THE ROLE OF VASOCONSTRICTOR AND VASODILATOR NERVES TO SKIN AND MUSCLE IN THE REGULATION OF THE HUMAN CIRCULATION

Arris and Gale Lecture delivered at the Royal College of Surgeons of England
on
20th November 1962
by

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AS YOU KNOW, it is usual to think of the nerves which influence the calibre of blood vessels as belonging to two main groups. First of all there are the vasoconstrictor fibres whose stimulation results in an increase in resistance to blood flow in the part supplied by the fibres. Impulses reaching these nerve endings are thought to release noradrenaline which contracts the smooth muscle in the blood vessel wall. Secondly there are the vasodilator fibres whose stimulation results in a decrease in resistance to flow. Impulses reaching these nerve endings are thought to release acetylcholine which relaxes the smooth muscle.

There is now evidence that both the skin and muscle in human limbs have a sympathetic vasoconstrictor and a sympathetic vasodilator innervation. Most of these ideas are inferences drawn from the effects of certain procedures on blood flow through the limbs. There is no direct evidence that these vessels are innervated nor that stimulation of sympathetic nerves results in contraction of the smooth muscle in their walls. Desirable though such evidence may be, it is difficult to obtain in the human subject. However, a general picture of the vasomotor innervation of human skin and muscle has been deduced from relatively simple experiments in man and it is this picture that I want to review to-day.

VASOMOTOR FIBRES TO SKIN

In the skin there seem to be two distinct patterns of vasomotor control. One type is seen in the extremities, that is, in the hands, fingers, feet, toes, ears and possibly the nose, and the other we see in the rest of the skin of the body, that is, in the skin of the trunk, the neck, the cheeks, the forearms, upper arms, calves and thighs (Blair, Glover and Roddie, 1960, 1961; Fox *et al.*, 1962). Figure 1 shows, schematically, experiments illustrating the difference between these patterns of innervation, the upper one showing the pattern in the extremities and the lower showing the pattern in the skin of the proximal part of the body.

In the upper experiment the subject was seated comfortably in a warm room. Blood flow was measured in both his hands by venous occlusion plethysmography. At the arrow marked C.N.B., the nerves to the hand whose blood flow is represented by the dotted line were blocked with local

anaesthetic. The blood flow rose from the normal value of about 10 ml. to about 30 ml./100 ml./min. There was no change on the control side. The conclusion can be drawn, as it was first drawn by Adson and Brown in 1929, that the blood vessels in the extremities are innervated by vasoconstrictor fibres and are normally subject to considerable vasoconstrictor tone. Between the first pair of dotted lines the subject was cooled by immersing his legs in cold water and directing a fine spray of iced water over his naked chest. This caused a fall in flow in the normal but not the nerve-blocked side. It can be concluded that vasomotor fibres are responsible for the fall in hand blood flow when the body is cooled. The fall could

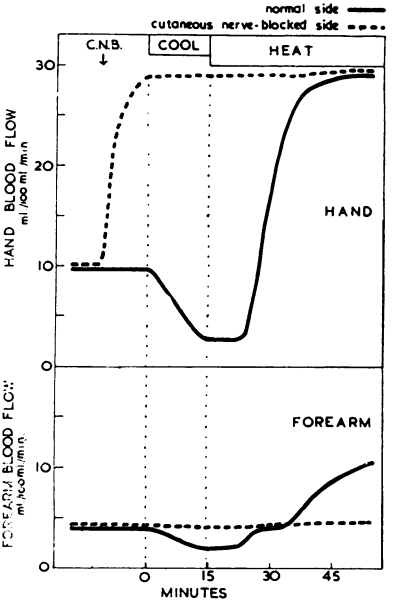

Fig. 1. The effect of blocking vasomotor nerves to skin on the response of hand and forearm blood flow to body cooling and heating. Solid line—blood flow in right hand or forearm; broken line—blood flow in left hand or forearm. At the arrow marked C.N.B., the vasomotor nerves to the left hand or forearm were blocked with local anaesthetic.

be prevented when the hand was treated with bretylium tosylate, an adrenergic blocking agent (Blair, Glover, Kidd and Roddie, 1960), suggesting that the vasomotor fibres involved were vasoconstrictor fibres.

