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RESPONSES OF MUSCLE BLOOD VESSELS TO INTRA-ARTERIALLY AND INTRAVENOUSLY ADMINISTERED NORADRENALINE

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There seems to be unanimous agreement in the literature that, when administered intra-arterially, noradrenaline constricts the blood vessels in skeletal muscle (Folkow, Frost & Uvnäs, 1948, the eviscerated hind-limb preparation in the cat; Barcroft & Konzett, 1949, man; Wakim & Essex, 1952, dog).

Reports differ in regard to its action when given intravenously. Some workers found it to have a purely vasoconstrictor effect (Goldenberg, Pines, Baldwin, Greene & Roh, 1948, man; Swan, 1949, man; de Largy, Greenfield, McCorry & Whelan, 1950, man; Burn & Hutcheon, 1949, cat). Others observed that it had a purely vasodilator action (Meier, Gross & Eichenberger, 1949, cat; McDowall, 1950, cat; Imig, Randall & Hines, 1952, small doses (0·2–0·4 μg/kg/min), unanaesthetized dog). A transient dilatation followed by constriction has been observed by Wakim & Essex (1952, dog), and Imig *et al.* (1952, 2 μg/kg body weight, unanaesthetized dog).

We have compared the action of intra-arterial and intravenous noradrenaline on the blood vessels of the skeletal muscle of the anaesthetized cat. The responses differed, but an adequate explanation capable of experimental proof has been obtained.

METHOD

Blood flow in response to noradrenaline was studied in the hind-leg (thigh) muscles of cats. Noradrenaline was administered by intravenous injection into a fore-limb vein via a polythene cannula and by intravenous infusion from a constant speed apparatus by the same route. Intra-arterial injections and infusions were given into the femoral artery; for this purpose a portion of a no. 16 hypodermic needle was sealed to a length of polythene tubing and after insertion into the artery left *in situ*. For intravenous injection the doses used ranged from 1 to 5 μg/kg and for intravenous infusion the concentration was adjusted to give a rate of 1–5 μg/kg/min. To obtain a comparable effect with intra-arterial injections and infusions one-tenth of the intravenous strengths was used.

The animals were anaesthetized with continuous ether or intravenous chloralose (70 mg/kg), or intraperitoneal pentobarbitone sodium (50 mg/kg), or were spinalized and the brain pithed

under ether. A second group of cats was sympathectomized, the sympathectomy being carried out 6 weeks prior to experiment, the thoracic and upper lumbar sympathetic chain was removed on one side. In addition, some cats were used after acute section of the sciatic nerve and treatment with a hexamethonium compound. In some experiments a blood-pressure compensator was employed (Delorme, 1951).

In each animal a hind-limb was skinned and all skin vessels were tied off. Vessels were tied so that the blood collected came from the thigh muscles only. A mass ligature placed round the leg at ankle level occluded the circulation of the pad of the paw. The skinned limb was kept warm throughout by cloths damped in 0·9% (w/v) saline. The femoral vein was isolated and cannulated proximally and distally using lengths of no. 2 size polythene tubing (Sterivac), filled with heparin-saline solution. The proximal cannula was passed steadily up the femoral vein until there was no backflow, but the cannula remained filled with blood. The ends of these cannulae were passed into 1 cm lengths of flexible Telcothene tubing making connexion with a length of no. 2 polythene tubing approximately 50 cm long which served as a flowmeter. When connexion was established through the tubing between the two ends of the femoral vein, the clip on the distal portion of the vein was removed, blood was allowed to flow, and heparin (1000 units/kg) was administered intravenously.

By clipping the distal Telcothene join, momentarily disconnecting the flowmeter tubing and replacing, a small bubble of air about 1 mm in length was introduced. On removal of the clip the bubble travelled forward and, after allowing time for it to attain a steady rate, its transit time between two fixed marks was observed, using a stop-watch. A bubble trap may be inserted to extract the bubble at the end of the meter, but we have generally allowed the small bubble to enter the circulation. No difficulty has been experienced as a result of this procedure since the volume of air so admitted is very small. At the end of the experiment the portion of tubing between the marks was cut out and its volume calculated from length and diameter, or calibrated by direct measurement of the volume of blood contained. Knowing the volume and the bubble transit time the rate of flow in ml./min was calculated.

