Vasomotor Responses in the Human Arm During Leg Exercise


The object of the experiments described in this paper was to see what part is normally played by vasomotor fibers to the limbs in the general circulatory response to exercise. It was not considered useful to make measurements of blood flow in actively exercising limbs, since any vasomotor effects in these parts would be obscured by the vasodilating effect of locally produced metabolites. Observations were, therefore, made on the resting hand and forearm during leg exercise.

It is now known that there are several systems of sympathetic fibers supplying the various tissues of the limb, and that the individual vasomotor centers which control these fibers seem able to function quite independently of each other. Skeletal muscle has both vasoconstrictor and vasodilator innervation. At rest, the muscle vessels are subjected to considerable vasoconstrictor tone. The activity of the fibers is varied reflexly, probably through alteration in the activity of baroreceptors in the central vascular area and possibly also in response to chemoreceptor stimulation. They play no part in the reflex changes of limb blood flow which occur in response to warming and cooling the body. Undergraduates are often taught that vasoconstriction in the inactive muscles during exercise leads to a redistribution of blood to the actively exercising muscles. There is no experimental evidence to support this. Using isotope clearance and change in the oxygen content of effluent venous blood to measure blood flow, results have been obtained which suggest that muscle blood flow in the forearm is little altered during leg exercise. Using venous occlusion plethysmography to measure forearm blood flow, Harpuder, Lowenthal, and Blatt came to a similar conclusion.

There is also evidence that human skeletal muscle is supplied with cholinergic vasodilator nerves. Though these fibers do not appear to be active at rest, they contribute to the muscle vasodilatation during emotional stress. It has been postulated that this type of fiber may be activated during the early stages of exercise but there is no experimental evidence on this point either in man or in other species.

The skin of the proximal parts of the limbs also has vasoconstrictor and vasodilator innervation. These nerve fibers are functionally distinct from those to muscle and there is no evidence as yet that they are activated in any but temperature-regulatory reflexes. Under comfortably warm conditions, neither set of fibers is active, so that blocking the cutaneous nerves to the limb results in very little change in flow. However, cooling the body results in increased vasoconstrictor fiber activity and heating the body results in active cholinergic vasodilatation. There is now evidence that the vasodilatation produced by these fibers may be secondary to the cholinergic excitation of the sweat glands.

The vasomotor control of blood vessels in the extremities of the limbs seems quite distinct from that of the skin in the proximal parts of the limbs. In the hands the vessels have a high degree of vasoconstrictor tone even when the subject is comfortably warm. Although these fibers take part in temperature-regulatory reflexes, they also show a high

From the Department of Physiology, The Queen's University of Belfast, Belfast, Ireland.
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degree of reactivity to a wide variety of stimuli, including many trivial and often unappreciated psychic stimuli. There is no evidence that vasodilator fibers play an important part in the reflex changes in hand blood flow seen in normal individuals. 20-22

From changes in the axillary arteriovenous oxygen differences, Bishop and his associates 9 deduced that total blood flow in the resting arm was reduced during leg exercise. Since they found no evidence for reduction in muscle blood flow, they concluded that the fall in flow occurred in the skin. Estimation of blood flow in the hand presents fewer technical difficulties than estimation of flow in other skin areas, and numerous workers have found that hand blood flow falls during leg exercise. 9-10, 23-25 This reduction usually occurs at the beginning of exercise. However, because of the specialized nature of the vascular bed in the hand and the specialized nature of its vasomotor innervation, it is not permissible to consider these changes as representative of those occurring in skin elsewhere in the body or in other tissues of the body. Further, the readiness of the hand blood vessels to constrict in response to minor psychic stimuli makes the results of such experiments difficult to interpret.

It is difficult to say whether the fall in flow described during exercise is a specific response to exercise or merely the consequence of the psychic disturbance which is occasioned by asking the subject to commence exercise and of his effort to cooperate. In this paper, therefore, more attention has been paid to the changes in vasomotor activity in the forearm than to those which occurred in the hand.

