Impaired sympathetic vascular regulation in humans after acute dynamic exercise

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1. The reduction in vascular resistance which accompanies acute dynamic exercise does not subside immediately during recovery, resulting in a post-exercise hypotension. This sustained vasodilatation suggests that sympathetic vascular regulation is altered after exercise.

2. Therefore, we assessed the baroreflex control of sympathetic outflow in response to arterial pressure changes, and transduction of sympathetic activity into vascular resistance during a sympatho-excitatory stimulus (isometric handgrip exercise) after either exercise (60 min cycling at 60% peak aerobic power ($\dot{V}_{O_2,peak}$)) or sham treatment (60 min seated rest) in nine healthy subjects.

3. Both muscle sympathetic nerve activity and calf vascular resistance were reduced after exercise ($-29{\cdot}7 \pm 8{\cdot}8$ and $-25{\cdot}3 \pm 9{\cdot}1$%, both $P < 0{\cdot}05$). The baroreflex relation between diastolic pressure and sympathetic outflow was shifted downward after exercise (post-exercise intercept, 218 ± 38 total integrated activity (heartbeat)$^{-1}$; post-sham intercept, 318 ± 51 total integrated activity (heartbeat)$^{-1}$, $P < 0{\cdot}05$), indicating less sympathetic outflow across all diastolic pressures. Further, the relation between sympathetic activity and vascular resistance was attenuated after exercise (post-exercise slope, $0{\cdot}0031 \pm 0{\cdot}0007$ units (total integrated activity)$^{-1}$ min; post-sham slope, $0{\cdot}0100 \pm 0{\cdot}0033$ units (total integrated activity)$^{-1}$ min, $P < 0{\cdot}05$), indicating less vasoconstriction with any increase in sympathetic activity.

4. Thus, both baroreflex control of sympathetic outflow and the transduction of sympathetic activity into vascular resistance are altered after dynamic exercise. We conclude that the vasodilatation which underlies post-exercise hypotension results from both neural and vascular phenomena.

The haemodynamic response to large-muscle, dynamic exercise is characterized by an increased mean arterial pressure, despite a profoundly reduced systemic vascular resistance. Although arterial pressure declines quickly after an acute bout of exercise, systemic resistance does not completely recover, resulting in a post-exercise hypotension (Coats, Conway, Isea, Pannarale, Sleight & Somers, 1989; Cléroux, Kouamé, Nadeau, Coulombe & Lacourcière, 1992*a*; Isea, Piepoli, Adamopoulos, Pannarale, Sleight & Coats, 1994) that lasts nearly 2 h in healthy individuals (Halliwill, Taylor, Hartwig & Eckberg, 1996). This sustained vasodilatation indicates that sympathetic vascular regulation may be altered after exercise. There are two possible sources for an alteration in sympathetic vascular regulation: arterial baroreflex control of sympathetic outflow and vascular responsiveness to sympathetic stimulation.

The arterial baroreflex exerts exquisite control over arterial pressure and should respond to the hypotension by increasing sympathetic outflow. However, despite the reduction in arterial pressure, sympathetic outflow to the vasculature is either unchanged or reduced compared with pre-exercise levels (Floras, Sinkey, Aylward, Seals, Thorén & Mark, 1989; Hara & Floras, 1992). Thus, baroreflex control of sympathetic outflow may be altered by prior exercise; however, it is unclear whether it is changes in gain and/or resetting of the reflex that are responsible. Further, data from animals suggest that vascular responsiveness to adrenergic stimulation is attenuated after exercise (Howard, DiCarlo & Stallone, 1992; Howard & DiCarlo, 1992; Patil, DiCarlo & Collins, 1993). If such vascular effects predominate in humans, a dissociation of vasoconstrictor responses from sympathetic activity could result in post-exercise

hypotension even if sympathetic outflow were *enhanced*. However, there are no data on the transduction of sympathetic nerve activity into vascular resistance after exercise in humans.

Changes in baroreflex control of sympathetic outflow and changes in the transduction of sympathetic outflow into vasoconstriction are not mutually exclusive; therefore, we investigated both baroreflex control of sympathetic nervous outflow and the transduction of sympathetic outflow into vascular resistance following moderate-intensity dynamic exercise in healthy humans. We have found previously that the baroreflex control of heart rate was augmented after exercise (Halliwill *et al.* 1996) and, therefore, hypothesized that alterations in sympathetic transduction to vascular resistance would be the predominant factor in generating post-exercise hypotension. However, our results indicate that alterations in both the baroreflex control of sympathetic nervous outflow and transduction of sympathetic outflow into vascular resistance contribute to post-exercise vasodilatation; thus, post-exercise hypotension appears to result from both neural and vascular mechanisms.

METHODS

This study was approved by the Human Research Committees of the Medical College of Virginia and the Hunter Holmes McGuire Department of Veterans Affairs Medical Center. Each subject gave his or her informed written consent prior to participation.

Subjects

Nine healthy, non-smoking, normotensive subjects participated in this study (five men and four women, aged 22–27 years). The subjects' average daily physical activity levels were within the normal range for a sedentary to moderately active population (Stanford Physical Activity Questionnaire (Sallis *et al.* 1985): 36·5–50·2 kcal day^{-1} kg^{-1}). Peak aerobic power ($\dot{V}_{O_2,peak}$) was determined with a graded maximal cycle ergometer test comprising 2 min workload increments sufficient to achieve exhaustion within 13 min, and $\dot{V}_{O_2,peak}$ was within the normal range for this population (36·5–51·0 ml min^{-1} kg^{-1}). This test was used to determine the exercise workloads used in the following protocol.