This type of flowmeter represents a simplification of the type described by Bruner (1948) and conforms with the theoretical considerations described by him.

The method undoubtedly measures only flow through the meter tubing and not absolute flow values since the tubing imposes some hindrance to flow. (Thus, whereas the normal resting venous flow as measured by the bubble flow averages 0·7 ml./min, if the blood runs out into a beaker from a polythene cannula of minimal length the flow averages 3 ml./min.) But it seems reasonable to suppose that it collects a constant proportion of the flow from the site studied and may, therefore, justifiably be used to examine the effect of agents like noradrenaline upon the extent of blood flow.

The procedure used was to obtain a steady rate of flow and then inject noradrenaline. With infusions, the control flow level was obtained using a constant rate infusion machine delivering an infusion of 0·9% saline intravenously or intra-arterially as required; then substituting noradrenaline made up in saline and infused at the same rate as saline alone, finally replacing the noradrenaline solution with saline for a further control period.

Simultaneous records of blood pressure were taken from the carotid artery. Resistance of the blood vessels was calculated:

$$\text{Resistance} = \frac{\text{Mean pressure (mm Hg)}}{\text{Flow (ml./min)}}.$$

RESULTS

Intra-arterial injections

Intra-arterial injections of noradrenaline (0·01–2·0 μg/kg) produced in all cats an immediate transient decrease in flow and an increase in vascular resistance with no change in the arterial blood-pressure level (Figs. 1 and 2).

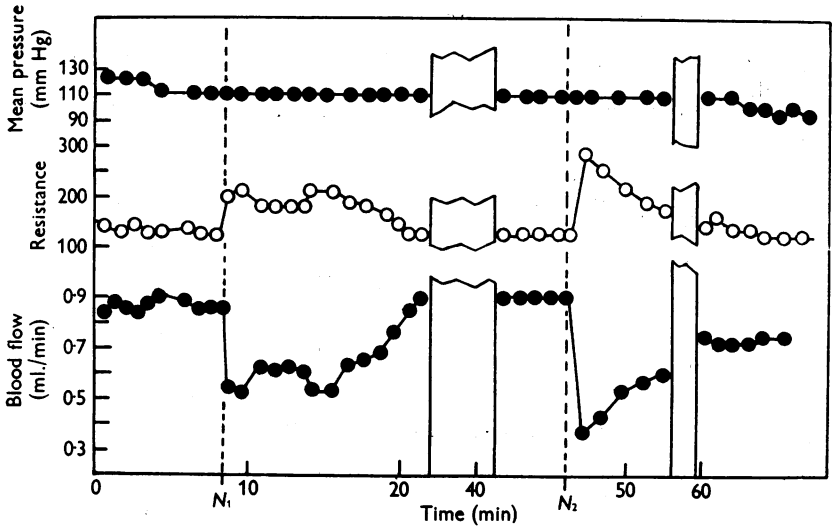

Fig. 1. Cat, 3 kg. Intraperitoneal pentobarbitone. Intra-arterial injection of noradrenaline 0·2 μg/kg at N_1; 0·4 μg/kg at N_2. From above: mean blood pressure, vascular resistance, blood flow.