Methods

The experiments were carried out on seven healthy young men. The subject lay supine on a firm platform in a laboratory with the temperature at 18 to 20 C.; both feet were on the pedals of a bicycle ergometer at a mean height of 10 cm. above the sternal angle. Forearm or hand blood flow was measured with the water-filled plethysmographs described by Greenfield. 26 Leg exercise was performed in time to a metronome. The degree of the exercise could be altered by changing either the rate of pedaling or the load on the wheel, and was estimated by measuring the increase in oxygen consumption during the exercise with a Krogh spirometer.

At first it was very difficult to measure forearm or hand blood flow during leg exercise because of arm movements. After many hours of practice, however, the authors were able to carry out exercise heavy enough to increase their oxygen consumption to over 1 L./min. without undue movements of the forearm. The main series of experiments was carried out on these three subjects. Slight movements were damped by including a 20-cm. length of capillary tubing (bore 1 mm.) in the tubing connecting the plethysmograph to the float recorder and by filling the latter with heavy gear oil. A record from one of these experiments, illustrated in figure 1, shows that the plethysmograms obtained were readily interpretable. In a series of experiments on these three subjects, each of the following procedures was carried out on one forearm.

1. The deep nerves above the elbow were blocked with 3 per cent ethoheaine hydrochloride containing 0.002 per cent epinephrine. 2 In two of these experiments, the pressure in the brachial artery was measured through a needle connected to a capacitance manometer.

2. The cutaneous nerves were blocked in the region of the elbow with the same anesthetic solution. The cutaneous nerves were first located by faradic stimulation. They were then palpated and picked up in a fold of skin between finger and thumb. Insertion of a needle into this fold of skin gave rise to a characteristic sensation which made it possible to locate the nerves very accurately; they could thus be blocked by the injection of a very small amount of solution.

3. Bretylium tosylate (Burroughs Wellcome), 12.5 mg. in 16 ml. saline, was infused into the brachial artery through an indwelling needle over a period of four minutes. This dose has been shown to block specifically the adrenergic vasoconstrictor nerves in the human forearm. 27

4. Atropine sulfate, 0.3 mg., was infused into the brachial artery over a similar period. This dose has been found to block the vasodilator activity of acetylcholine infused intra-arterially into
Figure 2
The effect of leg exercise on blood flow in the hand (v) and forearm (o) (Left panel): average result of 19 runs on three subjects when the increase in oxygen consumption above the resting level was less than 500 ml./min. (average 326 ml./min.). (Right panel): average result of 17 runs on the same subjects when the increase in oxygen consumption was greater than 500 ml./min. (average 780 ml./min.). The rectangle represents the five-minute period of leg exercise.

the same arm at the rate of 20 \mu g./min.; it also depresses, in the experimental but not the control arm, the vasodilatation in the skin during body heating18 and in the muscle during emotional stress.13

Forearm blood flow during leg exercise was also measured in four medical students who were not so highly practiced in pedaling the ergometer or in being subjects for physiological experiments. These subjects only carried out light work (average increase in oxygen consumption, 350 ml./min.); with heavier work, the plethysmograms were difficult to interpret because of arm movements. The effect of atropine on the response of these untrained subjects was also investigated.

Results
Effect of Leg Exercise on Blood Flow in Hand and Forearm in Practiced Subjects

Figure 1 shows the forearm blood-inflow curves recorded just before and immediately after the start of a period of leg exercise in one of the three trained subjects. This shows that there was a fall in forearm blood flow over the first minute of exercise. In 36 experiments on these subjects, hand and forearm blood flow and oxygen consumption were measured simultaneously. The average results of these experiments, arbitrarily divided into two groups, are shown in figure 2. In the left panel are shown the results of 19 experiments in which the increase in oxygen consumption above the resting value during exercise was less than 500 ml./min. (average 326 ml./min.), and the right panel contains the average results of the 17 experiments in which the increase in oxygen consumption was greater than 500 ml./min. (average 780 ml./min.). The pattern of response was the same in all these experiments. In the forearm, there was first a gradual fall in blood flow during exercise, which was more marked during the heavy exercise (0.001 > P) than during the light exercise (0.01 > P > 0.001). This was followed by a gradual return toward the resting level. Following heavy exercise, there was a significant increase in flow (0.001 > P), but after the light exercise there was no significant change from the resting level (0.8 > P > 0.7).

