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FURTHER OBSERVATIONS ON THE EFFECT OF ADRENALINE ON THE BLOOD FLOW THROUGH HUMAN SKELETAL MUSCLE

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In the human subject, Grant & Pearson (1938) found that single intravenous injections of adrenaline resulted in an increased blood flow in the forearm, which they considered mainly to represent an increased muscle blood flow. When, however, Holling (1939) and Allen, Barcroft & Edholm (1946) gave adrenaline in continuous intravenous infusions, the initial increase in blood flow was not maintained. Thus, Allen *et al.* observed that the intravenous infusion of 10 μg. of adrenaline per min., for 10 min., resulted in a sudden fivefold increase in blood flow during the first 2 min.; thereafter the flow decreased to about twice the resting rate, at which level it was maintained till the end of the infusion. These workers considered the initial great dilatation to be a direct local effect, for it was observed during intra-arterial infusions. They thought, however, that the subsequent phase of moderate but sustained increase in blood flow required elucidation.

Goldenberg, Pines, Baldwin, Greene & Roh (1948) have estimated that the peripheral vascular resistance in man is reduced during infusions of adrenaline. This may also be inferred from the earlier observations of Starr, Gamble, Margolies, Donal, Joseph & Eagle (1937), and McMichael & Sharpey-Schafer (1944), because adrenaline caused a proportionately greater increase in cardiac output than in the arterial blood pressure.

It is of interest, therefore, to know to what extent a decrease in the resistance of the vessels in skeletal muscle, during an infusion of adrenaline, leads to an increased blood flow in that tissue. Observations on the blood flow in human muscle, during continuous intra-vascular infusions of adrenaline, with particular reference to the later phase of sustained vasodilatation reported by Allen *et al.* (1946), are now presented.

METHODS

The subjects were all between 19 and 45 years of age, and comprised thirty healthy medical students and thirteen patients who had had one or more limbs sympathectomized for Raynaud's disease

(7), causalgia (4) or hyperhidrosis (2). All the patients had been submitted to a vigorous heat test and only those limbs with a complete absence of vasomotor activity were included. None showed any evidence of occlusive vascular disease.

Each subject first rested for at least half an hour in the laboratory, which was thermostatically maintained at a constant temperature, generally between 20 and 22° C. Plethysmographs were fitted to the forearm or calf, according to the technique of Barcroft & Edholm (1943, 1945). The plethysmographs were filled with water maintained at a temperature of 33–35° C. and blood flow was recorded usually every half minute. Blood pressure was recorded in the arm by the ordinary clinical sphygmomanometer, usually immediately after each recording of blood flow. However, in the upper limb experiments, as one arm was required for the intravenous infusion and the other for the measurement of blood flow or blood pressure, two separate infusions of adrenaline were given; during the first infusion, arterial blood pressure alone was recorded and 25–30 min. later the second infusion was given while blood flow was measured. This procedure was considered justifiable on the grounds that in eight subjects to whom two successive infusions of adrenaline were given, at intervals of 20 min. (while arterial blood pressure was measured continuously), the arterial blood pressure changes during the course of the second infusion differed by less than 10 mm. Hg from those recorded during the first infusion. Moreover, the results were essentially similar in a number of experiments in which blood flow was recorded during the first infusion and arterial blood pressure during the second. In all the experiments observations were made during a control period of at least 10 min. before and after each infusion of adrenaline.

Intravenous and intra-arterial infusions were carried out as described by Swan (1951), using local anaesthesia. When intra-brachial infusions were given to study the direct effect of adrenaline in the forearm, a needle was first inserted into the brachial artery just above its bifurcation, after which the plethysmograph was carefully drawn up the forearm as far as the needle itself. In all other experiments, blood flow measurements were started before commencing the saline infusion, to confirm that the actual insertion of the needle had little or no effect.

The observations presented here were all made during the course of continuous intravenous or intra-arterial infusions of saline. After a control period of 20 min. the saline was replaced for a period of exactly 10 min. with saline containing synthetic L-adrenaline tartrate, B.D.H. in the required concentration, after which the saline infusion was resumed for a further control period. The subjects were unaware of the time when the adrenaline was given except in so far as symptoms occurred during the intravenous infusions.

The dose of adrenaline for every intravenous infusion was 10 μg./min. In the intra-arterial infusions, however, a proportionately smaller dose was given. Taking into account the relative bulk of the tissue supplied, it was estimated that $\frac{1}{8}$–$\frac{1}{4}$ μg. into the brachial, and 1–2 μg. into the femoral artery, were approximately equivalent to the intravenous dose of 10 μg. The grounds on which this procedure was undertaken are outlined later.

This study is confined to the later phase of the adrenaline effect, after the initial marked dilatation has passed off, so the results have been analysed with regard to the change occurring during the later period of the adrenaline infusions, in relation to the resting levels. For this purpose, in each subject the average of the eight blood flow recordings during the last 4 min. of the adrenaline infusion has been compared with the average blood flow during the 4 min. immediately before the start of the infusion.

Blood flows are expressed as ml./min./100 ml. of tissue volume as obtained by water displacement.