Experimental protocol

Subjects underwent parallel experiments on two separate days. The order of the experiments was randomized between *sham*, a 60 min period of seated upright rest: and *exercise*, a 60 min period of seated upright cycling at 60% $\dot{V}_{O_2,peak}$ (Collins Pedalmate, W. E. Collins Inc., Braintree, MA, USA). We have previously shown that exercise of this intensity and duration produces a sustained (~2 h) post-exercise hypotension (Halliwill *et al.* 1996). During exercise and sham, subjects were allowed to drink water *ad libitum*. Ambient temperature ranged from 22 to 24 °C. During each experiment, heart rate, arterial pressure and cardiac output were measured in the supine position before and at 60 min post-sham or -exercise. Heart rate and arterial pressure were also recorded every 10 min during sham or exercise. The baroreflex control of sympathetic outflow was assessed 60 min post-sham or -exercise and sympathetic control of vascular resistance was assessed approximately 90 min post-sham or -exercise.

Baroreflex responsiveness. To assess the baroreflex control of sympathetic outflow, muscle sympathetic nerve activity was measured during arterial pressure changes induced by nitroprusside and phenylephrine (Ebert & Cowley, 1992). After a 5 min baseline period, 100 μg sodium nitroprusside was given intravenously as a bolus, followed 1 min later by 150 μg phenylephrine HCl. This protocol decreases arterial pressure ~15 mmHg below baseline levels and then increases it ~15 mmHg above baseline levels, over a short time course.

Vascular responsiveness. To assess the transduction of the sympathetic activity into vascular resistance, calf blood flow and muscle sympathetic nerve activity were measured during isometric handgrip exercise held to fatigue. Isometric exercise elicits a highly reproducible pressor response mediated by progressive, parallel increases in muscle sympathetic nerve activity and vascular resistance (Seals, 1989). Further, there is a causal relation between muscle sympathetic nerve activity and calf vascular resistance, providing a non-pharmacological method to quantify the transduction process. All subjects had undergone two previous training sessions in which they learned to perform isometric handgrip exercise to fatigue with either hand. In the training sessions, subjects were coached to avoid gasping breaths, Valsalva manoeuvers (forceful breath holding), and contraction of other limbs. During the experiments, the maximum voluntary contraction was determined from the best of three attempts after the subject had completed sham or exercise. After recovery from the baroreflex testing and a 5 min baseline period, the subject maintained an isometric forearm contraction at 35% of maximum voluntary contraction to the point of fatigue. Force from a dynamometer (Carolina Biological Supply Co., Burlington, NC, USA) was displayed to the subject on an oscilloscope with the target force. The end-point of fatigue was identified by an inability to maintain handgrip force within 10% of the target level for greater than 2 s and pronouncement of a maximal perceived exertion rating (Borg, 1970).

Measurements

Heart rate was determined from an electrocardiogram recording, beat-by-beat arterial pressure was measured in a finger using a Finapres blood pressure monitor (Model 2300, Ohmeda, Englewood, CO, USA), and standard arterial pressure was measured in an arm using a Dinamap blood pressure monitor (Model 1846SX, Critikon Inc., Tampa, FL, USA). Respiration was monitored continuously using a bellows placed across the subject's abdomen and linked to a pressure transducer.

Cardiac output. Cardiac output was estimated by the indirect Fick method of carbon dioxide (CO_2) rebreathing to equilibrium, as described previously (Collier, 1956; Halliwill *et al.* 1996).

Muscle sympathetic nerve activity. Muscle sympathetic nerve activity was recorded via microneurography, as described by Sundlöf & Wallin (1977). Briefly, multiunit, postganglionic muscle sympathetic nerve activity was recorded from the peroneal nerve posterior to the fibular head. Recordings were made with a tungsten microelectrode (0·2 mm diameter insulated shaft, tapered to an uninsulated tip of ~1–5 μm) inserted into the nerve bundle and an uninsulated reference electrode inserted near the fibular head (~2–3 cm from the recording electrode). The nerve was located by using the microelectrode first as a stimulating electrode to initiate muscle twitches, and then as a recording electrode to identify a fascicle which contained muscle sympathetic activity. Muscle sympathetic nerve activity was distinguished from other sources of nerve activity by the following criteria: (1) presence of spontaneous pulse synchronous bursts, (2) increased activity during Valsalva straining, (3) muscle afferent activity with muscle stretch, and (4) no change of activity during light stroking of the

Table 1. Systemic and regional haemodynamics and sympathetic outflow

	Post-sham	Post-exercise
Systolic arterial pressure (mmHg)	131 ± 3	123 ± 5*
Diastolic pressure (mmHg)	71 ± 2	65 ± 3
Mean arterial pressure (mmHg)	91 ± 2	84 ± 3*
Cardiac output (l min^{-1})	5·9 ± 0·4	7·0 ± 0·6*
Total peripheral resistance (units)	16·3 ± 1·5	12·8 ± 1·5*
Calf blood flow (ml min^{-1} (100 ml)$^{-1}$)	2·20 ± 0·34	2·86 ± 0·36
Calf vascular resistance (units)	47·4 ± 5·4	34·2 ± 4·9*
Muscle sympathetic nerve activity		
(bursts min^{-1})	15·7 ± 2·7	8·9 ± 1·5*
(total integrated activity (min)$^{-1}$)	2290 ± 340	1600 ± 300*
(bursts (100 heartbeats)$^{-1}$)	27·4 ± 5·0	14·8 ± 2·8*
(total integrated activity (100 heartbeats)$^{-1}$)	4000 ± 620	2660 ± 530*

