Differential control of heart rate and sympathetic nerve activity during dynamic exercise. Insight from intraneural recordings in humans.

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J Clin Invest. 1987;79(2):508-516. https://doi.org/10.1172/JCI112841.

Research Article

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Differential Control of Heart Rate and Sympathetic Nerve Activity during Dynamic Exercise

Insight from Intraneural Recordings in Humans

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Abstract

We used microelectrode recordings of muscle sympathetic nerve activity (MSNA) from the peroneal nerve in the leg during arm exercise in conscious humans to test the concept that central command and muscle afferent reflexes produce mass sympathetic discharge at the onset of exercise. Nonischemic rhythmic handgrip and mild arm cycling produced graded increases in heart rate and arterial pressure but did not increase MSNA, whereas ischemic handgrip and moderate arm cycling dramatically increased MSNA. There was a slow onset and offset of the MSNA responses, which suggested metaboreceptor mediation. When forearm ischemia was continued after ischemic handgrip, MSNA remained elevated (muscle chemoreflex stimulation) but heart rate returned to control (elimination of central command). The major new conclusions are that: (*a*) the onset of dynamic exercise does not produce mass, uniform sympathetic discharge in humans, and (*b*) muscle chemoreflexes and central command appear to produce differential effects on sympathetic and parasympathetic responses.

Introduction

The onset of dynamic exercise produces reflex changes in efferent autonomic activity that increase heart rate (HR),[1] cardiac output, vascular resistance, and arterial pressure (1–7). These neurocirculatory responses have been attributed both to reflexes arising within the exercising muscle (8–10), mediated by chemically sensitive and mechanically sensitive muscle afferents (11–13), and to neural impulses arising within the central nervous system, associated with the volitional component of exercise, termed central command (14–17).

Two related tenets have greatly influenced the thinking about the autonomic control of the circulation during exercise in humans. The first is that the onset of dynamic exercise produces generalized, uniform activation of sympathetic vasoconstrictor outflow as well as tachycardia (4, 18–20). This postulated mass sympathetic discharge is thought to produce widespread reflex vasoconstriction, which offsets metabolic vasodilation and helps to maintain arterial pressure during rhythmic muscle contraction. The second concept is that central command and muscle afferent reflexes are redundant control mechanisms that influence the same neural circuits in brainstem and produce comparable autonomic effects (12, 21). Thus, it has been assumed that both mechanisms promote sympathetic excitation at the onset of dynamic exercise.

The goal of this study was to test these concepts with direct measurements of sympathetic nerve traffic. In contrast to the previous studies of neurocirculatory regulation during dynamic exercise in humans, which used only indirect indices of sympathetic nervous activity, we used direct, microelectrode recordings of sympathetic action potentials (22) in conscious, exercising humans.

Our previous work on static exercise in humans emphasized the importance of chemosensitive muscle afferents in triggering sympathetic excitation in nonexercising skeletal muscles during static muscle contraction (23). In the present studies, we performed two series of experiments to examine the control of sympathetic nerve activity and HR during dynamic exercise. First, we studied responses to rhythmic handgrip (RHG) with and without forearm vascular occlusion to alter the metabolic state in the exercising muscle. We hypothesized that nonfatiguing, nonischemic rhythmic contractions would not trigger increases in muscle sympathetic outflow because the intermittent relaxation would promote muscle perfusion and washout of metabolites and thus minimize the stimulation of chemically sensitive muscle afferents. To increase the concentration of muscle metabolites in the vicinity of the afferent nerve endings within the exercising muscle, we had subjects perform RHG during forearm arterial occlusion with a pneumatic cuff on the upper arm. We postulated that increased stimulation of muscle chemoreflexes during RHG with ischemia would promote sympathetic excitation similar to that which we had observed previously during static exercise that is accompanied by sustained increases in tissue pressure and decreases in muscle blood flow.

In the second series, we used two-arm cycling to examine exercise of a larger muscle mass at graded exercise intensities. We predicted that sympathetic activation would develop and recover slowly at the beginning and end of exercise if the sympathetic response were governed by metaboreceptors that are influenced by the gradual accumulation and washout of muscle metabolites. In contrast, sympathetic excitation should begin and end promptly with the onset and offset of muscle contraction

A preliminary report of this work was presented at the meeting of the American Society for Clinical Investigation in Washington, D.C., May, 1985, and in the Young Investigator Competition of the American College of Cardiology in Atlanta, March, 1986.

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Received for publication 24 June 1985 and in revised form 6 October 1986.

1. *Abbreviations used in this paper:* HR, heart rate; MAP, mean arterial pressure; MSNA, muscle-sympathetic nerve activity; MVC, maximal voluntary contraction; RHG, rhythmic handgrip.

J. Clin. Invest.

0021-9738/87/02/0508/09 $1.00
Volume 79, February 1987, 508–516

if the response were mediated by either central command or mechanosensitive afferents. We also sought to determine if there was a threshold work load for sympathetic neural excitation and if there was a difference in the threshold for increases in muscle-sympathetic activity and in HR. A dissociation of HR and sympathetic nerve responses would support the concept that the two responses are governed by different mechanisms.

Methods

Subjects

22 men and 3 women, ages 18–30 yr, participated in this study after providing written informed consent. One subject participated in both series of experiments. The studies were approved by the institutional committee on human investigation.

Measurements

We measured arterial pressure, HR, and efferent muscle-sympathetic nerve activity (MSNA) in the leg during rhythmic arm exercise. HR (electrocardiogram), respiration (pneumograph), force of muscle contraction (dynograph), and MSNA (microneurography) were recorded continuously on a physiologic recorder (model 2800S; Gould Inc., Santa Clara, CA) at a paper speed of 5 mm/s. During handgrip exercise, blood pressure was measured by sphygmomanometry from the nonexercising arm. During arm cycling, systolic blood pressure was measured by sphygmomanometry from the leg; Korotkoff sounds were detected with a doppler probe placed over the posterior tibial artery. Arterial pressure was measured continuously with a brachial artery catheter (Seldinger technique) during intravenous infusion of sodium nitroprusside.

