ACTION OF ADRENALINE ON LIMB BLOOD VESSELS

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Both adrenaline and noradrenaline are secreted by the medulla of the adrenal gland, the proportions of the two varying in different circumstances, largely in relation to the type of stress to which the organism is subjected (von Euler, 1956). Both of the amines have marked actions on the cardiovascular system in man, and particularly on the peripheral circulation, but in most circumstances the actions of adrenaline will tend to predominate (de Largy, Greenfield, McCorry & Whelan, 1950). The effect of adrenaline on the limb vessels has been extensively studied in the last two decades, especially in the human subject. Although adrenaline is a pressor agent in most animals and constricts many vascular beds, its effect when circulating in the blood stream in man is to produce a fall in total peripheral resistance and a consequent lowering of the diastolic blood pressure. Much of this drop in resistance is attributed to arteriolar dilatation in the skeletal muscles, but the mechanism whereby this dilatation is brought about has not yet been fully elucidated and it is the purpose of this review to summarize the present situation.

1. Direct Effect of Adrenaline—Intra-Arterial Infusion

The local direct action of adrenaline on the circulation in the muscular segments of the limbs has been demonstrated by infusion of the drug into the brachial or femoral artery and measurement of forearm blood flow or calf blood flow by venous occlusion plethysmography (Allen, Barcroft & Edholm, 1946; Duff & Swan, 1951; Whelan, 1952). With all doses ranging from 0.001 \( \mu g./\text{mln.} \) to 1 \( \mu g./\text{mln.} \) for the forearm and 1 \( \mu g./\text{mln.} \) to 8 \( \mu g./\text{mln.} \) for the calf, given for periods of 5–10 min., the initial effect is a transient vasodilatation to a peak flow of two to five times the resting value during the first 1–2 min. of the infusion. This rapidly subsides so that the flow falls to or below the previous resting level and thereafter for the remainder of the infusion period the flow remains at, falls further below, or rises slightly above, the resting level. The larger the dose, the greater the likelihood of the flow’s falling below the resting level during the latter part of the infusion (fig. 1). An increase is more likely with moderate doses and, if it occurs, is rarely more than 20–30%. About

FIG. 1. Response of the Forearm Blood Flow to Intra-Arterial (I.A.) Infusions of Adrenaline before and after Intra-Arterial Infusion of Phenoxybenzamine

\[ \text{I.A. Adrenaline (0.05 \( \mu g./\text{min.} \))} \]

\[ \text{I.A. Adrenaline (1 \( \mu g./\text{min.} \))} \]

Results obtained on the same subject

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1–2 min. after the infusion ceases, the flow usually rises appreciably for 2–3 min. before settling back to the initial pre-infusion level. This after-dilatation is variable in degree and is not always seen, but tends to be more marked with larger doses.

a. Effect of Antagonists

It was concluded from this pattern of response of the forearm flow that adrenaline did not have a sustained direct dilator action on the forearm vessels, after its initial transient effect. However, the use of adrenaline antagonists in the analysis of the vascular response in the forearm has demonstrated that the flow pattern represents a balance between a constrictor action and a less potent and usually masked vasodilator effect. de la Lande & Whelan (1959) and Allwood & Ginsburg (1961) treated the forearm with chlorpromazine and phenoxybenzamine, which block the constrictor but not the dilator effect of adrenaline on animal tissues, and found that even large doses of adrenaline (1 μg./min.), which normally produced a sustained vasoconstriction, now had a very marked dilator effect, often such as to represent a continuation of the initial transient vasodilatation (fig. 1).