In the last part of the experiment the subject was heated by immersing his legs in water at 45° C. This caused a dramatic increase in the blood flow in the normal but not the nerve-blocked hand. Clearly, the increase in hand blood flow with body heating is due to vasomotor nerves. Since the level of flow in the normal hand did not exceed that in the nerve-blocked hand, it is not necessary to postulate the existence of vasodilator nerves to explain the result (Gaskell, 1956; Roddie *et al.*, 1957). The

increase in flow was not prevented by treating the hand with atropine (Gaskell, 1956; Roddie *et al.*, 1957). This supported the conclusion that the increase in flow was due to release of vasoconstrictor tone.

To summarize, the blood vessels in the hand like those in the other extremities are subjected to a high degree of vasoconstrictor tone even when the subject is comfortably warm. The level of tone is reflexly regulated to serve temperature regulation. Besides being involved in temperature regulation, vasoconstrictor fibres to the the extremities are active in response to a wide variety of seemingly trivial and often unappreciated stimuli. For example, if a subject sees the door of the laboratory being opened, his hand blood flow may fall to zero; merely inflating a cuff in one arm or taking a deep breath causes a significant fall in hand blood flow. This makes the study of vasomotor reflexes in the hand a difficult one. For example, it is very difficult to say whether a vasoconstriction in the hand is a specific response to a specific stimulus or whether it is just the consequence of the psychic activity which accompanies a stimulus.

In the experiment illustrated in the lower part of Figure 1, blood flow was measured in both forearms of a subject seated comfortably in a warm room. At the arrow the cutaneous nerves to the forearm whose blood flow is represented by the dotted line were blocked with local anaesthetic. As found by Edholm, Fox and Macpherson (1957) this caused no change in flow on either side. It can be concluded that the vessels of the forearm skin, unlike those of the hand, are not subjected to either vasoconstrictor or vasodilator tone when the subject is comfortably warm. When the subject was cooled the flow fell on the normal but not the nerve blocked side, indicating that vasomotor nerves were responsible for the fall. Since the fall could be prevented by treating the forearm with bretylium tosylate it seemed that the vasomotor nerves were adrenergic. Body cooling produced a fall in forearm blood flow of the same order as that produced by suppression of the skin circulation with adrenaline iontophoresis (Edholm *et al.*, 1956). This indicated that vasoconstrictor fibres could suppress the circulation to forearm skin.

When the subject was heated, blood flow increased on the normal side to a level considerably in excess of that on the nerve-blocked side which remained unchanged. Clearly vasomotor nerves were responsible for the rise, but equally clearly the rise could not be explained entirely by release of vasoconstrictor tone. Full release of vasoconstrictor tone would only bring flow to the level seen in the nerve-blocked forearm. It was necessary to postulate the existence of vasodilator fibres to forearm skin to explain this result. Treating the forearm with atropine delayed and reduced the rise in flow with heating, again suggesting that vasodilator fibres were involved (Roddie *et al.*, 1957c). Recent evidence has suggested that the active vasodilatation in the forearm with heating may be secondary to the

cholinergic activation of the sweat glands and the subsequent production of bradykinin-forming enzyme (Fox and Hilton, 1958), but unfortunately there is not time to elaborate this point further.

To summarize, the blood vessels in the skin in the proximal parts of the body are not subject to any vasomotor tone when the subject is comfortably warm. However, when the body is cooled the vessels constrict due to activity of vasoconstrictor fibres and when the body is heated they dilate due to an active vasodilator mechanism.

