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EXCITATION OF CHOLINERGIC VASODILATOR NERVES TO HUMAN SKELETAL MUSCLES DURING EMOTIONAL STRESS

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There is abundant evidence for the existence of cholinergic vasodilator fibres to the skeletal muscle in animals (Bülbring & Burn, 1935; Eliasson, Folkow, Lindgren & Uvnäs, 1951; Uvnäs, 1954). In anaesthetized cats these fibres have been stimulated by electrodes inserted into the brain and, particularly, into the motor cortex (Folkow & Gernandt, 1952; Lindgren, Rosén, Strandberg & Uvnäs, 1956). The fibres and their central connexions do not appear to be involved in baroreceptor or chemoreceptor reflexes (Folkow & Uvnäs, 1948; Frumin, Ngai & Wang, 1952, 1953; Lindgren & Uvnäs, 1954) and the effective physiological reflex stimulus has not been discovered. However, Abrahams & Hilton (1957) have recently shown that stimulation by electrodes, implanted into places in the brain stem which discharge these fibres in the anaesthetized cat, also provokes the 'flight or fight' reaction in conscious cats. It is therefore possible that the emotional stress associated with flight or fight may stimulate the vasodilator nerves.

In man the only evidence for the existence of vasodilator fibres to skeletal muscle comes from the experiments of Barcroft & Edholm (1945) on post-haemorrhagic fainting and it is not known if these fibres are used under more normal conditions of life. It has been known for a long time that emotional stress causes an increase in forearm blood flow (Wilkins & Eichna, 1941). This increase has been generally believed to be mainly due to the release of adrenaline (Golenhofen & Hildebrandt, 1957), although Wilkins & Eichna had claimed that sympathetic nerves contribute to it. The present experiments suggest that cholinergic vasodilator fibres to skeletal muscle contribute to the response, and it seems likely that such fibres are activated by the emotional experiences of everyday life.

METHODS

The experiments were carried out on male pre-clinical medical students, and on one female and four male patients from whom the stellate ganglion on one side had been removed as treatment for Ménière's disease. The subject, wearing normal indoor clothing, lay on a couch in a laboratory, the temperature in which was maintained constant in the range 18–22° C. Forearm blood flow was measured by venous occlusion plethysmography, with the water-filled, mechanically stirred plethysmograph described by Greenfield (1954), the water temperature being 35° C. In some experiments hand and calf blood flows were also measured simultaneously, by means of plethysmographs maintained at 32° and 35° C respectively. Changes in skin and muscle blood flow in the forearm were estimated from changes in the O_2 saturation of samples of superficial and deep venous blood (Roddie, Shepherd & Whelan, 1956). The pressure in the brachial artery was measured through a needle connected to a capacitance manometer. In some experiments the radial, median and ulnar nerves were blocked above the elbow with 3% ethocaine hydrochloride containing 0·002% adrenaline, as described by Roddie, Shepherd & Whelan (1957*a*). In other experiments the cutaneous nerves were blocked at the elbow as described by Edholm, Fox & Macpherson (1957). In six experiments atropine 0·1 mg in 4 ml. saline was infused through an indwelling needle into the brachial artery of one arm each minute for a total of 4 min. This dose has been found to block the vasodilator activity of acetylcholine infused intra-arterially into the same arm at the rate of 20 μg/min; it also depresses, in the ipsilateral but not the opposite arm, the vasodilatation in the skin during body heating (Roddie, Shepherd & Whelan, 1957*b*).

Stressing stimuli. For the present purposes we were interested in obtaining large responses rather than in the character and reproducibility of the emotional stimuli, and various stimuli were used. Before the experiments the subjects were told about the proposed measurements and injections, but they were not told that they would be emotionally stressed, since surprise was often an important feature of the stress. After the experiments a full explanation was given and the subjects were asked not to divulge this to other subjects.