RESULTS

Intravenous infusions, normal calves. The blood flow in twelve normal calves during intravenous infusions of adrenaline was studied. Fig. 1 illustrates a typical experiment in a man 38 years of age. After a latent period during which the adrenaline solution passes through the catheter into the circulation,

the systolic arterial blood pressure rises sharply by about 30 mm. Hg and remains elevated until after the end of the infusion. The diastolic blood pressure rises a little and then falls below the resting level for the remainder of the infusion. In many subjects the diastolic pressure fell initially; in every case the average diastolic pressure during the infusion was less than the resting level. The heart rate increases a little during the infusion; in some subjects a rather greater initial increase in rate was succeeded after 1–2 min. by restoration to a level slightly above the resting rate.

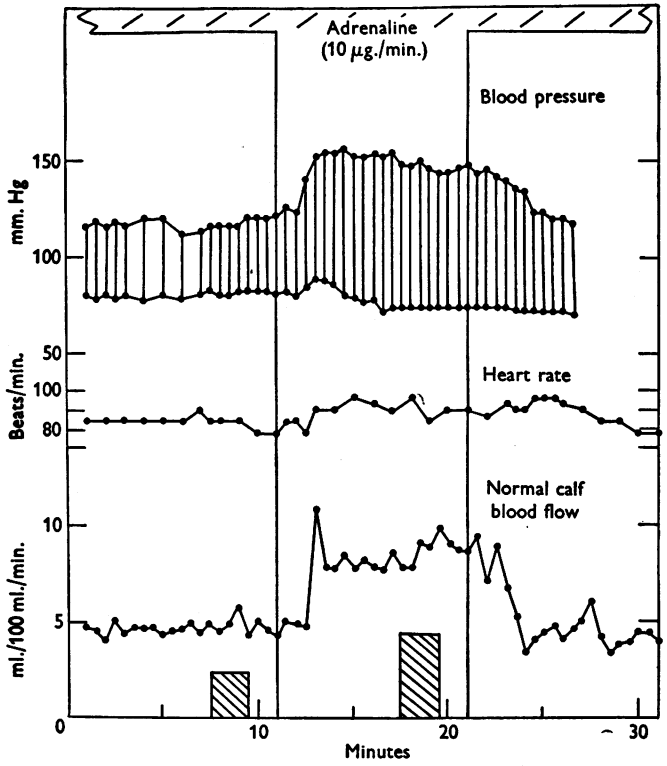

Fig. 1. Intravenous infusion of adrenaline, normal subject. Arterial B.P., heart rate and calf blood flow. The hatched blocks represent (in half scale) blood flow during control and response periods.

The blood flow in the calf increases suddenly to a peak from which it declines less rapidly to a level above the resting rate of 4·7 ml./100 ml./min. Thereafter the blood flow rises gradually; the average level during the last 4 min. of the infusion is 8·7 ml. In the whole group of twelve subjects, the average resting flow was 3·6 ml./100 ml./min. and the flow during the last 4 min. of the adrenaline infusions was 6·2 ml. (Table 1*a*). These figures differ significantly ($t=5{\cdot}46$, $P<0{\cdot}001$). The blood flow during the last 4 min. of the adrenaline infusions shows an average increase of 86% over the resting value.

During the intravenous infusions certain symptoms were consistently noted. The first sensation was a curious feeling of expectancy, amounting in some subjects to real anxiety, immediately followed by an awareness of the need for greater respiratory effort and an increase in depth and rate of breathing. About the same time a sudden increase in heart rate was noticed, and shortly afterwards the subject experienced a sensation of fatigue in the back and lower limbs, similar to that associated with strenuous exercise. A few subjects complained of slight frontal headache. The skin, especially of the face, remained pale throughout the infusion after which a sudden flush associated with a subjective feeling of warmth was frequently observed. In about half the subjects some degree of coarse irregular tremor of the limbs was seen. The subjective symptoms diminished after the first 2–4 min. despite maintenance of the adrenaline infusion at the same rate.

Intravenous infusions, sympathectomized calves. Six sympathectomized limbs were studied while intravenous infusions were given. The response in a typical experiment is illustrated in Fig. 2. The subject was a young woman who had had all four limbs sympathectomized for Raynaud's disease, with complete clinical cure. The systolic arterial blood pressure, in this case, rises from the resting level of 132 mm. Hg to reach the high level of 190 after the beginning of the infusion; it later settles at 180 mm. Hg till after the infusion, when it returns within a few minutes to the previous level. The diastolic pressure shows an average fall of about 10 mm. Hg during the infusion. The heart rate rises from 60 to 102/min., thereafter varying between 70 and 84 until after the infusion. The blood flow in the calf exhibits an initial rise and rapid fall to a low level from which it gradually rises a little; the average level, however, during the last 4 min. of the infusion is 2·6 ml./100 ml./min., compared with the resting level of 2·9 ml. The results in the six subjects are summarized in Table 1*b*. The differences between the resting levels and the blood flow during the last 4 min. of the adrenaline are not significant ($t=1{\cdot}72$, $P=0{\cdot}15$).

These results show that sympathectomized calves generally fail to show the normal rise in blood flow during the later period of the adrenaline infusions.