VASOCONSTRICTOR FIBRES TO MUSCLE

I would now like to turn to the muscle circulation. Almost 17 years ago, Barcroft and Edholm (1946) presented the first evidence that human skeletal muscle blood vessels had a vasoconstrictor and vasodilator innervation, in an Arris and Gale Lecture at this College. Their evidence for a vasoconstrictor innervation was as follows. Blocking the deep nerves to the forearm muscle with local anaesthetic was found to result in a two- to three-fold increase in forearm blood flow as measured by venous occlusion plethysmography. The increase appeared to be in muscle since suppression of the cutaneous circulation by iontophoresis of adrenaline into the skin did not prevent it, blocking the cutaneous nerves to the forearm did not produce it and what evidence there was suggested that bone blood flow was too small to account for it. It did not seem to be a result from the paralysis of the skeletal muscle fibres, since blocking the deep nerves to a forearm which had previously been sympathectomized did not increase forearm blood flow. It was concluded that blood vessels in human muscle were normally subject to appreciable vasoconstrictor tone through fibres distributed to the muscle with the motor nerves (Barcroft *et al.*, 1943).

The conclusion was later supported by other workers using different techniques to estimate muscle blood flow. Blocking the deep nerves to the forearm resulted in an increase in the oxygen saturation of blood sampled from the veins draining forearm muscle (Roddie *et al.*, 1957a) and in the apparent thermal conductivity of the tissue as measured by a heated thermocouple device introduced into the forearm muscle (Blair, Golenhofen and Seidel, 1959).

Initially there was no clear indication of the circulatory reflexes in which these fibres were involved. They did not take part in the reflex responses to a variety of stimuli, such as a pinch, a deep breath and the application of ice to the skin, which normally evoke strong vasoconstrictor responses in the hand. Despite some early evidence to the contrary (Barcroft, Bonnar and Edholm, 1947), they did not take part in the reflex vasodilatation which occurs in the forearm when the body is heated. This vasodilatation was confined to the skin. McGirr (1952) found that the rate of

clearance of Na^{24} from calf muscle fell when the subject was heated. Barcroft, Bock, Hensel and Kitchin (1955), using heated thermocouples to estimate muscle blood flow, found further evidence that muscle blood flow did not increase during body heating. Edholm, Fox and Macpherson (1956) found that effective suppression of the cutaneous circulation by iontophoresis of adrenaline into the skin prevented the increase in forearm blood flow when the body was heated. A method which we used in Belfast to look at this question is illustrated in Figure 2. Catheters were introduced into forearm veins, one into a superficial vein draining mainly skin tissue and another into a deep vein draining mainly muscle tissue (Roddie *et al.*, 1956). Millilitre samples of blood were taken via these catheters and their percentage oxygen saturation measured using a spectrophotometric technique. Forearm blood flow was simultane-

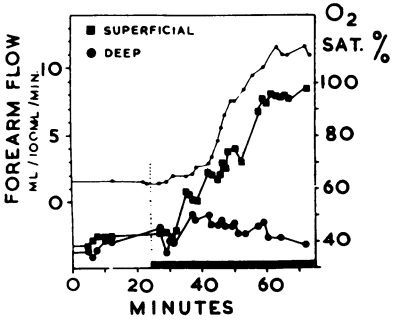

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Fig. 2. The effect of body heating on the oxygen saturation of deep and superficial venous blood and forearm blood flow. The black rectangle represents the period of body heating. O, left forearm blood flow; ■, oxygen saturation of superficial venous blood (right forearm); ●, oxygen saturation of deep venous blood (right forearm).

ously measured on the opposite forearm. The black rectangle represents the period during which the subject was heated. Heating caused the usual rise in forearm blood flow. This was paralleled by an increase in the oxygen saturation of the superficial venous blood but there was no comparable change in the oxygen saturation of the deep venous blood. If we assume that body heating did not greatly affect the metabolic requirements of the forearm tissues, this would suggest that the increase in flow during heating was almost entirely confined to the skin.

