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DIRECT EVIDENCE OF ACTIVE SYMPATHETIC VASODILATATION IN THE SKIN OF THE HUMAN FOOT

BY JOHAN LUNDBERG, LARS NORGREN, ELSE RIBBE, INGMAR ROSÉN, STIG STEEN, JOHAN THÖRNE AND B. GUNNAR WALLIN

From the Departments of Anaesthesia, Surgery and Clinical Neurophysiology, University Hospital Lund and Department of Clinical Neurophysiology, Sahlgren's Hospital, University of Göteborg, Sweden

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SUMMARY

1. During operative aorto-femoral vascular reconstructions on sixteen patients, the sympathetic chain was stimulated electrically between the L2 and L4 ganglia while blood flow was monitored by laser doppler flowmeters from the skin on the sole of the foot and the ankle and by an electromagnetic flowmeter from the deep femoral artery. Epidural anaesthesia to at least the T6 level was used which excluded reflex effects.

2. Stimulation (10 Hz) at 1–12 mA current strengths for 30 s evoked both reductions and increases of blood flow in glabrous and hairy skin. Initial short-lasting flow increases (durations 9–19 s) followed by sustained decreases were common; sometimes there were sustained flow increases at low and decreases at high current strengths.

3. In the deep femoral artery (supplying predominantly muscle) only flow reductions were evoked.

4. The results provide evidence for sympathetically mediated vasodilatation in the skin of the human foot whereas leg muscles may be supplied by vasoconstrictor nerves only.

INTRODUCTION

Both vasoconstrictor and vasodilator reflexes have been demonstrated in the skin of the human hand and foot. Reduction of ambient temperature causes reflex vasoconstriction (Pickering, 1933; Blair, Glover & Roddie, 1960) and (in warm subjects) transient reflex vasoconstriction is induced by a deep breath (Bolton, Carmichael & Sturup, 1936), arousal stimuli (Abramson & Ferris, 1940), mental stress (Abramson & Ferris, 1940) and by painful intraneural electrical stimulation (Oberle, Elam, Karlsson & Wallin, 1988). There is little doubt that these effects are due to increased activity in sympathetic vasoconstrictor neurones: adrenergic nerve fibres are present in the human skin and in microneurographic recordings of skin sympathetic activity these manoeuvres were associated with increases of nerve

traffic (Hagbarth, Hallin, Hongell, Torebjörk & Wallin, 1972; Delius, Hagbarth, Hongell & Wallin, 1972; Bini, Hagbarth, Hynninen & Wallin, 1980).

The mechanism behind reflex vasodilatation is less clear. Body heating leads to increased cutaneous blood flow, which in forearm, calf and thigh is due in part to a neurally mediated active vasodilator mechanism (Grant & Holling, 1938; Roddie, Shepherd & Whelan, 1957; Blair *et al.* 1960). In the hand and the foot, however, active vasodilatation during heating does not seem to occur (Sarnoff & Simeone, 1947; Gaskell, 1956; Roddie *et al.* 1957). In cold subjects painful intraneural electrical stimulation, mental stress, a deep breath and arousal stimuli all cause transient reflex vasodilatation in hands and feet (Blumberg & Wallin, 1987; Oberle *et al.* 1988), but it is unknown whether this is due to reduction of vasoconstrictor nerve traffic, increased activity in vasodilator neurones or whether it is a secondary response to sweating induced by increased activity in sudomotor nerve fibres.

The present study was undertaken to gain insight into sympathetic vasomotor mechanisms in the human leg. To this end we have stimulated electrically the lumbar sympathetic chain of patients undergoing reconstructive surgery of the abdominal aorta and measured the resulting blood flow changes in the skin of the foot and in the deep femoral artery. Our aim was to search for evidence of separate populations of sympathetic neurones, one inducing vasoconstriction and the other vasodilatation. If only vasoconstrictor neurones were present we expected a simple relationship between stimulus strength and vasoconstrictor responses whereas if both vasoconstrictor and vasodilator mechanisms were activated we expected more complex relationships or perhaps even changes between constrictor and dilator responses at different stimulus intensities.