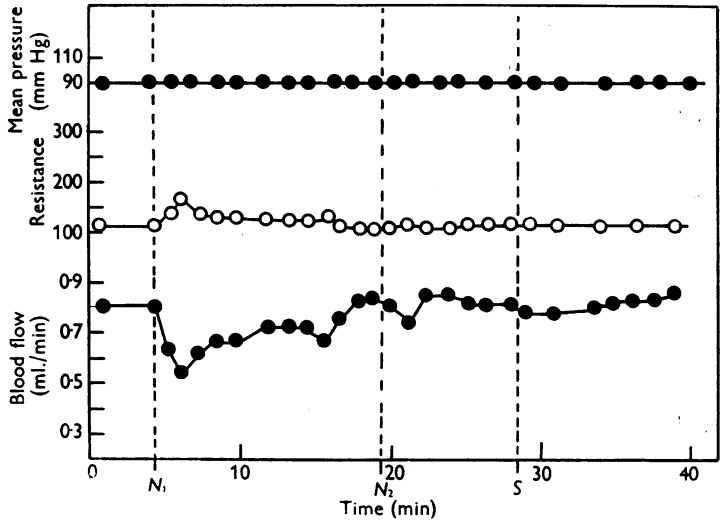

Fig. 2. Cat, 3 kg. Intraperitoneal pentobarbitone. Intra-arterial injection of noradrenaline 0·1 μg/kg at N_1; 0·01 μg/kg at N_2. Control injection of 0·9% NaCl solution at S.

Intra-arterial infusions

Intra-arterial infusions of noradrenaline (0·01–2·0 μg/kg/min) always caused a decrease in flow and an increase in resistance (Fig. 3). This constrictor effect persisted unchanged for as long as the infusion was maintained and the time of infusion was varied up to periods of about 1 hr. With high doses the venous outflow was completely stopped (Fig. 4).

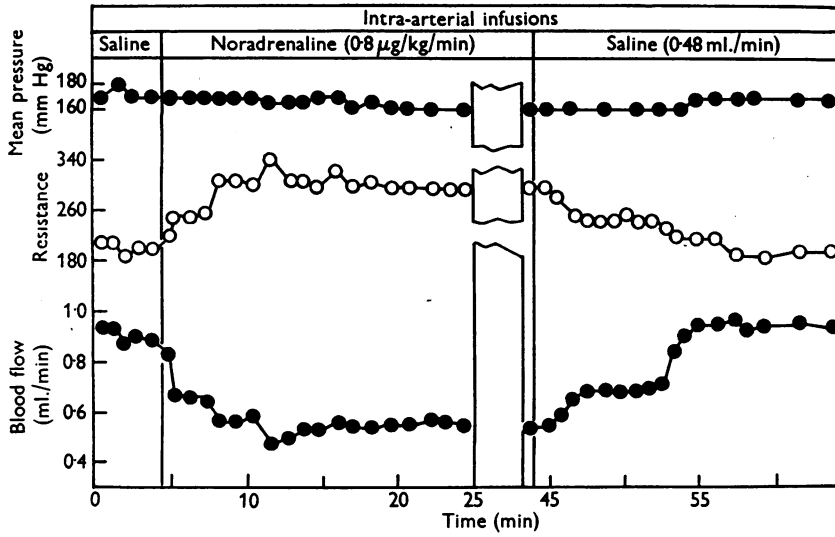

Fig. 3. Cat, 2·5 kg. Intraperitoneal pentobarbitone. Intra-arterial infusion of noradrenaline 0·8 μg/kg/min.

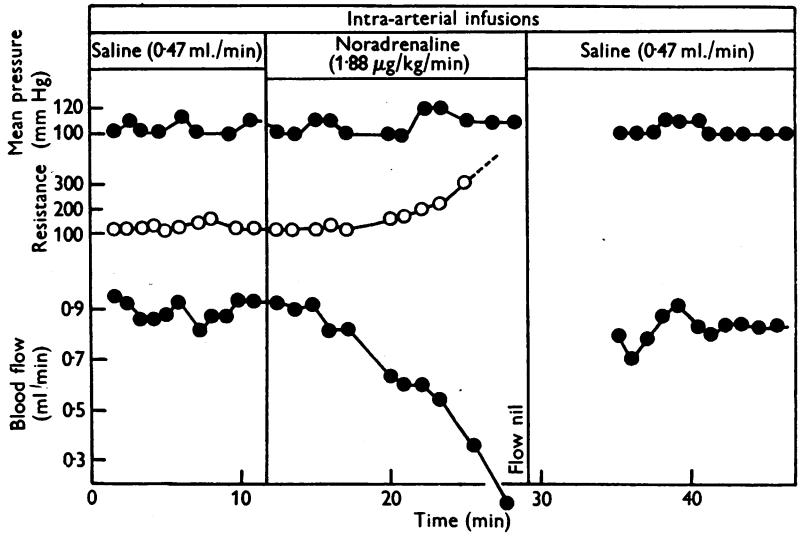

Fig. 4. Cat, 4 kg. Intravenous chloralose (70 mg/kg). Intra-arterial infusion of noradrenaline 1·88 μg/kg.