Periods of emotional stress lasting 2–3 min were produced by the following stimuli. (1) The subject was told that he would shortly be examined orally in physiology or that he would be tested in mental arithmetic. He was then kept in suspense for 2–3 min before being told that the test would not be applied, and that he could relax. (2) Some of the medical students were given a gruelling oral examination in physiology, and were severely criticized each time they gave wrong answers and sometimes when they gave correct answers. (3) Some subjects were tested in mental arithmetic. This has been found by several investigators to be a convenient emotional stimulus, capable of causing a considerable cardiovascular disturbance (Grant & Pearson, 1938; Abramson & Ferris, 1940; Figar, 1955; Golenhofen & Hildebrandt, 1957; Barcroft, Brod, Hayes & Hirsjarvi, 1958; Brod, Fencl, Hejl & Jirka, 1959). In our experiments the subject was asked to carry out a series of additions and subtractions of two- and three-digit numbers as quickly as possible in a dim or flickering light, with a metronome ticking, and with frequent distractions and criticisms. (4) The subject was asked to worry himself by thinking of unpleasant things. (5) In some of the experiments on the normal subjects a needle was inserted into the brachial artery for the recording of arterial pressure or the infusion of atropine. In other experiments, when arterial puncture was not necessary, a needle was inserted subcutaneously, and the subject was led to believe that this was in an artery. The insertion of the needle itself caused stress and an increase in forearm blood flow in some subjects. In each case time was allowed for the forearm blood flow to revert to resting level for several minutes. The subject was then deliberately frightened in the following way. The operators pretended that blood was leaking around the intra-arterial needle, that a haematoma was forming, and that there was a considerable loss of blood. By their conversation and demeanour they tried to indicate to the subject that they were worried and alarmed, and were thinking of abandoning the experiment. About half the subjects were hoaxed successfully; these became alarmed and some even complained of pain in the arm and throbbing in the head. After a few minutes the subject was reassured and consoled, and the real purpose of

the hoax was briefly explained. In every case anxiety was promptly relieved. Other subjects, some of whom were able to look at their arm and see for themselves that all was well, were not deluded by the acting and were not frightened. This particular stimulus, which is later referred to as 'severe stress' could, of course, be used only once for each subject.

RESULTS

In the experiment illustrated in Fig. 1, forearm and hand blood flow, arterial pressure and heart rate were measured during severe stress. The flow in the forearm reached 50 ml./100 ml./min, a level similar to that found immediately

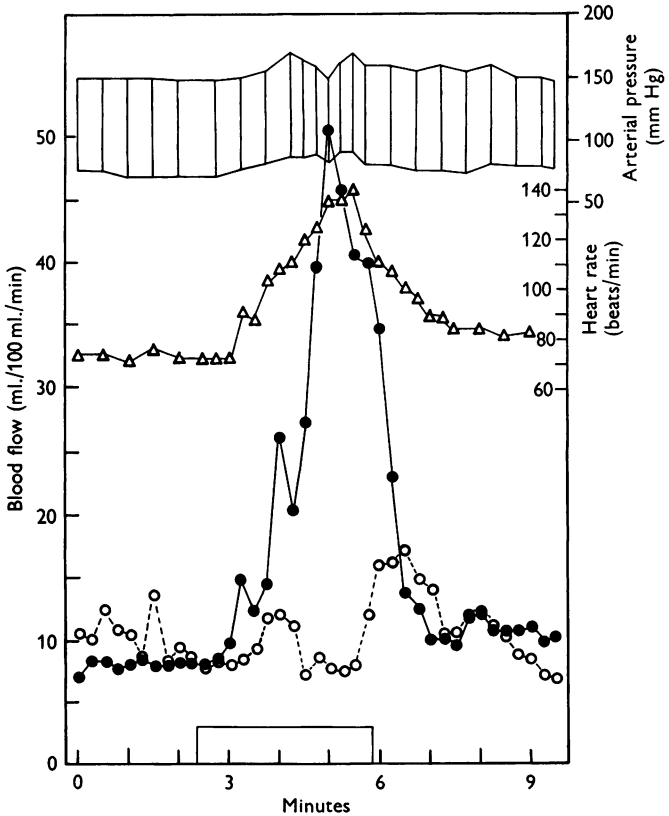

Fig. 1. Effect of severe emotional stress on arterial pressure; heart rate △, forearm blood flow ● and hand blood flow ○. During the time represented by the rectangle it was suggested to the subject that he was suffering from severe blood loss.

after severe exercise of the forearm muscles. Since there was no corresponding increase in arterial pressure the increase in flow was clearly due to vasodilatation in the forearm.

It is well known that an intravenous infusion of adrenaline causes vasodilatation in the forearm (Grant & Pearson, 1938; Allen, Barcroft & Edholm, 1946) and stress may cause release of adrenal medullary hormones (Cannon &

Britton, 1927). Thus the increase in forearm blood flow might be partly or wholly due to adrenaline. However, the response to stress seen in the present experiment differs from the response to intravenously administered adrenaline or adrenaline-noradrenaline mixtures in the following ways. (1) The size of the increase in forearm blood flow is greater than has to our knowledge been produced by intravenous infusion of adrenaline in man (Barcroft & Swan, 1953). (2) Infusions of adrenaline which cause a much smaller increase in flow in the forearm cause a marked reduction in flow in the hand (Swan, 1951) not seen in the present experiment. (3) The changes in arterial pressure in the present experiment are quite unlike those seen during infusion of adrenaline (Goldenberg, Pines, Baldwin, Greene & Roh, 1948; Barcroft & Starr, 1951) or adrenaline-noradrenaline mixtures (de Largy, Greenfield, McCorry & Whelan, 1950). (4) When an intravenous infusion of adrenaline is suddenly stopped the forearm flow takes 4–5 min to revert to resting level (Whelan, 1952), but in the present experiment the flow had returned very nearly to normal within 30 sec, and completely within 1 min.

