SUSTAINED DILATATION IN HUMAN MUSCLE BLOOD VESSELS UNDER THE INFLUENCE OF ADRENALINE

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Adrenaline has a direct effect on human muscle blood vessels. A single dose, or an infusion, causes a marked initial dilatation lasting 1–2 min, after which the dilatation rapidly disappears. In addition, during intravenous infusion adrenaline is considered to have a secondary effect via humoral agents which causes the sustained dilatation following the initial dilatation. However, it has been doubted that there is a sustained direct effect on muscle vessels (Duff & Swan, 1951; Whelan, 1952, 1954; summarized in Barcroft & Swan, 1953). On the other hand, Bock, Hensel & Ruef (1955) occasionally found a sustained increase in blood flow in the calf muscles (measured with a heated thermocouple probe) with intra-arterial infusion. Recent studies by the same method have shown that the direct effect of adrenaline on the vascular bed of the muscle is not limited to the initial dilatation, either with a single dose or with infusion (Golenhofen, 1959). Rather, the initial dilatation is always followed by a more or less marked, periodically damped, oscillation in the diameter of the muscle vessels; in the case of infusion there is usually a rise in the level of blood flow. Since these findings, which so far have been made only in calf muscles, contradict the prevailing view, it appeared advisable to examine further the sustained effect of adrenaline on the vascular bed of the muscle, especially in the forearm.

METHODS

Muscle blood flow was recorded continuously in the calf or forearm by means of Hensel's heated thermocouple probe (Wärmeleitsonde; Hensel & Ruef, 1954), which operates on the principle of a heated thermocouple as described by Gibbs (1933) and further developed by Grayson (1952). The probe consists of an injection cannula 60 mm long and 1 mm in diameter, the tip of which is soldered. In the lumen of the cannula there is an electric heating system and a thermo-electric measurement system. After the probe has been inserted into the muscle, the tip is warmed with constant alternating current. The thermocouple continuously measures the temperature difference between the heated tip and a reference junction 10 mm above the tip in the shaft of the probe. Changes in the absolute temperature of the muscle are eliminated because they influence both the heated and the reference junctions in the same way, which can be tested in each experiment by short occlusions of blood flow before heating the probe. The recorded temperature difference in the heated

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probe is therefore only dependent on the heat conductivity of the surrounding tissue. Changes in the conductivity of the tissue are indicative of changes in blood flow. The principle of the method is described by Grayson (1952) and Linzell (1953). For details of the special type of muscle probe used for this work see Hensel & Ruef (1954) and Golenhofen & Hildebrandt (1961). Results with this method have been published in this Journal by Barcroft, Hensel & Kitchin (1955), Allwood, Hensel & Papenberg (1959) and Blair, Golen-hofen & Seidel (1959).

In each case the probe reading was tested *in situ* by occluding the blood flow for 2 min, by means of a pneumatic cuff on the upper arm or thigh. The blood-flow zero point thus obtained makes it possible to calculate the responses approximately as a percentage of the initial value.

In some cases blood flow was also determined by a modified form of venous occlusion plethysmography, comparable to the procedure of strain-gauge plethysmography described by Whitney (1953; cf. Golenhofen, 1960). In certain cases there was an additional registration of skin blood flow with a heat-conductivity meter, which is placed on the skin and works on the same principle as the muscle probe (Hensel & Bender, 1956).

Intra-arterial injections were made in the femoral or brachial artery with a polyethylene catheter (inner diameter 0·3 mm, outer diameter 0·6 mm), which was introduced through a cannula. Physiological saline solution flowed constantly through the catheter. Injections and infusions were made through a two-way tap, the infusions by means of an infusion machine. Intravenous injections and infusions were made in the antecubital vein through an indwelling cannula. The tests were carried out on healthy males and females, mainly medical students, at room temperature (21–23° C). Each experiment lasted 5–8 hr.

