

REACTIONS OF ISOLATED SYSTEMIC AND CORONARY ARTERIES.

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RECENT studies of the coronary circulation on the whole animal and on the isolated heart have demonstrated certain differences between various reactions of coronary and systemic blood vessels. A number of observers(1, 2) have shown that the coronary circulation increases independently of changes in the heart rate when the blood or perfusing fluid is cooled, whereas the circulation through different denervated systemic organs increases on raising, and diminishes on lowering the temperature of the blood, or perfusion fluid(3). Experiments performed on whole organs do not permit of conclusions as to whether the differences in the reaction of blood vessels to temperature depend upon the response of the whole vascular system of the organ, or more exclusively upon the arteries or capillaries, nor still less as to whether or not the reactions are occasioned by changes in the metabolism of the organ. We resolved, therefore, to study first of all the reactions to heat of isolated coronary and systemic arteries, freed from their surrounding tissues. The arteries used were taken from animals immediately after death and placed in borate(4) or carbonate Ringer's solution of pH 7.50. Rings of about 2 to 4 mm. in length were cut from the arteries and connected in series with silver hooks, three rings being used in one chain, in a Dewar's flask of 50 c.c. capacity. The lever magnifying the movements 34 times was loaded by weights varying from 2 to 4 gm., according to the size of the artery. About 3 c.c. of fresh defibrinated blood were added to the solution, and a gentle stream of oxygen bubbled through it. The arterial rings were placed in the solution at room temperature and then slowly warmed by means of an electric bulb. The rate of the recording drum was 2.0 mm. per minute. Arteries which could not be used immediately were kept in oxygenated Ringer at about 0° C. Most of the experiments were performed upon arteries of the ox

and dog; a few experiments were made upon the coronary arteries of man.

TEMPERATURE REACTIONS. A distinct difference exists in the appearance of the coronary and systemic arteries as they are received fresh from the animal. At room temperature the coronary arteries are wholly relaxed, while the systemic arteries are markedly rigid.

(a) *Systemic arteries.* Temperature variations in systemic arteries were first studied by MacWilliam⁽⁵⁾ who described a contraction of the isolated artery occurring between 25° C. and 35° C., a second contraction between 45° C. and 50° C. and a final contraction occurring at between 60° C. and 65° C. After the first and second contractions the arteries relaxed to a variable extent. Great variations from this type of temperature curve were found, according to whether the artery was relaxed or contracted when the experiment was begun. Such variations may be expected when the arteries were used some time after death, and had been kept, sometimes for 24 hours or more, in oil or on ice. The most definite result of MacWilliam's experiments was what he termed "heat contraction" which took place between 60° C. and 65° C. Meyer⁽⁶⁾ has obtained similar results with arterial rings. Cow⁽⁷⁾ on the whole confirmed these results, and found on warming the perfusion fluid from 12° C. to 55° C., that a preliminary slight relaxation of tone of the systemic artery was followed, at about 25° C., by a slight but transient recovery of tone; this in its turn gave place to a further progressive relaxation which continued up to 50° C., beyond which point the heat contraction of MacWilliam supervened.

In our experiments upon fresh systemic arteries of the dog (renal, carotid, femoral and mesenteric) a relaxation following a transient increase in tone, as described by Cow, was the usual result. Fresh ox arteries suspended in oxygenated borate, Ringer's solution of pH 7.5 invariably give the type of curve (A) shown in Fig. 1. If the heating be not too rapid the fresh artery, after a transient contraction, starting at about 19°-21° C., begins to relax between 26° and 30° C., more usually in the neighbourhood of 27° C., and by the time the temperature has been raised to 37.5° C., the lumen of the artery is equal to or even greater than that obtaining at room temperature. Only in a few cases did the systemic artery at 37.5° C. fail to relax to the room temperature level, but in these cases also the maximal contraction was at about 27°-30° C. Maintenance of the temperature at 37.5° C. leads to a still further relaxation of the vessel wall until a base line is reached, which is far below the original. The degree of relaxation of the systemic artery

depends upon the extent of the tonic contraction existing when the warming is begun. Arteries which have been kept for some time in cold