Although sympathectomized subjects usually notice the same symptoms during an intravenous infusion as do normal subjects, a few who have had all four limbs sympathectomized experience more severe symptoms. In these subjects adrenaline causes a greater rise in arterial blood pressure than is usually seen in normal people. A similar observation was reported by Swan (1951).

Intra-arterial infusions, normal calves. Intra-arterial infusions of 1 μg. adrenaline/min. into the femoral artery were given to six normal subjects. During these experiments neither heart rate nor arterial blood pressure was influenced by the infusions. It is thought, since the dose of adrenaline was small and no systemic effects were observed, that the blood flow changes

during the infusion represent the direct local effect of adrenaline on the muscle blood vessels.

The response observed in a healthy young man is shown in Fig. 3. There is an initial increase in blood flow and then a fall; for the remainder of the infusion the level of flow is below the resting rate. During the last 4 min.

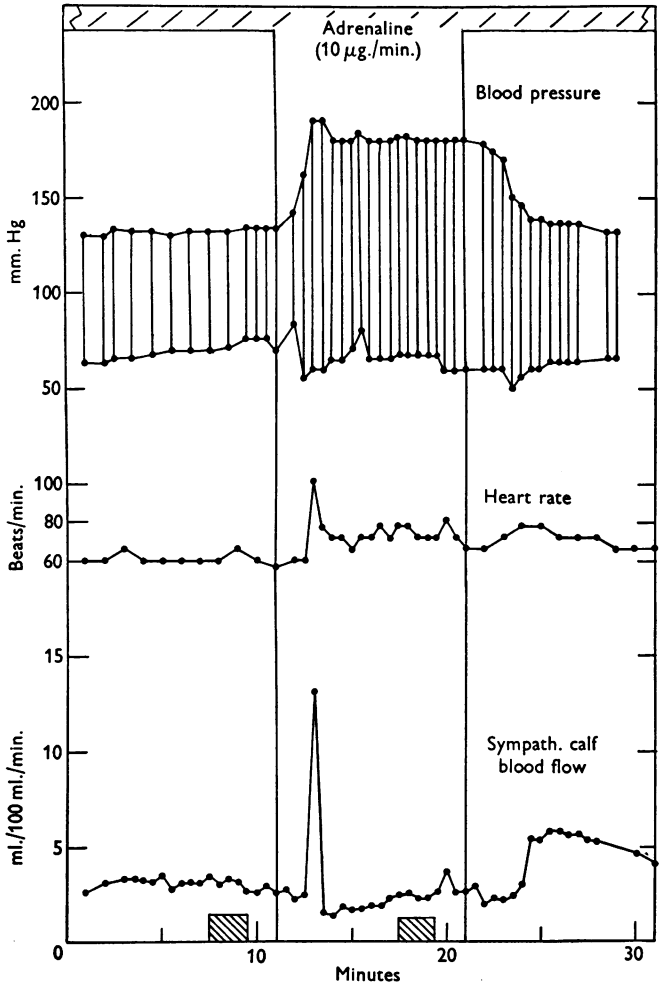

Fig. 2. Intravenous infusion of adrenaline, sympathectomized subject. Arterial B.P., heart rate and calf blood flow.

of the infusion it averaged 2·1 ml. as compared with the resting value of 2·5 ml./100 ml./min., a decrease of 16%. Only one of this series of six normal calves showed an appreciable increase in blood flow during the last 4 min. of the infusion. The average change in flow in the six subjects was an increase of 4%. The detailed results are given in Table 1*c*.

During the 10 min. test period a very much larger total amount of adrenaline is given in the intravenous infusion than in the intra-arterial infusion. It must now be considered whether this factor is in any way responsible for the difference in the response obtained. It seems unlikely that the adrenaline concentration in the circulation increases during a continuous infusion, for there is no progressive increase in arterial blood pressure, nor is there continuance of symptoms. After the infusion has been discontinued the arterial blood pressure falls within a very few minutes to the resting level. It is probable that the adrenaline is inactivated or withdrawn from the circulation by the tissues at a steady rate. Concerning the rate of inactivation of adrenaline by the tissues recent studies (Swan, 1951, Fig. 4) on the blood flow through the

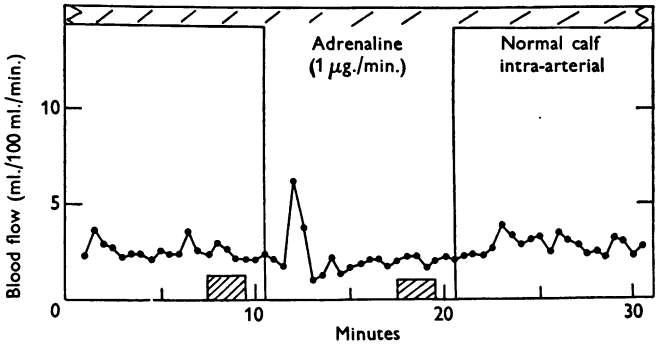

Fig. 3. Intra-arterial infusion of adrenaline, normal subject. Response of blood flow in calf.

human hand demonstrated that the constrictor action of even larger amounts of adrenaline did not persist after the end of the infusions, and the blood flow had frequently returned to normal values in 1–2 min. In the experiments described in this paper it is probable that inactivation of adrenaline took place at a steady rate, and that the relatively larger total intravenous dose was proportionately withdrawn from the general circulation by the tissues. Nevertheless, experiments were carried out using higher doses of adrenaline given intra-arterially and the responses in six normal calves to 2 μg. adrenaline/min. are detailed in Table 1*d*. Had the effect observed in the intravenous infusions been due to the accumulation of adrenaline in the blood stream a like response should have occurred in these experiments; on the contrary a decrease in blood flow of 34% resulted.