Intravenous injections

Intravenous injection of noradrenaline (1–5 μg/kg) under pentobarbitone, chloralose or ether anaesthesia produced a consistent pattern of response (Figs. 5 and 6). The effect on the blood pressure was uniformly observed. The initial rate of flow showed a marked increase coincident with the rise in the

blood pressure. This flow increase was rapidly followed by a decrease to below the pre-injection level where it remained for a variable period of time after the blood pressure had returned to its initial value. The vascular resistance

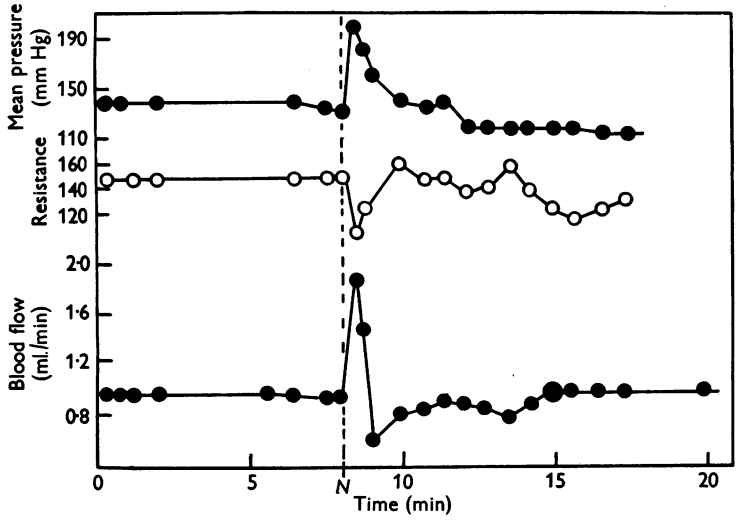

Fig. 5. Cat, 4 kg. Intraperitoneal pentobarbitone (50 mg/kg). Intravenous injection of noradrenaline 2 μg/kg at *N*.

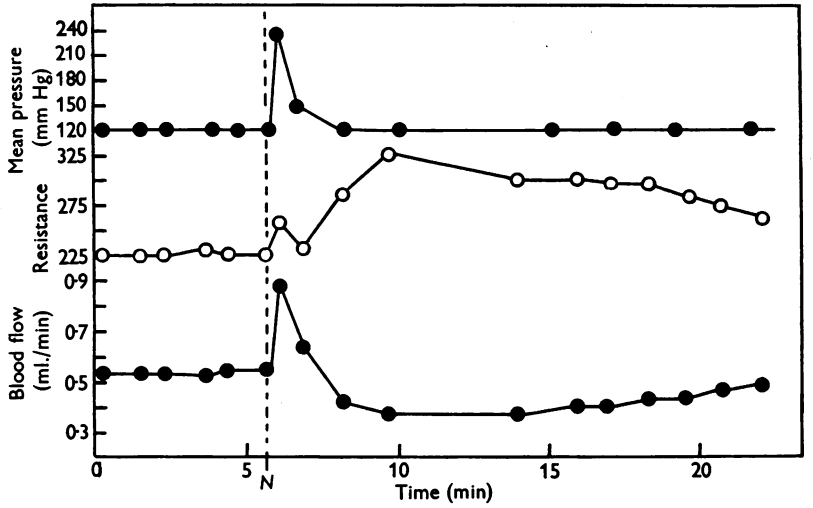

Fig. 6. Cat, 2·25 kg. Intraperitoneal pentobarbitone. Intravenous injection of noradrenaline 2·2 μg/kg at *N*.

usually displayed an initial fall but began to increase above its initial value prior to the decreased flow effect (Fig. 5). On occasions the resistance increased immediately (Fig. 6).

