# A COMPARISON BETWEEN THE VASCULAR RESPONSES TO ADRENALINE AND NORADRENALINE IN INDIVIDUAL SKELETAL MUSCLES OF THE CAT

BY W. C. BOWMAN

*From the Department of Pharmacology, School of Pharmacy, University of London, Brunswick Square, London, W.C.*1

Received October 13, 1958

The effects of intra-arterially and intravenously administered adrenaline and noradrenaline on the venous outflow from individual muscles in the hind limbs of cats under chloralose anaesthesia were studied. The various responses to these amines were shown to depend on the dose administered, the route of injection, the general arterial blood pressure and the vasomotor tone in the muscle. They did not vary with the type of muscle studied. When the vasomotor tone was high, intra-arterially administered adrenaline caused vasodilatation, vasoconstriction or a compound response according to the dose administered. Intra-arterially administered noradrenaline caused only vasoconstriction. However, both intravenously administered adrenaline and noradrenaline in small doses caused vasodilatation in skeletal muscles, the former being the more potent. That this effect depended on intact nervous connections was confirmed in cross-circulation experiments in which the muscle of one cat was perfused entirely by blood from a donor cat. When the vasomotor tone in the muscle was low, either naturally or as a result of acute denervation, it was difficult to produce any dilatation with adrenaline, and noradrenaline always caused vasoconstriction. Under these conditions, the increase in blood flow produced by the intravenous administration of the amines was shown, by means of a blood pressure stabiliser, to be a passive effect caused by the rise in blood pressure forcing more blood through the muscles.

IT is generally believed that the intravenous or intra-arterial administration of small doses of adrenaline produces vasodilatation in skeletal muscles while the administration of larger doses causes vasoconstriction[1–8]. Nevertheless, many workers have been unable to obtain such results. Some recorded only vasoconstriction after the intra-arterial administration of minimal effective doses of adrenaline[9,10]. Others[11,12] recorded a two-fold response of dilatation followed by constriction or dilatation preceded by constriction. Several workers[10,13,14] have reported that the only effect of intravenously administered adrenaline on skeletal muscle blood vessels is a vasoconstriction which may be preceded by a short-lasting passive increase in flow caused by the rise in blood pressure.

There is unanimous agreement that intra-arterially administered noradrenaline causes vasoconstriction in skeletal muscle vessels[6,8,10,15–18], but results differ about its effects when administered intravenously. Some workers have reported an immediate reduction in the blood flow following intravenous administration[19–22]. Others[10,17], described an initial increase in flow which they attributed to the rise in blood pressure and which was immediately followed by a decrease in flow. Still others[7,8,23,24] observed that intravenously administered noradrenaline, like adrenaline,

produced an increase in blood flow which was followed by vasoconstriction only when large doses were administered.

In the past, most workers have recorded blood flow changes in the muscles of the whole limb or in other large groups of muscles. The present experiments were designed to find out whether different types of skeletal muscles respond differently to these amines, thereby possibly accounting for some of the discrepancies. It was considered possible that during emergency states, adrenal medullary hormones might cause an increase in the blood supply to the quick acting white muscles, such as tibialis anterior but might have a different effect on the slow acting red muscles, such as soleus, which are known to contain their own oxygen storing pigments.

The results show that the various responses to adrenaline and noradrenaline depend on the dose administered, the route of injection, the general arterial blood pressure and the vasomotor tone in the muscle vessels but that they do not vary with the type of muscle studied.

## Methods

Cats were anaesthetised with chloralose only (80 mg./kg.) injected into the subcutaneous vein of the forelimb or into the internal saphenous vein. The blood flow in the femoral vein of one hind limb was then restricted to include only that from one of three muscles, the tibialis anterior, the gastrocnemius-plantaris or the soleus. The method used for recording the venous outflow from the tibialis anterior or the soleus muscle has been previously described[25]. When the blood flow from the gastrocnemius-plantaris muscle was studied, a similar procedure was carried out except that the circulation of this muscle was left intact while both arteries and veins supplying all other muscles were ligated. The blood flow in the femoral vein was recorded by means of the drop-chamber described by Hilton[26,27] and the Gaddum drop recorder[28]. To denervate the muscle during the experiment, the sciatic nerve was exposed high in the thigh.

In cross-circulation experiments, the gastrocnemius-plantaris muscle of one cat was prepared as described. A mass ligature was then made round the thigh just above the knee but excluding the femoral artery and vein and the sciatic nerve. Blood from the femoral artery of an anaesthetised, heparinised, donor cat was then led through polythene tubing into the cut peripheral end of the femoral artery of the first cat. The venous outflow from the perfused gastrocnemius-plantaris muscle was allowed to pass through the drop-chamber and then returned to the central end of the cut femoral vein of the donor cat. Thus the cross perfused muscle entirely lacked vascular connections with the recipient animal, only the nervous connections through the sciatic nerve being intact.

Blood pressure was recorded by means of a mercury manometer attached to a cannula in the right common carotid artery. In experiments in which the effects of intravenously administered adrenaline and noradrenaline were studied, the same doses were administered both

before and after connecting a blood pressure stabiliser[29] to the carotid artery.

Drugs were administered intravenously via a cannula in the jugular vein or intra-arterially by means of a needle cannula in the cut central end of a branch of the femoral artery—usually the small artery supplying the gracilis muscle. Before being tied and clamped in position, the needle cannula was inserted into the artery until its tip was level with the junction of the cannulated artery and the femoral artery. A micro-syringe was used for all intra-arterial injections. The drugs used were (—)-adrenaline bitartrate and (—)-noradrenaline bitartrate. Solutions were made in 0·9 per cent w/v NaCl saline. The doses quoted in the text refer to the quantity of amine calculated as base.

At the end of each experiment, Indian ink was injected through the arterial cannula to ascertain that the blood flow was restricted to the required muscle.