Values are means ± S.E.M. * indicates deviations from post-sham ($P < 0·05$).

skin or with startling the subject with loud noises, indicating lack of skin nerve activity. The recorded signal was amplified 70 000-fold, bandpass filtered (700–2000 Hz), rectified, and integrated (resistance–capacitance integrator circuit, time constant 0·1 s) by a nerve traffic analyser (Model 662C3, Biomedical Engineering, University of Iowa, Iowa City, IA, USA). The resulting signal was monitored on an oscilloscope and loudspeaker throughout the experiment. Sympathetic activity was recorded in the leg ipsilateral to the arm performing handgrip exercise and contralateral to the leg used for calf blood-flow measurements. The set-up was reversed on the second day of the experiment.

Calf blood flow. Calf blood flow was estimated by venous occlusion plethysmography, as described by Siggaard-Andersen (1970). An air-filled, latex plethysmographic cuff was placed mid-calf and connected to a volumetric pressure transducer (Model PT5, Grass Instrument Co., Quincy, MA, USA) for recording changes in calf volume. An arterial occlusion cuff around the ankle was continuously inflated to suprasystolic pressures (250 mmHg) during measurements, while a venous occlusion cuff around the thigh was inflated to 60 mmHg for 7·5 s out of every 15 s, providing one calf blood-flow measurement every 15 s. Calf blood flow was calibrated at the end of every experiment by adding known volumes of air to the plethysmographic cuff still in place on the subject. This blood flow was expressed as millilitres per minute per one hundred millilitres of tissue.

Data analysis

Data were recorded by electrostatic (Gould ES 1000, Gould Inc., Greenbelt, MD, USA) and FM tape (Model 3968A, Hewlett Packard) recorders. Data were analysed off-line with signal processing software (WinDaq, Dataq Instruments, Akron, OH, USA). The electrocardiogram, beat-by-beat arterial pressure, calf plethysmogram, integrated muscle sympathetic nerve activity, and respiration signal (bellows) were digitized at 250 Hz. Muscle sympathetic nerve activity was quantified as both the number of bursts and as total integrated activity, defined as the summed area of bursts. Data for derivation of ventilation volumes and CO_2 concentrations were digitized at 100 Hz. Total peripheral resistance was calculated by dividing mean arterial pressure by cardiac output, and calf vascular resistance was calculated by dividing mean arterial pressure by calf blood flow; both resistances were expressed as units. Since resistance values derived from Finapres and Dinamap pressures provided analogous results, only those based on Finapres pressures are presented.

A measure of baroreflex control of sympathetic outflow was provided by the relation between muscle sympathetic nerve activity and diastolic pressure during vasoactive drug boluses (Ebert & Cowley, 1992). We used diastolic pressure because muscle sympathetic nerve activity correlates closely with diastolic pressure but not with systolic pressure (Sundlöf & Wallin, 1978). Beat-by-beat values for nerve activity were averaged over 3 mmHg diastolic pressure ranges and a weighted linear regression between nerve activity and pressure was performed. This pooling procedure reduces the statistical impact of the inherent beat-by-beat variability in nerve activity due to non-baroreflex influences (e.g. respiration; Ebert & Cowley, 1992). The mean nerve activity and pressure during the 5 min baseline that preceded nitroprusside administration was included in the regression.

An index of the transduction of sympathetic activity into vascular resistance was derived from the relationship between calf vascular resistance and muscle sympathetic nerve activity. This was calculated from a weighted linear regression of 30 s values for calf vascular resistance and nerve activity (i.e. the mean of two calf blood-flow measurements were used for each point in the regression). The mean resistance and nerve activity during the 5 min baseline that preceded handgrip exercise were included in the regression.

Since regressions based on total integrated activity and burst number provided identical results, only those based on total integrated activity are presented.

Statistics. Variables which were measured after sham or exercise were compared using a paired Student's t test. All variables measured during sham or exercise were averaged for the entire 60 min period and compared with pre-exercise values by a repeated-measures analysis of variance. The baroreflex and transduction relations were analysed by multivariate linear regression models with repeated measures. All values are reported as means ± S.E.M.

