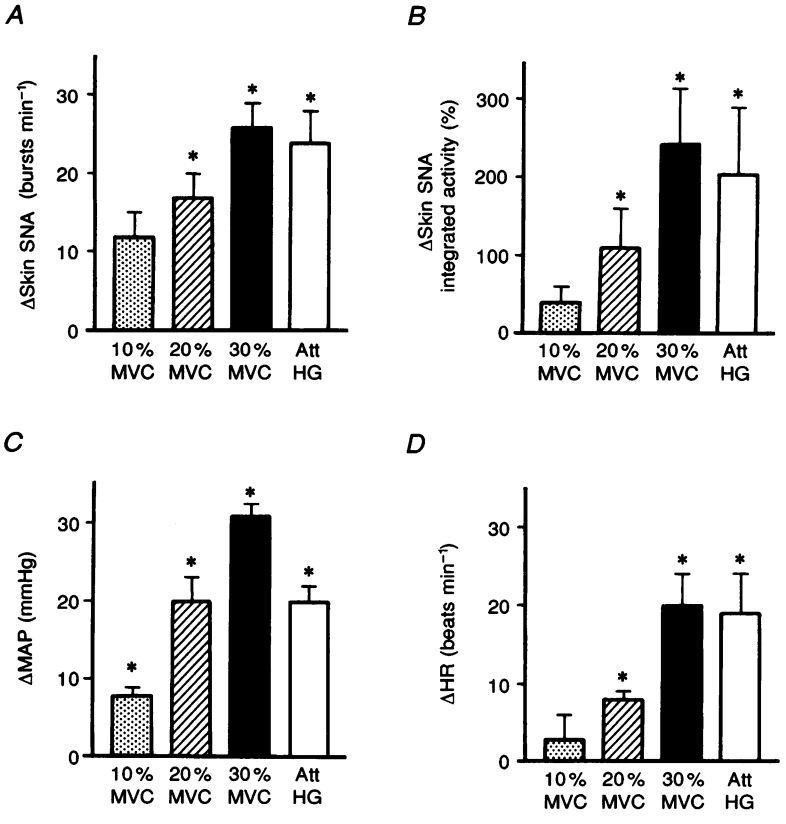

Figure 3. Effects of graded levels of static and attempted hand grip exercise during neuromuscular blockade on skin sympathetic activity, arterial pressure and heart rate

Effects of 2 min of static hand grip at 10% (▨), 20% (▨), and 30% (■) maximal voluntary contraction (MVC) and 2 min of attempted hand grip (Att HG) during partial neuromuscular blockade (□) on skin sympathetic nerve activity (SNA), expressed as changes in bursts per minute (*A*) and total integrated activity as a percentage (*B*), on mean arterial pressure (MAP; *C*) and on heart rate (HR; *D*). Data represent means ± S.E.M. for 8 subjects. * Significant responses, $P < 0.05$ *vs.* control.

Table 2. Skin sympathetic responses to mental arithmetic

	Skin sympathetic integrated activity (%)		
	Control	Mental stress 30 s	Mental stress 120 s
Before neuromuscular blockade	100	308 ± 60*	269 ± 38*
During neuromuscular blockade	100	281 ± 58*	218 ± 40*

Data are means ± S.E.M. for 7 subjects, * $P < 0.05$ *vs.* control.

Control for recruitment of other muscle groups during exercise

EMG in the exercising forearm increased with increasing levels of exercise from mean values of 0·003 mV (10% hand grip (HG)) to 0·1 mV (20% HG) to 0·22 mV (30% HG). Attempted hand grip during neuromuscular blockade increased EMG to a mean of 0·003 mV. In contrast, simultaneous recordings of EMG from the contralateral arm showed no activity (Fig. 4).

Static hand grip at 30% MVC produced a small increase in oxygen uptake from a mean value of 260 to 330 ml min^{-1}. During neuromuscular blockade oxygen uptake was increased to a mean value of 312 ml min^{-1} at rest. Attempted hand grip produced a small increase in oxygen uptake to a mean value of 366 ml min^{-1} (Fig. 5).

DISCUSSION

This study provides the first direct evidence in support of the hypothesis that central motor command is the primary mechanism that stimulates sympathetic outflow to skin during static hand grip exercise. This agrees with a recent study measuring sympathetic outflow to skin during static exercise that concluded that central motor command regulates sympathetic outflow to skin (Vissing *et al.* 1991).