## Results

Preliminary experiments showed that the intra-arterial administration of volumes of 0·9 per cent saline, greater than 0·02 ml., themselves usually caused an increase in venous outflow. For this reason adrenaline and noradrenaline were administered in volumes which did not exceed 0·01 ml. and control injections of saline were made throughout each experiment.

Throughout the experiments, similar responses were obtained whatever the muscle under study. The results to be described, therefore, apply to all three muscles, the tibialis anterior, the gastrocnemius-plantaris and the soleus.

### *Intra-arterially Administered Adrenaline and Noradrenaline*

The effect of intra-arterially administered adrenaline depended on the magnitude of the dose and the vasomotor tone in the muscle. When the vasomotor tone was shown to be high by the fact that later in the experiment acute denervation caused a marked and prolonged increase in venous outflow, the sequence of responses to ascending doses was as follows. Minimal effective doses (0·001–0·01 μg.) produced a short-lasting increase in flow only and this response at first increased as the dose was increased. With slightly larger doses (0·04–0·4 μg.), however, the increase in flow became progressively less and was followed by a small decrease in flow. As the dose was further increased, the initial increase in flow became still smaller and the following decrease larger, until, over a small range of doses (0·4–1·5 μg.), only a decrease in flow was recorded. Larger doses (greater than 1–2 μg.) produced an initial decrease in flow which was usually followed by an increase in flow of variable duration (from 90 seconds to 12 minutes). With the range of doses employed in this type of experiment the general arterial blood pressure usually remained unaltered. Figure 1 shows a characteristic sequence of responses to increasing doses of adrenaline.

In 2 out of 15 experiments, minimal effective doses caused an initial increase in flow which was followed by a decrease, that is, the pure dilator phase was absent. In 3 of the experiments minimal effective doses caused only a decrease in flow. These responses occurred in cats in which the vasomotor tone in the muscle was shown to be low by the fact that acute denervation later in the experiment caused only an initial short-lasting increase in flow. When the vasomotor tone was high, acute denervation of the muscle caused an initial short-lasting but marked increase in venous outflow accompanied by a rise in blood pressure of similar duration. The rate of flow subsequently subsided to a level 1·5–3 times greater than the flow from the innervated muscle, remaining there for several hours (Fig. 2).

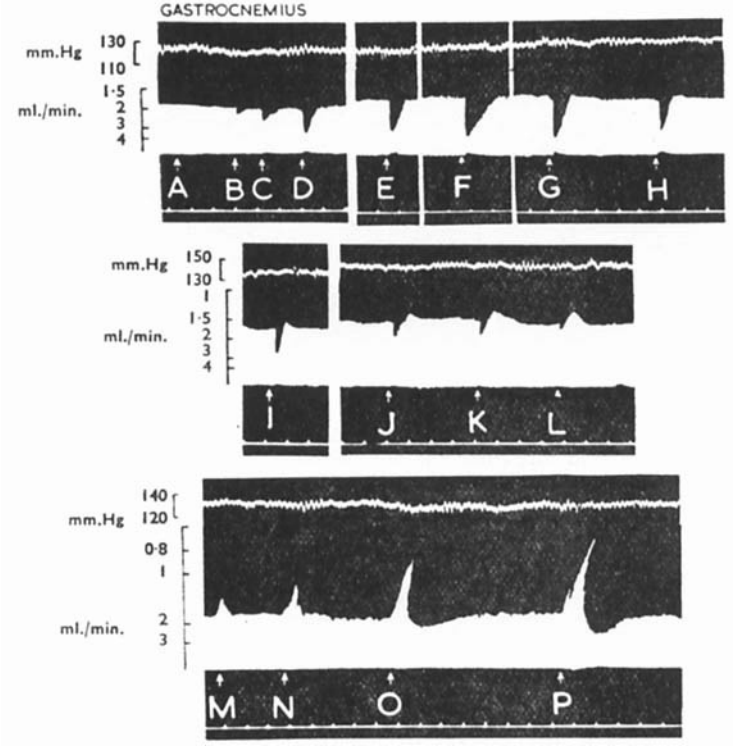


FIG. 1. Cat, 3·4 kg. The effect of intra-arterially administered adrenaline on the venous outflow from innervated muscle. Upper record: blood pressure; lower record: venous outflow. Time scale in min. At A, 0·0005; B, 0·001; C, 0·002; D, 0·004; E, 0·008; F, 0·01; G, 0·02; H, 0·04; I, 0·05; J, 0·1; K, 0·2; L, 0·4; M, 0·5; N, 1; O, 2; P, 3 $\mu$g.

After acute denervation, it was occasionally still possible to produce some dilatation with small intra-arterial doses of adrenaline. If, before denervation, the peak of the increase in flow caused by a certain dose of adrenaline was higher than the increased level of flow produced by

denervation, the adrenaline still had a slight dilator effect after denervation. Doses of adrenaline which produced in the innervated muscle a two-fold response of dilatation followed by constriction, caused only vasoconstriction during the hyperaemia produced by acute denervation (Fig. 2). Denervation did not always prevent the secondary increased flow which usually followed the vasoconstriction produced by large doses of adrenaline. When the vasomotor tone was low, the responses to intra-arterially administered adrenaline were the same before and after denervation.