Intravenous infusions, normal forearms. Intravenous adrenaline infusions were given to nine normal subjects while blood flow was measured in the forearm. As already stated, simultaneous blood pressure and forearm blood flow measurements were impracticable, so the blood pressure alone was first recorded while an infusion was given. After a control period of 25–30 min. during which the saline infusion continued, a second infusion of adrenaline was given

TABLE 1. Changes in calf blood flow in normal and in sympathectomized limbs during intravenous infusions of adrenaline, and in normal limbs during intra-arterial infusions of adrenaline. Blood flow in ml./min./100 ml. tissue

No.	Age (yr.)	Sex	Blood flow *A*	Blood flow *B*	Blood flow *B–A*	*B–A* % *A*	Blood pressure *A*	Blood pressure *B*	Condition	*D*
			(*a*) Normal calves, intravenous adrenaline 10 μg./min.							
1	21	F.	1·7	4·7	+3·0	+176	124/80	140/60	Normal	—
2	19	F.	4·6	5·4	+0·8	+18	116/55	148/48	Normal	—
3	19	F.	3·3	4·9	+1·6	+48	121/70	149/52	Normal	—
4	22	F.	4·2	8·2	+4·0	+95	—	—	Normal	—
5	22	F.	4·3	9·8	+5·5	+128	112/70	139/71	Normal	—
6	23	M.	4·5	5·4	+0·9	+20	142/78	152/58	Normal	—
7	20	M.	5·7	5·5	−0·2	−3	120/60	145/50	Normal	—
8	22	M.	2·1	4·3	+2·2	+105	118/76	144/66	Normal	—
9	28	M.	1·9	4·3	+2·4	+126	119/70	150/70	Normal	—
10	38	M.	4·7	8·7	+4·0	+85	116/81	148/74	Normal	—
11	32	F.	2·9	6·9	+4·0	+165	—	—	Normal	—
12	32	F.	3·2	6·1	+2·9	+69	110/68	140/65	Normal	—
		Av.	3·6	6·2	+2·6	+86%				
			(*b*) Sympathectomized calves, intravenous adrenaline 10 μg./min.							
1	19	F.	2·7	2·3	−0·4	−15	121/70	140/60	Causalgia	1
2	20	F.	2·9	2·6	−0·3	−10	132/72	180/66	Raynaud's disease	6
3	25	F.	5·6	4·4	−1·2	−21	116/65	150/60	Raynaud's disease	13
4	44	F.	3·2	3·0	−0·2	−6	103/60	140/70	Raynaud's disease	5
5	31	F.	2·4	2·7	+0·3	+12	118/78	118/76	Raynaud's disease	6
6	31	F.	2·8	2·5	−0·3	−10	118/78	118/76	Raynaud's disease	6
		Av.	3·3	2·9	−0·4	−8%	—	—	—	—
			(*c*) Normal calves, intra-arterial adrenaline 1 μg./min.							
1	27	M.	1·8	2·7	+0·9	+50	—	—	Normal	—
2	23	M.	3·2	3·6	+0·4	+13	—	—	Normal	—
3	21	M.	2·5	2·1	−0·4	−16	—	—	Normal	—
4	25	M.	3·5	2·9	−0·6	−17	—	—	Normal	—
5	22	M.	3·8	2·8	−1·0	−26	—	—	Normal	—
6	26	M.	3·3	4·0	+0·7	+21	—	—	Normal	—
		Av.	3·0	3·0	0·0	+4%	—	—	—	—
			(*d*) Normal calves, intra-arterial adrenaline 2 μg./min.							
1	23	M.	3·6	3·6	0·0	0	—	—	Normal	—
2	21	M.	2·3	1·6	−0·7	−30	—	—	Normal	—
3	25	M.	5·0	2·4	−2·6	−52	—	—	Normal	—
4	22	M.	3·8	1·9	−1·9	−50	—	—	Normal	—
5	25	M.	4·8	1·5	−3·3	−68	—	—	Normal	—
6	23	M.	7·8	7·4	−0·4	−5	—	—	Normal	—
		Av.	4·6	3·1	−1·5	−34%				

A = mean during the 4 min. prior to the start of the adrenaline; *B* = mean during the last 4 min. of the adrenaline infusion; *D* = duration of sympathectomy, in months.

while blood flow was recorded. In this group of subjects the changes in arterial blood pressure and in heart rate, and the symptoms, all closely resembled those already described in the previous group of normal subjects receiving intravenous infusions.