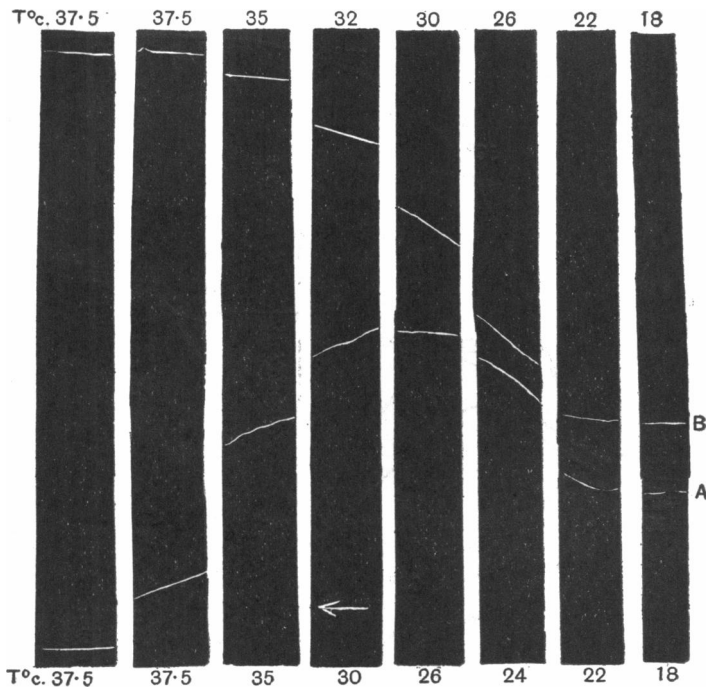


Fig. 1. Effect of warming of mesenteric (curve *A*) and coronary (curve *B*) arterial rings of the ox, about 20 minutes after death. Three rings were used together in each of the tracings; the inside diameter of the rings at room temperature was 1.9–2.1 mm.; each of the coronary rings contracted on warming by 1 mm., thus halving its diameter. Tracing to be read from right to left. Reduction $\frac{1}{2}$.

Ringer's solution, and especially in the absence of oxygen, give a considerably smaller contraction. If used about 6 to 8 hours after excision they fail to give any contraction but relax progressively as soon as the warming is begun (Fig. 2). The systemic arteries reach a maximum relaxation at about 39°–40° C. after which, and more usually at about 44° C., they again begin to contract, the contraction reaching an apex at about 48° C. In the great majority of cases this contraction did not raise the tone of the artery to that existing at room temperature, though in a few experiments the tone of the artery at 48° C. was equal to, or slightly greater than, that at room temperature.

At 48° C. or 50° C. a sudden and most profound relaxation takes

place; this continues until the temperature has reached 60°C . when the artery again contracts, never, however, reaching its original base line;