Site of the vasodilatation

In the experiment shown in Fig. 1 there was a great increase in the blood flow through the forearm, which is largely composed of muscle, but not through the hand, which is largely composed of skin. There were similar results in the five other experiments in which these measurements were made. In two of the latter experiments, the blood flow through the calf was also measured, and found to parallel that through the forearm. It is probable, therefore, that the vasodilatation was mainly in muscle. This suggestion was tested by making simultaneous observations on the oxygen saturation of the blood from superficial veins predominantly draining skin and from deep veins predominantly draining muscle (Fig. 2). At rest the blood from these veins differed in oxygen saturation, supporting the anatomical evidence for the differences in origin of the samples. During severe stress there was a marked rise in the oxygen saturation of the deep venous blood, paralleling the change in blood flow simultaneously recorded in the opposite forearm, but there was no change in the oxygen saturation of the superficial venous blood. Assuming that metabolism was unchanged, this indicates an increase in the blood flow through the muscle but not through the skin of the forearm. A second experiment on another subject gave a similar result.

Role of vasomotor nerves

Observations were made on five subjects from whom the stellate ganglion had been removed on one side as treatment for Ménière's disease, and in whom there was no known abnormality of the blood vessels of the arm. The stressing stimulus was mental arithmetic. One of these experiments is illustrated in

Fig. 3. During the stress there was a large increase in blood flow in the normal forearm but there was little change in that through the sympathectomized forearm. The results of all the tests carried out on the five patients are summarized in Fig. 4. In nine out of the eleven tests the stress produced a greater increase in mean flow in the normal (average 3·6 ml./100 ml./min) than in the

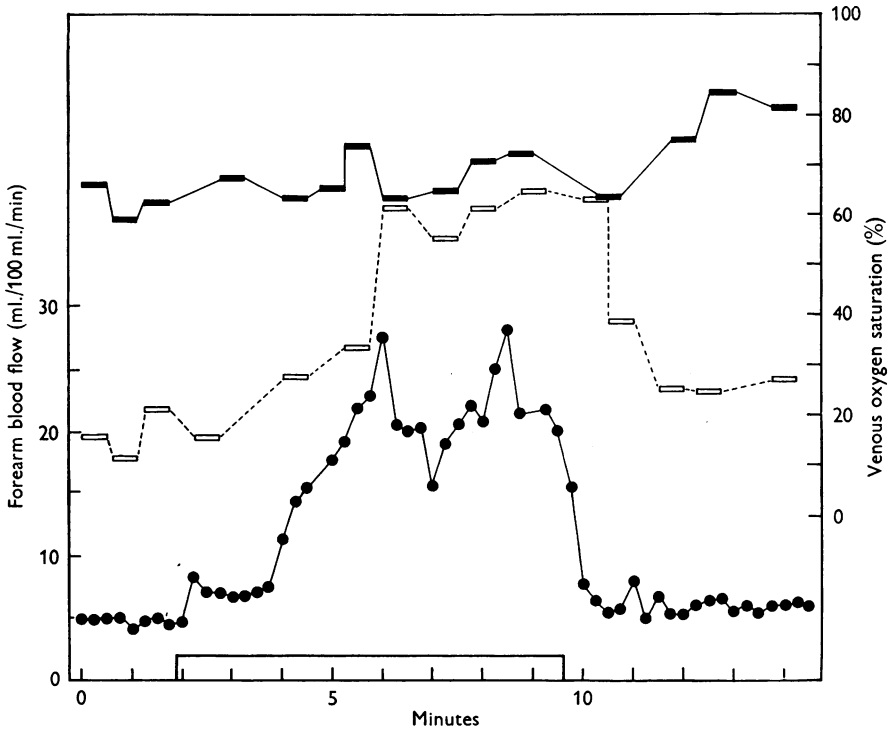

Fig. 2. Oxygen saturation of blood from superficial forearm veins ■, and deep forearm veins □; forearm blood flow in the opposite forearm ●. During the time represented by the rectangle it was suggested to the subject that he was suffering from severe blood loss.

sympathectomized forearm (average 0·8 ml./100 ml./min), and also a greater increase in peak flow in the normal (average 11·6 ml./100 ml./min) than in the sympathectomized forearm (average 7·7 ml./100 ml./min). In the remaining two of the eleven tests there was no increase in mean blood flow on the normal side, but there were increases of 0·8 and 2·8 ml./100 ml./min on the sympathectomized side; we can offer no satisfactory explanation for these two anomalous results. In general, however, the observations suggest that sympathetic nerves play a part in the response.