The effects of an infusion are depicted in Fig. 5. The first change in forearm blood flow is a sudden marked increase to between four and five times the mean

resting level. This increase is of short duration, and within a minute the blood flow returns to about twice the resting level. From this point to the end of the infusion the flow remains about this level, gradually rising a little during the last few minutes. After the end of the infusion, the blood flow soon returns to near the resting level. For the whole group of nine subjects, the mean resting level was 2·6 ml./100 ml./min., and the blood flow during the last 4 min. of the

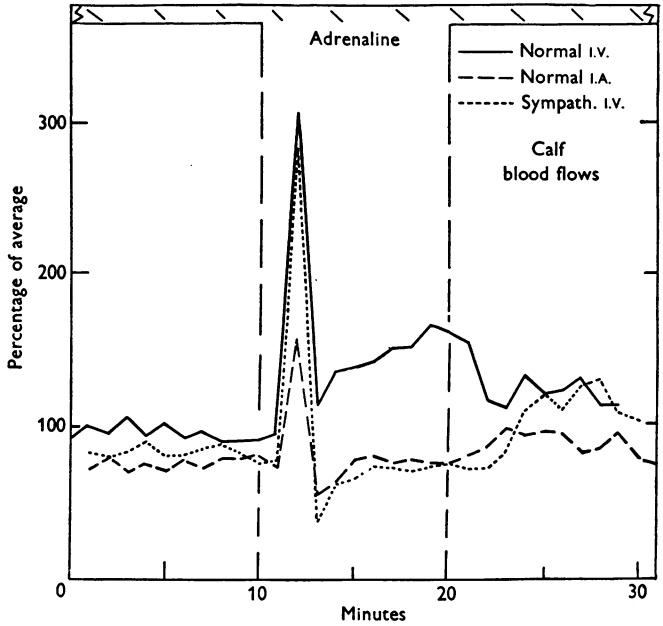

Fig. 4. Averages of the calf blood flow in three groups of subjects: ———, twelve normals, during intravenous infusions of adrenaline; - - - - - -, six sympathectomized, during intravenous infusions of adrenaline; — — —, six normals, during intra-arterial infusions of adrenaline.

adrenaline infusions was 5·1 ml. The difference between these figures is highly significant ($t=5·8$, $P<0·001$). The detailed results in this group are given in Table 2*a*.

Intravenous infusions, sympathectomized forearms. Observations on the effect of intravenous infusions in respect of seven sympathectomized forearms were made. The observations from a typical experiment are illustrated in Fig. 6. The subject was a man who had had a bilateral cervical sympathectomy, 1 year previously, for hyperhidrosis. In this instance, blood-pressure and heart-rate changes are similar to those found in normal subjects.

The forearm blood flow shows the initial brief rise to a peak from which it rapidly returns to below the resting level. During the rest of the infusion, however, the blood flow remains, with some fluctuation, near the resting level, and there is no substantial increase such as occurs in the normal forearm. The

resting blood flow in this subject was 4·6 ml./100 ml./min., while the corresponding value during the last 4 min. of the adrenaline infusion was 5·5 ml.

The results in the whole series of seven sympathectomized forearms are summarized in Table 2*b*. The average resting flow was 4·2 ml.; during the last

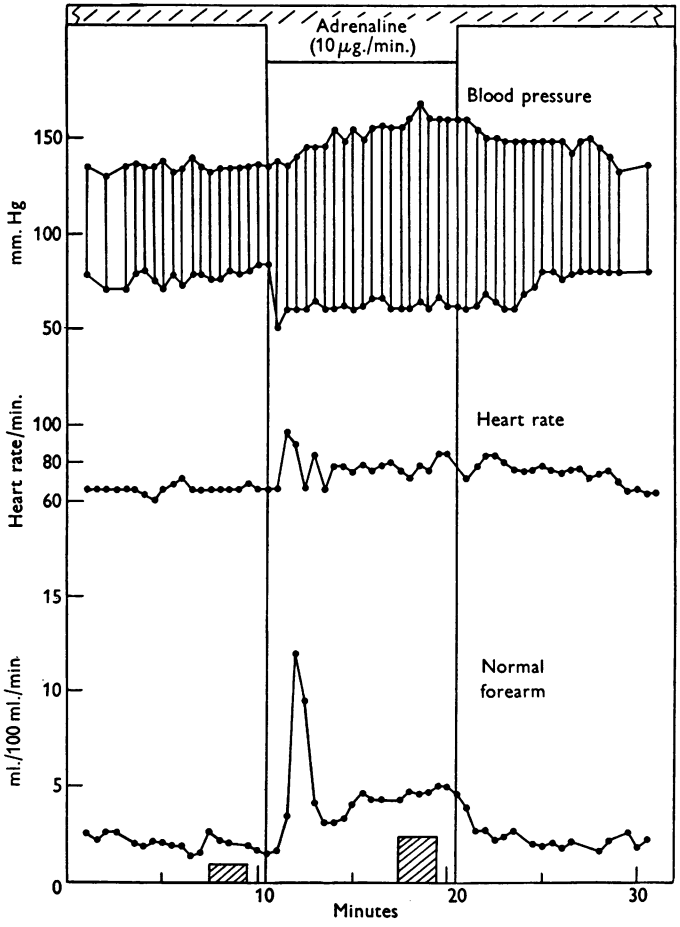

Fig. 5. Intravenous infusion of adrenaline, normal subject. Arterial B.P., heart rate and forearm blood flow.