Microelectrode recording of sympathetic nerve activity (microneurography)

Multiunit recordings of sympathetic nerve activity were obtained from a muscle nerve fascicle in the right peroneal nerve posterior to the fibular head (22). The recordings were made with tungsten microelectrodes 200 μm in diameter in the shaft, tapering to an uninsulated tip of 1–5 μm.

A reference electrode was inserted subcutaneously 1–3 cm from the recording electrode. The electrodes were connected to a preamplifier with a gain of 1,000 and an amplifier with a gain of 50. The neural activity was then fed through a band pass filter with a bandwidth of 700–2,000 Hz. For monitoring during the experiment, the filtered neurogram was routed through an amplitude discriminator to a storage oscilloscope and a loudspeaker. For recording and analysis, the filtered neurogram was fed through a resistance–capacitance integrating circuit (time constant 0.1 s) to obtain a mean voltage display of the neural activity.

There were three criteria for an acceptable recording of MSNA. First, weak electrical stimulation (1–3 V, 0.2 ms, 1 Hz) through the electrode in the peroneal nerve elicited involuntary muscle contraction but no paresthesias. Second, tapping or stretching the muscles or tendons supplied by the impaled fascicle elicited afferent groups I and II mechanoreceptor discharge, whereas stroking the skin in the distribution of the peroneal nerve did not evoke afferent discharge. Third, the neurogram revealed spontaneous, intermittent, pulse-synchronous bursts that increased during held expiration and phase 2 and phase 3 of a Valsalva maneuver, characteristic of MSNA (22). Evidence that such activity represents efferent sympathetic nerve activity has derived from earlier studies and includes (*a*) interruption of the activity by local nerve block proximal but not distal to the recording site in the leg; (*b*) elimination of the activity by ganglionic blockade; and (*c*) conduction velocity approximating 1 m/s (22). Neurograms that revealed spontaneous activity characteristic of cutaneous sympathetic activity were not accepted. This was assessed using an arousal stimulus (loud noise, skin pinch), which elicits bursts of cutaneous but not muscle-sympathetic activity. Three subjects were excluded from the protocols because we were unable to obtain satisfactory recordings of MSNA. Resting nerve activity was measured for 6–10 min before beginning the experimental protocols to ensure that a stable baseline level of nerve activity had been obtained.

Experimental protocols (exercise interventions)

SERIES I

In 14 subjects we studied responses to RHG using three protocols designed to examine the autonomic effects of central command and muscle afferents both alone and in combination.

With the subject in the supine position, maximal voluntary contraction (MVC) was determined before the exercise protocol using a Martin's dynamometer (Elmed, Inc., Addison, IL). Subjects performed brief, nonsustained, RHG contractions with the left hand (i.e., nondominant hand in all but one subject) at a rate of ~ 40 contractions/min with or without arrested forearm circulation.

Responses to RHG alone. After a 2-min control period, subjects performed three, 2-min bouts of RHG at 10, 30, and 50% MVC followed by a 2-min recovery period. The rationale was that RHG would primarily engage central command and mechanically sensitive muscle afferents.

Responses to RHG during forearm vascular occlusion. To increase the concentration of ischemic metabolites in the vicinity of the afferent nerve endings within the exercising muscle, subjects performed RHG during forearm vascular occlusion. After control measurements, blood flow to the left forearm was arrested by inflation of a pneumatic cuff on the upper arm to suprasystolic pressure (250 mmHg). Subjects then performed 2 min of RHG at 30% MVC followed by a 2-min recovery period (i.e., relaxation without ischemia).

Responses to muscle ischemia post-handgrip. Subjects performed 2 min of RHG during forearm ischemia with the vascular occlusion being maintained for an additional 2 min after the cessation of exercise. Vascular occlusion post-handgrip maintains the stimulation of muscle chemoreflexes, while musclar relaxation eliminates central command and mechanically sensitive muscle afferents.

The order of interventions was randomized with 10-min rest periods between interventions. During handgrip, subjects were instructed to relax the nonexercising limbs and to breathe rhythmically. No Valsalva maneuvers were observed.

SERIES II

To examine effects of exercise of a large muscle mass, we studied responses to two-arm cycling at increasing workloads in six subjects. Arm cycling was performed with subjects seated upright on an electronically braked bicycle ergometer (No. 8430, cardiac stress testing system; Engineering Dynamics Corp., Lowell, MA). After a 2-min control period, subjects performed 2-min bouts of two-arm cycling (~ 50 rpms) at increasing workloads from 0 to 80 W followed by 2 min of recovery measurements. Exercise bouts were separated by 10–20-min rest periods to allow the physiologic variables to return to control values and to prevent muscle fatigue. All six subjects reached 40 W, five subjects reached 60 W, and three subjects reached 80 W before leg motion made further microneurographic measurements impossible. Two additional subjects were excluded from analysis because of presyncopal vasodepressor reactions in the upright position.

Subjects also performed 2 min of RHG at 30 and 50% MVC in the sitting position before starting the arm-cycling protocol to examine effects of body position on responses to RHG.

HR and MSNA were measured simultaneously during arm cycling. The exercise protocol was repeated on a separate day to obtain measurements of systolic blood pressure by doppler-sphygmomanometry from the posterior tibial artery (along with simultaneous measurements of HR).

After completion of the exercise protocol, each subject performed additional 2-min exercise bouts at increasing workloads until fatigue to determine maximum exercise capacity.

HR responses to arm cycling after atropine. To examine the sympathetic component of the HR response during graded arm cycling, the exercise protocol was repeated on a separate day in five of the six subjects while HR was measured after parasympathetic blockade with atropine (0.04 mg/kg i.v. followed by small supplemental doses).