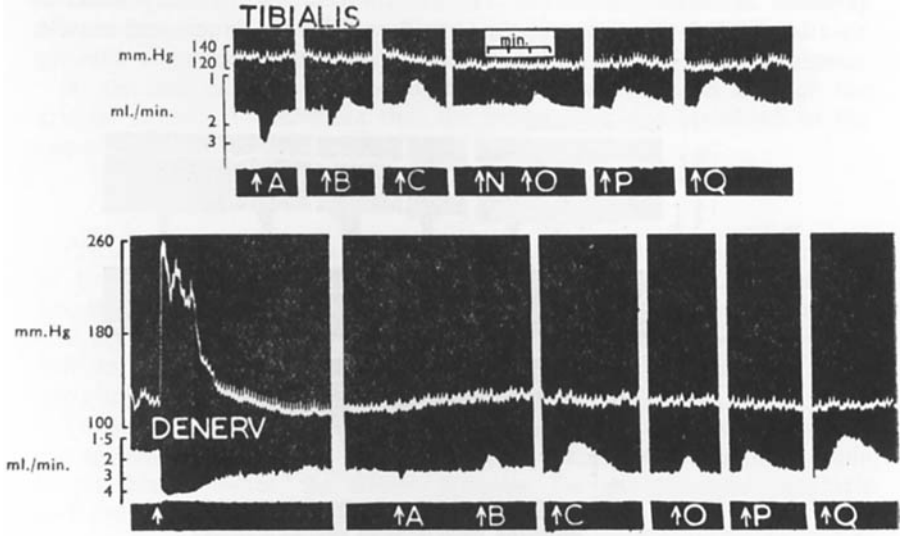


FIG. 2. Cat, 3·7 kg. The effect of acute denervation on the responses to intra-arterially administered adrenaline and noradrenaline. At A; 0·05, B, 0·2 and C, 0·5 μg. adrenaline. At N, 0·05; O, 0·1; P 0·2 and Q 0·5 μg; noradrenaline. At DENERV, scientic nerve severed. Time scale in min.

Minimal effective intra-arterial doses of noradrenaline (0·01–0·1 μg.) caused vasoconstriction only in the skeletal muscles and this response increased with increase in the dose. Doses of noradrenaline equivalent in size to purely dilator doses of adrenaline, were without effect (Fig. 2). In general, noradrenaline produced a greater and slightly longer lasting reduction in venous outflow than that produced by adrenaline (Fig. 2). However, in one animal in which the vasomotor tone in the muscle was later shown to be low, the vasoconstriction produced by adrenaline was equal to that produced by noradrenaline and was not altered by denervation. When denervation caused an increased flow through the skeletal muscle, noradrenaline subsequently injected produced a proportionately greater reduction in flow than when injected before denervation (Fig. 2).

*Intravenously Administered Adrenaline and Noradrenaline*

In general, the effects of intravenously administered adrenaline and noradrenaline were similar except that the vasopressor responses and the

reductions in venous outflow produced by noradrenaline were slightly greater than those produced by adrenaline, while the dilator effects were considerably weaker. The effects of the amines, when administered intravenously, depended on the general arterial blood pressure and the vasomotor tone in the muscle under study.

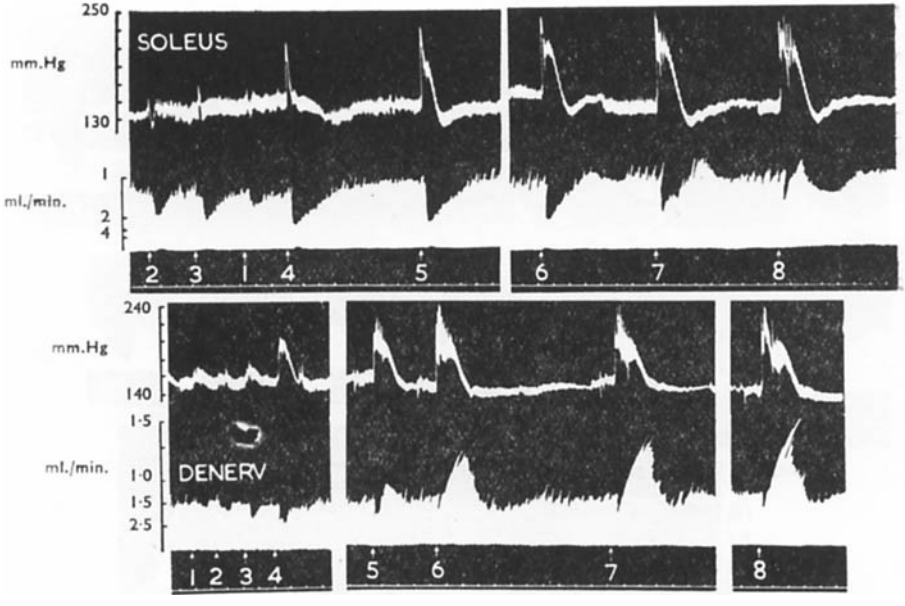


FIG. 3. Cat, 4·2 kg. The effect of acute denervation on the responses to intravenously administered adrenaline. Upper tracings: innervated muscle; lower tracings: acutely denervated muscle. Time scale in min. At **1**, 0·25; **2**, 0·5; **3**, 1; **4**, 5; **5**, 10; **6**, 20; **7**, 30; **8**, 50 $\mu$g.

In 21 out of 30 experiments in which the effects of intravenously administered adrenaline were studied, the blood pressure was greater than 100 mm. Hg and the vasomotor tone in the muscle was high, as shown by the fact that later in the experiment acute denervation caused a prolonged increase in venous outflow from the muscle. In these experiments both depressor and pressor doses of adrenaline, from 0·03 to 5–10 $\mu$g./kg., usually caused only an increase in venous outflow. This response increased with increase in dose. With larger doses (greater than 5–10 $\mu$g./kg.) the increase in flow became progressively less and was followed by a rapid return either to, or slightly below the normal level. Following this reduction in flow, even in preparations in which the flow was not reduced below normal, there was often a further increase in flow of longer duration (Figs. 3 and 5). After acute denervation of the skeletal muscle, it was usually still possible with small doses (up to 2–3 $\mu$g./kg.) to produce a small increase in venous outflow (Fig. 3). With larger doses, however, there occurred an initial short-lasting increase in venous outflow as the blood pressure rose, and this was followed immediately by vasoconstriction (Fig. 3). The vasoconstriction usually

occurred while the blood pressure was still rising, or at its maximum. Increase in dose caused an increase in vasoconstriction. Thus, a dose which was purely dilator in the innervated muscle, could cause a marked constriction in the acutely denervated muscle (Fig. 3). As in the innervated muscle an increase in flow often followed the vasoconstriction.