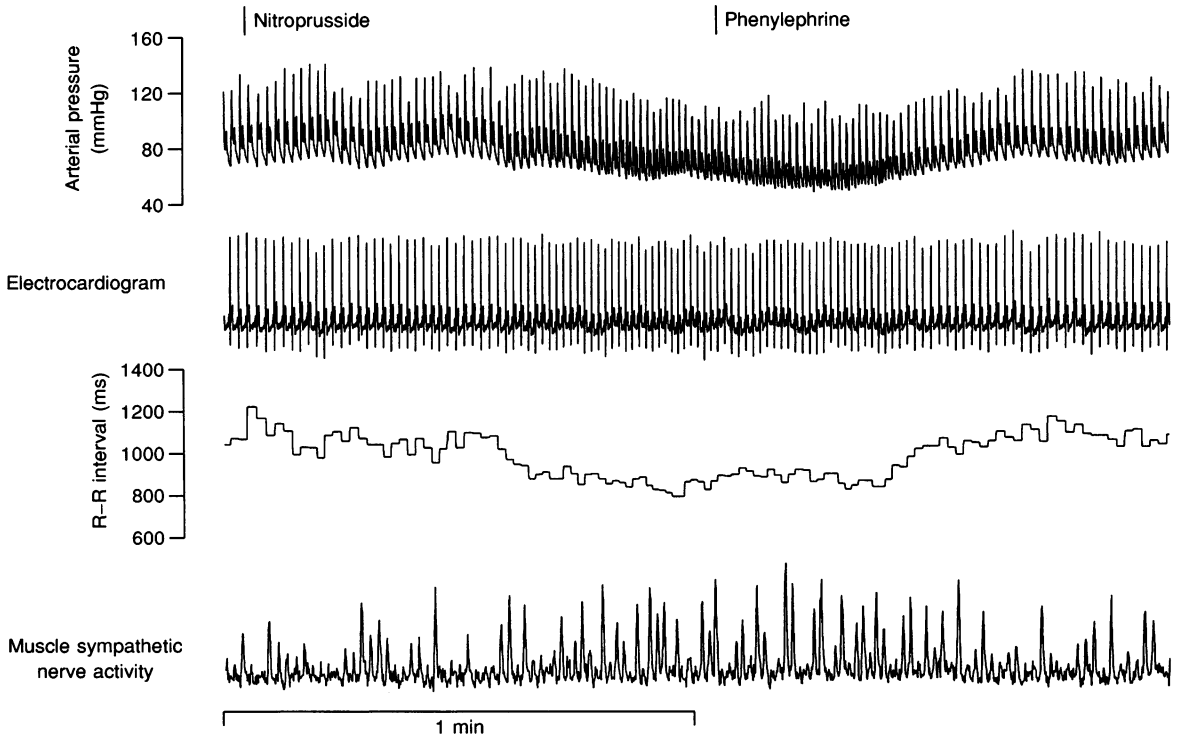

Figure 1. Representative vascular baroreflex data

Representative data from one subject showing beat-by-beat arterial pressure, electrocardiogram, beat-by-beat R–R interval, and integrated muscle sympathetic nerve activity during nitroprusside and phenylephrine baroreflex testing.

RESULTS

Exercise

The mean exercise workload was 130 ± 10 W. During this time heart rate increased from 62·0 ± 2·2 beats min^{-1} at rest to 138·2 ± 3·1 beats min^{-1} during exercise (mean for entire 60 min of exercise, $P < 0·05$). This represented, on average, 63·0 ± 1·9% of heart rate reserve (heart rate reserve is defined as resting supine heart rate minus maximum heart rate achieved during $\dot{V}_{O_2,peak}$ test), indicating the targeted relative workload had been reached. Systolic pressure increased 34 ± 4 mmHg ($P < 0·05$), while diastolic pressure was unchanged (0 ± 4 mmHg) during exercise. As a result, mean arterial pressure increased with exercise (+11 ± 3 mmHg, $P < 0·05$). Neither heart rate nor arterial pressure changed with sham.

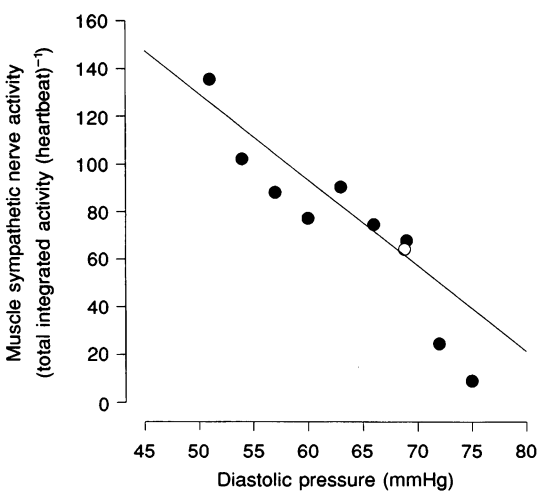

Figure 2. Representative vascular baroreflex relation

Representative baroreflex relation derived from data in Fig. 1. ○, 5 min baseline that preceded nitroprusside administration. ●, the mean nerve activity across a 3 mmHg range of pressure. Regression: muscle sympathetic nerve activity (MSNA) = 310 − 3·61 diastolic pressure (DBP); r, −0·88.

Systemic and regional haemodynamics and sympathetic outflow

Table 1 shows systemic and regional haemodynamics and sympathetic outflow at 1 h recovery post-sham and post-exercise. Mean arterial and systolic pressures were less post-exercise (both $P < 0{\cdot}05$). Cardiac output was higher after exercise ($P < 0{\cdot}05$), whereas both total peripheral and calf vascular resistances were lower ($-21{\cdot}7 \pm 4{\cdot}9$ and $-25{\cdot}3 \pm 9{\cdot}1$%, both $P < 0{\cdot}05$) after exercise. Concurrent with these haemodynamic changes, muscle sympathetic nerve activity was lower after exercise, regardless of whether it was assessed as burst number or total integrated activity.