2-Isopropylamino-1-(2-naphthyl)ethanol (pronethalol) (Alderlin\(^1\)), when given intra-arterially, has the effect of abolishing all dilator manifestations of adrenaline in the forearm. The initial transient dilatation, any sustained increase, and the after-dilatation are all replaced by an immediate and maintained vasoconstriction, the flow slowly returning to the resting level within 1–2 min. after the infusion is stopped (Dornhorst & Robinson, 1962; Lowe & Robinson, 1963a). A similar effect is produced by dichloroisopropylnoradrenaline (Shanks, personal communication).

b. Local Dilator Effect of Adrenaline

The finding of a dilator component of the local action of adrenaline on skeletal muscle vessels has been confirmed by Golenhofen (1962), who found a sustained though fluctuating increase in the heat conductivity from the forearm and calf muscles during intra-arterial infusions of doses of 0.04–8 μg./min., and by Skinner & Whelan (1962), who showed the relative effects of adrenaline on the two major divisions of the forearm circulation, namely the skin and muscle blood flow. The total blood flow of the forearm segment was measured by venous occlusion plethysmography, and changes in skin and muscle circulations were followed by determination of the oxygen saturation of venous blood samples obtained by cannulation of deep and superficial forearm veins. These have been shown to drain the vascular beds of muscle and skin respectively (Roddie, Shepherd & Whelan, 1956). The changes in oxygen saturation of the effluent venous blood were taken to represent changes in blood flow, on the assumption that the oxygen consumption of the tissues was not altered.

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\(^1\) Imperial Chemical Industries proprietary name.—Ed.
The oxygen saturation of skin blood fell during infusions of adrenaline into the brachial artery in doses ranging from 0.05 μg/min. to 0.2 μg/min., indicating a reduction in blood flow, and with larger doses (0.5 μg/min. and 1 μg/min.) samples were impossible to obtain, demonstrating that the skin circulation was shut down. With doses of 0.05-0.2 μg/min., the muscle blood oxygen saturation showed an initial transient rise and then fell to a less marked, but still elevated, level which was sustained during the remainder of the infusion at a time when the total forearm blood flow had either returned to, or was reduced below, the initial resting level (fig. 2). With doses of 0.5 μg/min. and 1 μg/min., both the muscle oxygen saturation and the blood flow fell below their respective resting levels after the initial transient rise. After the infusions ceased, the after-dilatation in forearm flow was accompanied by a similar increase in muscle oxygen saturation.

c. Influence of the Skin Circulation

In addition to illustrating a local direct dilator action of adrenaline on muscle vessels with all but the largest doses, the findings described above also demonstrate that the influence of the changes in skin circulation on the response of the total forearm blood flow may in certain circumstances be more marked than had been previously considered. The dilatation of muscle vessels produced by adrenaline may be more than balanced by a powerful skin constriction so that the total forearm flow may be reduced. In these circumstances the total forearm flow is not a good index of changes occurring in the muscle vascular bed. An experiment carried out a good many years ago on the limb of the cat, which demonstrated this influence of the skin circulation on the response to adrenaline, is described by Dale (1960).

Further observations supporting the importance of the changes in skin circulation in the response of the total forearm segment to adrenaline are illustrated in fig. 3 (Barcroft and Whelan, 1962, unpublished work). When the subject was cooled by immersing the feet in water at 0°C. and exposing the trunk to a stream of cold air, the forearm blood flow was about 1 ml/100 ml/min., and during intra-arterial infusion the initial transient vasodilatation was followed by a sustained increase to about 3 ml/100 ml/min. (fig. 3A). As the subject was warmed, the forearm flow rose. This increase has been shown to be due to vasodilatation of the skin vessels only (Roddie et al. 1956). Adrenaline in the same dose then resulted in a fall in forearm flow below the resting level after a less marked transient vasodilatation (fig. 3B). When the effect of heating was at its maximum (forearm flow, 10 ml/100 ml/min.), infusion of adrenaline resulted in a fall in forearm flow, even the transient increase being completely masked (fig. 3C). The flow did not fall to the level reached during the previous infusions, probably because the concentration of the drug arriving at the skin vessels was reduced by dilution by the increased blood flow.