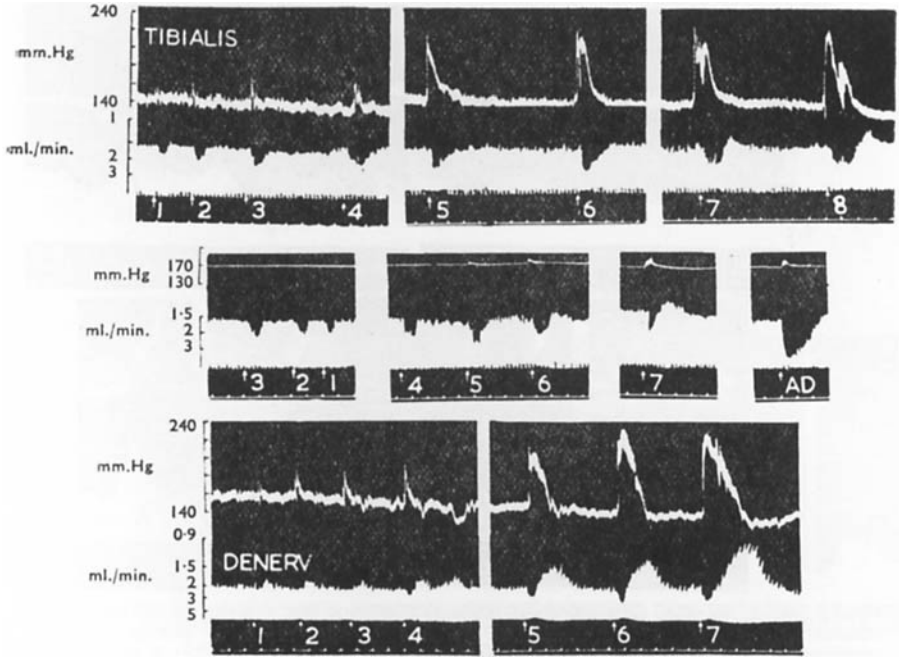


FIG. 4. Cat, 3·8 kg. The effect of stabilising the blood pressure and of acute denervation on the responses to intravenously administered noradrenaline. Upper tracings: innervated muscle; middle tracings; innervated muscle, blood pressure stabilised; lower tracings: acutely denervated muscle. Time scale in min. At **1**, 0·1; **2**, 0·25; **3**, 0·5; **4**, 1; **5**, 5; **6**, 10; **7**, 20; **8**, 40 μg. noradrenaline. At **AD**, 10 μg. adrenaline for comparison.

In 22 out of 28 experiments in which the effects of intravenously administered noradrenaline were studied, the blood pressure and vasomotor tone were high. In 12 of these 22 experiments intravenously administered noradrenaline produced effects similar to those described for adrenaline except that the increases in flow were smaller, while the decreases in flow were larger and usually occurred with smaller doses. Figure 4 illustrates one of these experiments. Unlike the effect of adrenaline, vasoconstriction produced by large doses of noradrenaline was not followed by a secondary increase in flow. In none of the experiments did small doses of noradrenaline cause a fall in blood pressure like that reported by West[30], but in two experiments in which the general arterial blood pressure was exceptionally high, the smallest doses of noradrenaline which increased the venous outflow from the muscle, were without effect on the blood pressure (Fig. 4). In the remaining 10 of these 22

experiments, intravenously administered noradrenaline in all effective doses produced only vasoconstriction. Intravenously administered adrenaline on the other hand, produced vasodilatation even in these experiments. Acute denervation later in these experiments caused a prolonged increase in the venous outflow from the muscle but it was much smaller in extent than that which occurred in the other 12 experiments. After acute denervation, in all experiments, effective doses of noradrenaline produced a vasoconstriction which, particularly with large doses, was preceded by a short-lasting increase in flow as the blood pressure rose (Fig. 4).

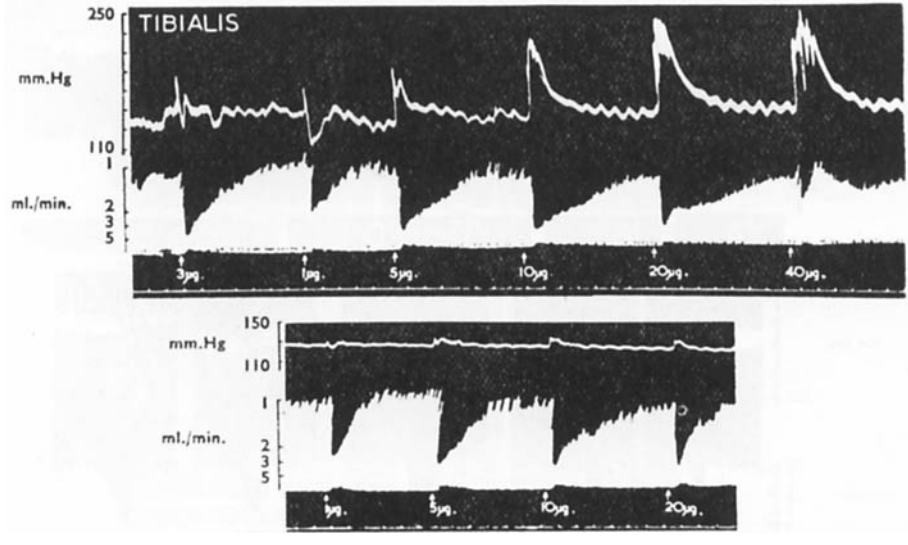


FIG. 5. Cat, 3·8 kg. The effect of stabilising the blood pressure on the responses to intravenously administered adrenaline in the innervated muscle. Time scale in min.