METHODS

Material. After giving their informed consent, sixteen patients aged 45–76 years (mean 64) participated in the study, which was approved by the Human Ethics Committee of the University of Lund. The patients suffered from vascular occlusive disease and were scheduled for aorto-bifemoral reconstructions. Patients with diabetes mellitus were excluded, as were patients with weak or absent skin conductance responses in the soles of the feet when tested pre-operatively.

Procedure. Lumbar epidural anaesthesia with mepivacaine, 20 mg ml^{-1}, was applied via a lumbar catheter up to at least the T6 level. General anaesthesia was then initiated with thiopenthal, fentanyl and succinyl-choline and was maintained with nitrous oxide–oxygen (65–35%), diazepam and pancuronium. After laparotomy and dissection of the vessels in the groin the left lumbar sympathetic chain was dissected between the second and fourth lumbar sympathetic ganglia. Needle electrodes, insulated except at the tip, were positioned about 10 mm apart in the sympathetic chain and used for stimulating the chain with electrical pulses (0·5 ms duration) delivered from a constant current stimulator (Disa 1505 or 1507, Skovlunde, Denmark). In early experiments both stimulation frequency and strength were varied and in those experiments the duration of and interval between stimulation periods were not constant. However, in the last nine patients (aged 59–75 years) 30 s stimulation periods were delivered with intervals of 2 min between the beginning of successive periods. Data from these patients are summarized in Table 1. In seven of these cases stimulation frequency was kept at 10 Hz while stimulation strength was varied between 1 and 12 mA. In the other two cases stimulation frequency was varied between 1 and 20 Hz at constant stimulation currents of 5 and 8 mA, respectively.

Measurements. Cutaneous blood flow was measured with two laser doppler flowmeters (Periflux, PF 1, Perimed AB, Stockholm, Sweden) the probes of which were positioned on the sole and the medial aspect of the ankle (posterior to and slightly above the medial malleolus), respectively, of the left foot. In one control experiment probes were attached to the soles of both feet. Electrical

calibration for zero blood flow was made in all recordings. Several gains were selectable by switches. The maximum output of a given gain level (defined electrically) was taken as 100%. The analog output of this equipment gives no absolute values but relative changes of cutaneous blood flow (for technical details and evaluation of the laser doppler flowmeter see Holloway & Watkins, 1977; Nilsson, Tenland & Öberg, 1980; Johnson, Taylor, Shepherd & Park, 1984). In addition, blood flow

TABLE 1. Blood flow effects of sympathetic stimulation

		Sole of foot		Ankle		A. femoralis	
Subject	Stimulation parameter	Dilatation	Constriction	Dilatation	Constriction	Dilatation	Constriction
G.O. (♀)	Current	Yes*	Yes	Yes*	Yes	No	Yes
B.S. (♀)	Current	No	Yes	Yes*	Yes	No	Yes
T.J. (♂)	Current	Yes**	Yes	Yes**	Yes	No	Yes
C.C. (♂)	Current	No	Yes	Yes*	Yes	No	Yes
A.S. (♂)	Current	Yes**	Yes	Yes*	Yes	No	Yes
H.P. (♂)	Current	No	No	No	No	No	No
O.N. (♂)	Current	No	Yes	Yes	Yes	n.t.	n.t.
G.J. (♂)	Frequency	Yes*	Yes	n.t.	n.t.	n.t.	n.t.
E.L. (♂)	Frequency	Yes*	Yes	n.t.	n.t.	No	Yes

* Initial transient dilatation followed by vasoconstriction.
** Sustained dilatation at low and vasoconstriction at high current strengths.
n.t. = not tested.

in the left deep femoral artery was monitored with an electromagnetic flowmeter (Cliniflow, Carolina Medical Electronics Inc., NC, USA). The outputs from the flowmeters were recorded on a 4 channel chart recorder (Kipp & Zonen BD 101, Holland) at a speed of 2 mm s^{-1}. For analysis the flow records were fed into a computer (PDP 11/70) with the aid of a digitizing board (Calcomp 2000, Calcomp, Anaheim, CA, USA). The computer then calculated mean blood flow during 60 s from the start of the stimulation in relation to the control flow during the 30 s immediately prior to the stimulation. The control flow was taken as 100%.