Comparison of MSNA and HR responses during intravenous infusion of sodium nitroprusside

In three additional subjects, we monitored intra-arterial pressure and compared HR and MSNA responses to arterial baroreceptor inhibition during intravenous infusion of sodium nitroprusside. The drug was diluted in 5% dextrose in water and infused into a peripheral vein at rates of 0.5–1.0 μg/kg per min for 2 min. The dose of nitroprusside was individualized for each subject to produce a maximal reduction in mean arterial pressure (MAP) of 10–15% below the baseline value. Baroreceptor inhibition during nitroprusside provided an internal control, i.e., a nonexercise stimulus for producing increases in HR and MSNA.

Data analysis

Sympathetic bursts were identified by inspection from the mean voltage neurogram and expressed as bursts per minute. The intraobserver variability in identifying bursts is < 5% while interobserver variability is < 10% (23).

Measurements of blood pressure were obtained during the last half of each minute. Values for MSNA and HR reflect the mean either for the entire minute or for each 30-s interval.

Statistical analysis was performed using analysis of variance and the Bonferroni method for multiple comparisons (24). Values of $P < 0.05$ were considered significant. Results are expressed as mean±SE.

Results

Exercise interventions

SERIES I

Responses to RHG alone (Table I and Figs. 1 and 2). RHG at 10, 30, and 50% MVC produced graded increases in arterial pressure and HR but did not increase MSNA. For example, during RHG at 50% MVC, MAP rose by + 13±3 mmHg ($P < 0.05$) and HR rose by + 11±3 beats/min ($P < 0.05$), but MSNA did not change (ΔMSNA = − 1±3 bursts/min, $P > 0.10$).

Basal MSNA was significantly increased ($P < 0.05$) from 19±1 bursts/min sitting to 28±4 bursts/min supine. However, the MAP, HR, and MSNA responses to RHG at 30 and 50% MVC were comparable in both positions (Table I).

Responses to RHG during arrested forearm circulation (Table II and Figs. 1 and 2). During forearm vascular occlusion, RHG at 30% MVC produced an augmented pressor response and a striking increase in MSNA (Fig. 2). However, the increase in sympathetic activity did not begin with the onset of muscle contraction. The MSNA did not change during the first minute, but increased markedly over control values (from 20±2 to 36±2 bursts/min, $P < 0.05$) during the second minute of ischemic handgrip (Table II).

Table I. Responses to RHG

	MAP		HR		MSNA	
	Supine	Sitting	Supine	Sitting	Supine	Sitting
	mmHg	*mmHg*	*beats/min*	*beats/min*	*bursts/min*	*bursts/min*
Control period						
1st min	90±1		61±1		18±1	
2nd min	92±1		64±1		18±1	
RHG at 10% MVC						
1st min	93±1*		64±1		15±1	
2nd min	94±1*		64±1		16±1	
Recovery period						
1st min	92±1		61±1		20±1	
2nd min	91±1		62±1		18±1	
Control period						
1st min	94±1	95±4	63±1	64±5	19±1	29±4
2nd min	95±1	95±4	63±1	63±6	19±1	27±3
RHG at 30% MVC						
1st min	98±1*	100±5*	67±1*	68±6	17±1	23±4
2nd min	101±1*	102±5*	68±1*	66±6	18±1	26±3
Recovery period						
1st min	96±1	96±4	62±1	61±6	21±1	28±3
2nd min	94±1	95±4	63±1	62±6	21±1	30±4
Control period						
1st min	94±1	94±5	63±1	61±2	19±1	25±4
2nd min	94±1	92±6	64±1	59±3	20±1	27±4
RHG at 50% MVC						
1st min	102±1*	103±8*	74±1*	71±3*	18±1	23±5
2nd min	107±1*	108±7*	75±1*	72±3*	18±1	23±5
Recovery period						
1st min	96±1	93±5	65±1	58±2	20±1	29±6
2nd min	94±1	92±5	64±1	58±1	20±1	29±4

Entries are mean±SE for 6 subjects at 10% MVC, 14 subjects at 30% MVC, and 9 subjects at 50% MVC in the supine position and for 6 subjects at 30% MVC and 4 subjects at 50% MVC in the sitting position. * $P < 0.05$ vs. control values.

Table II. Responses to RHG during Forearm Vascular Occlusion

	MAP	HR	MSNA
	mmHg	*beats/min*	*bursts/min*
Control period			
1st min	95±1	64±1	19±2
2nd min	95±1	65±1	20±2
RHG at 30% MVC during vascular occlusion			
1st min	105±1*	74±1*	17±2
2nd min	115±1*	77±1*	36±2*
Recovery period			
1st min	96±1	63±1	26±2*
2nd min	96±1	63±1	23±2
Control period			
1st min	95±2	62±1	19±2
2nd min	94±2	62±1	18±2
RHG at 30% MVC during vascular occlusion			
1st min	104±2*	70±1*	20±2
2nd min	117±2*	73±1*	33±2*
Vascular occlusion post-RHG			
1st min	113±2*	64±1	38±2*
2nd min	115±2*	62±1	39±2*
Recovery period			
1st min	96±2	65±1	24±2
2nd min	94±2	62±1	21±2

Entries are mean±SE for 9 subjects in the first sequence and for 12 subjects in the second sequence.
* $P < 0.05$ vs. control values.