When the blood pressure stabiliser was connected to the carotid artery, the dilatation produced by intravenously administered adrenaline was only slightly reduced in extent and duration (Fig. 5). The dilator response to noradrenaline was reduced but not abolished when the blood pressure was prevented from rising (Fig. 4). With the stabiliser connected, even large doses of adrenaline and noradrenaline, of about 20 $\mu$g./kg., produced a rise in blood pressure of only 5–10 mm. Hg. After denervation, the reduction in blood flow produced by adrenaline and noradrenaline was slightly greater than that produced when the blood pressure was allowed to rise, and with large doses of adrenaline and all doses of noradrenaline there was no initial short increase in flow preceding the vasoconstriction.

The results so far described indicate that both adrenaline and noradrenaline can produce a vasodilatation in skeletal muscles which is not due to a direct action on the vessels but which is activated through

the nerves. Further support for this conclusion was provided by experiments in which the effects of intra-arterially and intravenously administered adrenaline were compared. In such experiments, it was always possible to produce a greater increase in venous outflow from the skeletal muscle with intravenously administered adrenaline than with intra-arterially administered adrenaline. Even in the range of intravenous vasodepressor doses, it was always possible to find a dose which produced a greater increase in venous outflow than any dose administered intra-arterially. Figure 6 illustrates such an experiment.

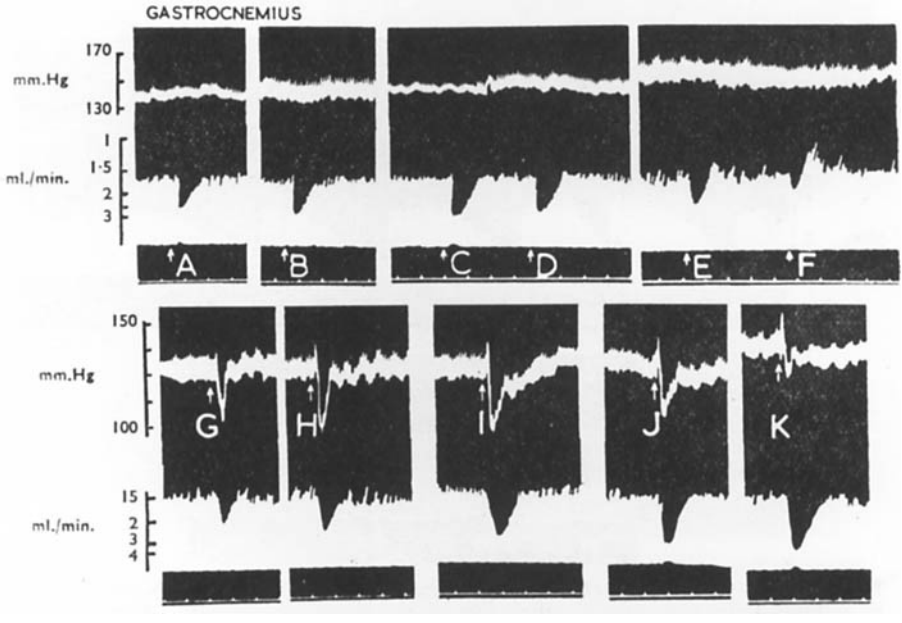


FIG. 6. Cat, 4·1 kg. Comparison between responses to intra-arterially and intravenously administered adrenaline in the innervated muscle. Upper tracings: intra-arterial administration; lower tracings: intravenous administration. Time scale in min. At A, 0·025; B, 0·04; C, 0·06; D, 0·08; E, 0·15; F, 0·3; G, 0·1; H, 0·25; I, 0·5; J, 1; K, 2 $\mu$g.

Cross-circulation experiments confirmed that the vasodilatation produced by intravenously administered noradrenaline and part of that produced by adrenaline, is dependent on intact nervous connections. In 3 out of 5 such experiments, the intravenous administration of adrenaline to the recipient cat caused vasodilatation in the skeletel muscles and in 2 of them, noradrenaline caused a similar but smaller response. Figure 7 illustrates an experiment in which both adrenaline and noradrenaline caused such a vasodilatation. These effects occurred despite the fact that there was no circulation connection between the recipient cat and the muscle under study. The absence of a pressor response in the donor cat confirmed the lack of circulatory connection. In the other experiments the amines were without effect when administered to the

recipient cat. In these experiments the vasomotor tone in the perfused muscle was later shown to be low. After acute denervation of the muscle the administration of the amines to the recipient animal was without effect in every experiment. With the doses used, the administration of the amines to the donor cat caused vasoconstriction in the perfused muscle both before and after denervation. The vasoconstriction was preceded by a brief passive increase in flow as the blood pressure of the donor animal rose (Fig. 7).