This suggestion is supported by the results of experiments on normal subjects in whom the median, radial and ulnar nerves to one arm had been blocked above the elbow with local anaesthetic solution. Five subjects were

exposed to one or more of the stimuli previously described, and the results of these experiments are summarized in Fig. 5. On all fifteen occasions the stress produced a greater increase in mean flow on the normal (average 5·0 ml./100 ml./min) than on the nerve-blocked side (average 2·4 ml./100 ml./min), and also a greater increase in peak flow on the normal (average 9·0 ml./100 ml./min) than on the nerve-blocked side (average 5·4 ml./100 ml./min). These experiments

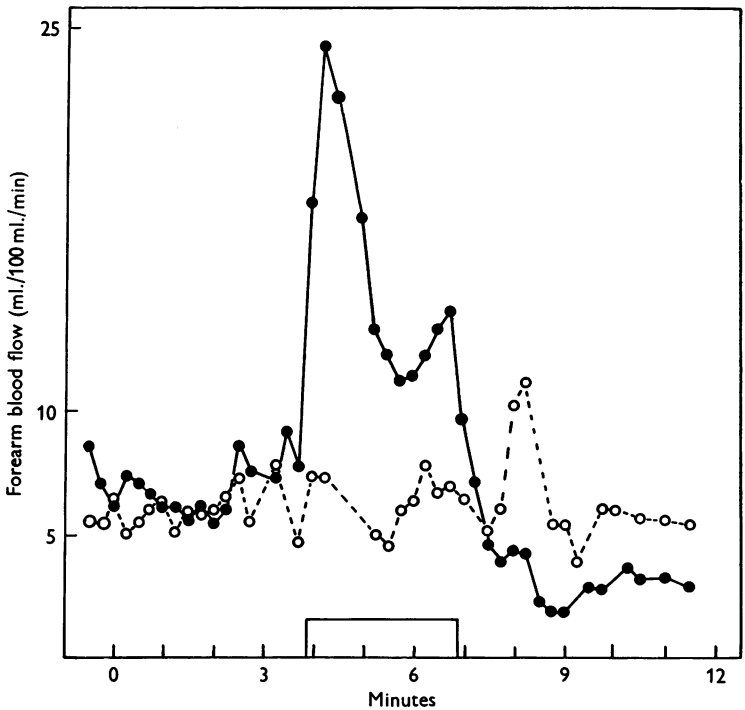

Fig. 3. Effect of stress on blood flow through a normal, ●, and a sympathectomized, ○, forearm. During the time represented by the rectangle a mental arithmetic test was given.

indicate that the response is partly dependent on fibres travelling with the deep nerves to the forearm.

The following experiments suggest that the cutaneous nerves to the forearm are not involved in the response (Fig. 6). In four subjects the cutaneous nerves to one forearm were blocked with local anaesthetic. In the ten tests made in these experiments stress produced a similar increase in mean flow on the normal (average 3·5 ml./100 ml./min) and the nerve-blocked sides (average 3·4 ml./100 ml./min).

We conclude that nerves, which are interrupted by stellate ganglionectomy and are distributed with the deep somatic nerves, but not with the cutaneous nerves, to the forearm, contribute to the vasodilatation during stress.

Contribution of vasodilator fibres

Figure 7 shows part of an experiment in which emotional stress was produced in a subject in whom the deep nerves to one forearm had been blocked with local anaesthetic. Before stress the blood flow was somewhat higher in the blocked forearm than in the normal. Over a period of 6 min a series of stres-

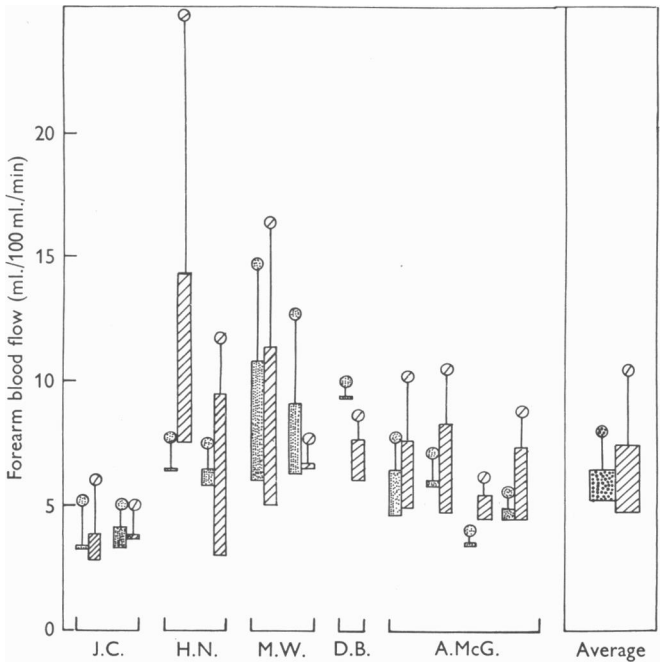

Fig. 4. The effect of sympathectomy on the increase in forearm blood flow during stress; summary of results of eleven experiments on five subjects. The blood flow was simultaneously measured in a sympathectomized ▦ and a control (normal) forearm ▨. The base of each rectangle shows the mean level of blood flow at rest, the top shows the mean level during stress and the circle shows the peak flow observed during stress. The symbols in the panel at the right of the diagram represent the average of all the results.