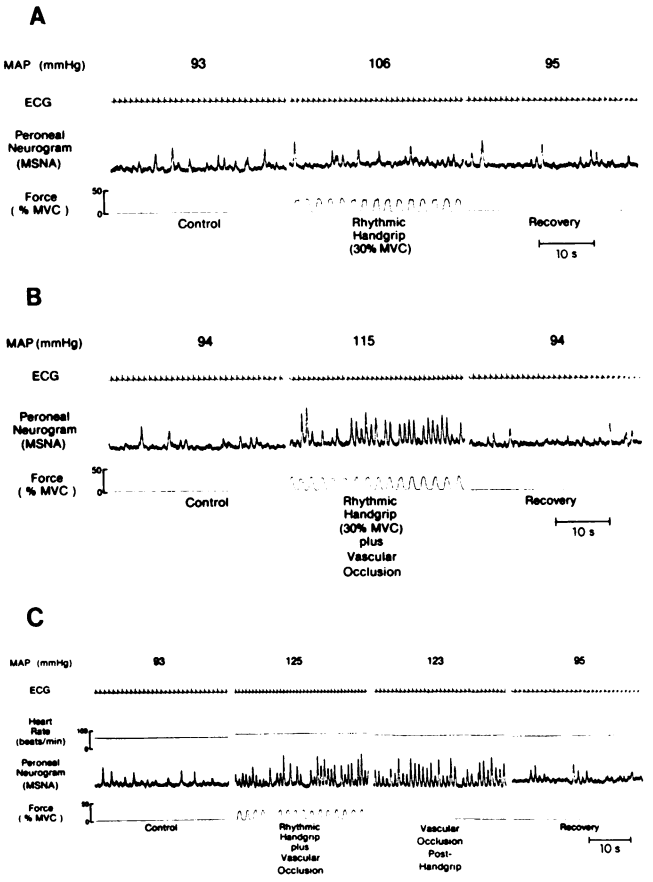

Figure 1. Recordings of MSNA from one subject during three experimental interventions vs. rhythmic handgrip at 30% of MVC. Data represent the last 30 s of each 2-min measurement period. (*a*) RHG alone did not increase MSNA. (*b*) RHG during forearm vascular occlusion produced a striking increase in MSNA. (*c*) During maintenance of forearm vascular occlusion (muscle ischemia) after cessation of ischemic handgrip, HR returned to control but MSNA remained elevated.

Responses to muscle ischemia post-handgrip (Table II and Fig. 1). When forearm circulatory arrest was maintained after the cessation of RHG, HR returned promptly to control values, but MAP and MSNA remained significantly ($P < 0.05$) elevated. Indeed, MSNA tended to be higher during post-handgrip muscle ischemia than during the second minute of RHG.

Three subjects experienced pain in the forearm during vascular occlusion and most subjects experienced mild paresthesias. However, there was no correlation between pain and the increased MSNA produced by forearm ischemia during or after RHG. The most striking increases in MSNA occurred in four subjects who experienced no pain.

SERIES 2

Responses to two-arm cycling (Table III and Figs. 3, 4, and 5). Mild arm cycling at 0, 10, and 20 W had no effect on MSNA but produced graded increases in HR and MAP. For example, during arm cycling at 20 W, HR increased by 24 beats/min over control valves in session A and by 22 beats/min in session B and systolic blood pressure rose by 25 mmHg but MSNA did not change (Table III).

In contrast, MSNA increased markedly during heavier exercise. Cycling at 40 and 60 W increased MSNA by 69±16% and 121±29% respectively over control valves ($P < 0.05$).

At workloads that produced significant increases in sympathetic nerve activity (e.g., 40 W), there was a temporal dissociation between responses of HR and MSNA (Fig. 4). HR rose most rapidly in the first 30 s of arm cycling (64±5 to 94±4 beats/min, $P < 0.05$) and showed little additional increase between the first and second minutes of exercise at 40 W (97±6 to 100±9 beats/min, $P > 0.10$). In contrast, MSNA did not increase significantly from control in the first 30 s of cycling at 40 W (from 31±5 to 34±6 bursts/min; $P > 0.1$) but increased to 41±6 bursts/min at the end of the first minute of cycling ($P < 0.05$ vs. control) and increased further to 54±10 bursts/min after the second min ($P < 0.05$ vs. first minute).

Fig. 5 depicts the relationship between changes in HR and MSNA for RHG at 10–50% MVC (both supine and upright) and arm cycling at 0–80 W. During RHG and during arm cycling at low workloads, HR increased by up to 25 beats/min but MSNA did not increase. In contrast, during arm cycling at higher workloads, which increased HR by > 25 beats/min, MSNA increased in proportion to the increases in HR.

Maximal exercise capacity for the six subjects during arm cycling was 120±6 W. In all six subjects, the lowest workload, which increased MSNA by at least 25% over control values, was between 30 and 40% of the subject's maximum exercise capacity.

HR responses to arm cycling after atropine (Fig. 6). Before atropine, graded arm cycling produced HR responses that were matched to the intensity of the exercise. Atropine increased basal

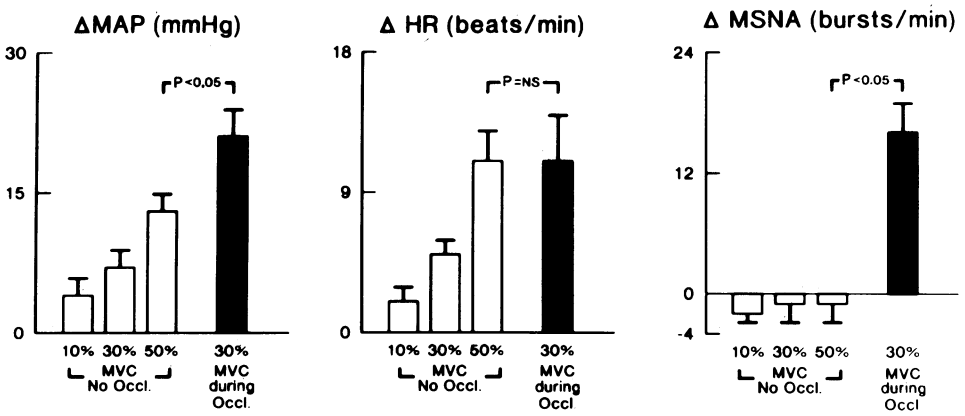

Figure 2. Effects of forearm vascular occlusion (muscle ischemia) on responses during the second minute of RHG. Values are mean±SE for 6 subjects at 10% MVC, 14 subjects at 30% MVC, and 9 subjects at 50% MVC. During nonischemic handgrip at 10, 30, and 50% MVC (*clear bars*), MAP and HR increased in proportion to intensity of contraction, but MSNA did not increase. In contrast, during muscle ischemia RHG at only 30% MVC (*solid bars*) produced an augmented pressor response and a striking increase in MSNA.