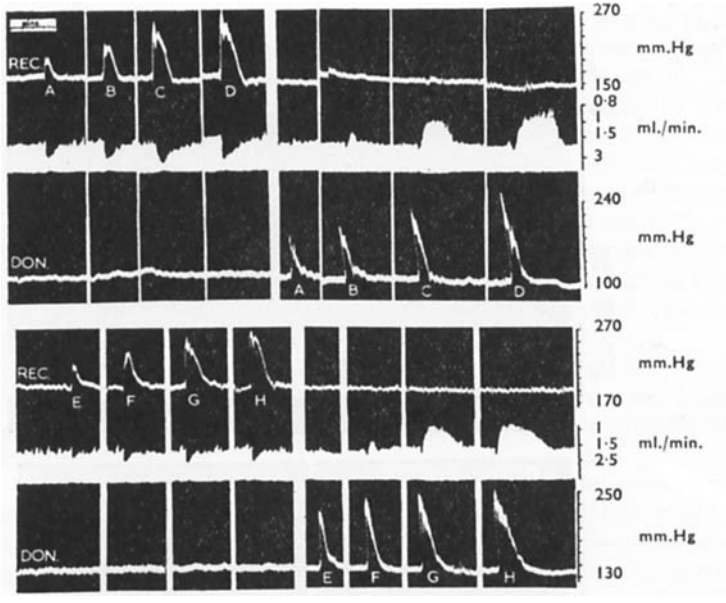


FIG. 7. Recipient cat, 3 kg; donor cat, 3·7 kg. Cross-circulation experiment. REC:—blood pressure of recipient cat. DON:—blood pressure of donor cat. Middle record:—venous outflow from perfused muscle. At A, B, C, D, 5, 10, 20 and 30 $\mu$g. adrenaline. At E, F, G, H, 5, 10, 20 and 30 $\mu$g. noradrenaline. The doses are marked under the blood pressure record of the cat to which they were intravenously administered.

In 9 out of 30 experiments with adrenaline and in 6 out of 28 with noradrenaline, the blood pressure was lower than 100 mm. Hg and the vasomotor tone in the muscle under study was later shown to be low. In these experiments minimal effective doses of adrenaline and noradrenaline (0·02–0·1 $\mu$g./kg.) produced a rise in blood pressure and an increase in venous outflow from the muscle. These effects increased in magnitude with increase in dose, up to a maximum with doses of 5–20 $\mu$g./kg. Larger doses caused an increase in flow which was followed by vasoconstriction (Fig. 8). The vasoconstriction occurred as the blood pressure was returning to normal. A further dilatation of longer duration followed the vasoconstriction produced by adrenaline on only 2 occasions (Fig. 8). However, on several occasions the vasoconstriction produced by both adrenaline and noradrenaline showed two distinct peaks. That

is, a short-lasting dilatation of variable extent was superimposed on the vasoconstriction 20 to 60 seconds after its onset. This dilatation, which occurred less often and was always smaller with noradrenaline, was then followed by a further vasoconstriction. Acute denervation did not alter the responses to adrenaline and noradrenaline in these experiments. By connecting the blood pressure stabiliser to the carotid artery the initial increase in venous outflow was prevented and all effective doses of adrenaline and noradrenaline caused an immediate vasoconstriction which was slightly greater than that which occurred when the blood pressure was allowed to rise. However, the vasoconstriction still often showed two distinct peaks. Figure 8 illustrates an experiment in which a single large

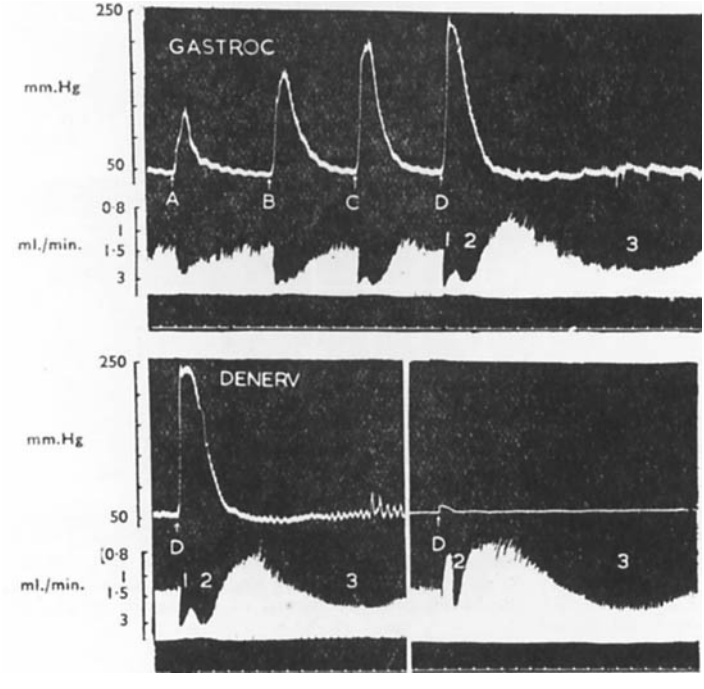


FIG. 8. Cat, 3·9 kg. The effect of intravenously administered adrenaline when blood pressure and vasomotor tone low. Upper tracing: innervated muscle; left lower tracing: acutely denervated muscle; right lower tracing: acutely denervated muscle, blood pressure stabilised. Time scale in min. At A, B, C and D, 2, 10, 20 and 40 $\mu$g. adrenaline.

vasoconstrictor dose of adrenaline produced three distinct and separate increases in flow; an initial increase as the blood pressure rose, a second increase which occurred immediately after the onset of vasoconstriction and a third increase which followed the vasoconstriction. The same response was produced in the acutely denervated muscle. When the blood pressure stabiliser was connected, the initial increase was absent and vasoconstriction occurred immediately but the second increase was still superimposed upon it and the third increase still occurred after the

vasoconstriction. These increases in flow are marked 1, 2 and 3 in Figure 8.

## Discussion

When vasomotor tone is high, the intra-arterial administration of small amounts of adrenaline causes vasodilatation in skeletal muscles. With increase in dose, the response changes through a dual effect of dilatation followed by constriction, to a pure reduction in venous outflow. Girling[14] recorded a similar sequence of responses to ascending doses of adrenaline in rabbits. In most experiments the vasoconstriction produced by large doses of adrenaline was followed by a secondary increase in blood flow, an effect previously described in the dog by Green[31] and by Dörner[8]. Dörner[8] thinks no great importance should be attributed to the vasodilatation produced by small intra-arterial doses of adrenaline. He showed that even physiological saline injected intra-arterially may cause vasodilatation in the femoral artery. In the present work, the volume of injections administered intra-arterially was restricted to 0·01 ml. and control saline injections of the same volume as the adrenaline solutions were without effect. Furthermore, the intra-arterial administration of noradrenaline causes only vasoconstriction, the minimal effective dose being roughly equal to the smallest dose of adrenaline which shows some vasoconstrictor action. Doses of noradrenaline equivalent in size to purely dilator doses of adrenaline are without effect on the blood flow. The dilatation must, therefore, be attributable to a specific effect of adrenaline.