RESULTS

In most patients stimulation of the sympathetic chain evoked well-defined blood flow responses in the stimulated leg. However, in one patient there were no clear flow responses (currents up to 10 mA). With few exceptions the current threshold for flow effects was 2 mA or less and the responses began only a few seconds after the beginning of the stimulation. Data from nine patients are summarized in Table 1.

Changes of blood flow in the sole of the foot (glabrous skin)

Stimulation of the lumbar sympathetic chain could evoke both increases and decreases of blood flow in the sole of the foot on the stimulated side but no changes occurred in the opposite foot (one experiment). In three of nine patients only flow reductions occurred but in five experiments there were both increases and decreases of blood flow. When mixed responses occurred different patterns were observed. One is illustrated in Fig. 1. In this patient all (six) stimulation periods were associated with almost immediate, fairly steep flow increases which after about 15 s turned into flow reductions lasting a minute or more after the end of the stimulation. The mean duration of the flow increase (from the start of the stimulation) in the three patients

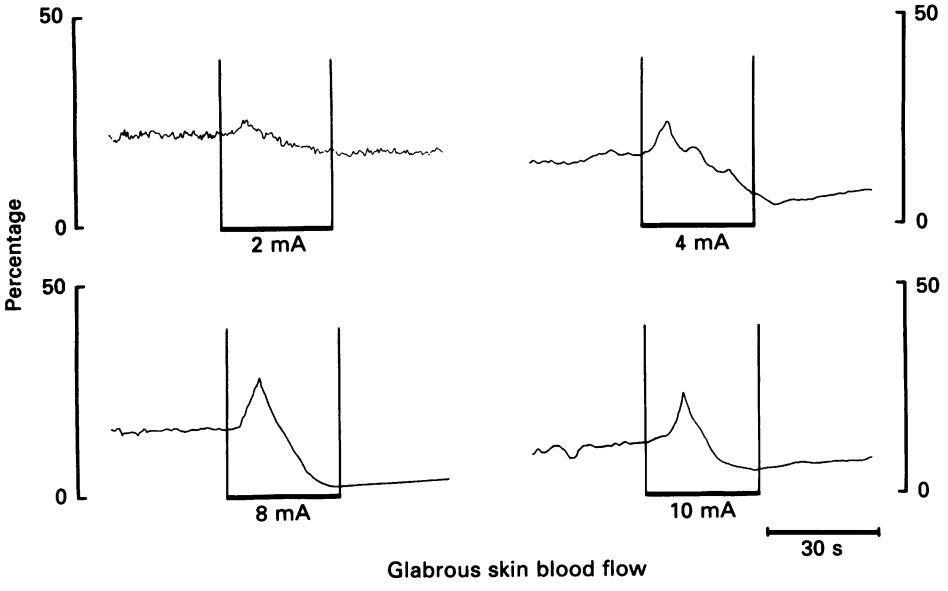

Fig. 1. Changes of blood flow recorded with a laser doppler flowmeter from the plantar side of the big toe during 10 Hz electrical stimulation (indicated by horizontal bar under each flow curve) of the lumbar sympathetic chain beween the L2 and L4 ganglia at different current intensities (indicated below horizontal bars). Subject G.O. Pulse duration 0·5 ms. Note initial transient flow increases followed by long-lasting decreases at all current intensities.