HR from 63±5 to 119±10 beats/min ($P < 0.05$) and significantly decreased the percent increase in heart during all intensities of arm cycling. Most importantly, atropine prevented the matching between exercise intensity and HR during mild cycling because heart increased consistently by only 6–8% over control values during mild exercise at either 0, 10, or 20 W. In contrast, there was a significant increase ($P < 0.05$) in the magnitude of HR response after atropine during arm cycling as the work load was increased from 20 to 40 W and from 40 to 60 W.

Responses to intravenous infusion of sodium nitroprusside (Table IV and Fig. 7). Nitroprusside infusion produced progressive decreases in arterial pressure and progressive increases in HR and MSNA. The HR and MSNA responses to nitroprusside infusion followed parallel time courses without a lag in the onset of the MSNA response.

Discussion

This study provides the first direct measurements of sympathetic nerve traffic during dynamic exercise in humans. The major new conclusions are that central command appears to initiate parasympathetic withdrawal and tachycardia at the onset of exercise, whereas muscle chemoreflex activation is important in producing parallel activation of sympathetic outflow to the nonexercising skeletal muscles and the heart (sinus node) during dynamic exercise. An important corollary is that the onset of rhythmic muscle contraction does not produce mass, uniform sympathetic discharge in humans because the muscle chemoreflex is not engaged during the initial stage of mild or moderate dynamic exercise.

Differential control of sympathetic and parasympathetic responses by central command and muscle chemoreflexes. HR and MSNA responses were dissociated during each of several different exercise interventions. The observations provide strong evidence that the two responses are regulated at least in part by different mechanisms.

The most striking example of this dissociation occurred during graded arm cycling when the increases in MSNA lagged considerably behind the increases in HR, with respect to both time course and exercise intensity. This cannot be explained by an inherent lag in sympathetic vs. parasympathetic responsiveness because arterial baroreceptor deactivation during vasodilator infusion produced parallel increases in HR and MSNA without any delay in the onset of the MSNA vs. HR response.

The lag in the onset of sympathoexcitation in nonexercising muscle during moderate and heavy contractions of large muscles and during ischemic contraction of small muscles suggests metaboreceptor mediation. Mense and Stahnke (27) and Kaufman et al. (28) have identified populations of group IV muscle afferents in cats that are activated predominately or exclusively by ischemic rather than nonischemic contractions. During ischemic exercise, impulse activity in these afferents exhibited a delay in

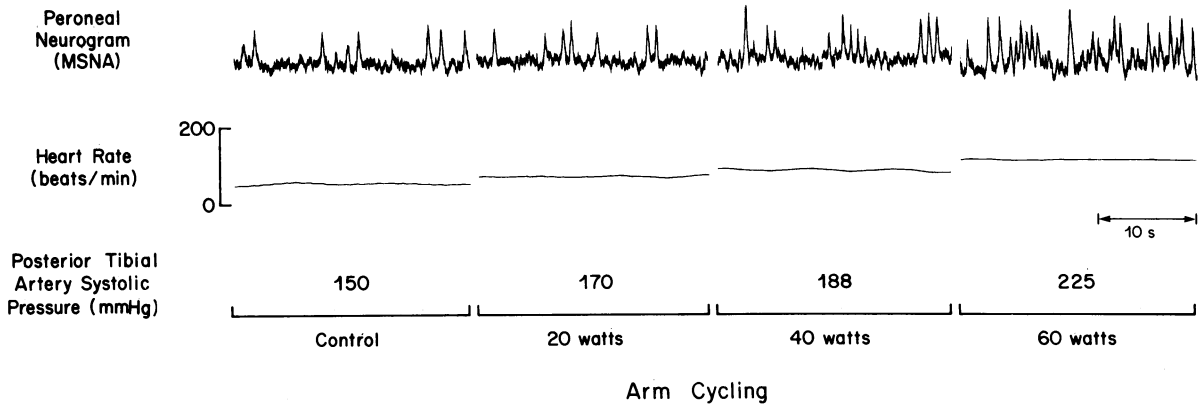

Figure 3. Recording of MSNA in the leg during two-arm cycling at mild, moderate, and heavy levels of intensity. Data represent the last 25 s of each 2-min measurement period. Mild exercise at 20 W had no effect on sympathetic neural activity but produced a 25 beat/min increase in heart rate and a 20 mmHg rise in systolic blood pressure. In this subject, the threshold workload for sympathetic activation was 40 W.