Lundholm[32] and Celander[18] have suggested that the dilatation of the blood vessels of skeletal muscles produced by adrenaline might be due to the increased lactic acid concentration resulting from changes in the carbohydrate metabolism. However, from the present experiments it appears unlikely that lactic acid can account for the initial dilatation obtained with small amounts of adrenaline. The onset of this dilatation is rapid, in many cases starting before the injection is completed. A direct action on the walls of the vessels is, therefore, more probably the cause since a secondary effect due to metabolic changes would involve first the penetration of adrenaline from the lumen of the vessel to the skeletal muscle, secondly, the break-down of glycogen and finally the return of lactic acid to the blood stream. Increased lactic acid formation may, however, account for the secondary dilatation which usually follows vasoconstriction produced by adrenaline. The time lag between injection and the appearance of secondary dilatation is more in accordance with what might be expected if the effect were due to metabolic changes. It is unlikely that the secondary dilatation is caused by the concentration of adrenaline, as it passes from the circulation, again entering the dilator range. Vasoconstriction is abruptly cut short by the secondary dilatation and if the above were the explanation, a more gradual change from constriction to dilatation might be expected. Furthermore, secondary dilatation often occurred in acutely denervated muscles in which no initial dilatation with small doses of adrenaline could be demonstrated. A

comparison between the secondary dilatation and the reactive hyperaemia which follows a short period of ischemia resulting from mechanical occlusion of the femoral artery, showed, in accordance with the results of Lanier and others[33] that, while the adrenaline effect in different experiments lasted from 90 seconds to 12 minutes, the duration of the reactive hyperaemia rarely exceeded 45 seconds. Moreover, the vasoconstriction produced by noradrenaline was not succeeded by a secondary increase in flow. Finally, the secondary adrenaline dilatation often occurred after the intravenous administration of large doses of adrenaline which, however, did not reduce the rate of flow below the normal level.

Acute denervation of the muscle usually caused an increase in venous outflow which on some occasions was as great as three times that of the flow from the innervated muscle. The extent of the increase in flow after acute denervation provided some indication of the degree of vasomotor tone, dependent on autonomic nerves. It was occasionally still possible to cause some dilatation in the acutely denervated muscle with small doses of adrenaline administered intra-arterially but constriction was the more usual response. Thus when the vasomotor tone is low and the vessels are consequently widely dilated, it is difficult to produce any further dilatation with intra-arterially administered adrenaline.

Noradrenaline, when administered intra-arterially, produced an immediate vasoconstriction. These results confirm the findings of others[6,8,10,15–17]. In most of my experiments, the vasoconstriction produced by noradrenaline was slightly greater and longer lasting than that produced by adrenaline, but it is difficult to determine the relative potency of the two amines in producing vasoconstriction because the effect of adrenaline is the overall result of two opposing actions. In the experiments of Wakim and Essex[10] adrenaline and noradrenaline were equally potent in producing vasoconstriction and this was found to be so in one of the present experiments in which the vasomotor tone in the muscle was low. It is therefore probable that adrenaline is at least as potent a vasoconstrictor substance as noradrenaline but when the vasomotor tone is high this action is masked to some extent by its vasodilator action.

When the general arterial blood pressure and the vasomotor tone in the muscles are high, intravenously administered adrenaline, and, to a smaller extent, noradrenaline cause, except in large doses, an increase in the blood flow through skeletal muscles. The use of the blood pressure stabiliser showed that only a small part of this effect is brought about through the rise in blood pressure and the buffer reflexes. With the intravenous administration of small amounts of adrenaline, the direct vasodilator action, as seen after intra-arterial injection must take part in the effect. However, a direct action on the blood vessels cannot account for the vasodilatation produced by the intravenous administration of noradrenaline or of large amounts of adrenaline. That the dilatation is partly activated through the nerves is shown by the following results.

1. After acute denervation of the muscle, intravenous doses of adrenaline or noradrenaline, which previously caused vasodilatation, frequently

produced a marked vasoconstriction, the flow often being reduced to a level below that of the normal flow from the innervated muscle. Several workers have explained this effect with adrenaline on the grounds that the widely dilated vessels of the acutely denervated limb cannot be further dilated. This explanation, however, does not account for the marked vasoconstriction which occurs after denervation. Certainly it cannot be said that acute denervation sensitises the vessels to the constrictor action of adrenaline because no such marked sensitisation occurs when it is administered intra-arterially.

2. The dilatation produced by intravenously administered adrenaline, even when it caused a fall in blood pressure, was very much greater than that produced by any dose administered intra-arterially. Similar results were obtained in the dog by Dörner[8].

3. When the vasomotor tone was high, the intravenous administration of adrenaline or noradrenaline to the recipient cat in a cross-circulation experiment caused vasodilatation in the muscle despite the fact that the only connection between the muscle and the recipient cat was through the nerves. After acute denervation of the muscle, a similar administration to the recipient cat was without effect on the muscle blood vessels. On the other hand, the intravenous administration of adrenaline or noradrenaline to the donor animal caused, after an initial passive increase in flow, only vasoconstriction in the perfused muscle. These results confirm those obtained in the dog by several other workers[2,34–38] with adrenaline and those of Gruhzit and others[38] with noradrenaline.