Thus it seems clear that adrenaline has a direct dilator action on muscle vessels in the forearm in doses of up to 0.2 μg/min. intra-arterially, but that a constrictor component also operates, since the initial dilator effect is not maintained, since larger doses result in a reduction of blood flow in muscle as well as in the total forearm flow and since, after administration of phenoxybenzamine, adrenaline produces a marked sustained vasodilatation.

d. The Receptor Concept

The balance of opposing constrictor and dilator actions of adrenaline so as to produce the characteristic pattern of blood-flow change in the forearm has been explained in a number of ways. The concept of separate constrictor and dilator adrenotropic receptors in the vessel wall was proposed by Ahlquist (1948) and elaborated by Youmans, Green & Denison (1955), Green & Kepchar (1959) and Ginsburg & Cobbold (1960). According to this concept, the initial increase in blood flow is attributed to stimulation of β
that the change in lactic acid is not responsible, de la Lande metabolic activity in muscle might account for or contribute potassium and phosphate levels in the effluent venous blood.

by an increase in lactic acid and pyruvic acid and a fall in glycogenorytic activity in the forearm muscles, as manifested aline given intra-arterially was found to cause an increase in draining an area which was being perfused (de la Lande, catheter, providing evidence that the blood being sampled was dye infused into the artery was recovered through the venous local dilator effect, since Hildes, Purser & Sherlock (1949) had not been able to demonstrate an increase in the femoral concentration has been shown in animals and in man (Grif- that the muscle vasodilatation is accounted for by release of adrenaline in a patient whose muscles contained no phos-phyrase, and concluded that the dilator effect could not be accounted for the lactic acid output of the muscles. Whether any of the other products of the metabolic action of adrena-line participate in the vascular responses remains to be decided. Potassium uptake by the muscles is increased by adrenaline (de la Lande et al. 1961), and potassium has been shown to dilate forearm vessels (Glover, Roddie & Shanks, 1962; Lowe & Thompson, 1962; Skinner and Whelan, unpublished work) but its role in the vascular effects of adrenaline has not been elucidated. Barcroft and McArdle (unpublished work) found a normal response of the forearm vessels to intravenous adrenaline in a patient whose muscles contained no phosphorylase, and concluded that the dilator effect could not be due to the action of adrenaline on carbohydrate metabolism in muscle.

Effects on Different Parts of the Vascular Bed

Dale & Richards (1918) suggested that separate segments of the vascular bed, such as arteries and capillaries, may respond differently to adrenaline. Apart from the different behaviour of the skin and muscle vessels (fig. 2 of this paper; Skinner & Whelan, 1962; Barcroft and Whelan, 1962, unpublished work), there is so far no evidence in the human limb of differential effects on muscle arteriolar vessels, but such data are difficult to obtain.

The possibility exists that the pattern of blood flow and of venous oxygen saturation changes during adrenaline infusions might be accounted for by the opening-up of arteriovenous shunts or diversion of blood into non-metabolic capillary channels. Rosell & Uvnäs (1960) have put forward evidence from cat experiments to support the view that hypothalamic stimulation alters the distribution of the blood in the vascular bed in muscle, but so far data on this possibility in man are lacking. Skinner & Whelan (1962) attributed the increased oxygen saturation of venous blood from muscle during adrenaline infusions to vasodilatation, and the fact that in many instances this was not accompanied by an increase in total forearm blood flow was attributed to the opposing fall in skin blood flow. While it is possible that the increased oxygen saturation was due to shunting of arterial blood through non-metabolic pathways, not all of the blood could have been shunted in this way, since the venous effluent shows evidence of metabolic changes (de la Lande et al. 1961).

2. Indirect Effect of Adrenaline—Intravenous Infusion

The pattern of response of the forearm vessels to adrenaline given by continuous intravenous infusion in doses ranging from 5 µg./min. to 30 µg./min. is similar to the direct effect seen on intra-arterial infusions, in that 40–50 sec. after the infusion commences there is a transient vasodilatation which lasts for
1–2 min. This can be attributed to the arrival of adrenaline in the arteries of the limb, the longer delay in onset being due to the circulation time. After this the response differs from the direct one. The flow settles out to a level at least double the resting value, and this is sustained or even somewhat increased as the infusion continues. When the infusion ceases, no after-dilatation is seen, the flow gradually returning to the resting value within 3–5 min. This pattern of response was first defined by Allen et al. (1946). The sustained increase in forearm flow on intravenous infusion of adrenaline is always marked and is usually much greater than the slight increase in flow sometimes seen with intra-arterial infusion. For this reason it was concluded that some additional dilator mechanism was involved when adrenaline was given intravenously, other than the direct action of adrenaline itself.