Over the last few years, a number of stimuli have been described which cause changes in the activity of vasomotor fibres to muscle. Figure 3 shows schematically some of the peripheral vascular effects of these stimuli. In the top experiment blood flow was measured in both forearms by venous occlusion plethysmography. At the first arrow, the deep nerves to the forearm whose blood flow is represented by the dotted line

were blocked with local anaesthetic. This resulted in a doubling of flow due to release of vasoconstrictor tone. Four stimuli were then applied which are thought to result in release of vasoconstrictor tone, raising the legs of a recumbent subject (Roddie and Shepherd, 1956; Roddie *et al.*, 1957b), negative pressure breathing (Blair, Glover and Kidd, 1959), squatting (Sharpey-Schafer, 1956) and causing large intrathoracic pressure transients by coughing or voluntary contractions of the respiratory muscles (Sharpey-Schafer, 1953; Roddie *et al.*, 1958). When the stimuli were applied, the blood flow on the normal but not the nerve-blocked arm

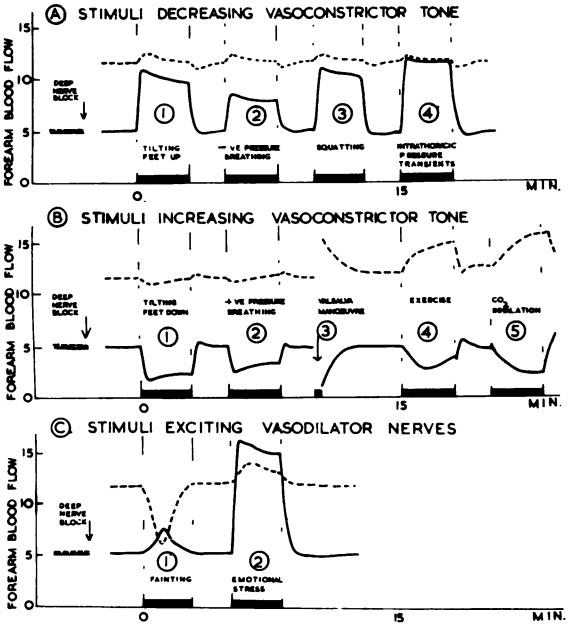

Fig. 3. The effect of various stimuli on blood flow in normal and nerve-blocked forearms. Solid line—blood flow in right forearm; broken line—blood flow in left forearm. At the first arrow in each experiment the deep nerves to the left forearm were blocked with local anaesthetic.

increased. This indicated that vasomotor nerves were responsible for the increases. Since the vasodilatations were blocked by intra-arterial infusions of the adrenergic blocking agent, bretylium tosylate, but not by similar infusions of atropine, it seemed that release of vasoconstrictor tone was responsible for them. The middle experiment indicates some stimuli which result in an increase in vasoconstrictor tone in muscle. They include tilting a subject from the horizontal to the vertical position (Brigden *et al.*, 1950), positive pressure breathing (Blair, Glover and Kidd, 1959), the Valsalva manoeuvre (Sharpey-Schafer, 1955; Roddie *et al.*, 1958), muscular exercise (Blair, Glover and Roddie, 1961a) and inhalation

of carbon dioxide (McArdle *et al.*, 1957; Blair, Glover, McArdle and Roddie, 1960). These stimuli produced a fall in the blood flow in the normal forearm though the flow on the nerve-blocked forearms either remained unchanged or actually increased. This again indicated that vasomotor nerves were responsible for the changes in flow in the normal forearms. Since the changes were again abolished by bretylium yet were not affected by atropine, it seemed that the vasomotor fibres concerned with the responses were vasoconstrictor ones.

The receptors concerned in the reflex regulation of vasoconstrictor tone in human muscle are not known. Many of the stimuli just described