The observations presented here are based on 32 experiments on 19 persons, in which the periodically damped fluctuations in blood flow in the calf muscles under the influence of adrenaline and other stimuli were examined. Some of the results have already been published (Golenhofen, 1959). Altogether 52 intravenous infusions of adrenaline were made (in 15 experiments), mainly with 10 μg/min but also with 4–5 μg/min, and 53 intra-arterial infusions in the femoral artery (in 12 experiments), with doses between 0·05 and 8 μg/min. In five additional experiments on various persons 14 adrenaline infusions were made into the brachial artery, with doses between 0·04 and 0·4 μg/min (Table 1).

RESULTS

After the application of stimuli causing sudden alterations in muscle blood flow (mediated by changes in the diameter of the blood vessels), the blood flow returns to normal by periodically damped oscillations. Figure 1 shows typical examples taken from two different experiments. If the blood flow is stopped for a short time, or if vasodilator drugs are administered, these reactive-periodic fluctuations in blood flow appear. The periods always have approximately the same duration, about 2–3 min under normal conditions. During adrenaline infusion these periodic fluctuations in blood flow are particularly marked, as is shown in Fig. 1, and in the same way for both intravenous and intra-arterial administration. Following intra-arterial administration the response is confined to the area supplied by the artery; it must, therefore, be due to a direct local effect of the adrenaline on the vascular bed of the muscle. In this connexion, 'direct' means that there are no central, generalized effects produced by nerves or hormones. The question whether adrenaline has a

direct local effect on the vessels, or whether its influence is indirect by way of metabolic effects or other local reflexes, will not be discussed here.

The periodic fluctuations in blood flow during administration of adrenaline are not bound up with corresponding fluctuations in the adrenaline concentration in the arterial blood; rather they depend upon the ability of the vascular bed to respond periodically even to sustained stimuli. This is shown in Fig. 2. Here an intravenous infusion of adrenaline led to a periodic
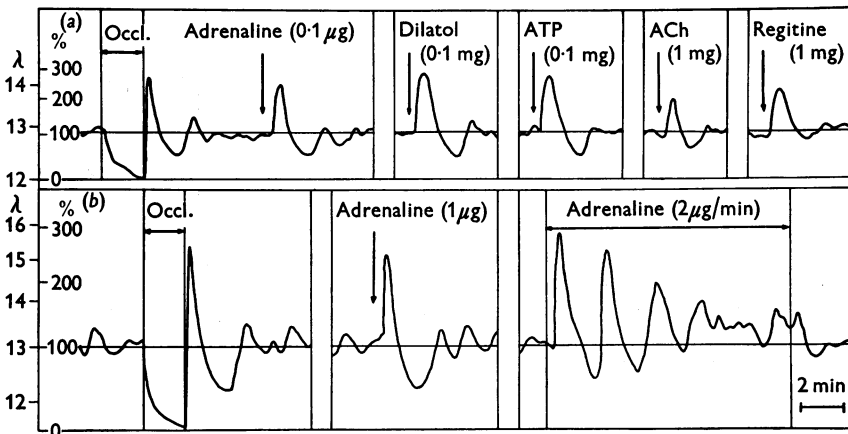

Fig. 1. Reactive-periodic fluctuations in muscle blood flow in the calf after 2 min occlusion and injection into femoral artery of various dilatants: Dilatol, phenyl-butyl-noroxyephedrine chlorohydrate (Troponwerke, Köln-Mühlheim); ATP, adenosine triphosphoric acid ('ATP Homburg', Chemiewerk Homburg A.G., Frankfurt); ACh, Acetylcholine; Regitine, imidazoline derivative (Ciba A.G., Basel). Curves taken from two experiments (*a* and *b*). In all Figs. (except Fig. 4) ordinates show: thermal conductivity of the muscle, λ (10^{-4} cal/cm. sec. °C); and calculated blood flow as a percentage of the average initial value.

damped fluctuation of the blood flow in both calves, although the after-waves which followed the initial dilatation did not run synchronously. In the left calf the duration of the periods was approximately 2·0 min under normal conditions, but in the right calf it was 2·3–2·4 min. A reduction of the surrounding pressure in the left leg (by means of a pressure chamber on the lower leg) markedly prolonged the duration of the periods in this area (by *ca*. 0·6 min), whereas the periods for the right calf remained the same. Likewise the period duration of the reactive oscillations after stoppage of blood flow or application of other drugs depends upon the transmural pressure of the vessel (for further details, see Golenhofen, 1960).