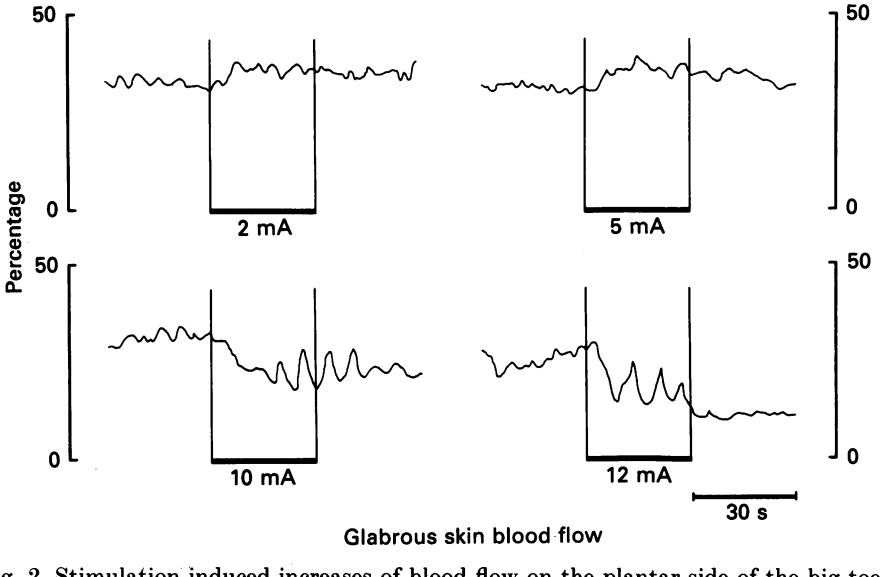

Fig. 2. Stimulation-induced increases of blood flow on the plantar side of the big toe at low and decreases at high current intensities in subject T.J. Same conditions and symbols as in Fig. 1.

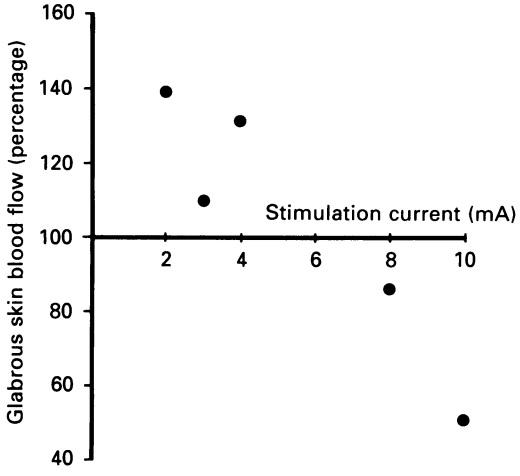

Fig. 3. Blood flow recorded with a laser doppler flowmeter on the plantar side of the big toe during 30 s of 10 Hz electrical stimulation of the sympathetic chain between the L2 and L4 ganglia at different current intensities. Subject A.S. Each data point shows mean blood flow during 60 s after start of stimulation compared to mean flow during a 30 s control period immediately prior to the stimulation (equal to 100%).