4 min. of the infusions the average blood flow was 4·7 ml. These figures do not differ significantly ($t = 1{\cdot}2$, $P = 0{\cdot}25$).

Intra-arterial infusions, normal forearms. Intra-brachial arterial infusions were given to six normal subjects. The result in a typical experiment on a normal subject aged 21 years is represented in Fig. 7. No alteration in arterial blood pressure was observed.

The characteristic initial increase in blood flow is followed by a rapid decline

to below the resting level of 3 ml./100 ml./min. The blood flow then rises slightly, but remains at about the resting level throughout the remainder of the infusion. During the last 4 min. the average blood flow was 3·1 ml./100 ml./min., an increase of only 3% over the resting level.

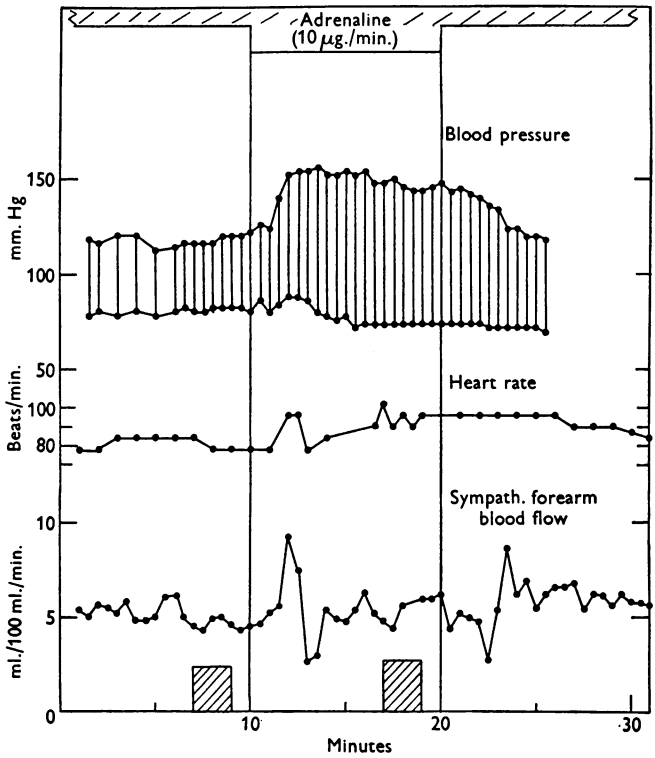

Fig. 6. Intravenous infusion of adrenaline, sympathectomized subject. Arterial B.P., heart rate and forearm blood flow.

In none of the six experiments in this group was there a sustained increase in flow. The observations are summarized in Table 2*c*. The average change in this group is a decrease of 5%. The difference in blood flow during the later adrenaline period, by comparison with the resting period, is not significant ($t=0{\cdot}5$, $P=0{\cdot}6$).

In the normal forearm, therefore, as in the normal calf, the blood flow increases markedly for a brief period at the beginning of an intravenous infusion of adrenaline, and then remains moderately elevated till the end of the infusion.

In the sympathectomized forearm, as in the sympathectomized calf, an intravenous infusion causes an initial transient increase in blood flow but no

TABLE 2. Changes in forearm blood flow in normal and in sympathectomized limbs during intravenous infusions of adrenaline, and in normal limbs during intra-arterial infusions of adrenaline. Blood flow in ml./min./100 ml. tissue.

No.	Age (yr.)	Sex	Blood flow *A*	Blood flow *B*	*B–A*	*B–A*% *A*	Blood pressure *A*	Blood pressure *B*	Condition	*D*
			(*a*) Normal forearms, intravenous adrenaline 10 μg./min.							
1	18	M.	3·4	5·6	+2·2	+65	128/80	160/65	Normal	—
2	19	M.	3·4	6·4	+3·0	+88	116/85	140/80	Normal	—
3	18	M.	3·4	7·7	+4·3	+127	135/80	165/65	Normal	—
4	19	M.	2·0	4·6	+2·6	+130	135/80	155/70	Normal	—
5	19	M.	2·4	3·2	+0·8	+33	135/80	150/75	Normal	—
6	19	M.	1·7	3·9	+2·2	+130	—	—	Normal	—
7	19	M.	3·5	5·4	+1·9	+54	134/80	160/62	Normal	—
8	33	M.	1·9	4·7	+2·8	+147	—	—	Normal	—
9	33	M.	1·8	4·2	+2·4	+133	—	—	Normal	—
		Av.	2·6	5·1	+2·4	+101%				
			(*b*) Sympathectomized forearms, intravenous adrenaline 10 μg./min.							
1	22	M.	3·1	3·9	+0·8	+26	122/76	140/76	Hyperhidrosis	6
2	43	M.	4·0	3·5	−0·5	−13	130/74	156/60	Causalgia	7
3	32	M.	4·6	5·5	+0·9	+19	—	—	Hyperhidrosis	12
4	32	F.	2.6	4·4	+1·8	+69	118/92	148/74	Raynaud's disease	24
5	29	M.	5·9	5·2	−0·7	−12	110/66	140/64	Causalgia	4
6	29	M.	6·7	5·9	−0·8	−12	—	—	Causalgia	4
7	22	F.	2·5	4·4	+1·9	+76	112/70	140/68	Raynaud's disease	18
		Av.	4·2	4·7	+0·5	+22%	—	—	—	—
			(*c*) Normal forearms, intra-arterial adrenaline, $\frac{1}{8}$ μg./min.							
1	21	M.	3·0	3·1	+0·1	+3	—	—	Normal	—
2	29	M.	8·7	3·8	−4·9	−56	—	—	Normal	—
3	21	M.	1·9	1·7	−0·2	−10	—	—	Normal	—
4	21	M.	6·0	6·3	+0·3	+5	—	—	Normal	—
5	20	M.	6·0	7·0	+1·0	+17	—	—	Normal	—
6	20	M.	5·3	6·0	+0·7	+13	—	—	Normal	—
		Av.	5·2	4·7	−0·5	−5%	—	—	—	—