In the hand, there was an immediate decrease in flow at the start of exercise, which was, if anything, greater during light exercise (0.001 > P) than during heavy exercise (0.01 > P > 0.001). As in the forearm, flow returned toward the resting level during the five-minute period of exercise and rose substantially above it after exercise. There was a more significant increase in flow after heavy exercise (0.01 > P > 0.001) than after light exercise (0.02 > P > 0.01).

Effect of Nerve Block on Response of Forearm Blood Flow to Leg Exercise in Practiced Subjects

Deep Nerve Block

In the experiment illustrated in figure 3, forearm flow was simultaneously measured in both forearms. The deep nerves to the muscles of the left forearm had been blocked. This caused the blood flow on the left side to be higher than that in the control arm, due to the release of vasoconstrictor tone. Forearm vascular resistance was calculated by dividing the mean arterial pressure by mean flow, and is shown in arbitrary units. During the period of exercise there was a fall in blood flow in the control forearm, yet the mean arterial pressure was increased by

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The effect of deep nerve block on forearm blood flow and forearm vascular resistance during leg exercise. Nerve-blocked forearm (●); normal forearm (○); heart rate (▲). The rectangle represents the period of leg exercise and the number within the rectangle shows the increase in oxygen consumption above the resting level during exercise.

About 20 mm Hg. This showed that marked vasoconstriction occurred in the forearm during exercise, causing a considerable rise in forearm vascular resistance. As there was no change in vascular resistance in the nerve-blocked forearm, it was clear that the vasoconstriction was due to vasomotor nerve activity. The increase in flow observed on the nerve-blocked side could be explained as a passive response to the increase in arterial pressure. A similar result was obtained in one other experiment of this type.

In a series of 10 experimental runs on the three subjects, forearm blood flow was compared in the normal and nerve-blocked sides during exercise. The average result of these experiments is shown in figure 4. Although there was a significant fall in blood flow on the control side (0.01 > P > 0.001), there was a significant rise in flow on the nerve-blocked side (0.01 > P > 0.001). The difference between the response of the two sides was also significant (0.01 > P > 0.001). These results indicated that the vasoconstriction in a normal forearm during exercise is mediated through vasomotor fibers distributed to the forearm in the deep nerves.

Adrenergic Block

In twelve runs on the same subjects, forearm blood flow was measured bilaterally following intra-arterial infusion of 12.5 mg. bretylium tosylate into one side (fig. 5). This dose has been shown to cause a selective block of sympathetic adrenergic nerve
endings. The picture was very similar to that in the experiments in which the deep nerves to one forearm were blocked. The blood flow in the control side fell, whereas that in the experimental side rose; the difference between the responses of the two sides was highly significant (0.01 > P > 0.001). This result indicated that the vaso- motor fibers responsible for the vasoconstriction in the control forearm are adrenergic. In one experiment, the effect of bretylium tosylate on the response of the hand blood vessels to exercise was studied. Bretylium reduced the degree of both the initial fall in flow and the subsequent rise in flow in the experimental hand.

**Cutaneous Nerve Block**

In 10 runs on the three subjects, the cutaneous nerves to one forearm were blocked, thus paralyzing vasomotor activity in the skin without interfering with the vasomotor fibers to the muscle vessels. The average result of these experiments is shown in figure 6. The initial vasoconstriction was unaffected by the procedure, and there was no significant difference between the response of the two sides (0.4 > P > 0.3). This indicated that the vasoconstrictor fibers involved in this response are not distributed with the cutaneous nerves.