The reactive-periodic fluctuations in blood flow can also be recorded by measuring blood flow in the calf with an occlusion plethysmograph, as is shown by the examples in Fig. 3. Figure 3(*a*) shows a simultaneous
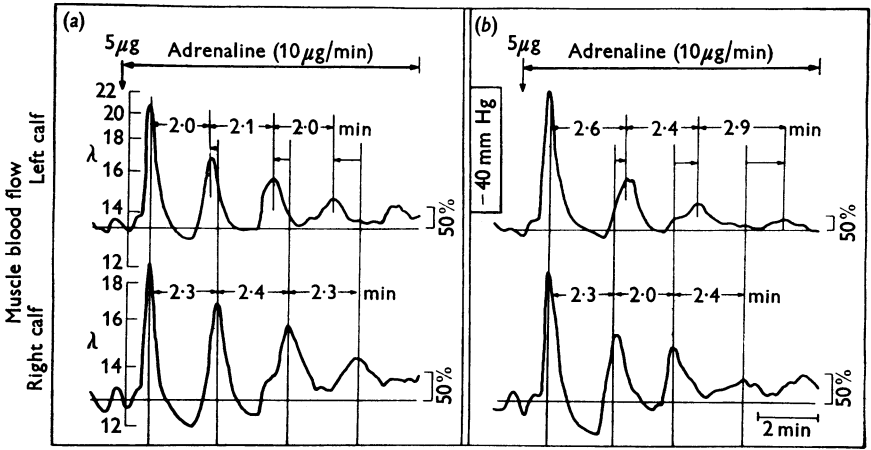
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Fig. 2. Reactive-periodic fluctuations in muscle blood flow in the right and left calves during intravenous infusion of adrenaline (10 μg/min, simultaneous registration). (a), Both calves under normal pressure conditions. (b), Decreased pressure (−40 mm Hg) around the left calf. For approximate estimation of the changes in blood flow, the extent of deflexion is given for 50 % of the initial value (Golenhofen, 1959).
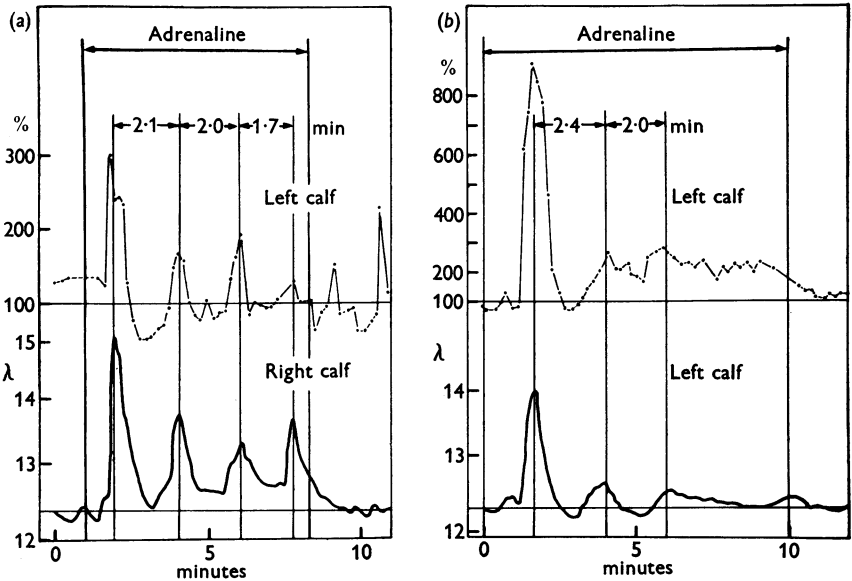