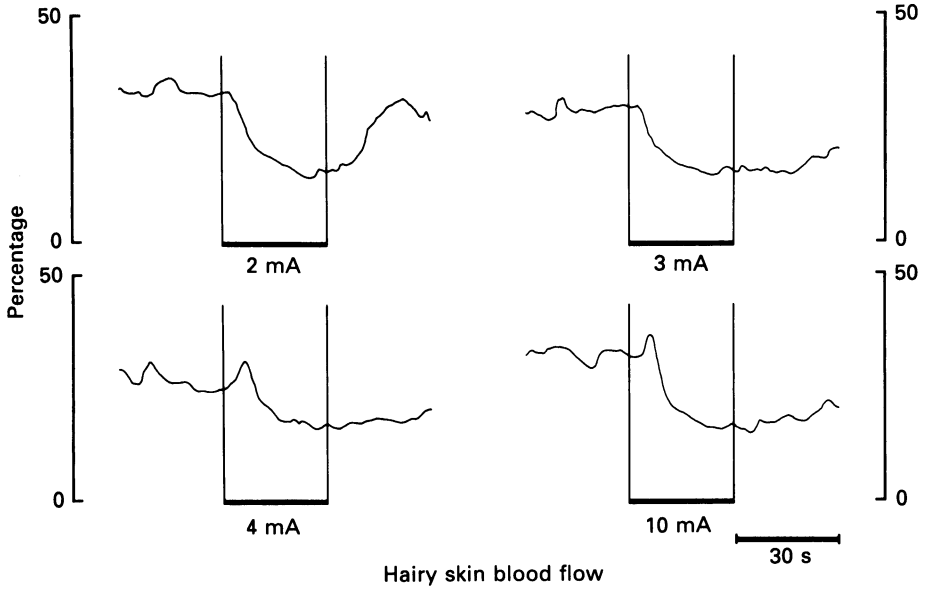

Fig. 4. Stimulation-induced sustained flow reductions in hairy skin at the ankle in subject C.C. Note initial transient flow increases at 4 and 10 mA current intensities. Same symbols as in Fig. 1.

who displayed this pattern was 19, 15 and 15 s, respectively. Another pattern (two cases) showed moderate sustained flow increases at low and clear reductions at high stimulation strengths (Fig. 2) with mixed responses at intermediate currents. Figure 3 summarizes quantitatively the stimulation-induced flow changes 0–60 s from the start of the stimulation in the other case (subject A.S.).

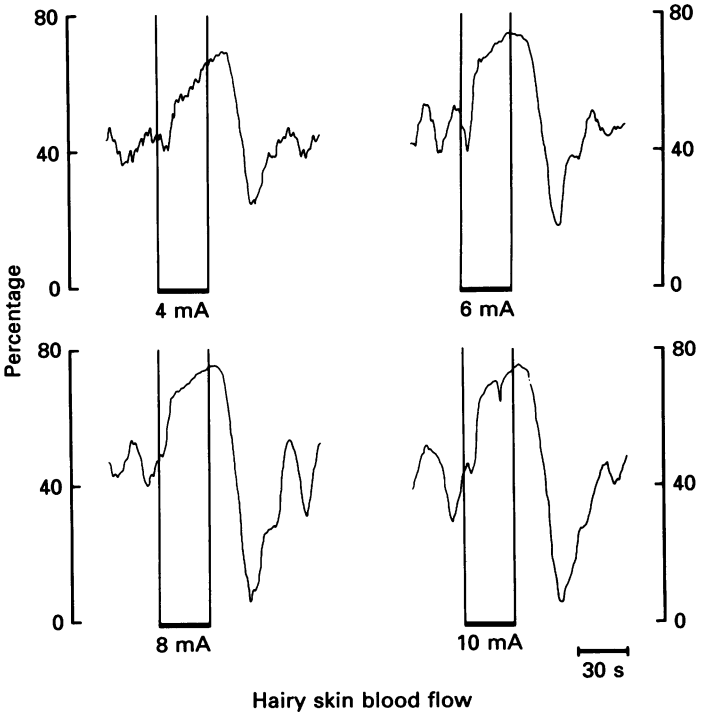

Fig. 5. Stimulation-induced sustained increases of blood flow in hairy skin at the ankle followed by marked transient flow reductions after the end of the stimulation. Subject O.N. Same symbols as in Fig. 1.

Changes of hairy skin blood flow at the ankle

In four patients there were transient early flow increases (mean durations of 12, 11, 10 and 9 s, respectively) in hairy skin at the ankle followed by long-lasting signs of vasoconstriction. In three of the cases the transient flow increases occurred at all current strengths and in the fourth case (Fig. 4) only at high strengths. In one patient sustained increases of blood flow occurred during all current strengths and in this case there were also short but marked transient flow decreases after the end of the stimulation (Fig. 5). There was also one case with more variable and less marked increases of flow at low current strengths and a clear decrease at the highest strength.

Changes of blood flow in the deep femoral artery

In the deep femoral artery which is dominated by flow to leg muscles the stimulation periods caused sustained blood flow reductions only. Usually the

threshold was similar to that for skin blood flow changes, i.e. around 2 mA, and the latency to the beginning of the response was also similar, i.e. a few seconds only. With increasing currents the flow sometimes decreased linearly (Fig. 6) but sometimes levelled off more or less completely at higher currents.