A = mean during the 4 min. prior to the start of the adrenaline; *B* = mean during the last 4 min. of the adrenaline infusion; *D* = duration of sympathectomy, in months.

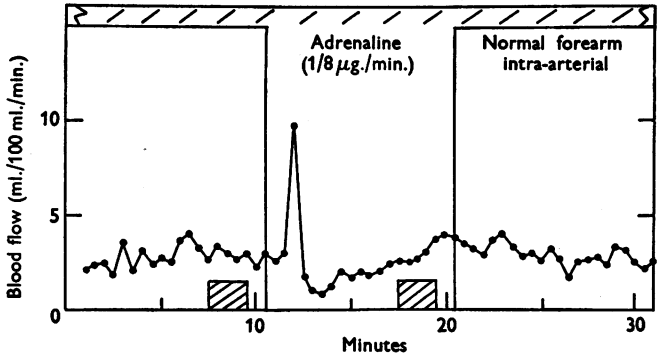

Fig. 7. Intra-arterial infusion of adrenaline, normal subject. Effect on forearm blood flow.

subsequent rise. Likewise an intra-arterial infusion of adrenaline causes only an initial brief rise, but not a sustained increase in forearm blood flow.

In the forearm, it will be noted (Table 2) that the mean control blood flow was greater in the group receiving intra-arterial infusions and in the sympathectomized group, than in the normal group receiving intravenous infusions. The higher control level in the first group might be due to the saline infusion, for the same infusion rate (4 ml./min.) was used in all intravenous and intra-arterial infusions, and while this might have no effect upon the circulation in a large bulk of tissue like the leg, it might alter in some way the circulatory dynamics in a smaller bulk of tissue such as the forearm. These differences in the control blood flow levels might be responsible in some degree for the different responses observed in the three groups of forearms. When the blood flow means during the adrenaline infusion are adjusted by covariance analysis for the inequality in resting values there remains a statistically significant difference between the normal and the sympathectomized forearms during intravenous infusions.

DISCUSSION

The changes in blood flow in the calf induced by adrenaline infusions (Fig. 4) reveal a distinctive pattern of response which is supported by the results obtained in the forearm experiments. By whatever route the adrenaline is infused, a marked but transient increase in blood flow is the first change in every subject whether normal or sympathectomized. In the three groups of calf experiments the resting blood flow means are clearly comparable, yet only in the normal group receiving intravenous adrenaline was this initial rise followed by a significant change in blood flow during the last 4 min. of the infusion, this being an increase of 86%. Thus in the two groups of subjects receiving the same total dose of adrenaline by intravenous infusion, the normal group exhibits a second phase of increased blood flow while the sympathectomized group does not.

In the forearm also a similar increase in blood flow (101%) was found when intravenous adrenaline was given to normal subjects, this response being significantly different from the effects observed in sympathectomized forearms. However, when the response of the normal forearm to intravenous adrenaline is compared with the response to intra-arterial adrenaline it loses its statistical significance because of an elevated control level of blood flow in the latter group. It is considered probable that in fact both calf and forearm respond alike to intravenous and intra-arterial adrenaline. Nevertheless, for the purpose of discussion reliance will only be placed on the statistically significant results obtained in the calf experiments.

In Fig. 4 the graphs of the average blood flow results in the three groups of calves have been superimposed. For purposes of comparison, in this figure,

small differences in timing have been eliminated by aligning each series in relation to the maximum blood flow during the initial brief increase which occurs in all groups. Usually, of course, with intra-arterial infusions the blood flow changes earlier because the adrenaline passes directly into the limb. This figure demonstrates in diagrammatic fashion the differences between normal and sympathectomized limbs in the response to intravenous adrenaline infusions—the latter have no secondary increase in blood flow.