In the experiments illustrated in figure 6, the blood flow on the two sides diverged toward the end of exercise and during recovery. Whereas the flow returned as usual...
toward the resting level on the normal side, the fall in flow was more persistent on the side with cutaneous nerve block. After exercise, there was a significant increase in flow on the control side above the initial resting level (0.02 > P > 0.01), but no such increase was seen on the experimental side (0.1 > P > 0.05). This indicated that the increase in flow on the control side at these times is mediated through fibers running with the cutaneous nerves and occurs mainly in skin vessels. Moreover, since the flow on the control side rose higher than the flow on the side with cutaneous nerve block, the vasodilation could not be explained by release of vasoconstrictor tone. It is likely, therefore, that it was mediated by vasodilator fibers to the skin vessels.

**Cholinergic Block**

The fact that there is vasoconstriction in the forearm muscle at the start of exercise does not exclude the possibility that an increase in vasodilator fiber activity might occur at the same time. If this were the case, blocking the vasodilator fibers to muscle would result in an even greater vasoconstriction in the experimental forearm. To test this possibility, the effect of intra-arterial atropine on the response was studied in nine runs on the three subjects. The average result is illustrated in figure 7. There was no significant difference between the responses on the two sides (0.9 > P > 0.8); therefore, it was concluded that cholinergic fibers do not play an important part in the vasomotor response to exercise under these conditions. However, although blood flow usually rose in the control arm after exercise, a similar increase was often not seen in the atropinized forearm; the difference reached a significant level (0.05 > P > 0.02). This can probably be explained as due to block of cholinergic fibers to skin on the atropinized side.

**Effect of Leg Exercise on Blood Flow in Forearm in Unpracticed Subjects**

Ten experimental runs were performed by four subjects unaccustomed to the procedure. The average change in blood flow in these runs is compared with that which occurred in 10 similar runs carried out by the three experienced subjects (fig. 8). To avoid movements of the forearm, only light work was performed in these experiments. The average increases in oxygen consumption were 350 ml./min. for the untrained subjects and 397 ml./min. for the trained subjects. Whereas the usual fall in flow was seen in the trained subjects, the untrained subjects responded with a small increase in flow. In the experiment illustrated in figure 9, the effect of atropine on the response of an untrained subject was studied. The increase in flow was slightly reduced on the atropinized side, suggesting that the cholinergic vasomotor fibers to the forearm contributed to the increase in flow during leg exercise. However,
Changes in Local Blood Flow During Attempted Exercise of Paralyzed Forearm

Blood flow was measured simultaneously in both forearms in four unpracticed subjects. Gallamine triethiodide (Flaxedil) was infused into the left brachial artery at a rate of 4 mg./min. for six to nine minutes at the beginning of each experiment. The dose used was sufficient to cause paralysis of the muscles of the left forearm without obviously affecting muscle power elsewhere in the body. Three of the subjects, however, experienced some blurring of vision. When paralysis was complete, the subject was asked to try to open and close his left hand rhythmically, in time with a metronome. The result of one of these experiments is illustrated in figure 10. In this case, the blood flow through both forearms increased, presumably because of associated emotional stress; but the increase in the left arm was no greater than that in the right. A similar result was obtained in two other experiments, and in the fourth there was no increase on either side. Although gallamine triethiodide blocked cholinergic transmission at the myoneural junction, it did not seem to block the activity of vasodilator fibers. When the subject was subsequently exposed to emotional stress, a symmetrical vasodilatation occurred in both forearms. This type of vasodilatation could be reduced on one side by atropinizing one forearm.

Discussion
Vasoconstrictor Fibers to Muscle

Leg exercise normally resulted in a small fall in flow in the resting forearm. When vasoconstrictor fibers in the forearm were blocked by bretylium tosylate, or when the deep nerves to the forearm had been blocked with local anesthetic, exercise caused a large increase in flow which could be explained by the associated increase in arterial pressure. It was clear, therefore, that leg exercise caused an increase in vasoconstrictor tone in the forearm. The increase occurred in muscle rather than skin, since blocking only the vasomotor fibers to the skin did not prevent vasoconstriction in the forearm during exercise.