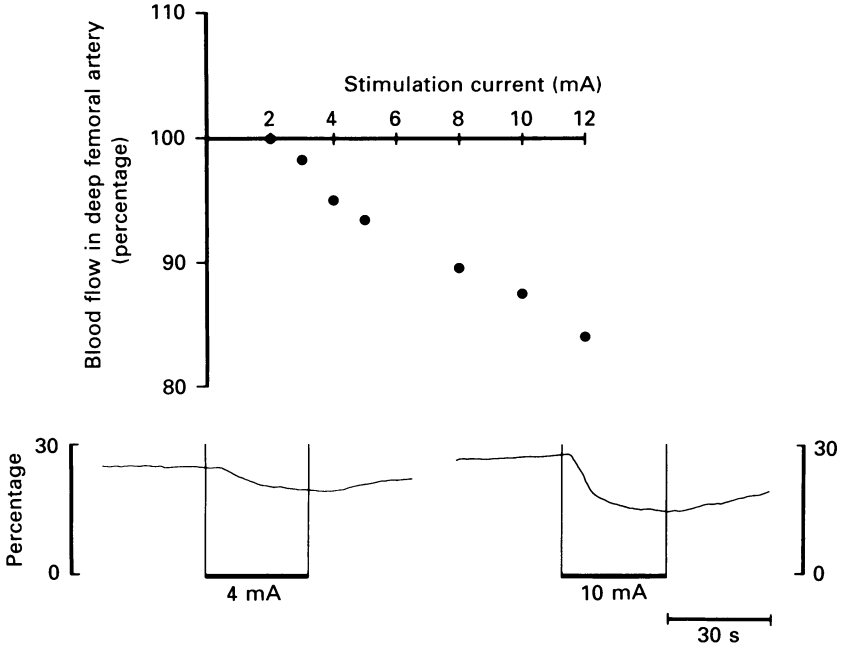

Fig. 6. Blood flow in deep femoral artery recorded with electromagnetic flowmeter during 30 s of 10 Hz electrical stimulation of the sympathetic chain between the L2 and L4 ganglia at different intensities in subject T.J. Each data point shows mean blood flow during 60 s after start of stimulation compared to mean flow during a 30 s control period immediately prior to the stimulation (equal to 100%). Examples of individual flow records shown below.

DISCUSSION

Skin blood flow

Our main finding was that electrical stimulation of the lumbar sympathetic chain may lead to either increases or decreases of cutaneous blood flow in the foot on the stimulated side. If afferent unmyelinated cutaneous nerve fibres from the foot were present in the sympathetic chain, electrical stimulation of the chain could in theory evoke antidromic vasodilatation in the foot. To our knowledge, however, there is no evidence that such fibres exist and the most likely explanation for both the increases and decreases of blood flow is activation of sympathetic fibres. The duration of the dilator responses was shorter than that of the constrictor responses which also agrees with a sympathetic mechanism; antidromic vasodilator responses are usually much more long lasting (Blumberg & Wallin, 1987).

Sympathetic outflow to the foot reaches the sympathetic chain through

preganglionic fibres in the T9–L2 ventral roots (Normell, 1974). Since lumbar epidural anaesthesia was applied to at least the T6 level and since in a control experiment no changes of blood flow occurred in the opposite foot, the responses must have been evoked by centrifugally conducted impulses and not via a reflex pathway. General anaesthesia inhibits skin sympathetic activity (König & Wallin, 1976) which in combination with epidural anaesthesia should ensure that all spontaneous preganglionic activity destined to the foot was eliminated. It is also unlikely that there should be spontaneous activity in the postganglionic neurones since sympathetic recordings in patients with traumatic spinal cord injury show that decentralized postganglionic sympathetic neurones have virtually no spontaneous activity in the peroneal nerve (Wallin & Stjernberg, 1984; Stjernberg, Blumberg & Wallin, 1986). In addition, no spontaneous postganglionic sympathetic activity remains in the peroneal nerve after epidural anaesthesia above the T9 level (Lundin, Elam & Wallin, 1988). With no spontaneous postganglionic vasoconstrictor activity present the increase of blood flow seen in our experiments must have been due to active vasodilatation and not to inhibition of vasoconstrictor activity (via stimulation-induced activity in preganglionic inhibitory neurones or pre-junctional neuro-effector mechanisms).