Fig. 3. Blood flow measured simultaneously with a modified form of venous-occlusion plethysmography (above) and heated thermocouple probe (below) during intravenous infusion of adrenaline 10 μg/min. Examples taken from two experiments, a and b.

measurement of blood flow in the left calf by means of venous occlusion plethysmography (original in Fig. 4) and in the right calf by means of a heated thermocouple probe. Figure 3(b) presents part of another test, in which blood flow in the left calf was measured by both methods simultaneously. The duration of the periods cannot be determined exactly from the occlusion plethysmogram alone because of the discontinuity of the recording. In addition, changes in the skin blood flow, which often take
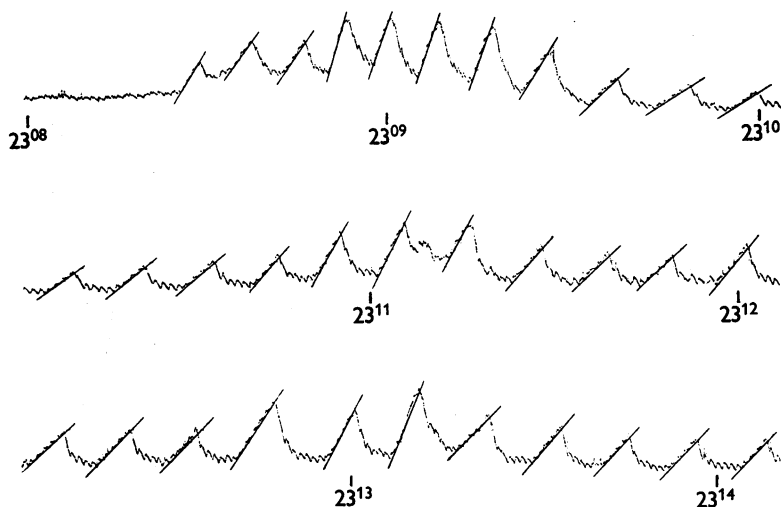

Fig. 4. Original recording of a modified venous-occlusion plethysmograph during intravenous infusion of adrenaline (part of the blood-flow course shown in Fig. 3a). Infusion began a few seconds before the recording shown here. During the rise of the curve (slanting lines) venous flow was occluded. In Fig. 3 the increase in volume during occlusion is given as a percentage of the initial value.

opposite courses, can blur the fine points in the course of muscle blood flow, or can completely conceal slight oscillations.

Usually the oscillations of the blood flow in the right and left calf are closer to being synchronous under normal pressure conditions than in the example given in Fig. 2. This is evidently due to the fact that the oscillatory ability of each side is well adjusted to that of the other (Fig. 3a), since when there is an isolated change in the transmural pressure on one side the frequency of the oscillation is changed in this area too, which shows the local nature of the oscillation. It seems possible that in the example of Fig. 2 the venous flow in the right leg was hindered and the venous pressure raised. Such elevations in venous pressure have the same effect on the frequency of the oscillations as reducing the surrounding pressure. Occasionally we observed an irregular succession of blood-flow peaks; these are probably

caused by fluctuations in the adrenaline concentration in the blood and can be thought of as repeated initial effects. They were always synchronous.