sing stimuli was applied. At (1) a rabbit which had been dissected after death was produced, at (2) it was held close to the subject's face and he was asked to smell it, at (3) the heart was opened and blood collected in a beaker, and at (4) he was asked to drink this blood. He was prepared to do this and opened his mouth in anticipation but the request was withdrawn. At (5) the stomach was opened, and he was offered a meal of stomach contents but again the offer was withdrawn, and at (6) he was told to relax. On three occasions during this period of stress the blood flow through the normal forearm exceeded that through the nerve-blocked forearm, and on two of these occasions the difference was much greater than could be accounted for by errors of

measurement. Careful inspection of the plethysmographic record failed to indicate any muscular movements in the normal forearm which might have been responsible for increasing the blood flow. The difference between the blood flow in the normal and the nerve-blocked sides cannot be explained by humoral agencies, which presumably act symmetrically, nor by release of vasoconstrictor tone, which is presumably more nearly complete on the nerve-blocked than on the normal side. It can, however, be readily explained by the activity on the normal side of vasodilator fibres which are partially or completely prevented from acting on the nerve-blocked side.

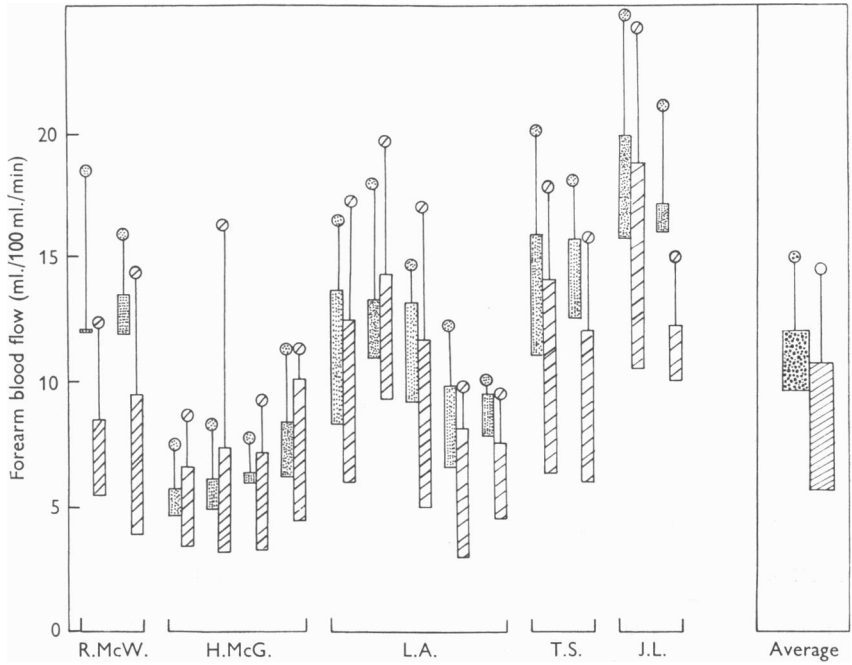

Fig. 5. The effect of blocking the deep nerves to the forearm on the increase in forearm blood flow during stress. Summary of the results of fifteen experiments on five subjects. ▦ nerve-blocked side; ▨ normal side; conventions as in Fig. 4.

In the other nerve-block experiments (Fig. 5) the blood flow in the normal arm never exceeded that in the nerve-blocked arm by a convincing amount. The increase in blood flow in the normal arm could be explained, therefore, by a release of vasoconstrictor tone. It could also be explained by the addition of vasodilator activity to an unchanged level of vasoconstrictor activity in the normal arm. These other experiments therefore neither prove nor disprove the participation of vasodilator nerves. Only when very high levels of blood flow are attained, as is seen in Figs. 1, 2 and 7, can vasodilator activity be detected by this sort of experiment.