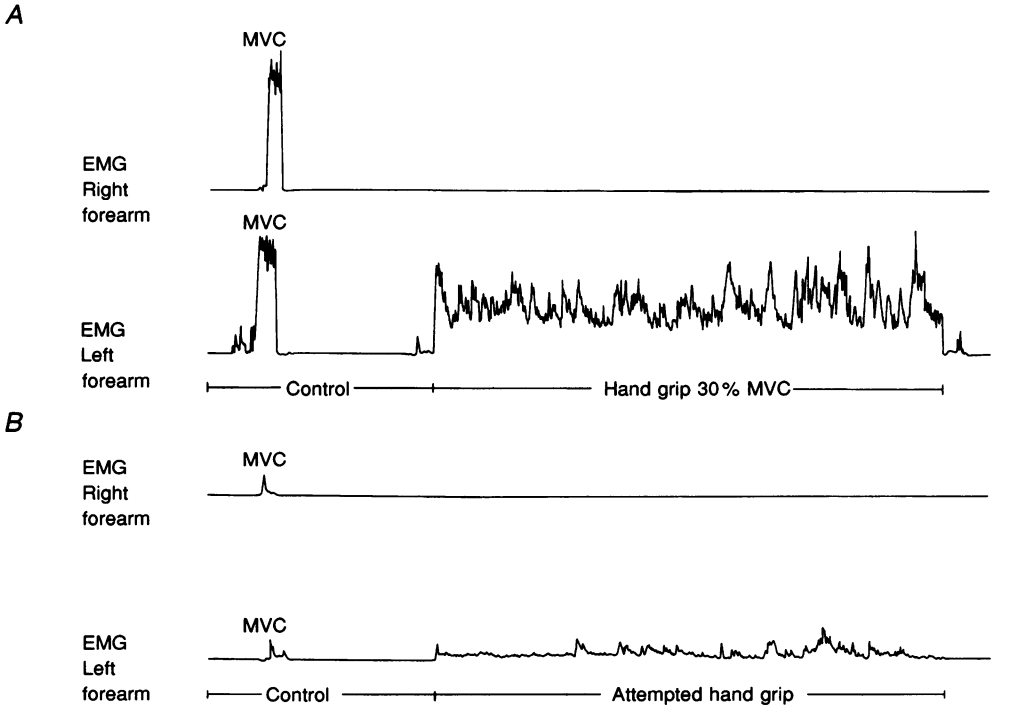

Figure 4. Electromyographic responses to static hand grip exercise and to attempted hand grip during neuromuscular blockade

Original record from one subject showing electromyographic (EMG) responses in left (exercising) and right (resting) forearm. During the control period the subject performed a maximal voluntary contraction (MVC) on both sides. *A*, control followed by 2 min of static hand grip at 30% MVC in the left forearm with right forearm at rest. *B*, control followed by 2 min of attempted static hand grip in the left forearm with right forearm at rest.

This interpretation, however, was based on several lines of indirect evidence.

Static hand grip at 10% had no effect on skin SNA. Static hand grip at 20 and 30% MVC evoked increases in skin SNA that were graded to the level of exercise. During vecuronium-induced neuromuscular blockade subjects were so weak that even though maximal effort was applied, they failed to maintain a force output equivalent to the output produced during 10% MVC before vecuronium. This attempted hand grip exercise consistently evoked increases in skin SNA that were equivalent to the increases produced by static hand grip at 30% MVC. The increases in skin SNA were maintained throughout the entire duration of exercise and while the force output became smaller the skin SNA became larger over the 2 min of attempted hand grip, further emphasizing the dissociation of skin sympathetic activation from force development (with muscle afferent activation).

The most likely explanation is that central motor command plays a major role in the stimulation of sympathetic outflow to skin during static hand grip while mechano- and metaboreceptor afferents play, at most, a minor modulatory role. This interpretation is based on the following findings.

First, partial neuromuscular blockade augmented central command because near-maximal motor effort was needed to maintain force output. Attempted static hand grip during partial neuromuscular blockade evoked increases in heart rate equivalent to the increases evoked during static hand grip at 30% MVC, suggesting that the central motor efforts might be comparable. It is well acknowledged that exercise-induced increases in heart rate are elicited by an autonomic drive of central origin (Freyschuss, 1970; Victor *et al.* 1989).

Second, during attempted hand grip the rate of perceived exertion, a subjective index of central motor command, was submaximal indicating that central motor command was high (Borg, 1970). Furthermore, during graded levels of hand grip the rate of perceived exertion was directly related to the increase in skin SNA, and the rate of perceived exertion during attempted hand grip was comparable to the level reported during hand grip at 30% MVC.

Third, during partial neuromuscular blockade, stimulation of mechanoreceptor afferents was minimized. During the first minute of attempted hand grip the force developed was equivalent to the force produced during hand grip at 10% MVC. During the second minute of attempted hand grip, subjects were unable to maintain the force development, so afferent stimulation should be almost zero. Animal experiments have shown that static exercise-induced reflex increases in SNA evoked by mechanoreceptor afferents are characterized by an initial burst of activity beginning approximately 1 s after onset of tension development, followed by rapid adaptation (Kaufmann *et al.* 1983; Victor, Rotto, Pryor & Kaufmann, 1989). In our human experiments, the increases in skin SNA preceded