Sustained dilatation in the calf muscles is usually slight, as can be determined by integration of the waves (by planimetry) following the initial dilatation, or from the final oscillation value. Intra-arterial application of optimal doses (0·5–2 μg/min) seldom leads to an increase of more than 50 % (Fig. 1). In some cases there is also an oscillatory adjustment to a value which is not significantly higher than the initial value; the resulting increase in the mean value is caused only by the repeated waves which run asymmetrically around the normal value. This behaviour of blood flow
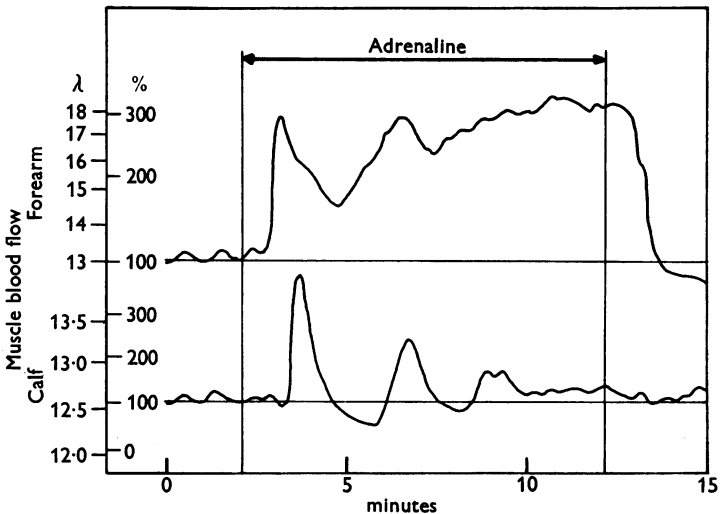

Fig. 5. Simultaneous registration of muscle blood flow in the forearm and calf during intravenous infusion of adrenaline 10 μg/min.

during intra-arterial application is not, however, essentially different from that during intravenous infusion (Fig. 5). In contrast, it is evident that the sustained dilatation in the forearm is always greater, and the course of the periodic reaction considerably more damped. Often only a single after-wave can be traced with certainty, and occasionally there is an aperiodically damped transition to a higher blood flow level following the initial dilatation. Figure 5 shows an example of the characteristic differences between the course of the reaction in the forearm and in the calf. The cause of these differences is not known.

As Table 1 shows, it is possible to produce a large sustained dilatation of the muscle blood vessels in the forearm by intra-arterial administration of adrenaline. In the example given in Fig. 6 (Table 1, test 3, measure-

ment point *a*) there was a sustained increase in blood flow of approximately 140 %.

No generally valid assertions can be made in regard to optimal dosage for intra-arterial infusion, since mixing in the arterial blood is certainly not completely uniform. It probably averages about 0·1 *μ*g/min for the

TABLE 1. Infusion of adrenaline in the brachial artery: muscle blood flow in the forearm following the initial dilatation

In experiments 3, 4 and 5 records were obtained simultaneously with two heated thermocouple probes, *a* and *b*, placed a few centimetres apart.

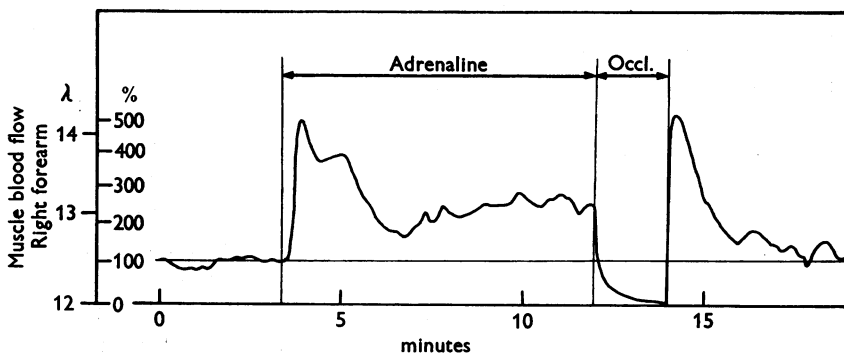| Exp. no.	Dose/min (*μ*g)	Sustained change in blood flow (% of initial value)	
1	0·1	+ 25	
2	0·05	0	
	0·1	+ 40	
	0·2	+115	
3	0·05	*a* +160	
		b + 50	
	0·1	*a* +140	
		b + 30	
	0·1	*a* +230	
		b + 30	
4	0·04	*a* 0	
		b 0	
	0·08	*a* + 65	
		b + 45	
	0·1	*a* + 80	
		b + 30	
5	0·1	*a* 0	
		b + 70	
	0·1	*a* 0	
		b − 20/0	
	0·2	*a* − 30/0	
		b − 15/+ 25	
	0·4	*a* − 60	
		b − 50	