The same pattern of response occurred also in the spinal pithed cat and in the denervated hind-limb muscles whether after chronic sympathectomy or after acute section of the sciatic nerve together with blockade using hexamethonium bromide. Since the initial increase in flow might have been a passive effect due to the increased perfusion pressure, the experiments were repeated on the cat in which the carotid artery was connected to a compensating system of the type described by Delorme (1951) to prevent any pressure rise. Injection of noradrenaline now produced little or no rise in pressure and the initial increase in flow was absent, the response was one of pure vasoconstriction with an increased vascular resistance (Fig. 7).

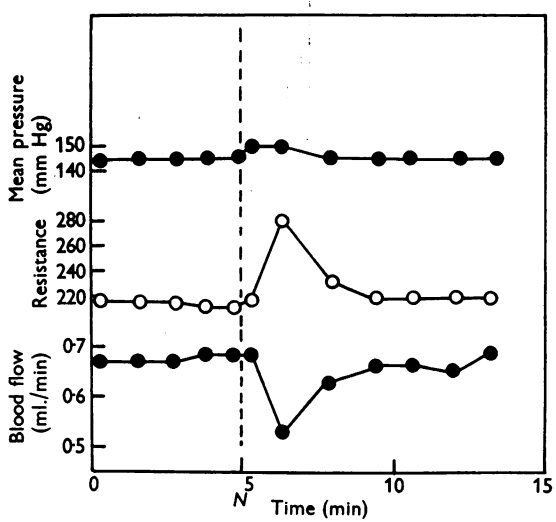

Fig. 7. Cat, 3·25 kg. Intraperitoneal pentobarbitone. Intravenous injection of noradrenaline 3 μg/kg at *N*. Blood-pressure compensator in vascular system.

Intravenous infusions

The concentration of noradrenaline was adjusted to give a dose level with the range 1–5 μg/kg/min. The response of the muscle blood flow to such doses consisted of an initial increase in flow which might be short-lived or might persist for some minutes; however, the flow then fell to the resting level or slightly below despite the increased head of pressure (Figs. 8 and 9). This response was typical of cats under various anaesthetics, in the spinal cat and in the chronically sympathectomized and acutely denervated limb (Fig. 10). The resistance of the muscle vessels was similar to the effects observed with intravenous injections except that the increased resistance after the initial decrease persisted for as long as the infusion of noradrenaline continued and for a variable time afterwards. The time of the infusions was varied

from intervals of 5 to 60 min without any alteration of response being observed.

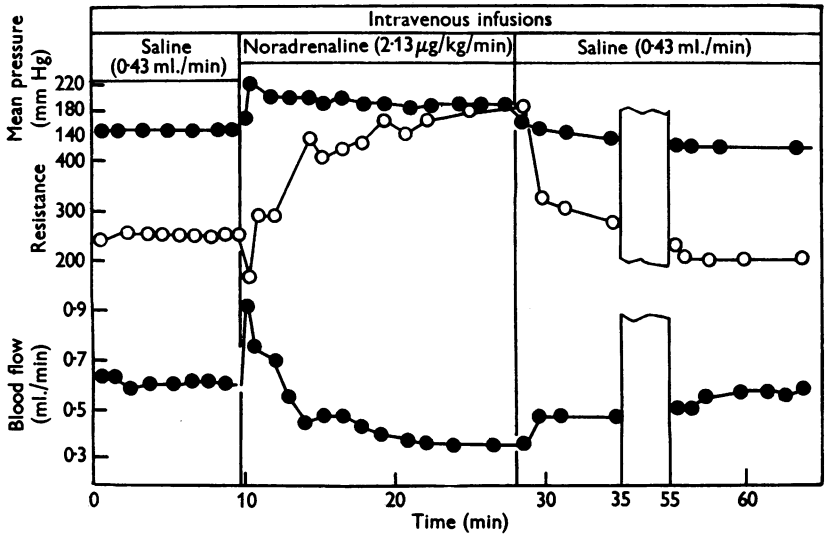

Fig. 8. Cat, 2·25 kg. Intraperitoneal pentobarbitone. Intravenous infusion of noradrenaline 2·13 μg/kg/min.