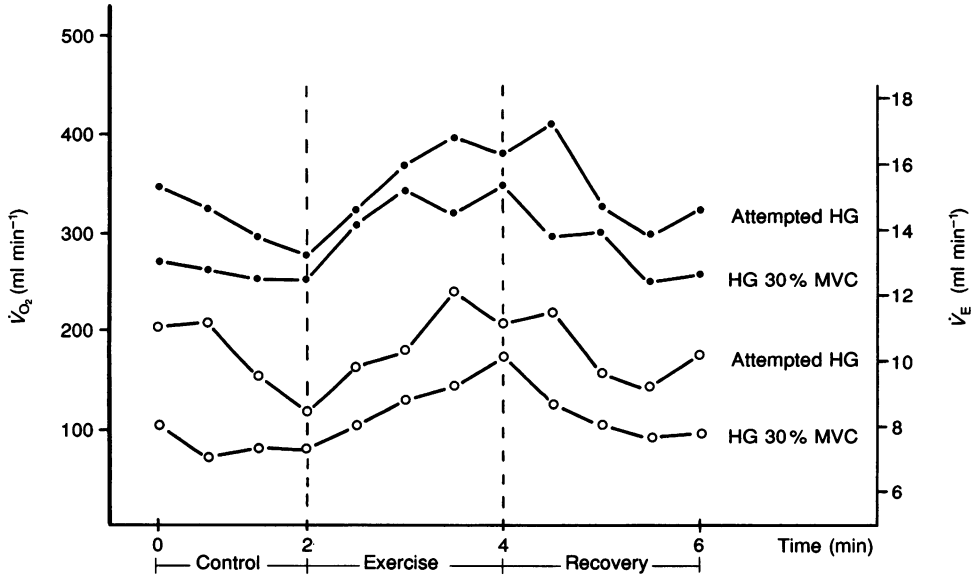

Figure 5. Changes in metabolism during static hand grip at 30% MVC and during attempted hand grip with neuromuscular blockade

Temporal pattern of oxygen uptake, $\dot{V}_{O_2}$ (●), and minute ventilation, $\dot{V}_E$ (○) estimated by open air spirometry during 2 min of control followed by 2 min of either static hand grip at 30% MVC or attempted hand grip with neuromuscular blockade, both followed by 2 min of recovery. Data represent means of average values for 30 s periods in 3 subjects.

the onset of tension development and increased rather than decreased, during both attempted and normal contraction.

Fourth, during partial neuromuscular blockade, stimulation of metaboreceptor afferents was minimized. When stimulated by static contraction in anaesthetized animals the metaboreceptor afferents show a slow and progressive increase in activity that corresponds to the progressive accumulation of intramuscular metabolites within the vicinity of these afferent endings (Kaufmann *et al.* 1983; Mitchell & Schmidt, 1983; Rotto, Stebbins & Kaufmann, 1989). Metaboreceptor afferents are unlikely to have caused the increase in skin SNA because during normal hand grip, skin SNA increased immediately with the initiation of the hand grip and even during attempted hand grip skin SNA increased, despite almost no force development and, therefore, almost no accumulation of metabolites.

The possibility was considered that the vecuronium-induced increase in baseline values of skin SNA influenced the response evoked by attempted hand grip exercise, i.e. it would have 'turned on' the sympathetic system and increased responses to any stimulus. This does not appear to be the case because vecuronium had no effect on the mental arithmetically induced increases in skin SNA. Mental arithmetic is a non-exercise stimulus to skin SNA (Delius *et al.* 1972). The increase in skin SNA produced during vecuronium-induced neuromuscular blockade probably was a non-specific side effect of vecuronium rather than an arousal response. An arousal response is characterized by being transient and to habituate with repeated presentations. Throughout the period with neuromuscular blockade, the increased level of skin SNA did not level off, but rather remained at a stable increased level.

It has been shown previously that during static hand grip exercise activation of muscle groups in the 'resting' limb may interfere with the interpretation of the resulting autonomic responses (Lind, Dahms, Williams & Petrofsky, 1981). Therefore, to test if activation of resting muscles could explain the increase in skin SNA during attempted hand grip, the muscle activity of three subjects was recorded using the electromyographic technique (EMG). During both static hand grip and attempted static hand grip no EMG activity was recorded in the non-exercising forearm, while there was a characteristic increase in skin SNA. In the present study, activation of leg muscles to explain responses to hand grip exercise also may be excluded. Even the slightest muscle tension in the leg where microneurographic measurements are performed produces electromyographic noise that drowns the sympathetic signal. Electromyographic artifacts are easily distinguished from sympathetic activity and such recordings were excluded from analysis. Measurements of oxygen uptake during this form of exercise and using such a small muscle mass is not a sensible way to estimate muscle activation. The data suggest an increase in oxygen uptake during attempted hand grip with neuromuscular blockade. There is a close temporal correlation between changes in ventilation and changes in oxygen uptake. Therefore, the tendency of increased oxygen uptake may be ascribed to the increased energy cost of ventilation. However, these experiments cannot completely exclude the possibility that the increase was due to increased metabolism somewhere else in the body. The finding of an increase in oxygen uptake during intended exercise is in accordance with a previous study showing that mental simulation of exercise can activate respiratory control mechanisms (Decety, Jeannerod, Durozard & Baverel, 1993).

In conclusion, this study provides direct neurophysiological evidence that central motor command can activate sympathetic outflow. During static hand grip central motor command is the primary mechanism that stimulates sympathetic outflow to skin.

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