Baroreflex control of sympathetic outflow

Figure 1 shows data from one subject during injections of vasoactive drugs. Nitroprusside and phenylephrine elicit a sequential fall and rise in pressure that provoke reflex changes in heart period (R–R interval), and muscle sympathetic outflow. Changes in diastolic pressure were similar after sham and exercise (mean fall: $-13{\cdot}2 \pm 1{\cdot}6$ *vs.* $-15{\cdot}6 \pm 2{\cdot}4$ mmHg, $P = 0{\cdot}37$; mean rise: $11{\cdot}6 \pm 2{\cdot}0$ *vs.* $12{\cdot}0 \pm 2{\cdot}4$ mmHg, $P = 0{\cdot}79$). The relation between muscle sympathetic nerve activity and diastolic pressure derived from the data in Fig. 1 is shown in Fig. 2. This relation was used to assess baroreflex control of sympathetic outflow. A close relation between nerve activity and pressure was seen in each subject (mean correlation coefficient, $r = -0{\cdot}74 \pm 0{\cdot}08$). Figure 3 shows the mean baroreflex relations. Although the slopes of the relations were not different ($-3{\cdot}96 \pm 0{\cdot}72$ *vs.* $-3{\cdot}05 \pm 0{\cdot}70$ total integrated activity (heartbeat)$^{-1}$ mmHg^{-1}, $P = 0{\cdot}10$), the intercept was less post-exercise (318 ± 51 *vs.* 218 ± 38 total integrated activity (heartbeat)$^{-1}$, $P < 0{\cdot}05$), indicating that the entire relation was shifted downward, and that across all diastolic pressures, muscle sympathetic nerve activity was less. In contrast, the relation between heart rate and arterial pressure was unaltered, as we have found previously (intercept: 201 ± 23 *vs.* 174 ± 17 beats min^{-1}, $P = 0{\cdot}13$; slope: $-1{\cdot}05 \pm 0{\cdot}16$ *vs.* $-0{\cdot}91 \pm 0{\cdot}14$ beats min^{-1} mmHg^{-1}, $P = 0{\cdot}36$; Halliwill *et al.* 1996).

Transduction of sympathetic activity into vascular resistance

Figure 4 shows data from one subject during the handgrip portion of the protocol. Isometric handgrip exercise elicits a progressive rise in arterial pressure and parallel increases in muscle sympathetic nerve activity and vascular resistance. Handgrip strength and time to fatigue were consistent on each day of the experiment (35% maximal voluntary contraction: $12{\cdot}3 \pm 0{\cdot}9$ *vs.* $12{\cdot}0 \pm 1{\cdot}3$ kg, $P = 0{\cdot}70$; time to fatigue: 237 ± 24 *vs.* 252 ± 41 s, $P = 0{\cdot}70$). The relation between calf vascular resistance and muscle sympathetic nerve activity derived from the data in Fig. 4 is shown in Fig. 5. A close relation between calf vascular resistance and nerve activity was seen in each individual (mean r, $0{\cdot}76 \pm 0{\cdot}04$). This relation was used to assess the transduction of sympathetic activity into vascular resistance. Figure 6 shows the mean transduction relations expressed as total integrated activity. The slope of the relation was greatly attenuated post-exercise ($0{\cdot}0100 \pm 0{\cdot}0033$ *vs.* $0{\cdot}0031 \pm 0{\cdot}0007$ units (total integrated activity)$^{-1}$ min, $P < 0{\cdot}05$), but the intercept was unaltered ($19{\cdot}6 \pm 11{\cdot}1$ *vs.* $26{\cdot}1 \pm 4{\cdot}2$ units, $P = 0{\cdot}12$), indicating that with any increase in muscle sympathetic nerve activity, there is less of an increase in calf vascular resistance after exercise, and that this disparity becomes more apparent with greater sympathetic activation.

DISCUSSION

These data provide conclusive evidence for altered sympathetic vascular regulation after acute dynamic exercise in humans. Despite strong evidence for a persistent post-exercise vasodilatation, there are no previous data on baroreflex control of sympathetic outflow or sympathetic control of vascular resistance after exercise in humans. Our findings are schematically summarized in Fig. 7. First, we found striking reductions in baseline muscle sympathetic nerve activity, which were associated with a downward shift of the sympathetic nerve activity–arterial pressure relation.

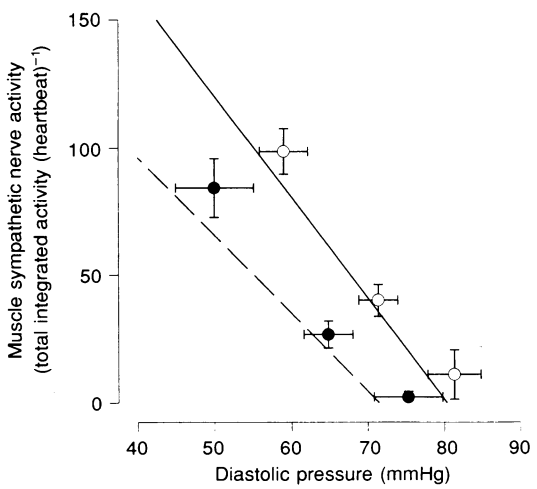

Figure 3. Mean vascular baroreflex relations

Mean baroreflex relations after sham (continuous line) and after exercise (dashed line; $n = 9$). Also shown are the baseline values for post-sham (○) and post-exercise (●), and the mean values from each subject's lowest and highest diastolic pressures post-sham (○) and post-exercise (●). Error bars indicate S.E.M. Post-sham regression: MSNA = 318 − 3·96 DBP; r, −0·88; post-exercise regression: MSNA = 218 − 3·05 DBP; r, −0·83.