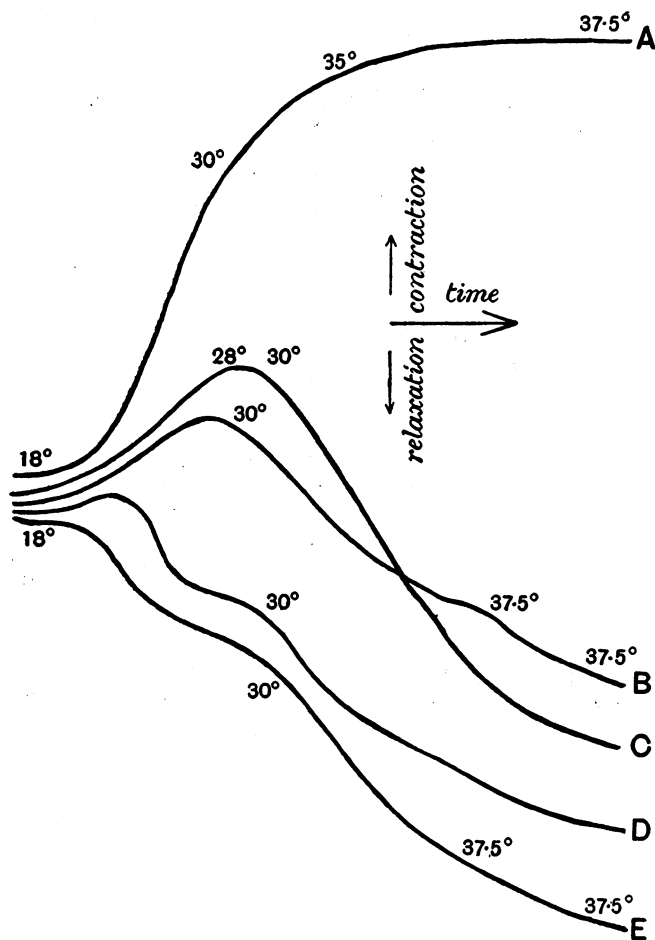


Fig. 2. Re-drawn superimposed curves; to read from left to right. Effect of warming of:

Curve A. Coronary rings, 24 hours old, kept in Ringer's fluid.

„ B. Mesenteric rings of the same diameter, 6 hours old, kept in oxygenated Ringer's fluid.

„ C. Mesenteric rings, fresh.

„ D. Mesenteric rings, 8 hours old, kept in Ringer's fluid.

„ E. Mesenteric rings, 24 hours old, kept in Ringer's fluid.

Ox arteries. Reduction $\frac{1}{2}$.

further heating has no effect. The temperature reactions of the systemic rings are reversible up to 45°C . and at the latter temperature only when

it was not maintained for more than a few minutes. Approximately at this temperature the arteries cease to respond to adrenaline. The profound relaxation of arteries (at 48°–50° C.) has been described for other types of smooth muscle⁽⁸⁾ under the name of heat paralysis. Evans states that if a guinea-pig's uterus—in which heat paralysis occurs at about 49° C.—is quickly cooled, it regains its excitability and once more responds to drugs. In the case of arteries we found no such return of excitability on cooling the rings after heat paralysis had taken place.

(b) *Coronary arteries.* Within the range of temperatures from 18° C. to about 38° C. the coronary arteries behave differently from the systemic. The coronary artery progressively contracts with increase of temperature from 18° C. to 37·5° C. If the heating be gradual the maximal contraction is reached at about 37·5° C. (Fig. 1 B). If, however, the temperature be raised rapidly, the contraction will continue for some considerable time after the temperature has reached 37·5° C. The time taken to raise the temperature was generally, as in the case of the systemic arteries, about 30 minutes. In arteries which are not quite fresh the uniformity of the temperature curve may be broken by a small transitory relaxation. The artery at 37·5° C. is contracted well above the base line at room temperature so that the diameter at the higher temperature may be reduced by as much as half. The artery remains contracted so long as this temperature is maintained. This contraction is reversible, and provided the artery is kept well oxygenated it can be repeated many times during two or three days after excision. In some experiments we repeated the cooling and warming of the coronary artery up to body temperature six times, in all cases obtaining the same degree of contraction. In contrast with this the systemic artery when tested a few hours after excision, fails to give even the transitory contraction described above (Fig. 2). Above 38° C. the coronary artery relaxes; from about 45° C. it behaves in the same manner as the systemic artery, *i.e.* it contracts up to 48°–50° C., then completely relaxes to the base line, and at 60° C. gives a final and vigorous contraction. The difference in the response of systemic and coronary arteries at the higher temperatures is mainly quantitative: the contraction between 45° C. and 50° C. occurs in the case of the systemic artery when it is relaxed, in the coronary when it is still in a state of partial contraction. In the first case the base line at room temperature is reached or approximated during the periods of contraction between 45° C. and 50° C. and above 60° C.; in the second it is reached or approximated during the period of relaxation between 50° C. and

60° C. This behaviour of the arteries is represented in the following table:

Changes in tone of the isolated arterial rings related to the tone of the artery at 22° C.					
Temperature ° C.	Systemic artery		Coronary artery		
	Below	Above	Below	Above	
22-30	.	+	.	+	
30-38	-	.	.	+	
38-44	-	.	.	-	
44-50	+	or +	.	+	
50-60	-	.	.	-	
About 61	+	.	.	+	

Base line

↓

+ Above = contraction above base line.
 - Above = relaxation but not below base line.
 + Below = contraction but not up to base line.
 - Below = relaxation below base line.