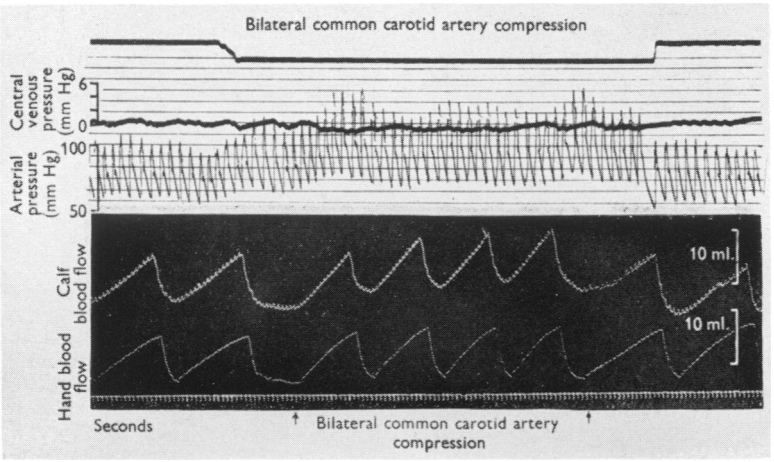

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Fig. 4. Top: records from above downwards show signal, central venous pressure and brachial arterial pressure. Depression of signal indicates the period during which both common carotid arteries were compressed. Bottom: plethysmographic tracings of calf and hand blood flow before, during and after compression of both common carotid arteries: arrows mark the beginning and end of compression. The static calibrations on the plethysmographic records show 10 ml. volume increases.

which result in vasodilatation such as tilting feet-up, negative pressure breathing, and squatting probably increase the intrathoracic blood volume. Conversely, tilting feet-down, positive pressure breathing and the Valsalva manoeuvre decrease intrathoracic blood volume. These changes in volume could stimulate some of the many receptors which have been described in the walls of the low pressure vascular compartments in the chest. Sharpey-Schafer (1956) has found that there is frequently a relationship between the changes in arterial pulse pressure and the changes in forearm blood flow during these reflexes, a decrease in pulse pressure associated with vasoconstriction and an increase with vasodilatation. Nevertheless it seems unlikely that changes in the activity of the stretch

receptors in the carotid sinus area are very important in the reflex regulation of vasoconstrictor tone in muscle. Changes in posture can result in large changes in vasoconstrictor tone in muscle without much change in pulse pressure (Roddie *et al.*, 1957b). Ernsting and Parry (1957) found that raising the effective pressure at the carotid sinus by applying subatmospheric pressure to the neck did not decrease resistance to blood flow in the forearm though it produced hypotension. In Belfast we looked at some of the peripheral vascular effects of lowering the pressure at the level of the carotid sinuses by compression of the common carotid arteries (Roddie and Shepherd, 1957). This caused the mean pressure at the sinus to fall to about 40 mm. Hg. and abolished pulsations. Some of the results are shown in Figure 4. The upper record shows the increase in arterial pressure recorded in the brachial artery when both common carotid arteries were compressed. One would have expected to see an increase in resistance to blood flow in the limbs associated with this pressor response. However, this was not the case as can be seen from the

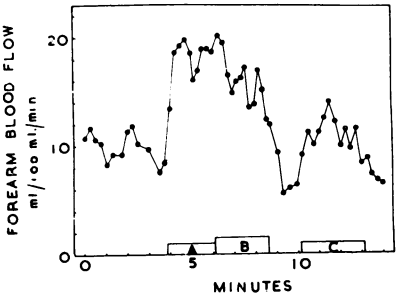

Fig. 5. Forearm blood flow during emotional stress. For explanation see text.

plethysmographic records of blood flow in the hand and calf shown in the bottom panel. When the carotids were compressed calf and hand blood flow increased as shown by the increase in the slope of the inflow curves. Vascular resistance was either unchanged or slightly decreased during compression. In view of these findings it seems likely that the receptors concerned in the reflex regulation of vasoconstrictor tone lie in a low-pressure vascular compartment.