The most likely explanation for the variability of responses is that the stimulation evoked impulse activity in two types of fibres, one causing vasodilatation and the other vasoconstriction. The differences in response patterns between experiments probably arose because both the destination and number of fibres of the different types close to the stimulating electrodes varied randomly. However, when increases of blood flow occurred they were usually most prominent at low stimulus strengths. Furthermore, transient flow increases preceding vasoconstrictor responses were more common than the reverse sequence. These results may indicate that stimulation thresholds were lower and response latencies shorter for neurones inducing vasodilatation than for vasoconstrictor neurones. On the other hand, since blood flow reductions dominated at high stimulus strengths, neurones causing vasoconstriction may be more numerous than those causing vasodilatation and/or having more long-lasting effects. In addition, the possibility exists that the time course of the responses may be modified by pre-junctional neuro-effector mechanisms. It is also conceivable that with a physiological irregular impulse pattern the balance between dilator and constrictor responses would differ from that found with even stimulation.

The present results provide the first evidence for active sympathetic vasodilatation in the skin of the human foot. The vasodilatation may be due to impulse traffic in sympathetic vasodilator neurones. However, it has also been suggested that active cutaneous vasodilatation is a secondary effect to activity in sympathetic sudomotor neurones (see Rowell, 1983). Human postganglionic sudomotor neurones have higher conduction velocity than vasoconstrictor neurones (Fagius & Wallin, 1980) which suggests larger diameters and a lower threshold to electrical stimulation for sudomotor neurones. Thus, if sudomotor neurones were responsible for the vasodilatation one would expect the vasodilation to have a lower threshold for electrical stimulation than the vasoconstriction, which in fact was the case in our experiments. Consequently, the results are compatible with the sudomotor alternative but provide no evidence for or against true vasodilator neurones.

It has recently been shown that cutaneous reflex vasodilatation occurs in hands and feet in response to a number of short-lasting reflex stimuli (Blumberg & Wallin, 1987; Oberle *et al.* 1988). Although it is unclear whether these effects are due to active vasodilatation the present results show that such a mechanism is present at least in the foot. This raises the possibility that earlier failures to demonstrate active vasodilatation during heating are due to methodological difficulties. Previous conclusions have been based on measuring changes of skin temperature or blood flow when anaesthetizing nerves supplying the skin area under study (Sarnoff & Simeone, 1947; Gaskell, 1956). In hands and feet temperature or blood flow did not decrease after such nerve blocks. This was in contrast to findings in forearm and calf and therefore it was suggested that hands and feet did not have active vasodilatation. However, the skin of hands and feet have a much higher density of AV shunts than that of forearm and calf (Grant & Bland, 1931). AV shunts are controlled predominantly via adrenergic vasoconstrictor nerves (see Hales, 1985) and since flow through fully relaxed AV shunts is very high, the additional flow obtained by blocking vasodilator nerve traffic may be too small to be detected by occlusion plethysmography or temperature measurements.

Flow in the deep femoral artery

In the deep femoral artery the stimulation induced only reductions of blood flow, suggesting that sympathetic regulation of skeletal muscle blood flow is dominated by vasoconstrictor mechanisms. In addition, the results also show that in patients with severe arteriosclerotic narrowing of large arteries, sympathetic vasoconstrictor impulses can still induce substantial reductions of muscle blood flow. It has been suggested previously that muscles are innervated both by sympathetic vasoconstrictor and vasodilator fibres (Golenhofen & Hildebrand, 1957; Blair, Glover, Greenfield & Roddie, 1959). Our results do not exclude the possibility that vasodilator fibres exist but if they do, their effects are overridden by those of vasoconstrictor fibres when both types of fibres are stimulated simultaneously.

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