Table III. HR, Arterial Pressure, and Sympathetic Nerve Responses to Arm Cycling

Session A

Exercise intensity	HR						MSNA					
	Control period		Exercise period		Recovery period		Control period		Exercise period		Recovery period	
	1st min	2nd min	1st min	2nd min	1st min	2nd min	1st min	2nd min	1st min	2nd min	1st min	2nd min
W	*beats/min*	*beats/min*	*beats/min*	*beats/min*	*beats/min*	*beats/min*	*bursts/min*	*bursts/min*	*bursts/min*	*bursts/min*	*bursts/min*	*bursts/min*
0	63±6	64±5	74±7*	74±6*	62±6	61±5	28±6	32±5	28±5	27±5	32±3	30±4
10	63±5	63±5	81±6*	79±6*	63±6	60±5	33±3	31±3	30±4	30±4	32±3	30±3
20	62±5	63±5	84±5*	87±7*	65±7	61±6	31±5	28±4	31±6	33±8	33±5	31±6
40	63±5	64±5	96±5*	101±9*	76±9	64±8	33±5	28±5	38±6	49±11*‡	38±7	32±5
60	60±2	60±3	104±4*	110±5*‡	78±3*	61±2	29±4	27±3	51±12*	67±15*‡	40±7*	31±5

Session B

Exercise intensity	HR						Posterior tibial artery systolic pressure					
	Control period		Exercise period		Recovery period		Control period		Exercise period		Recovery period	
	1st min	2nd min	1st min	2nd min	1st min	2nd min	1st min	2nd min	1st min	2nd min	1st min	2nd min
W	*beats/min*	*beats/min*	*beats/min*	*beats/min*	*beats/min*	*beats/min*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*
0	59±4	61±4	73±5*	70±5*	56±5	58±4	166±8	165±8	179±8*	178±7*	168±8	170±7
10	60±3	61±4	79±5*	76±5*	57±4	58±4	167±8	167±8	184±7*	187±7*	172±7	170±6
20	60±4	59±4	84±5*	82±6*	59±4	58±4	165±7	167±8	186±7*	191±5*	175±7	170±7
40	58±4	61±4	91±6*	94±6*	65±6	59±4	168±8	167±8	200±6*	208±5*‡	184±8*	180±8*
60	57±3	59±4	105±7*	109±7*	72±4*	58±3	162±5	164±8	212±7*	223±4*‡	192±7*	185±10*

Entries are mean±SE for six subjects at 0–40 W and five subjects at 60 W during two separate experimental sessions, A (simultaneous measurements of HR and MSNA) and B (simultaneous measurements of HR and posterior tibial artery systolic pressure). HR responses to exercise where comparable in sessions A and B. * $P < 0.05$ vs. control values. ‡ $P < 0.05$ 2nd vs. 1st min of exercise.

the onset of the excitatory response in the first minute of muscle contraction, increased progressively during the second minute of exercise, was maintained at a high level during postcontraction ischemia, and decreased gradually during relaxation without ischemia (27). The striking similarity between the behavior of these group IV afferents in cats and the MSNA responses during ischemic contractions in humans supports the view that chemosensitive muscle afferents are important in the control of MSNA during dynamic exercise in humans.

Our findings are consistent with previous hemodynamic observations, which suggest that the neurocirculatory adjustments to mild dynamic exercise are not dependent upon muscle chemoreflexes (29, 30). In humans, elimination of muscle afferent input with selective sensory nerve block did not attenuate the increases in arterial pressure and HR during mild, nonischemic

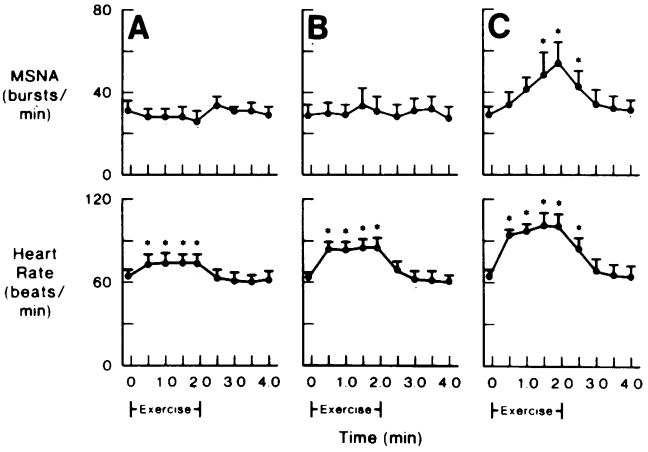

Figure 4. Comparison of sympathetic nerve (MSNA) and HR responses during 2 min of arm cycling at (*A*) 0, (*B*) 20, and (*C*) 40 W. Values are mean±SE for six subjects. Mild exercise at 0 and 20 W produced rapid, graded increases in HR but had no effect of sympathetic traffic. During more intense exercise at 40 W, sympathetic activity increased significantly; however, the neural response developed more slowly than the chronotropic response.

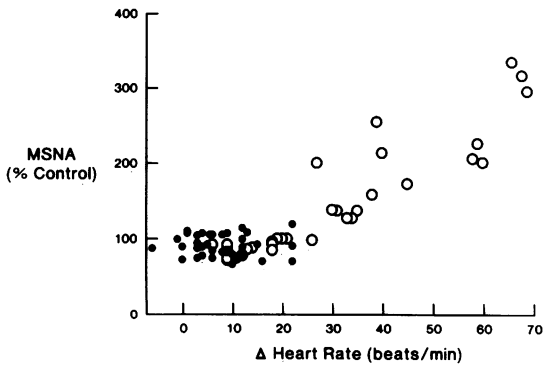

Figure 5. Relationship between the HR and sympathetic nerve responses to RHG at (*filled circles* 10–50% MVC) for 19 subjects and to arm cycling (*open circles*) at 0–80 W for 6 subjects. MSNA is expressed as a percentage of the control values. During RHG and arm cycling at low workloads, HR increased by up to 25 beats/min but MSNA did not increase. In contrast, during arm cycling at higher workloads, which increased HR by > 25 beats/min, MSNA increased in proportion to the increases in HR.