VASODILATOR FIBRES TO MUSCLE

The first evidence that human skeletal muscle had a vasodilator nerve supply was provided by Barcroft and Edholm, 1945. They found that forearm blood flow increased during fainting induced by trapping blood in the limbs with venous tourniquets and by venesection (Fig. 3*c*1.) Since the skin appeared pale, it seemed reasonable to suppose that the increase was occurring deep to skin, that is, in the skeletal muscle. Since arterial pressure was falling rapidly at the time of the faint, the increase

in flow was clearly due to vasodilatation. Blocking the deep nerves to the forearm changed this picture. During the faint, the blood flow in nerve-blocked forearms fell, passively following the changes in arterial pressure. This suggested that the vasodilatation in the normal forearm was mediated by vasomotor nerves. The average blood flow at the height of a faint in nine normal forearms was higher than the average blood flow in six nerve-blocked forearms. In other words the blood flow in the normal forearms during fainting rose to a level which could not readily be explained by release of vasoconstrictor tone alone. It was concluded that the vasodilatation in the normal forearm was due to activity of vasodilator fibres rather than to release of vasoconstrictor tone. Though the evidence was suggestive, it was not conclusive, since the observations on the normal and nerve-blocked forearms were not made simultaneously on the same subject. In that it seemed unlikely that a powerful vasodilator system to muscle should exist merely to facilitate fainting, the work of Barcroft and Edholm (1945) provided a strong incentive to find stimuli which might

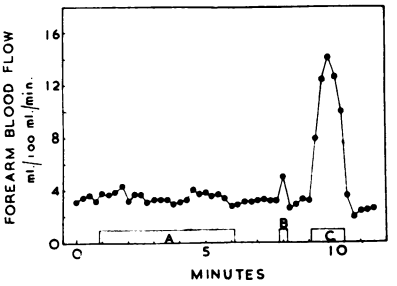

Fig. 6. Forearm blood flow during emotional stress. For explanation see text.

excite these fibres under more normal physiological conditions. In the cat and dog strong evidence for a cholinergic innervation of blood vessels in skeletal muscle had been found (Bülbring and Burn, 1935) and the central connections and efferent distributions of these fibres was extensively studied (Uvnäs, 1954). However, the nature of the stimulus which normally excited these fibres remained obscure. The fibres and their central connections were not involved in baro- or chemo-receptor reflexes in dogs and cats (Folkow and Gernandt, 1952; Frumin, Ngai and Wang, 1952; Lindgren and Uvnäs, 1954). In man no evidence was found that they normally played a part in the reflex changes in muscle blood flow during posture change or exercise (Roddie, Shepherd and Whelan, 1957b; Blair, Glover and Roddie, 1961a). A clue to the nature of the stimulus which normally excited these fibres was provided by Abrahams and Hilton (1958). They found that stimulation by electrodes of places in the brain, which excited vasodilator fibres to muscle in anaesthetized cats, provoked a "flight or fight" reaction in conscious cats. It seemed possible, therefore, that emotional stress might be associated with excitation of vasodilator

fibres to muscle. We therefore tried to devise ways of inducing " flight or fight " reactions in our subjects (Blair, Glover, Greenfield and Roddie, 1959).

It was known that the performance of mental arithmetic by a subject often led to an increase in his forearm blood flow (Abramson and Ferris, 1940; Wilkins and Eichna, 1941; Golenhofen and Hildebrandt, 1957; Brod *et al.*, 1959, Barcroft *et al.*, 1960).

We had quite a lot of fun thinking out ways in which we could frighten or annoy our subjects more effectively than was possible using mental arithmetic as a stressing stimulus. A method which we tried was one that Greenfield had used some years ago to produce fainting (1951); that

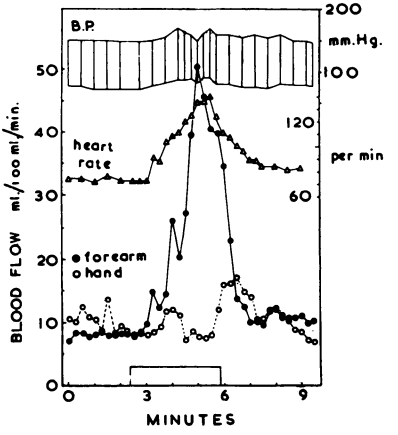

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Fig. 7. Effect of severe emotional stress on arterial pressure; heart rate Δ, forearm blood flow ● and hand blood flow O. During the time represented by the rectangle it was suggested to the subject that he was suffering from severe blood loss.