a. Sympathetic Nerves

Duff & Swan (1951) found that the sustained vasodilator response was absent in the limbs of patients who had been subjected to sympathectomy 1–24 months previously, and also observed that it was absent or small when the drug was given by arterial infusion. They concluded that the sustained vasodilator effect of adrenaline could be attributed to a sympathetic reflex. Whelan (1952), however, demonstrated that the pattern of response was not altered by blocking the nerves to the forearm with local anaesthetic and also found that, while the dilatation was absent in chronically sympathectomized# limbs, it was present in the acutely sympathectomized* limb, gradually diminishing over the subsequent weeks after operation. It was concluded that the sustained vasodilatation was indirect, but that it was not mediated by the sympathetic nerves. The diminished response in the chronically sympathectomized limb could be attributed to the development of increased sensitivity to the constrictor effect of adrenaline. The release of an intermediate vasodilator substance was invoked to account for the difference between the intravenous and the intra-arterial routes of administration.

b. Histamine

Staub (1946) found an increase in the plasma histamine level in human subjects during intravenous infusions of adrenaline and credited histamine with the indirect dilator action. Mongar & Whelan (1953) were unable to confirm the finding of an increased histamine level either in the antecubital venous blood or in the arterial blood arriving at the forearm in the brachial artery. Furthermore, antihistamines, such as tripelennamine and antazoline, which could be shown to abolish or very considerably reduce the dilator responses of the forearm to quite large doses of histamine given intra-arterially, did not have any effect on the pattern of the response to adrenaline (Whelan, 1956).

c. Lactic Acid

If a product of muscle metabolism which is dilator to muscle vessels were released into the blood stream during adrenaline infusions, the amount circulating, on being added to that locally produced in the limb, could result in a greater dilator effect of intravenous compared to intra-arterial infusions. The failure of lactic acid to provoke vasodilatation when infused into the brachial artery (de la Lande & Whelan, 1962) suggests that this substance plays no role in adrenaline dilatation. It is possible, however, that some other products of muscle metabolism are involved, but no investigation of these has been made.

d. Thyroid

McDermott, Fry, Brobeck & Long (1950) demonstrated that adrenaline stimulates the release of thyrotrophin and it seemed conceivable that release of thyroid hormone could be responsible for the muscle dilatation. However, the limited evidence available appears to exclude rather than favour this possibility. The vasodilator responses in patients with myxoedema and thyrotoxicosis were within the range observed in normal subjects (Whelan, 1954). Tri-iodothyronine does not produce vasodilatation in forearm or hand when infused intra-arterially in relatively high concentrations (Hodge, 1962, personal communication).

e. Isopropylnoradrenaline

This is an amine with an uncomplicated vasodilator action on muscular limb segments (Koncett, 1940; Barcroft & Koncett, 1949; Cobbolt, Ginsburg & Paton, 1960). The dilator effect of intra-arterial infusions of this substance on human limb vessels is not augmented by adrenergic blocking agents (Ginsburg & Cobbolt, 1960) but is abolished by dichloroisopropylnoradrenaline (Shanks, personal communication) and by pronethalol (Dornhorst & Robinson, 1962). If this amine were released into the blood during adrenaline infusions, it could satisfactorily account for the increased sustained vasodilator effect. Eakins & Lockett (1961) found that an isopropylnoradrenaline-like substance was released from the liver during intravenous infusions of adrenaline in the cat, and Dorner (1953) observed that in dogs adrenaline infused into the thoracic and upper abdominal aorta caused a dilatation in the leg muscles, but that infusion below the coeliac axis and superior mesenteric arteries did not. While these observations suggest the possibility that adrenaline releases some dilator substance from the liver or elsewhere, there are so far no data in man to support this view.

f. Respiratory Effects

That the hyperventilation induced by intravenous adrenaline is not responsible for the forearm dilatation was shown by Dornhorst and Whelan (1952, unpublished work) who found that voluntary hyperventilation of a comparable degree does not have a dilator effect.