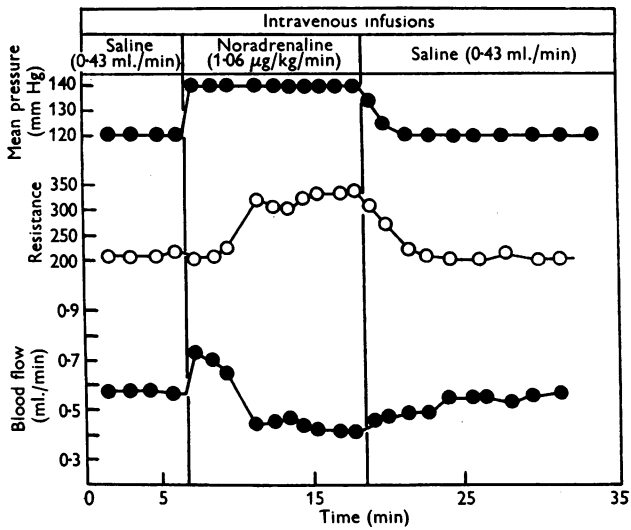

Fig. 9. Cat, 2·25 kg. Intraperitoneal pentobarbitone. Intravenous infusion of noradrenaline 1·06 μg/kg/min.

The initial increase in flow was absent when the pressure rise was prevented by compensation (Fig. 11).

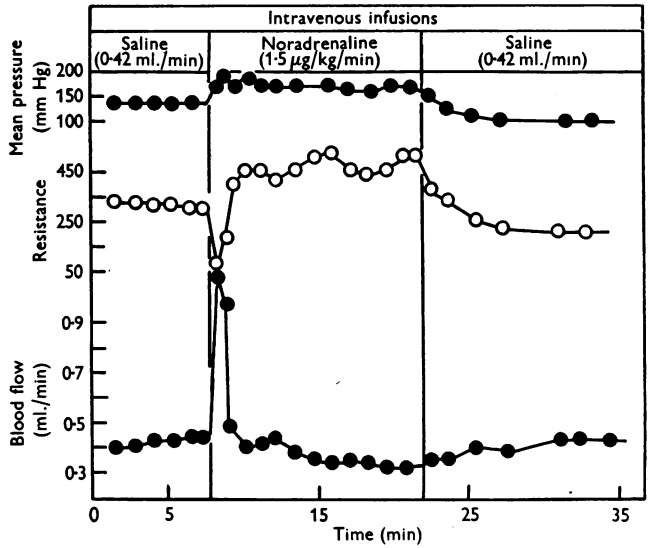

Fig. 10. Cat, 3 kg. Intraperitoneal pentobarbitone. Chronic sympathectomy, right sympathetic chain removed T6–L3. Flow from right femoral vein. Intravenous infusion of noradrenaline 1·5 μg/kg/min.

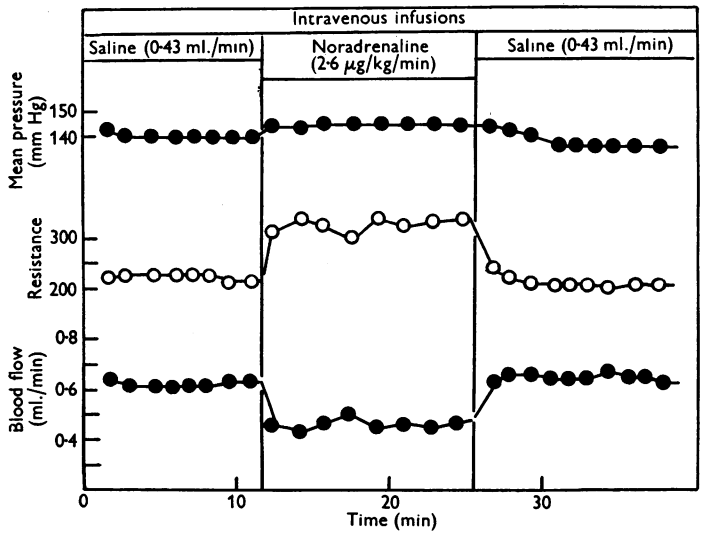

Fig. 11. Cat, 3·25 kg. Intraperitoneal pentobarbitone. Intravenous infusion of noradrenaline 2·6 μg/kg/min. Blood-pressure compensator in vascular system.