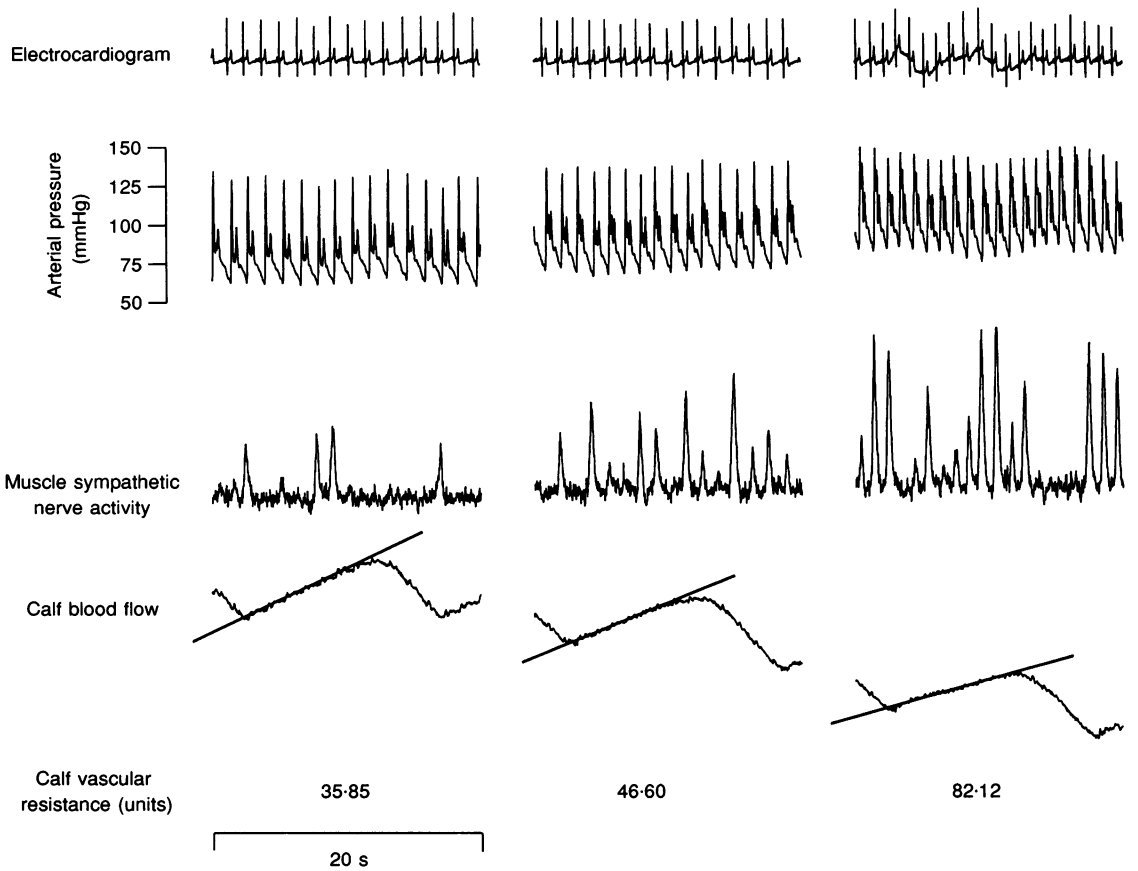

Figure 4. Representative handgrip data

Representative data from one subject showing electrocardiogram, arterial pressure, integrated muscle sympathetic nerve activity, calf blood flow, and the derived calf vascular resistance during the handgrip part of the protocol.

This indicates that an alteration in baroreflex control of sympathetic outflow does contribute to post-exercise vasodilatation. Second, we found a dramatic attenuation of the vascular resistance–sympathetic nerve activity relation. This indicates that an impairment in the transduction of nerve activity into vascular resistance also contributes to post-exercise vasodilatation. Thus, the reduced vascular resistance which underlies post-exercise hypotension results from both neural and vascular phenomena.

Although we document changes in sympathetic vascular regulation only to skeletal muscle, these alterations have an important functional impact on systemic haemodynamics.

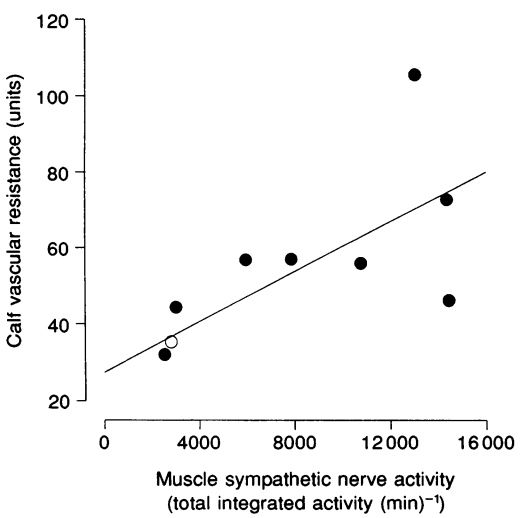

Figure 5. Representative handgrip transduction relation

Representative transduction relation derived from data in Fig. 4. ○, 5 min baseline that preceded handgrip exercise. ●, the mean nerve activity and vascular resistance during a 30 s period. Regression: calf vascular resistance (CVR) = 27·4 + 0·0033 MSNA; r, 0·78.