g. Dilation Effects

While consideration has been paid to the appropriate dose of intra-arterial adrenaline necessary to match a given intravenous dose, and the smaller intra-arterial doses have been shown to have a dilator action on forearm vessels (Whelan, 1952; Skinner & Whelan, 1962), little attention has been given to the possible consequences of alteration in blood flow and hence of concentration on the response to intra-arterially administered drugs.
Lowe & Robinson (1963b) have put forward the suggestion that the difference in patterns of response to intravenous and intra-arterial infusions of adrenaline can be accounted for by differences in the blood concentrations of the drug during infusions by the two routes. During intravenous infusions the concentration in the blood arriving in the limb will not be affected by the changes in blood flow, but will remain constant or slowly increase owing to accumulation during the infusion. The dilator (Σ) effect will tend to predominate and will not be limited, since the increased flow will bring more drug at the same concentration. With intra-arterial infusions, where the rate of addition of the drug into the blood stream is constant, the sustained vasodilatation of the forearm flow to intravenous infusion matched that of the intravenous infusion in the same way that the rate of addition of the same mixture, by the two routes. During intravenous infusions the rate of addition of the drug into the blood stream is constant, while a reduction in flow will increase the concentration and hence tend to be self-perpetuating, and the constrictor effect will therefore tend to predominate. To test this hypothesis, isopropylnoradrenaline, which is dilator (β stimulant) to forearm vessels, and noradrenaline, which is constrictor (α stimulant), were made up in a mixture such that the pattern of the forearm flow to intravenous infusion matched that of adrenaline. Intra-arterial infusion of the same mixture, appropriately diluted, gave a response which differed from that of the intravenous infusion in the same way that the response to intra-arterial adrenaline differed from that to intravenous adrenaline, in that the sustained vasodilatation was much smaller or even absent.

This is a new approach to the problem and indicates that more attention should be paid to the effect of blood-flow changes and consequent dilution effects when vascular responses to drugs are analysed.

3. Skin Circulation

Adrenaline given intravenously, intra-arterially, or by iontophoresis, causes a reduction in skin blood flow both in the hand and the forearm (Barcroft & Swan, 1953; Skinner & Whelan, 1962). An after-dilatation of hand vessels follows the cessation of intravenous infusions, which appears to be nervously mediated, since it is absent in sympathectomized limbs and after intra-arterial infusions. It is concluded that the principal action of adrenaline on skin vessels is to cause constriction and that the after-dilatation is due to depression of vasoconstrictor tone to the hand, possibly an action at sympathetic ganglia (Barcroft & Swan, 1953).

4. Capillaries

The pallor of the skin of the limb seen on infusion, iontophoresis, or intradermal injection of adrenaline, is usually attributed to constriction of capillaries, and direct observation of the vessels in the nail fold (Greisman, 1952) showed obliteration of the arterial segments of the terminal capillary loops by intravenous adrenaline. As Greisman pointed out, however, it is difficult to be certain that the effect was not due to constriction of the parent metarteriole. No data are available about the action of adrenaline on the capillaries of the skeletal muscle of the limb.

5. Veins

The changes in the limb circulation brought about by adrenaline so far described are attributable to its action on the smooth muscle of the arterioles, these in turn regulating the blood flow through the vascular bed.

Adrenaline, however, also acts on the venous side of the limb circulation, and its effect is to increase venous tone and hence reduce the volume of blood in the part and the capacity of the limb to hold blood when the outflow is obstructed. Lewis (1924) showed that the venules in the skin contracted, following local application of adrenaline, and Page, Hickam, Sieker, McIntosh & Pryor (1955) demonstrated an intense constriction of an isolated segment of superficial forearm vein. Allen et al. (1946) observed that the volume of the forearm decreased during intravenous infusions at a time when the rate of blood flow was increased.

Sharpey-Schafer (1961)4 measured volume and venous-pressure increases in the forearm with venous occlusion during intravenous and intra-arterial adrenaline and demonstrated that the venous pressure was raised while the flow showed either an increase or an increase followed by a fall. These findings indicated that adrenaline had a direct action in increasing the tone of the veins of the limb.

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4 See also Sharpey-Schafer, p. 145 of this number of the Bulletin.—Ed.
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