was asking the subject to drink some of his own blood! This was often quite effective. In Figure 5 is shown an experiment on an honours B.Sc. student shortly before his professional examination. At the beginning of rectangle A, he was told that within a few minutes he would be given a gruelling oral examination in physiology, and his blood flow promptly doubled. During B, he was actually given the oral. It didn't seem to be quite as bad as he had expected and the blood flow level fell somewhat. At this point we apologized for the indignity and his blood flow rapidly came back to normal. Then, at the beginning of C, some disparaging remarks were made about a young lady in whom we had heard that this subject was romantically interested. Though he showed no outward signs of emotion, the blood flow response was quite informative. Figure 6 shows another type of experiment. This we tried on the head of our de-

partment. During A he was given quite a severe test in mental arithmetic, and though there were some mistakes there was very little change in flow. We got a slight response during B when we pretended to pour some boiling water over his hand. The only good response we got here was at C when our head technician came into the laboratory and said that a fire had broken out in the departmental office. I do not think he really believed this, but there was enough emotional content in the situation that his blood flow rose considerably. These experiments do not really help very much, but I think they do indicate that this vasodilatation in muscle is due more to the stress associated with mental exercise than to the mental exercise itself.

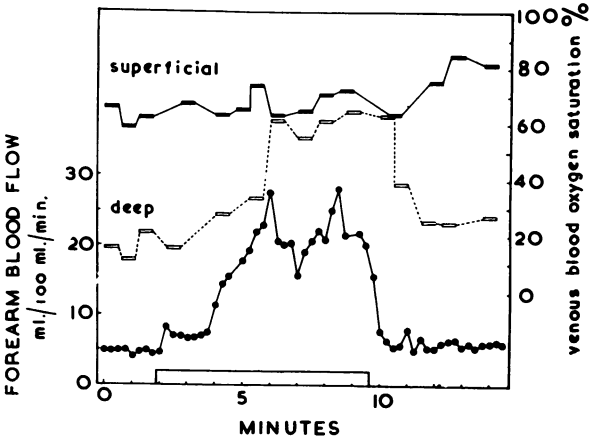

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Fig. 8. Oxygen saturation of blood from superficial forearm veins □, and deep forearm veins ■; ● forearm blood flow in opposite forearm. The rectangle represents the period when the subject was emotionally stressed.

Our best response is illustrated in Figure 7. We led the subject, a medical student, to believe that he was losing blood very rapidly from an arterial puncture site, that his blood pressure was falling rapidly, and that his state of health was very precarious. This was all done by whispered conversation so that the subject could just hear. Though some of the people conducting the experiment made an effort to stop the experiment, one " hard-hearted " experimenter insisted that it must go on. The subject became quite worried and alarmed about this. His forearm blood flow rose to 50 ml./100 ml./min., a level as high as that seen after severe exercise of the forearm muscles. We then apologized and reassured the subject, explained the hoax, and his blood flow in the forearm fell very rapidly to the control level. During this time he really felt ill. He complained of throbbing in the head and his arm was very sore where the blood was supposedly leaking. Though emotional stress is known to

result in the release of adrenaline, this response did not show many of the characteristics of an adrenaline infusion. The rate of onset of vasodilatation and the rapidity of the fall were too great. The blood pressure response and the response of hand blood flow were not typical of adrenaline infusions. One would expect a much greater pressor response and vasoconstriction in the hand with doses of adrenaline that would cause such a large vasodilatation in the forearm.

In the experiment shown in Figure 8, samples of blood from the superficial veins draining the forearm skin and from the deep veins draining the muscle were collected. Forearm blood flow was measured on the opposite side. During the time shown by the length of the bar it was quite easy to convince the subject here that he had lost too much blood. Forearm