The reactions to temperature changes do not depend upon the diameter of the arteries, large and small arteries giving precisely similar results.

The main point demonstrated by these experiments is that, within the viable range of rise in temperature, the systemic arteries relax while the coronary arteries contract; when excised from the body the coronary artery is completely relaxed, while the systemic artery is almost fully contracted. In the case of arteries kept for several hours without sufficient oxygen, the differences described become more pronounced. The results of these experiments should not be regarded as showing a fundamental difference between coronary and systemic arteries in general, for it is possible that systemic arteries other than those examined may show temperature reactions similar to those of the coronary arteries. The observations are important in that they provide an interpretation of the experiments on the effect of temperature upon the coronary circulation in the isolated heart and in the heart-lung preparation.

ACTION OF ADRENALINE AND ERGOTOXIN. It is well known that in most animals adrenaline dilates the coronary and contracts the systemic arteries. We investigated the action of adrenaline upon these arteries after previous application of ergotoxin. The action of ergotoxin upon the peripheral blood vessels has been demonstrated by Dale⁽⁹⁾ and by Barger and Dale⁽¹⁰⁾, who showed that after the injection of ergotoxin, injection of adrenaline or stimulation of the splanchnic nerve causes a peripheral vaso-dilatation. This reversed effect of adrenaline was tentatively explained as being due to ergotoxin paralysing the sympathetic vaso-constrictor nerve endings, without, however, paralysing the sympathetic vaso-dilator nerve endings, and thus leaving the latter free to

respond to adrenaline or to stimulation of the sympathetic nerves. The vaso-dilator effect of adrenaline after ergotoxin depends upon the relative doses of the two drugs, and a large dose of adrenaline is known to overcome the effect of ergotoxin and so produce vaso-constriction. As regards isolated arterial rings, the effect of ergotoxin and the reversal phenomenon of Dale have not previously been investigated. In the coronary and systemic arteries we have vessels which behave oppositely towards adrenaline. If Dale's explanation of the reversal is correct we should expect to find that the vaso-dilator action of adrenaline upon the coronary arteries would remain unaffected by a previous application of ergotoxin in doses which in systemic arteries are sufficient to produce the reversal phenomenon.

Before settling this question it was necessary to determine whether a distinct reversed reaction to adrenaline can be observed on isolated systemic rings and whether ergotoxin by itself has any effect upon systemic and coronary rings.

(a) *Systemic arteries.* Ergotamine tartrate in concentrations below 1 : 500,000 at 37.5° C. failed to produce any effect, while concentrations between 1 : 500,000 to 1 : 100,000 produced a more or less conspicuous constriction which was followed by a slight dilatation or a return to the previous line. Still higher concentrations produced a pure dilatation which in many cases was so intense that the diameter of the artery was more than doubled. Ergotoxin added at room temperature even in the larger doses has no effect, but on warming, the systemic rings instead of their usual response relax progressively. This relaxation is very conspicuous and at 37.5° C. the rings may be doubled in diameter. In this relaxed state they continue to respond to barium chloride by contraction if the latter is added in large doses; after washing off the ergotoxin and cooling, they regain their tone and then show a normal temperature curve. As regards the action of adrenaline (tabloid form without chloreton) after the larger doses of ergotoxin we find that even large doses of adrenaline (up to 1 : 50,000) fail to have any effect. It is probable that in high concentration ergotoxin affects the muscle of the arteries, which relax, cease to react to temperature and react but slightly to vaso-constrictor substances. When ergotoxin is added in doses which, following the immediate constrictor effect, produce little or no vaso-dilatation, the addition of adrenaline either ceases to produce vaso-constriction, or causes dilatation. Whether ergotoxin abolishes or reverses the action of adrenaline depends upon the systemic artery employed. In the renal, carotid and the larger mesenteric arteries ergotoxin only abolishes the

effect of adrenaline; in small arteries it reverses the action of adrenaline. In this relation experiments upon the mesenteric arteries are instructive (Fig. 3). Curve *A* in Fig. 3 shows the response of a small mesenteric