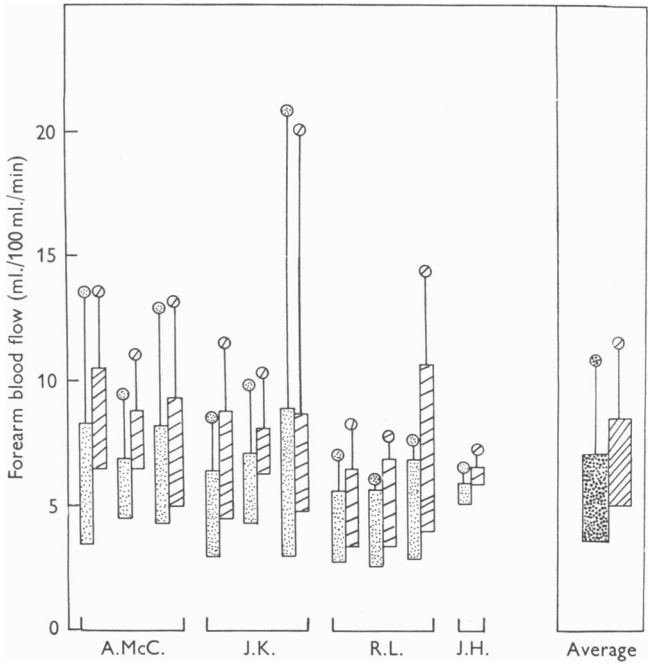

Fig. 6. Effect of blocking the cutaneous nerves to the forearm on the increase in blood flow during stress; summary of results of ten experiments on four subjects. ▦ nerve-blocked side; ▨ normal side; conventions as in Fig. 4.

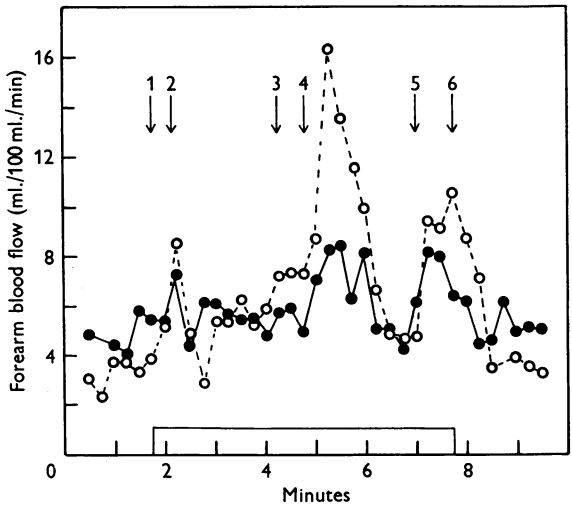

Fig. 7. Effect of blocking the deep nerves to the forearm on the increase in forearm blood flow during stress. The subject was stressed during the period represented by the rectangle; for detail of stimuli 1–6 see text. ●, Nerve-blocked side; ○, normal side.

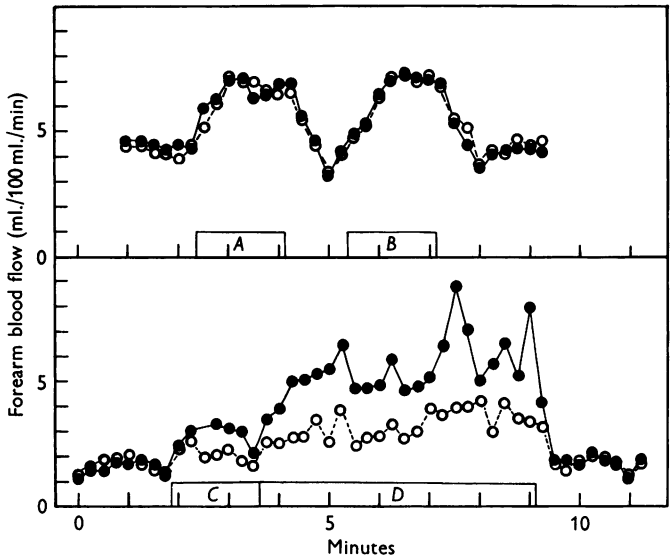

Fig. 8. The effect of atropine on the increase in forearm blood flow during stress. Upper panel: response in the two forearms to two periods of anticipation of mental arithmetic (*A* and *B*) before atropine infusion. Lower panel: response to anticipation of mental arithmetic (*C*) and to a mental arithmetic test (*D*), after atropinization of the left (○) forearm.