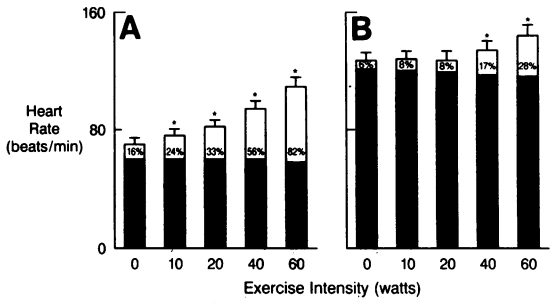

Figure 6. HR in the control state (*open bars*) and during the second minute of graded arm cycling (*open bars*) before (*A*) and after (*B*) atropine (0.04 mg/kg i.v.). Data are mean±SE for five subjects. Percent changes in HR from control to the second minute of exercise are also shown. Before atropine, HR responses were matched to the intensity of the exercise ($P < 0.05$ vs. response at 0 load). When the parasympathetic component of the HR response to exercise was markedly attenuated after atropine, graded arm cycling began to produce graded increases in HR ($P < 0.05$ vs. response at 0 load) once subjects attained a work load of 40 W.

exercise (29). In dogs, moderate decreases in muscle perfusion that would potentiate muscle chemoreflexes did not accentuate the arterial pressure and HR responses to mild dynamic exercise (30).

The present study supports previous reports that the chronotropic responses during the initial stages of exercise are due to withdrawal of vagal tone (6, 7, 31). The small residual increases in HR during mild arm exercise after atropine were most likely due to incomplete muscarinic blockade (limited by the central neural side-effects of atropine in human subjects). Because the parasympathetically mediated tachycardia began promptly at the onset of exercise, we suggest that this autonomic adjustment is mediated by central command rather than by muscle chemoreflexes.

Our data also suggest that there is a comparable lag in the activation of sympathetic drive to the sinus node and to the nonexercising skeletal muscles during graded exercise in humans. This relative delay in the onset of sympathetic activation compared with the rapid onset of parasympathetic withdrawal is consistent with the view that muscle chemoreflexes are important in the control of sympathetic outflow to the heart as well as skeletal muscle. However, we cannot exclude the possibility that the onset of sympathoexcitation during dynamic exercise is also related in part to a critical level of central command and/or mechanosensitive muscle afferent discharge.

Mechanisms of exercise pressor responses. The mechanisms responsible for these increases in arterial pressure during exercise appear to differ depending upon the intensity of the exercise and the presence or absence of muscle ischemia.

During mild exercise that did not produce muscle sympathetic activation, arterial pressure increased in proportion to exercise intensity and in parallel with the graded increases in HR. Thus, it is likely that the pressor response to mild exercise is mediated importantly by concomitant increases in HR and cardiac output.

However, because there is increasing evidence that regional sympathetic responses can be highly differentiated (22, 32, 33), we cannot exclude the possibility that sympathetic activation in vascular beds other than that in skeletal muscle might also contribute to the pressor response in the early stage of exercise. We speculate that the prompt forearm vasoconstrictor responses, which have been reported at the onset of leg exercise, are mediated by increased sympathetic outflow to skin rather than muscle. Because skin sympathetic activity, unlike muscle sympathetic activity, is extremely responsive to arousal stimuli (22), cutaneous vasoconstriction at the onset of exercise probably represents an arousal response. In addition, previous studies indicate that the onset of exercise is accompanied by vasoconstriction in the renal and splanchnic beds (4). Sympathetic activation in the skin and viscera during exercise may be mediated by mechanisms other than muscle chemoreflexes.

During exercise that increased MSNA, reflex sympathetic activation appeared to have an important influence on the exercise pressor response. The striking increase in MSNA during ischemic handgrip was associated with a markedly augmented

Table IV. Responses to Intravenous Infusion of Sodium Nitroprusside

	Control period		Nitroprusside infusion				Recovery period	
	60 s	120 s	30 s	60 s	90 s	120 s	60 s	120 s
Subject 1								
MAP (*mmHg*)	123	128	125	117	115	113	107	117
HR (*beats per minute*)	76	76	76	86	92	102	106	84
MSNA (*bursts per minute*)	26	16	28	50	60	64	54	22
Subject 2								
MAP (*mmHg*)	79	78	73	73	71	71	74	77
HR (*beats per minute*)	48	46	48	52	62	64	50	44
MSNA (*bursts per minute*)	16	14	18	28	38	40	22	14
Subject 3								
MAP (*mmHg*)	90	89	83	83	83	82	85	94
HR (*beats per minute*)	54	54	60	60	62	60	70	54
MSNA (*bursts per minute*)	32	24	40	40	42	44	50	18
Mean±SE								
MAP (*mmHg*)	97±13	98±15	94±16	91±13	90±13	89±13	89±10	96±12
HR (*beats per minute*)	59±9	59±9	61±8	66±10	72±10	75±13	75±16	61±12
MSNA (*bursts per minute*)	25±5	18±3	29±6	39±6	47±7	49±7	42±10	18±2

Entries are data for MAP, HR, and MSNA during nitroprusside infusion in three subjects.