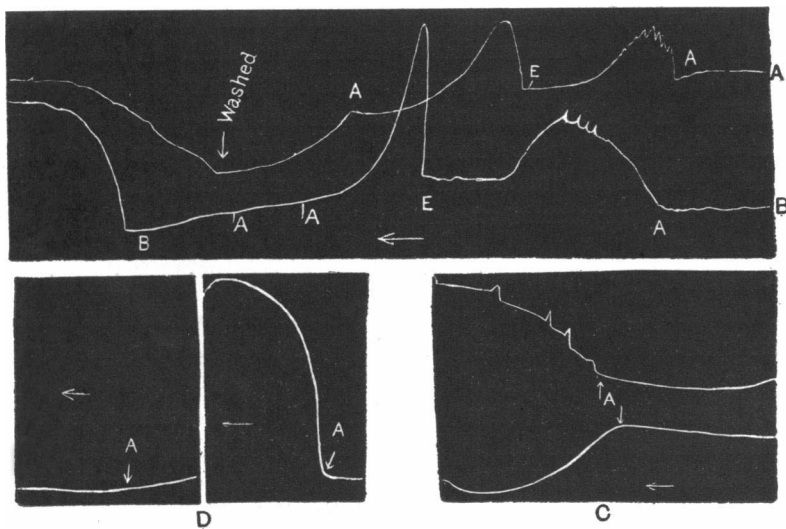


Fig. 3. All curves to be read from right to left.

- Curve A.* Small mesenteric arterial rings (1.5 mm. in diameter); at A adrenaline 1 : 1,000,000; at the apex of the contraction the rings are washed with about 100 c.c. of fluid; at E ergotamine tartrate 1 : 100,000, this is followed at A by a second dose of adrenaline 1 : 1,000,000; the rings are then again washed with about 100 c.c. of fluid.
- Curve B.* The same as curve A but larger mesenteric rings (4.0 mm. in diameter); adrenaline and ergotamine followed by another dose of adrenaline were added in the same concentrations as in curve A. The third dose of adrenaline (second after ergotamine) was 1 : 100,000; this was followed at B by barium chloride 1 : 15,000.
- Curve C.* Small mesenteric rings. Upper tracing—effect of adrenaline 1 : 800,000 before ergotamine. Lower tracing—same dose of adrenaline after ergotamine.
- Curve D.* Large mesenteric rings, same concentration of adrenaline as in curve C. Right-hand tracing before and left-hand tracing after ergotamine. All tracings were taken at a temperature of 37.5° C. Reduction $\frac{1}{2}$.

artery which was taken close to the intestine; curve *B* is that of the same mesenteric artery but taken at the root of the mesentery. In both cases the first administration of adrenaline gave a definite constrictor effect. The Ringer's fluid in the Dewar's flask was then changed and time was allowed for the rings to relax. Administration of ergotoxin

was followed in both cases by a transitory constriction after which the arteries relaxed to slightly below their respective base lines. A second administration of adrenaline caused a conspicuous dilatation of the smaller rings but had no effect upon the larger ones. In the latter case even a considerably larger dose of adrenaline which was administered next also failed to have any effect. The smaller rings returned after washing to their original base line; the larger rings though they did not respond to adrenaline constricted on administration of barium chloride. Curve *C* shows the response to adrenaline of a small mesenteric artery before and after ergotoxin; curve *D* shows a response of a large artery. Similar results were obtained in every experiment in which the reversal phenomenon was studied on rings taken from the main trunks of different arteries and from their smaller branches.

On the basis of these experiments we may conclude that isolated arterial rings are suitable for the study of the reversal phenomenon. If the reversal is due to paralysis of the sympathetic vaso-constrictors then we have to assume that only the smaller ramifications of the arteries are supplied with sympathetic vaso-dilators.