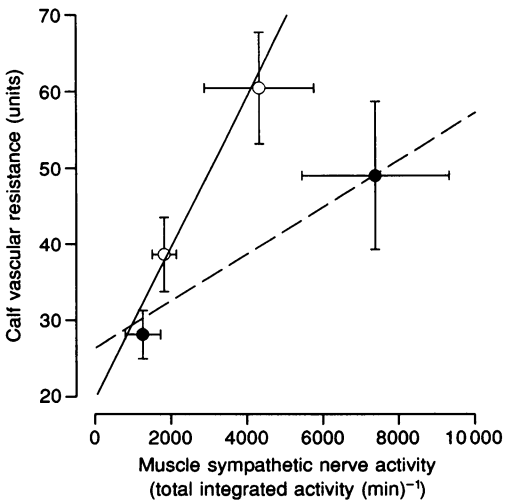

Figure 6. Mean transduction relations

Mean transduction relations after sham (continuous line) and after exercise (dashed line; $n = 9$). Also shown are the baseline values for post-sham (○) and post-exercise (●), and the mean values from each maximal nerve activity post-sham (○) and post-exercise (●). Post-sham regression: CVR = 19·6 + 0·0100 MSNA; r, 0·93; post-exercise regression: CVR = 26·1 + 0·0031 MSNA; r, 0·93.

Skeletal muscle can receive up to 88% of systemic blood flow during exercise (Rowell, 1993) and changes in skeletal muscle blood flow at rest can profoundly affect systemic arterial pressure (Rowell, Detry, Blackmon & Wyss, 1972). Further, we found that total peripheral resistance and calf vascular resistance changed in parallel, strongly suggesting that what occurs in the lower leg does indeed reflect what occurs systemically. Therefore, our findings of regional neural and vascular changes underlying a vasodilatation after exercise are likely to have a functional significance in mediating post-exercise hypotension.

Neural mechanisms

All our subjects had a decreased sympathetic nerve activity within the 2 h immediately following acute dynamic exercise. Previous assessments of sympathetic outflow after exercise have yielded equivocal results (Floras *et al.* 1989; Floras & Senn, 1991; Hara & Floras, 1992), perhaps because the exercise protocols used did not consistently produce post-exercise hypotension. In association with the reduced nerve activity, we also found that the relation between sympathetic activity and arterial pressure is shifted downward after exercise. Thus, sympathetic vasoconstrictor outflow is less at any pressure, contributing to the reduced

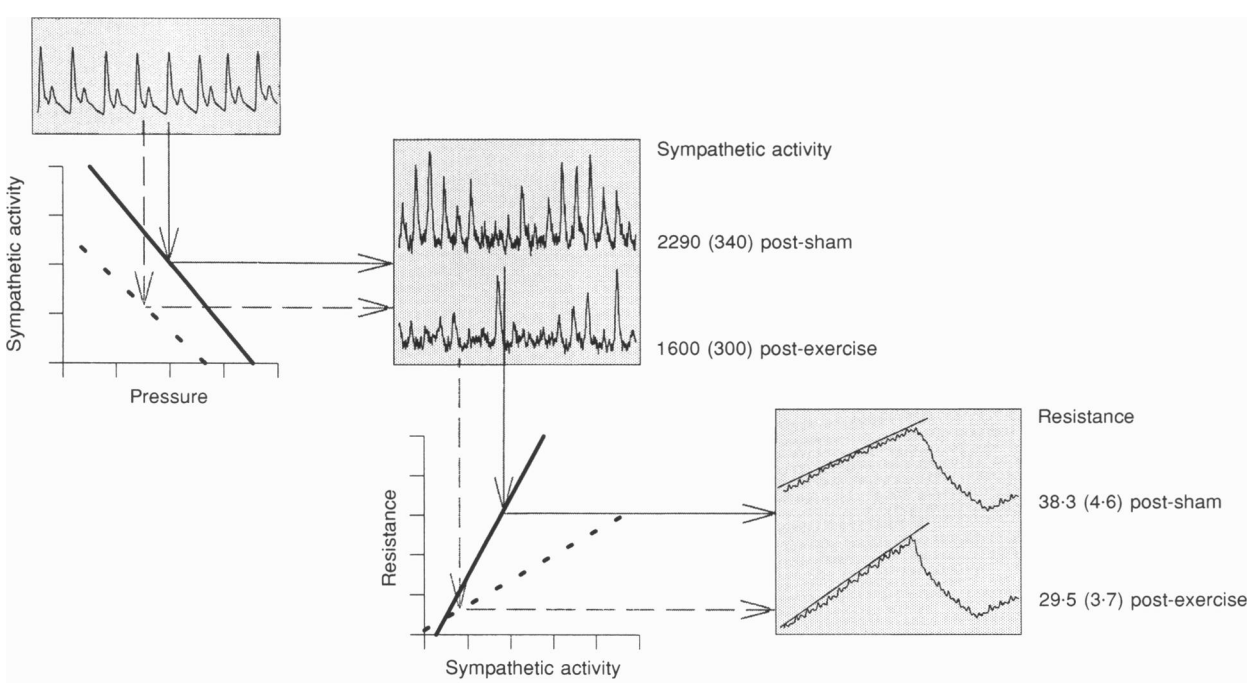

Figure 7. Schematic summary of results

Model of altered vascular regulation after exercise, incorporating shift in baroreflex control of sympathetic outflow and attenuation of the transduction of sympathetic activity into vascular resistance. Sham relations are continuous lines; exercise relations are dashed lines.