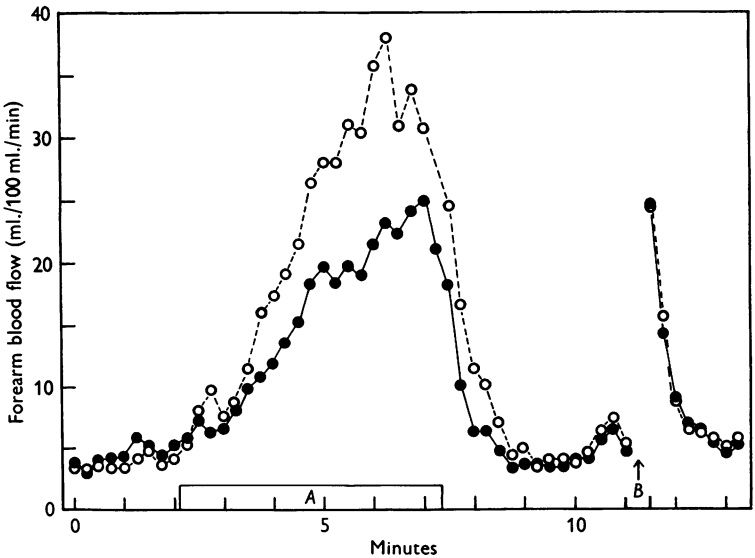

Fig. 9. The effect of atropine on the increase in forearm blood flow during stress. The rectangle *A* represents the period of stress; at *B* the circulation to both forearms was arrested for 2 min. ● normal forearm; ○ atropinized forearm.

Activity of vasodilator nerves against a background of vasoconstrictor activity can, however, be demonstrated by the selective block of vasodilator nerves in one arm. Figure 8 shows the result of an experiment in which this was done. Mild stress was applied before and after atropine had been infused through an indwelling needle into one brachial artery. Initially the blood-flow responses in the two forearms were symmetrical. After the infusion of atropine the resting blood flow was equal in the two arms, although at a lower level than previously, but during emotional stress there was a very much

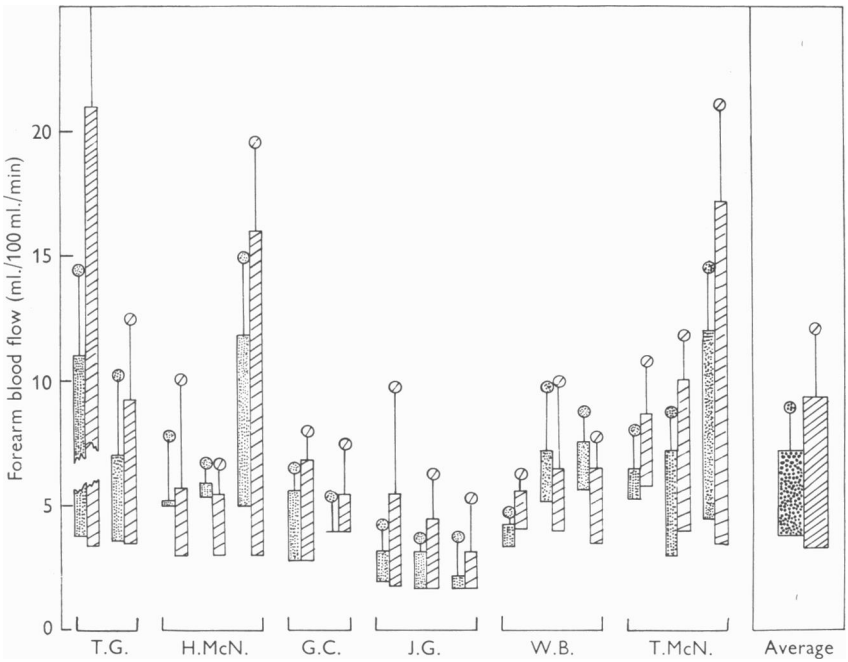

Fig. 10. Effect of atropine on the increase in forearm blood flow during stress; summary of results of sixteen experiments on six subjects; ▦ atropinized side, ▨ normal side; conventions as in Fig. 4. Values in the first experiment on T.G. were 10 ml./100 ml./min greater than those shown here above the breaks in the columns, and the peak flow on the normal side was 38 ml./100 ml./min.

smaller response in the atropinized forearm than in the normal. Figure 9 shows an experiment in which severe stress was applied. Again the response was much smaller on the atropinized side than on the normal side. It was not possible to test for symmetry of response before giving atropine in this experiment, because this type of stress is not repeatable. However, both before and after the infusion of atropine the resting levels of blood flow in the two arms were almost identical. There was also a symmetrical response after arrest of the circulation for 2 min. Figure 10 summarizes the results of these and fourteen other tests in which a wide range of stimuli was applied to six subjects.

In every experiment the response was smaller or absent on the atropinized side. The average increase in mean flow was 3·4 ml./100 ml./min on the atropinized side compared with 6·0 ml. on the normal, and the average increase in peak flow was 5·1 ml./100 ml./min on the atropinized side compared with 8·7 ml. on the normal. It seems clear therefore that cholinergic vasodilator nerves contribute to this response.

DISCUSSION

There are three main problems concerning the mechanism of the vasodilatation observed in the forearm during emotional stress. (1) Is it in muscle or in skin? (2) Is it nervous or humoral? (3) If nervous, is it due to increased activity in vasodilator fibres or to reduced activity in vasoconstrictor fibres? To obtain simultaneous answers to all three questions in one experiment would facilitate interpretation, but would require an amount of interference with the subject which we consider undesirable and perhaps unphysiological. Our experiments were therefore designed to answer one question at a time.