The increase in vasoconstrictor tone in the forearm was sufficient, not only to prevent flow from increasing in spite of the increase in arterial pressure during exercise, but usually to cause an actual reduction in flow. The increase in vasoconstrictor tone seemed to be related to the degree of exercise. Increasing the degree of exercise usually increases the degree of rise in arterial pressure. In the
present experiments the fall in blood flow was, if anything, greater during heavy exercise than during light exercise. It was clear, therefore, that the increase in vasoconstrictor tone was able to overcome the effect of the increased blood pressure on flow at all the levels of exercise studied. Undergraduates have usually been taught that vasoconstriction in the inactive muscles during exercise leads to a redistribution of blood flow from these muscles to those which are actively engaged in the exercise. Although there is no previous evidence, to our knowledge, that this is the case, the present experiments would seem to justify it. However, the fall in flow was very small in most cases, and it would seem that the main effect of the increase in vasoconstrictor tone was to prevent an increase in flow rather than to cause a reduction in flow. The present experiments do not throw light on the afferent mechanisms responsible for these changes in vasoconstrictor tone.

Vasodilator Nerves to Muscle

If vasodilator fibers to muscle were active during exercise, they might act either in a general way causing vasodilation in all the muscle beds, or they might act in a specific way causing vasodilation confined to the actively exercising muscles.

In the present experiments, it was found that atropinization of the forearm did not affect the blood flow response of the forearm to leg exercise in the highly practiced subjects. Since atropine has been shown to block the effect of vasodilator fibers to forearm muscle, it is clear that a widespread discharge of these fibers is not an integral part of the general vasoconstrictor response to exercise. However, it should be stressed that the subjects in these experiments (the authors) were so highly trained in the experimental procedure and so accustomed to acting as subjects in physiological experiments that the emotional disturbance during exercise was minimal.

A different picture was seen in subjects whose emotional reactions to the procedure were less dulled by repetition. During even light exercise, a small increase in forearm blood flow was often present in these subjects, and the increase was sometimes reduced by atropinizing the forearm. It seems, therefore, that a general discharge of vasodilator fibers can occur during exercise, but probably only if the exercise is associated with some degree of emotional stress. Since emotional stress causes vasodilator discharge, and since exercise is accompanied by emotional stress in many situations of everyday life, it is only to be expected that a general discharge of vasodilator fibers to muscle must often modify the circulatory response to exercise. In competitive athletics, vasodilator discharge may even be the dominant feature of the vasoconstrictor response. In the laboratory, it is not
easy to make subjects carry out exercise under experimental conditions without causing them some emotional disturbance. It seems that careful allowance must be made for such disturbance in the interpretation of the results of this type of experiment.

Another way in which vasodilator fibers to muscle might be concerned in the vasomotor response to exercise is that their activity might be confined to the actively exercising muscle. In this way the vasodilator activity of the locally produced metabolites might be supplemented by nerves and thus allow an immediate and considerable increase in muscle blood flow. Eliasson, Lindgren, and Uvnäs found evidence that the sympathetic vasodilator outflow was represented in the motor cortex. Vasodilator responses were obtained in the dog on electrical stimulation of the area between the cruciate sulcus and the sulcus considered to be homologous to the central sulcus. This being the case, it is conceivable that activity of the pyramidal tract neurones, through some nervous integration at cortical level, might induce activity in vasodilator neurones supplying the same muscle area. If the hypothesis were correct, a voluntary effort to exercise a forearm paralyzed with a myoneural blocking agent should be accompanied by vasodilation in the forearm, provided the agent did not also block the activity of cholinergic vasodilator fibers. However, it was found that when one forearm was treated with gallamine triethiodide, attempts to exercise the paralyzed forearm did not cause a greater vasodilatation in the treated forearm than that seen in the untreated forearm. Gallamine triethiodide did not reduce the forearm vasodilatation during emotional stress. The results did not, therefore, support the possibility that the specific vasodilator outflow to a specific group of muscles is activated when the muscle group in question is exercised.