The possibility of an increased sensitivity of the denervated blood vessels to adrenaline cannot yet be entirely excluded. Hypersensitivity to adrenaline has been observed to follow sympathectomy in animals (Dale & Richards, 1918), and is thought by some (Smithwick, Freeman & White, 1934) to occur in the human subject. Conceivably, therefore, sympathectomized limbs in virtue of an enhanced sensitivity to the constrictor phase of the local action of adrenaline might fail to show the secondary increase, whatever its mechanism in normal limbs. The effect of an intra-arterial infusion of adrenaline on the muscle blood flow in a sympathectomized upper limb was studied in two subjects. The result did not differ from that found when intra-arterial infusions are given to normal subjects.

Changes in blood flow in forearm and calf may be ascribed largely to changes in the flow of blood through skeletal muscle (Allen *et al.*, 1946). The above results therefore confirm that in normal subjects the vessels in skeletal muscle show two phases of dilatation when an intravenous infusion of adrenaline is given. The second phase results in an increase of blood flow, of almost twice the resting rate, in the latter half of the infusion. Allen *et al.* (1946) observed, and it is herein confirmed, that the initial large dilatation is due to a direct action of adrenaline on the blood vessels of skeletal muscle, for it occurs with intra-arterial infusions, and in sympathectomized vessels. The sustained rise in blood flow in normal muscle, which follows this initial vasodilatation, when intravenous infusions of adrenaline are continued, must be due to a different mechanism, for it is absent during intra-arterial infusions. What, then, is its nature?

The sustained increase in blood flow occurs at a time when the arterial blood pressure is elevated, so it might be considered to be a passive consequence of the increased 'perfusion pressure'. But the increase in systolic blood pressure averaged about 30 mm. Hg, while the diastolic pressure was reduced by about 10 mm. Hg. If conditions are such that the blood flow is directly proportional to the head of perfusion pressure, the mean increase in arterial pressure alone could account at most for an increase in blood flow of about 10%, which is much less than the observed increase of 80–100%. Further, the blood pressure rises rapidly after the start of the infusion to a fairly steady level during the remainder of the infusion, while the secondary rise in blood flow often takes 1–3 min. to appear. Indeed, it is usual for the blood flow to continue to increase

slowly during the remainder of the infusion, while further elevation in blood pressure usually does not occur. Moreover, when fluctuations in blood pressure and in blood flow occur, these are seldom coincident; nor is there any general association between the degree of blood pressure rise in different subjects, during this period, and the actual level of blood flow (Tables 1 and 2).

Green, Lewis, Nickerson & Heller (1944) found that the pre-existing level of tonicity of a vascular bed greatly modified the increase in flow resulting from a given increase in perfusion pressure. If the vascular tone of the vessels in sympathectomized limbs may be presumed to be not greater than normal, then this group should have exhibited an increase in blood flow equal to that in normal limbs, if the effect were due simply to the increased arterial pressure resulting from the adrenaline.

Is the secondary rise in blood flow in normal muscle during the intravenous infusion of adrenaline due to the arrival at the periphery of some vasodilating substance liberated elsewhere into the circulation in response to the adrenaline? If this were so, sympathectomized limbs would be expected also to exhibit this increase in muscle blood flow. Moreover, unless the dilating action of this hypothetical substance were confined to the vasculature of muscle, generalized vasodilatation resulting in a significant fall in arterial blood pressure would be expected. However, the blood pressure is maintained at about the same level during the course of the infusion, falling only after the end of the infusion.

It therefore seems likely that the sustained rise in muscle blood flow in normal limbs during intravenous infusions of adrenaline is due to an alteration in vasomotor tone. Blood vessels in human skeletal muscle are supplied with both constrictor and dilator sympathetic nerves (Barcroft, Bonnar, Edholm & Effron, 1943; Barcroft & Edholm, 1945). Changes in vasomotor tone might result from activity of either or both groups of nerves; they probably act reciprocally to influence blood flow.

Vasodilatation is known to result from stimulation of the baroceptors of the carotid sinus and aortic arch (Heymans & Bouckaert, 1933). This effect is mediated by the sympathetic pathway and is abolished by sympathectomy. This mechanism may be responsible in some degree for the increase in blood flow in normal limbs.

Adrenaline has been shown to depress transmission in sympathetic ganglia (Marrazzi, 1939), thereby inhibiting vasoconstrictor tone (Bülbring & Burn, 1942). In this connexion Swan (1951) has demonstrated a central inhibition of sympathetic vasoconstrictor tone in the skin in man following short intravenous infusions of adrenaline. Although the effect described in the present study differs in that it occurs in muscle blood vessels during the course of infusions of adrenaline, it may well be of the same nature.

SUMMARY

1. The changes in skeletal muscle blood flow have been studied by venous occlusion plethysmography in the human forearm and calf, during the course of intravenous infusions of adrenaline at a rate of 10 μg./min. for 10 min., in normal and in sympathectomized limbs.

2. Both groups exhibit an initial brief but marked dilatation; in the normal muscle this is succeeded by a phase during which blood flow is approximately twice the resting level.

3. This second phase does not usually occur in sympathectomized limbs, and it is absent in normal limbs when adrenaline is given by intra-arterial infusion.

4. Evidence is presented that the secondary vasodilatation in normal skeletal muscle is mediated by the sympathetic nerves.

5. The possible mechanisms which might lead to this vasomotor effect are discussed.

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