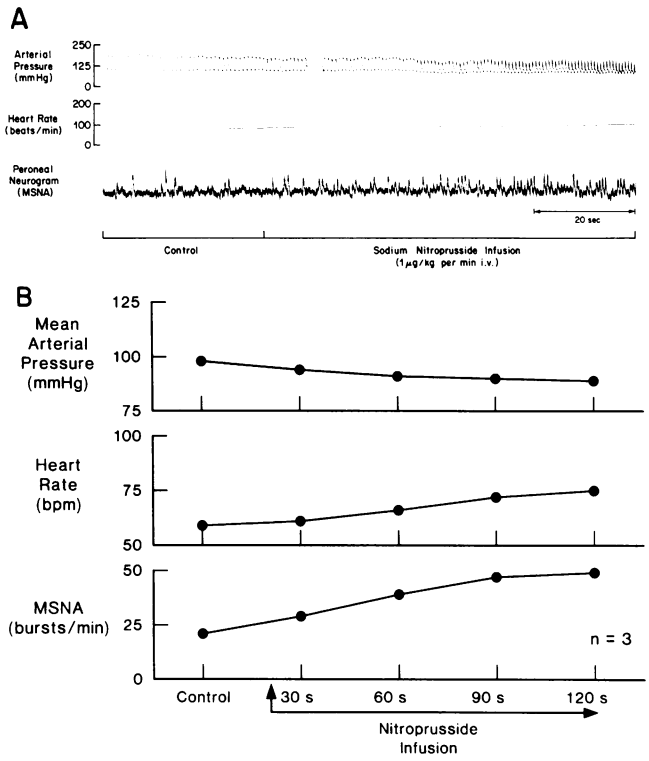

Figure 7. Comparison of MSNA and HR responses to arterial baroreceptor inhibition during decreases in arterial pressure produced by intravenous infusion of sodium nitroprusside. (*A*) A continuous recording of arterial pressure, HR (cardiotachometer), and muscle sympathetic activity in one subject. (*B*) Average responses in three subjects. Nitroprusside infusion produced parallel increases in MSNA and HR without any lag in the onset of the sympathetic nerve response relative to the HR response.

rise in arterial pressure. This augmentation appeared to be due primarily to an increase in sympathetic vasoconstrictor tone rather than HR (and cardiac output) because ischemic handgrip at only 30% MVC produced a significantly larger pressor response than nonischemic handgrip at 50% MVC even though these two exercise interventions produced comparable increases in HR.

Mechanosensitive muscle afferents. In anesthetized cats, mild rhythmic contractions activate mechanosensitive group III muscle afferents and produce a reflex pressor response that is presumably mediated by increased sympathetic outflow (34). However, in conscious humans MSNA did not increase during nonischemic RHG contractions or during mild arm cycling. Although mild rhythmic contraction does not appear to be a sufficient condition to reflexly increase MSNA in humans, we cannot exclude the possibility that mechanosensitive thin fiber afferents may contribute to sympathetic regulation during intense rather than mild rhythmic contractions.

Influence of body position and low pressure cardiopulmonary baroreceptors. Activation of cardiopulmonary baroreceptors inhibits and unloading of these receptors augments the reflex vasoconstrictor responses to muscle afferent stimulation (35, 36). One reason why MSNA did not increase during RHG in the supine position might be that cardiopulmonary baroreceptor activation inhibited the excitatory influence from the muscle afferents. This explanation is unlikely because MSNA did not increase during RHG at either 30 or 50% MVC when cardiopulmonary receptors were unloaded in the upright position.

Rhythmic vs. static exercise. During nonfatiguing exercise, static muscle contraction characteristically produces much larger increases in MAP than does rhythmic contraction, even when the two forms of exercise are performed to equivalent increases in oxygen consumption (37–39). The comparatively greater pressor response to nonfatiguing static vs. rhythmic contraction has been attributed traditionally to two factors. First, during static exercise, sustained increases in intramuscular pressure causes passive (i.e., nonreflex) increases in vascular resistance because of mechanical hindrance to blood flow within the contracted muscle (39, 40). Second, it has been proposed that reflex vasoconstriction is offset by greater metabolic vasodilatation during dynamic than during static exercise (39–41). An important feature of this study is the suggestion that the augmented pressor response to static vs. rhythmic contraction is explained in part by a difference in reflex rather than mechanical mechanisms in these two modes of exercise (41).

In a previous study (23), we found that static handgrip at 30% MVC produced an average increase in MAP of 18 mmHg and increased MSNA from 21±3 to 33±4 bursts/min. In contrast, we found in this study that RHG at 30% MVC increased mean pressure by only 7 mmHg and did not increase MSNA. A major factor in the discrepancy between the pressor responses to these two forms of exercise may be that static contraction produces chemoreflex-mediated increases in MSNA, whereas rhythmic contraction does not. The evidence for this postulate is that RHG at 30% MVC during arrested forearm circulation increased MAP by 20 mmHg and increased MSNA from 20±2 to 36±2 bursts/min. These responses to ischemic rhythmic contraction are comparable to those seen during static handgrip, which causes sustained increases in tissue pressure.

Clinical implications. These findings in healthy subjects would predict that sympathetic nerve responses to dynamic exercise should be augmented in patients with cardiovascular disorders that impair perfusion of the exercising muscles. When patients with unilateral iliofemoral stenosis and intermittent claudication performed rhythmic leg exercise, increases in aortic pressure were much greater during contraction of the poorly perfused leg than during contraction of the well perfused leg before the onset of ischemic pain (42). In addition, peripheral vasoconstrictor responses to dynamic exercise in conscious dogs were markedly enhanced when oxygen delivery to the exercising muscles was impaired by heart block, anemia, or congestive heart failure (7).

In conclusion, the present study challenges two traditional concepts of cardiovascular regulation during dynamic exercise. First, during the initiation of dynamic exercise in humans there is a concomitant delay in the onset of sympathetic activation to nonexercising skeletal muscle and to the heart. This challenges the concept of mass sympathetic discharge at the onset of exercise. Second, this study documents the complexity in the control of HR, arterial pressure, and MSNA during dynamic exercise. Although both central neural and peripheral reflex mechanisms contribute to the maintenance of arterial pressure during dynamic exercise, the data suggest that central command and muscle chemoreflexes do not exert comparable effects on sympathetic and parasympathetic responses.

Acknowledgments

We thank Dr. B. Gunnar Wallin for advice and support and Dr. Jere H. Mitchell for his advice and thoughtful comments. We also thank Christine Sinkey for technical assistance and Sara Jedlicka and Cynthia Lawson for secretarial assistance.

This work was supported by a Clinical Investigator Award (HL01362) to Dr. Victor from the National Heart, Lung, and Blood Institute

(NHLBI) and by research grants HL24962 and HL14388 from the NHLBI and by research funds from the Veterans Administration.

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