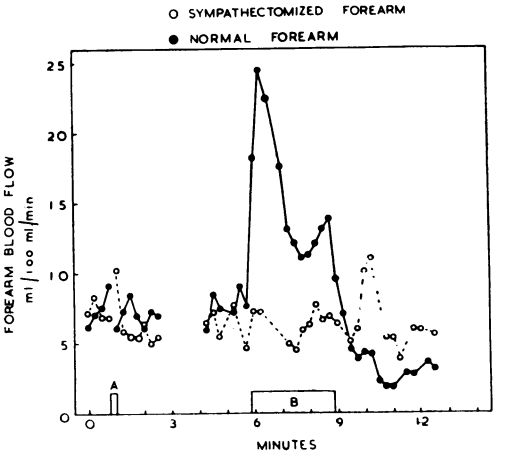

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Fig. 9. Effect of stress on blood flow through a normal ●, and a sympathectomized O, forearm. During the period represented by the rectangle B the subject was emotionally stressed. At A, he performed a valsalva manoeuvre.

blood flow went up four- or five-fold. This was accompanied by an increase in the oxygen saturation of the deep blood, but there was no comparable change in the superficial, suggesting that the increase in blood flow was mainly in muscle.

In the experiment illustrated in Figure 9 the subject was a patient who had had a unilateral sympathectomy. To emotionally stress this subject we criticized his behaviour and he became rather irritated. A large vasodilatation occurred on the normal side but not on the sympathectomized side. It was concluded that sympathetic nerves must contribute to the vasodilatation in muscle during stress.

The experiment illustrated in Figure 10 would suggest that cholinergic fibres contribute to this. We measured the forearm flow on two sides, and at the beginning of the experiment atropine was infused into one

forearm. When the subject was frightened during period A, the vasodilatation on the atropinized side, though not abolished, was considerably reduced. In addition the level of blood flow reached during stress in normal forearms often exceeded that reached in the opposite nerve-blocked forearms. In other words the vasodilatation could not always be explained by release of vasoconstrictor tone. Finally, treating the forearm with bretylium did not greatly affect the response.

Presumably a large number of factors go into the final vasodilatation during emotional stress, but it would seem that cholinergic vasodilator fibres to muscle contribute to it. It was concluded that skeletal muscle, besides having a vasoconstrictor nerve supply, has a vasodilator nerve supply and that these fibres are involved in the circulatory adaptations to emotional stress. Actually, looking back, it would not be surprising if

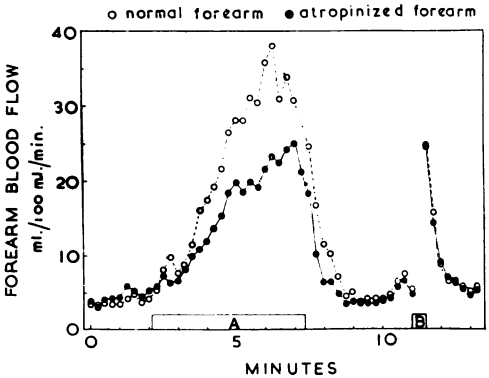

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Fig. 10. The effect of atropine on the increase in forearm blood flow during emotional stress. O, Normal forearm; ●, atropinized forearm. A, period of emotional stress. B, period of circulatory arrest in both forearms.

emotional stress accounted in part for the vasodilatation in muscle which was seen when subjects were made to faint. Just before fainting, the subjects presumably felt a little frightened.

SUMMARY

Evidence is presented that the resistance blood vessels in human skeletal muscle have both a dilator and constrictor innervation. At rest the vessels are subjected to considerable constrictor tone and this is varied reflexly in the circulatory adaptations to a variety of stimuli such as change in posture, exercise and changes in intrathoracic pressure. The vasodilator fibres to muscle are not active at rest but contribute to the vasodilatation muscle during emotional stress. The blood vessels of the skin of the extremities seem to have an exclusively vasoconstrictor innervation and are normally subject to considerable vasoconstrictor tone. This tone is reflexly varied in temperature regulation. The vessels of the skin

in the proximal parts of the body are not subjected to either vasoconstrictor or vasodilator tone when the subject is comfortably warm. However, skin blood flow falls when the body is cooled, due to vasoconstrictor fibre activity, and rises when the body is heated, due to an active vasodilator mechanism mediated through sympathetic fibres.

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