Fig. 6. Muscle blood flow in the forearm during infusion of adrenaline 0·1 *μ*g/min in the brachial artery (test 3, measurement point *a* in Table 1).

brachial artery. Smaller doses (0·04 and 0·05 μg/min) usually produce only an initial dilatation, or have no effect at all, whereas greater doses frequently lead to constriction. Occasionally the range of doses which produce dilatation is so small that with increasing dosage at a low value sustained dilatation does not appeal, whereas doubling the dose leads to constriction (Table 1, test 5, measurement point a). The tests in which muscle blood flow in the forearm was measured simultaneously with two probes also show that the muscle areas did not all react uniformly, probably because they did not all receive the same amount of adrenaline (Table 1).
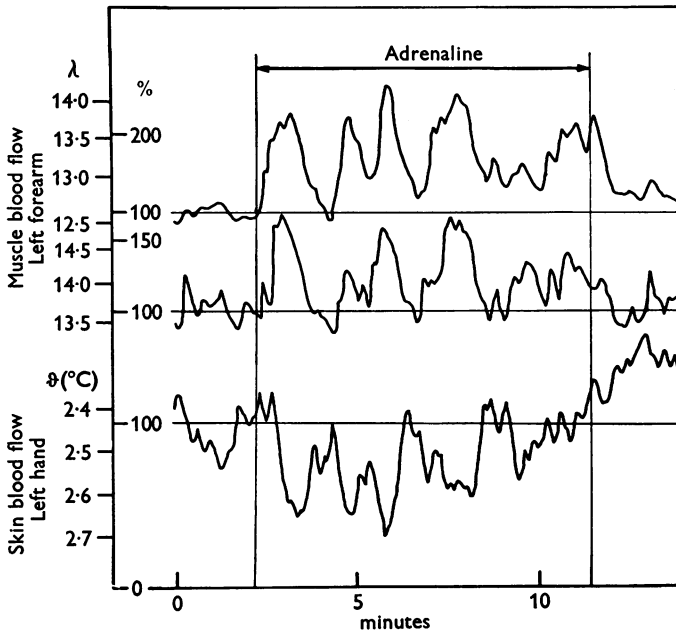

Fig. 7. Simultaneous registration of muscle blood flow with two heated thermocouple probes in the left forearm (a few centimetres apart) and of skin blood flow in the left hand during infusion of adrenaline 0·1 μg/min in the brachial artery. ϑ, temperature of the skin-flow meter above skin temperature.

In the test shown in Fig. 7 (Table 1, test 4) there was also considerable fluctuation in muscle blood flow in the arm during adrenaline infusion. The irregular distances between the peaks of the big waves, however, indicate that this may be attributed mainly to fluctuations in adrenaline concentration, and less to a periodic reaction of the vessels. Here the skin blood flow ran strictly in the opposite direction, which would necessarily produce more equalized curves if measurement were made with an occlusion plethysmograph.

DISCUSSION

Our observations show that we are not justified in making a fundamental distinction between initial and sustained effect in regard to adrenaline. Rather they are only parts of a unified oscillatory blood-flow pattern. It is easy to understand why this oscillation following a single injection of adrenaline, either intravenous or intra-arterial, was not previously detected in occlusion plethysmograph recordings, since it is often strongly damped. A small after-wave can easily be overlooked if the measurement points are fairly far apart, or it can be concealed by reactions in skin vessels. Temporary decreases to below the initial blood-flow value following initial dilatation are frequently recognizable in occlusion plethysmogram curves (cf. Barcroft & Swan, 1953), but these could have been caused by vascular constrictions in the skin lasting longer than the initial dilatation of the muscle vessels.

Discrepancies have been found in regard to sustained dilatation during intra-arterial infusion of adrenaline in measuring total blood flow by means of occlusion plethysmography on the one hand (Duff & Swan, 1951; Whelan, 1952, 1954), and measurements of blood flow in small sections of muscle by means of a heated thermocouple probe on the other hand. Since these discrepancies are not due to differences in dosage, they can only be explained by the non-uniform distribution of adrenaline in the blood which is connected with the intra-arterial mode of application.