Even large doses of adrenaline administered intravenously often caused only an increased flow through the muscle, although, as shown by cross-circulation experiments in which adrenaline was administered to the donor animal, the local action of such doses is vasoconstriction. Thus in the innervated muscle, the dilatation due to nervous activity is often sufficiently great to mask completely the local constrictor action. Gruhzit and others[38] showed that, in the dog, mechanoreceptors along the course of the thoracic aorta, activated by the inotropic cardiac action of adrenaline and noradrenaline may be the afferent source of a reflex vasodilatation produced in skeletal muscles.

When the general arterial blood pressure and the vasomotor tone in the muscle were low, intravenously administered adrenaline and noradrenaline did not cause reflex dilatation in the skeletal muscles. A similar result was obtained in dogs by Gruhzit and others[38]. The marked increases in venous outflow produced by adrenaline and noradrenaline under these conditions was unaltered after acute denervation and was shown, by the use of the blood pressure stabiliser, to be simply a passive effect caused by the large rise in blood pressure.

Several workers have been unable to record any vasodilatation with intra-arterially or intravenously administered adrenaline or with intravenously administered noradrenaline. Such results were occasionally obtained in the present experiments but only in animals in which the vasomotor tone in the muscles was shown to be low. Species difference

may account for the observations of some of these workers. For example, the experiments of Girling[14] were made on rabbits, animals which, according to Hartman, Kilborn and Lang[39] lack vasodilator mechanisms sensitive to intravenously administered adrenaline. Others[19,20,22], worked with human subjects and there is no evidence that adrenaline or noradrenaline causes reflex dilatation in the skeletal muscles of man. However, some workers[9–12,17] used the cat or the dog as their experimental animals and it seems probable, therefore, that the vasomotor tone in the muscles must, for some reason, have been low. Several factors are known to influence vasomotor tone. For example, Folkow[40] has shown that the use of many types of arterial flow meter causes a loss of vasomotor tone in the muscle vessels and the importance of anaesthetics in its maintenance has often been emphasised[8,24]. In the present experiments the blood flow was continuously recorded on the venous side; chloralose was the anaesthetic used and it is known that under chloralose anaesthesia vasomotor tone is well maintained.

From a physiological point of view the results are of interest since they indicate that, in emergency states, the relatively small amounts of both adrenaline and noradrenaline liberated from the adrenal medullae will cause vasodilatation in skeletal muscles.

## References


1. Hoskins, Gunning and Berry, *Amer. J. Physiol.*, 1916, **41**, 513.
2. Hartman and Fraser, *ibid.*, 1917, **44**, 353.
3. Dale and Richards, *J. Physiol.*, 1918, **52**, 110.
4. Dale and Richards, *ibid.*, 1927, **63**, 201.
5. Gruber, *Amer. J. Physiol.*, 1929, **89**, 650.
6. Folkow, Frost and Uvnäs, *Acta physiol. scand.*, 1948, **15**, 412.
7. Imig, Randall and Hines, *Amer. J. Physiol.*, 1952, **169**, 22.
8. Dörner, *Arch. exp. Path. Pharmak.*, 1954, **221**, 286.
9. Puccinelli, *Riv. di Pat. Sper.*, 1934, **12**, 261.
10. Wakim and Essex, *Circulation*, 1952, **5**, 370.
11. Clark, *J. Physiol.*, 1934, **80**, 429.
12. Roome, *Amer. J. Physiol.*, 1938, **123**, 543.
13. Mertens and Rein, *Pflüg. Arch. ges. Physiol.*, 1938, **241**, 402.
14. Girling, *Amer. J. Physiol.*, 1951, **164**, 400.
15. Barcroft and Konzett, *J. Physiol.*, 1949, **110**, 11P.
16. Barcroft and Konzett, *ibid.*, 1949, **110**, 194.
17. Cobbold and Vass, *ibid.*, 1953, **120**, 105.
18. Celander, *Acta physiol. scand.*, 1954, **32**, Suppl. 16.
19. Goldenberg, Pines, Baldwin, Greene and Roh, *Amer. J. Med.*, 1948, **5**, 792.
20. Swan, *Lancet*, 1949, **2**, 508.
21. de Largy, Greenfield, McCorry and Whelan, *Clin. Sci.*, 1950, **9**, 71.
22. Barcroft and Swan, *Sympathetic Control of Human Blood Vessels*, Edward Arnold and Co., London, 1953.
23. von Meier, Gross and Eichenberger, *Helv. physiol. acta*, 1949, **7**, 230.
24. McDowall, *J. Physiol.*, 1950, **111**, 1.
25. Bowman and Zaimis, *ibid.*, 1958, **144**, 92.
26. Hilton, *ibid.*, 1952, **117**, 48P.
27. Hilton, *ibid.*, 1953, **120**, 230.
28. Gaddum and Kwiatkowsky, *ibid.*, 1938, **94**, 87.
29. Ginzel and Kottegoda, *ibid.*, 1954, **123**, 277.
30. West, *J. Pharm. Pharmacol.*, 1951, **3**, 340.
31. Green, *Science*, 1953, **118**, 570.
32. Lundholm, Communication at VIIth Scand. Physiol. Congr. 1951, quoted by Celander.[18]
33. Lanier, Green, Hardaway, Johnson and Donald, *Circulation Research*, 1953, **1**, 40.

34. Gayet, Gayet and Guillaume, *C.R. Soc. Biol. Paris*, 1927, **97**, 1145.
35. Gayet, Gayet and Quivy, *ibid.*, 1933, **114**, 619.
36. Tournade and Malméjac, *ibid.*, 1933, **114**, 1247.
37. Binet and Burstein, *ibid.*, 1947, **141**, 630.
38. Gruhzit, Freyburger and Moe, *J. Pharmacol.*, 1954, **112**, 138.
39. Hartman, Kilborn and Lang, *Endocrinology*, 1918, **2**, 122.
40. Folkow, *Acta physiol. scand.*, 1952, **27**, 118.