vascular resistance after exercise. This resetting of the arterial baroreflex to lower pressures could occur either at the level of the baroreceptors themselves or in the central nervous system. It is unlikely that the baroreceptors themselves are reset, since baroreflex control of heart rate is not altered at the time when our sympathetic recordings were made (Halliwill *et al.* 1996). As afferent baroreceptor activity does not subserve specific efferent outflows, this excludes baroreflex resetting at the baroreceptor level and indicates a change in the central nervous system control of vascular sympathetic outflow. A central opioid pathway, activated by exercise, has been suggested to mediate post-exercise vasodilatation by inhibiting sympathetic vasoconstrictor outflow (Thorén, Floras, Hoffman & Seals, 1990). However, recent studies have found no role for a central opioidergic mechanism in mediating post-exercise hypotension (Hara & Floras, 1992; Sebastian, Moran & Tipton, 1995). Nonetheless, it is apparent that some central alteration in the arterial baroreflex results in a downward shift in the sympathetic outflow–arterial pressure relation.

It is possible that the alteration is not due to a change in the arterial baroreflex *per se*, but is due to increased sympatho-inhibitory input from cardiopulmonary receptors. Although exercise usually produces hypovolaemia (sweating and extravascularization of fluids lead to plasma volume loss), plasma volume returns to normal and can even increase during recovery from exercise due to changes in fluid-regulating hormones or elevations in plasma protein (leading to fluid shifts from the extravascular space; Röcker, Kirsch, Heyduck & Altenkirch, 1989; Gillen, Lee, Mack, Tomaselli, Nishiyasu & Nadel, 1991). Some volume expansion may have occurred prior to our measurements (we did not measure plasma volume); however, volume expansion of greater than 1 l would be required to elicit the magnitude of sympatho-inhibition that we found (Vissing, Scherrer & Victor, 1989) and volume expansion of this magnitude is unlikely to have occurred as quickly as 1–2 h post-exercise (Röcker *et al.* 1989; Gillen *et al.* 1991). Nonetheless, the influence of cardiopulmonary reflexes could be enhanced by a single bout of exercise. Indeed, Collins & DiCarlo (1993) reversed the post-exercise hypotension in rats by blocking cardiopulmonary afferent nerves. It is unclear if this mechanism is responsible in humans. Reductions in central blood volume presumed to unload the cardiopulmonary baroreceptors have been shown to produce both unchanged and augmented forearm vascular resistance responses (Bennett, Wilcox & Macdonald, 1984; Cléroux, Kouamé, Nadeau, Coulombe & Lacourcière, 1992*b*). However, these data are insufficient to derive any conclusions concerning cardiopulmonary responses in humans due to methodological limitations (Taylor, Halliwill, Brown, Hayano & Eckberg, 1995) and to measurement limitations (i.e. no information on sympathetic responses). Regardless, it may be that increased cardiac filling pressures secondary to modest hypervolaemia interact with augmented responsiveness of cardiopulmonary reflexes to inhibit sympathetic outflow, thus shifting the nerve activity–arterial pressure relation in humans.

Vascular mechanisms

We found not only a clear sympatho-inhibition, but also a striking attenuation of the relation between sympathetic activity and vascular resistance during recovery from exercise. Thus, even if sympathetic vasoconstrictor outflow were unchanged, impaired vascular responsiveness would result in reduced vascular resistance after exercise. Ineffective transduction of nerve activity into vasoconstriction could result from less neurotransmitter release. For example, circulating opioids may be increased after a single bout of exercise (Schwarz & Kindermann, 1992). Sympathetic nerve terminals possess presynaptic inhibitory opioid receptors (Wong-Dusting & Rand, 1989) that may be occupied after exercise, effectively reducing noradrenaline release. Although systemic opioid blockade with naloxone has been shown to reverse post-exercise hypotension in animals (Shyu & Thorén, 1976; Devine, Sebastian, Monnin & Tipton, 1991; Sebastian *et al.* 1995), it has had mixed results in humans (Boone, Levine, Flynn, Pizza, Kubitz & Andres, 1992; Hara & Floras, 1992), and the role of opioids remains controversial (Sebastian *et al.* 1995). Presynaptic inhibition can also be caused by neuropeptide Y (Lundberg & Stjärne, 1984), which is co-released with noradrenaline during exercise (Pernow *et al.* 1986). After exercise, neuropeptide Y may remain bound to presynaptic receptors, reducing noradrenaline release (Pernow *et al.* 1986).

The most likely site for ineffective transduction of sympathetic outflow into vascular resistance is arterial smooth muscle, through receptor downregulation or local vasodilatator substances. Post-exercise reductions in vascular responsiveness to adrenergic stimulation have been shown in isolated aortic strips (Howard *et al.* 1992) and in conscious rabbits (Howard & DiCarlo, 1992) and rats (Patil *et al.* 1993). Using nitric oxide synthetase blockade in rats, Patil *et al.* (1993) were partially able to reverse the attenuated adrenergic responsiveness of smooth muscle after exercise, strongly supporting a role for enhanced nitric oxide activity in post-exercise vasodilatation. While there are no analogous data from humans, the strongest effect on vascular responsiveness may be that of nitric oxide.

In conclusion, we found that persistent vasodilatation following a single bout of moderate-intensity dynamic exercise is mediated in two ways. First, baroreflex control of sympathetic outflow is altered, such that sympathetic outflow at any given pressure is less. Second, transduction of sympathetic activity into vascular resistance is also altered, such that vascular resistance is even further reduced. Thus, post-exercise hypotension appears to result from both neural and vascular mechanisms.

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