Of the twelve infusions which Whelan (1952) made into the brachial artery, only three were made with a dosage which, according to the findings reported here, could be expected to produce a sustained effect (0·05–0·1 μg/min). No significant conclusions can be drawn from the other doses (1/40–1/1000 μg/min). The two infusions with 0·05 μg/min led to a sustained increase (18 and 35 % respectively) of blood flow in the forearm; in the other case with 1/8 μg/min, no sustained rise was recognizable. The six infusions which Duff & Swan (1951) made into the brachial artery with 1/8 μg/min produced an average sustained reduction in blood flow of 5 % (a rise up to 17 % in four cases and falls of 10 and 56 % in the other two cases). From these findings it was concluded that sustained dilatation of the muscle vessels in the forearm, which is around 100 % during intravenous infusion of adrenaline at 10 μg/min, does not depend upon a direct local effect of the adrenaline.

However, one may assume that in the intra-arterial experiments performed by Duff & Swan (1951), as well as in those of Whelan (1952, 1954), there were larger sustained dilatations in various muscle areas as a result of the physiological effect of adrenaline. Because of the non-uniform distribution of the adrenaline in the arterial blood, however, these

dilatations were probably decreased by the unchanged blood-flow values in other sections and were compensated by constrictions in still other sections.

We believe that our infusion technique, with very thin polyethylene catheters (0·3 mm inner diameter), ensures an adequate mixing of adrenaline with the blood as a result of the high influx speed against the blood stream, since the relation between dose and effect was quite uniform throughout a large number of tests with injections in the femoral artery (Golenhofen, 1959). However, simultaneous measurements with two probes have shown (Table 1) that individual sections of muscle vessels can remain unchanged while others are dilated or constricted. If infusion is carried out through other cannulae (usually wider), the mixture is obviously worse. Thus, using the same method for measuring muscle blood flow, Bock et al. (1955) found a sustained dilatation of the muscle vessels with adrenaline 10 µg/min in the femoral artery in one case, and with 0·001 µg/min in another case. In the first case occlusion plethysmography would certainly have revealed a reduction in blood flow, since most of the muscle sections undoubtedly received a concentration sufficient to cause constriction, whereas in the other case a change in the total blood flow does not appear to be possible.

Since a completely uniform distribution of adrenaline in the blood cannot be achieved by intra-arterial application, the local effect of adrenaline produced by intravenous infusion cannot be duplicated in the forearm by intra-arterial application. This is only possible (within limits) for smaller areas of muscle, such as can be tested with the related technique of heat-conductivity measurement.

Our findings thus lead to the conclusion that the local sustained effect of adrenaline on the muscle blood vessels fundamentally produces the same changes in blood flow as intravenous infusion. This agrees with Celander's (1954) findings in the cat. It cannot yet be decided to what degree the extent of the reaction during intravenous administration is also changed by additional secondary neural or humoral influences. Such reflex influences have been demonstrated in animal experiments (Dörner, 1956). Combined measurements with occlusion plethysmography and heated thermocouple probes must still be made in order to determine to what extent the hitherto divergent results can be brought into agreement by improved techniques of intra-arterial infusion.

SUMMARY

1. Muscle blood flow in the calf and forearm was examined with continuous heat conductivity measurement in healthy subjects during intravenous and intra-arterial injections and infusions of adrenaline.

2. In contrast to the results obtained by occlusion plethysmography, it was found that intra-arterial infusions produced sustained increases in blood flow similar to intravenous infusions.

3. The causes of these differences are discussed.

4. The sustained dilatation of the muscle vessels during intravenous infusion of adrenaline cannot be attributed entirely to secondary neural or humoral influences. Here, however, it is not yet known to what extent these influences may be involved in addition to the local adrenaline effect.

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