DISCUSSION

The results presented confirm the work of Folkow *et al.* (1948), of Burn & Hutcheon (1949) and of Wakim & Essex (1952), and show that in the skinned limb noradrenaline acts as a vasoconstrictor. This is shown most clearly with

intra-arterial administration where the effects are uncomplicated by those due to blood-pressure changes, and is supported by experiments with intravenous administration where the pressure changes are eliminated by inserting a pressure stabilizer in the arterial system.

Except for an initial increase in muscle blood flow which accompanied the elevation of blood pressure in intravenous injections or infusions, vasoconstriction was consistently obtained. The increase in flow cannot be ascribed to local vasodilatation since it did not occur following intra-arterial infusions or injections. That it might passively follow changes in the pressure head of the perfusing fluid, was suggested by its absence when the pressure rise was prevented by the insertion of a compensator in the arterial system, whereupon the flow response was identical with that obtained with intra-arterial injections or infusions. The possibility of a reflex vasodilatation could be ruled out since the initial rise in flow was present in the acutely denervated ganglion-blocked leg, in the chronically sympathectomized and in the pithed spinal preparation.

It is suggested, therefore, that the initial increase observed with intravenous administration is a passive consequence of the increased perfusion pressure, and in this we differ from Meier *et al.* (1949), who consider that changes in flow are largely independent of the blood-pressure increase and attribute little importance to this as determining the extent of peripheral blood flow.

If the relationship between pressure and flow be plotted for a series of pressures, the rate of change of flow decreases in the higher pressure range indicating that for a small increase in pressure at low pressures there is a considerable increase in flow. The rapidly occurring, relatively large pressure increment seen on the intravenous injection of noradrenaline therefore tends to produce the initial effects observed—an effect which is then overcome by the gradually developing constrictor action. The 'dilatation' observed, then, is not due to the action of noradrenaline on the muscle vessels where its action is purely constrictor.

Vascular resistance as measured by the ratio of blood pressure to blood flow usually showed a decrease coincident with the initial increase in flow observed with intravenous injections or infusions. This, we believe, reflects the fact that the relationship between pressure and flow for small flows is not linear (Pappenheimer & Maes, 1942) and the curves expressing resistance record only an arbitrary arithmetical relationship. It would therefore appear that for brief rapid changes in blood flow the ratio of blood pressure to muscle flow is not a true measure of the vascular resistance.

Imig *et al.* (1952) state that they obtained an increase in blood flow with an intravenous infusion of noradrenaline (0·2–0·4 μg/kg/min) which did not cause significant changes in blood pressure; we have not been able to confirm these results.

SUMMARY

1. The blood flow through skeletal muscle vessels in the skinned limb of the cat under a number of anaesthetics, or in a spinal preparation, or in a sympathectomized limb, in response to noradrenaline has been studied by a bubble flow technique.

2. Intra-arterial injections (0·01–2·0 μg/kg) or infusions (0·01–2·0 μg/kg/min) cause a decrease in flow and an increase in peripheral resistance.

3. It is concluded that noradrenaline exerts a vasoconstrictor action in respect to skeletal muscle blood vessels.

4. Intravenous injections (1–5 μg/kg) or infusions (1–5 μg/kg/min) produce an initial increase in flow followed by a decrease in flow and an increase in peripheral resistance.

5. The initial increase in muscle blood flow is due to the abrupt rise in the arterial blood pressure. It is a passive effect; a reflex mechanism is not involved. As the constrictor action of noradrenaline develops it causes the decrease in flow which follows the initial increase.

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