**Vasomotor Fibers to Skin**

**Forearm**

Blocking the cutaneous nerves to the forearm did not impair the vasoconstriction in the forearm during exercise. There was, thus, no evidence that vasoconstrictor fibers to skin vessels took part in the reflex vasoconstriction in the forearm during exercise. However, cutaneous nerve block did reduce the small rise in blood flow toward the end of, and after, exercise. This suggested that reflex vasodilatation was occurring in skin at these times. The finding that the blood flow rose to a higher level in the normal side than in the nerve-blocked side indicated that the vasodilatation was not due to release of vasoconstrictor tone in skin, but rather to an active vasodilator mechanism mediated through fibers running with the cutaneous nerves. Body heating causes such a reflex vasodilatation in forearm skin, and it is likely that the increase in heat production during exercise was responsible for the vasodilatation in the present experiments. The fact that the subjects often felt hot and were sweating after the period of exercise would support this.

**Hand**

The present results are in agreement with observations of many previous workers that...
there is a reduction in hand blood flow at the beginning of a period of leg exercise. It is difficult to say, however, whether the vasoconstriction is a specific vasomotor response to exercise or merely the normal sequence of the psychic disturbance which the exercise unavoidably causes. Hand blood flow is notoriously labile and, under comfortably warm conditions, strong vasoconstriction can occur in response to quite trivial stimuli. If the subject sees the door of the laboratory being opened or if he begins to wonder when the experiment will end, his hand blood flow often drops to practically zero. A deep breath may stop hand blood flow for several seconds, and merely inflating a pneumatic cuff on one arm causes a significant reduction in blood flow through the opposite hand. Great caution must always be used, therefore, in interpreting the significance of vasoconstriction in the hand in response to a particular stimulus. In the present experiments, the initial vasoconstriction in the hand differed in several ways from that seen in the forearm. The initial fall in hand blood flow was, if anything, greater during mild exercise than during severe exercise (fig. 2). The greatest fall in flow was usually seen in the first few seconds of exercise. This was the time when the subject made an effort to pick up the correct rhythm of exercise on the bicycle ergometer, when some degree of psychic disturbance would not be surprising. In the forearm the greatest fall in flow was not seen until about one minute after exercise had started. It is, therefore, not possible to say from the present experiments that vasoconstriction in the hand is a specific response to exercise.

After some minutes of exercise, however, the hand blood flow often rose to above the resting level, and after exercise stopped, rose to yet higher levels. A similar result was found by Muth et al. using hand calorimetry to estimate blood flow. Since the initial vasoconstriction and the later vasodilatation were reduced when the hand had been treated with bretylium tosylate, it is likely that they were both due to alterations in vasoconstrictor tone. Since the vasodilatation after exercise in the hand, like that in the forearm, was greater with heavy than with light exercise, it is likely that the increase in heat production during exercise was responsible for the reflex release of vasoconstrictor tone.

Summary

Blood flow was measured in the hands and forearms of recumbent subjects by venous occlusion plethysmography during leg exercise on a bicycle ergometer. In three highly practiced subjects, exercise resulted in a small fall in forearm flow and a moderate rise in arterial pressure. Resistance to blood flow was therefore considerably increased. Blocking the vasomotor fibers to forearm skin did not affect this, but blocking the deep nerves to the muscle vessels prevented the increase in vascular resistance during exercise. Treating the forearm with bretylium tosylate had the same effect as deep nerve block. It was concluded that vasoconstrictor tone in muscle is increased during exercise.

Since treating the forearm with atropine did not affect the normal response, it was concluded that activation of vasodilator fibers to muscle is not an integral part of the general vasomotor response to exercise. Evidence was also found that the vasodilator outflow to a specific muscle group is not specifically activated when the muscle group in question is exercised.

During fairly heavy exercise, vasodilatation occurred in both hand and forearm skin. In the hand this was preceded by vasoconstriction. Evidence was found that the vasodilatation in the hand was due to release of vasoconstrictor tone, whereas that in the forearm was mediated through vasodilator fibers. It is likely that the increase in heat production during exercise was responsible for the reflex vasodilatation in skin.

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References


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DAVID A. BLAIR, WALTER E. GLOVER and JAN C. RODDIE

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