In the experiments in which emotion caused an increase in the oxygen saturation of blood from the deep veins in the forearm there was no increase in the oxygen saturation of the blood coming from the veins draining the skin of the forearm. In experiments in which the forearm and hand blood flow were measured simultaneously only the blood flow in the forearm was increased by emotion. This evidence strongly suggests that the vasodilatation is mainly in muscle. Golenhofen & Hildebrandt (1957), using Hensel's heated thermocouples to measure skin and muscle blood flow during mental arithmetic, came to the same conclusion.

The evidence suggests that the response is at least partly under nervous control. Although the vasodilatation was usually not abolished, it was much reduced on the side in which the nervous control of the vessels was interrupted by sympathectomy or deep nerve block. We are therefore in agreement with Wilkins & Eichna (1941), who found a nervous contribution to the increase in forearm blood flow during mental arithmetic. The residual vasodilatation in our experiments may have been due either to incomplete interruption of nervous pathways or to a humoral mechanism, or to both. It is difficult to estimate the humoral contribution, which may vary from subject to subject, and from one type of stimulus to another.

The reduction in the response following the infusion of atropine into the brachial artery provides strong evidence for the participation of cholinergic vasodilator nerves. The residual vasodilatation may have been wholly or partly due to failure of the injected atropine to reach all the cholinergic nerve endings, as it is very unusual for substances injected into the brachial artery to be uniformly distributed to all the tissues of the forearm. For example, when histamine is injected in this way the flushing of the skin is patchy, and

some areas may not flush at all. Thus the contribution of cholinergic nerves may well have been greater than the reduction of the response by atropine seems to indicate.

It is known that cholinergic vasodilator fibres supply forearm skin vessels (Roddie *et al.* 1957*b*). They are activated during body heating, and the vasodilatation is probably secondary to stimulation of the sweat glands (Fox & Hilton, 1958). If emotional stress causes sweating in the forearm this would presumably be associated with a vasodilatation in the skin which could be blocked by atropine. However, the response is not regularly affected, and is on the average unaltered by blocking the superficial nerves which supply the skin blood vessels and sweat glands. As an increase in skin blood flow was not observed in any of the experiments in which it was sought, it seems most unlikely that it occurred in each of the sixteen atropine experiments. We conclude, therefore, that the increase in forearm blood flow during stress is mainly due to activation of cholinergic vasodilator nerves to muscle.

From the present experiments it would be difficult to say whether or not vasoconstrictor fibres to muscle also contribute to the forearm vasodilatation during stress. These fibres, but not vasodilator fibres, normally participate in certain baroreceptor reflexes both in man (Roddie, Shepherd & Whelan, 1957*c*, 1958) and in animals (Lindgren & Uvnäs, 1954). A variation in vasoconstrictor activity during stress could only be excluded if the response to stress was completely abolished in an atropinized forearm. This was the case in only two experiments, and it would not be possible to draw firm conclusions from such meagre data. In the other atropine experiments we cannot distinguish between the contributions to the residual response of unblocked vasodilator nerves, constrictor nerves and humoral substances. To supply positive evidence for release of vasoconstrictor tone during stress it would be necessary to show that selective block with a sympatholytic drug reduced the response, but we have not tried this as yet. It seems, likely, however, that vasodilator fibres are active before vasoconstrictor tone is fully released, because there was evidence of vasodilator activity at low levels of flow in the atropine experiments. We cannot exclude, but have no reason to expect, a contribution from release of vasoconstrictor tone to the response during stress. Animal experiments suggest that the vasomotor centres controlling vasoconstrictor and vasodilator fibres to muscle are anatomically and physiologically distinct; the vasoconstrictor outflow participates in certain baroreceptor reflexes and the vasodilator outflow in the circulatory adjustments to emotional stress.

SUMMARY

1. Emotional stress was produced in medical students, and in subjects who had had a unilateral sympathectomy, by means judged likely to be most effective for each individual.

2. There was little change in arterial pressure, but a large increase in blood flow through both forearm and calf, indicating vasodilatation in these regions.

3. There was no consistent change in the total blood flow through the hand. There was an increase in the oxygen saturation of blood from the deep but not from the superficial forearm veins. These results suggest that the forearm vasodilatation occurs in muscle.

4. The vasodilatation in the forearm was reduced and occasionally abolished in the nerve-blocked or sympathectomized forearm.

5. The vasodilatation was always smaller in an atropinized forearm than in the control forearm, and occasionally was abolished.

6. It is concluded that cholinergic vasodilator nerves to muscle contribute to the forearm vasodilatation during stress.

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