(b) *Coronary arteries.* Small doses of ergotoxin (1 : 500,000–1 : 100,000) added at 37.5° C. produce either no effect or a transitory vaso-constriction, followed by a vaso-dilatation, the extent of which depends on the dose. In either case adrenaline continues to produce a marked vaso-dilatation. This was observed even when ergotoxin was added in doses considerably larger than those sufficient to abolish or reverse the effect of adrenaline upon systemic rings. Fig. 4 shows curves obtained from a series of experiments upon the same three rings of a coronary artery. Curve *A* is a normal temperature reaction with the vaso-dilator response to a dose of 1 : 800,000 of adrenaline at 37.5° C. The arterial rings were thoroughly washed in Ringer's solution at 37.5° C. and cooled to 15° C. The temperature was again raised to 37.5° C., and ergotoxin, 1 : 50,000 added (curve *B*). After a transient contraction, a definite relaxation occurred; after which adrenaline (1 : 800,000) added to the perfusion fluid produced a complete relaxation, the curve nearly returning to its original base line. The arterial rings were now thoroughly washed with warm Ringer's solution of 37.5° C. After the original tone was regained ergotoxin was added in two doses, giving a final concentration of 1 : 37,500. The degree of relaxation was comparable to that in the previous experiment; adrenaline was then added to a concentration of 1 : 800,000, the completion of the curve of relaxation being again comparable to the preceding one. In no case have we found

ergotoxin plus adrenaline to relax the coronary artery below its original base line at room temperature. Curve *D* shows the temperature reaction

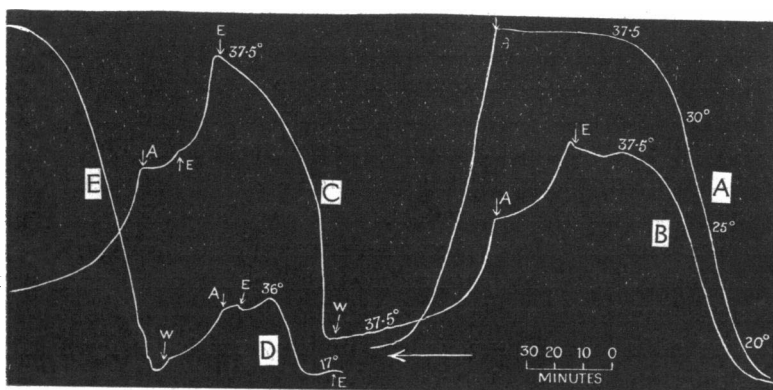


Fig. 4. All curves to be read from right to left.

Curve A. Normal temperature curve of fresh coronary rings. At A adrenaline 1 : 800,000 was added; the rings were then washed with cold fluid. The effect of re-warming is shown by curve B.

Curve B. Ergotamine 1 : 50,000 was added at E and adrenaline same dose as before, at A. The rings after thorough washing with warm fluid spontaneously regain their tone (curve C).

Curve C. Ergotamine is added in two doses making a final concentration of 1 : 37,500; adrenaline 1 : 800,000 again relaxes the rings. The rings are thoroughly washed with cold fluid and ergotamine 1 : 50,000 is added before warming.

Curve D. Shows the effect of warming in presence of ergotamine. At E another dose of ergotamine was added making the final concentration 1 : 37,500; adrenaline 1 : 800,000 added at A relaxes the rings to the original base line. The rings are thoroughly washed in a stream of warm fluid.

Curve E. Shows the recovery of the rings on washing.

All the curves were obtained from the same rings. Rate of drum 1 mm. per minute. Reduction $\frac{1}{2}$.

in the presence of ergotoxin (1 : 50,000), and curve *E* the recovery of the artery on washing. It is thus seen that in large doses ergotoxin antagonises the temperature response of the coronary rings. From a comparison of curves obtained from rings taken from the coronary artery at its origin, and from the smaller arteries within the muscle at the heart's apex, it can be seen that the small coronary vessels are proportionally more reactive to adrenaline than the larger; this would

indicate that the smaller the vessel and the finer its ramification, the richer is it in vaso-dilator supply.

THE EFFECT OF HISTAMINE ON CORONARY ARTERIES. We have found that in the coronary and systemic arterial rings of the dog, man and the ox histamine always caused contraction (Fig. 5). In perfusion experiments on non-beating strips of the ventricular muscle of the rabbit's heart, histamine produced diminution in the rate of perfusion. In experiments with perfusion of long pieces of coronary arteries taken from the heart of the rabbit, histamine also caused contraction. The doses of histamine used varied in the case of perfusion experiments from 1 in 10,000,000 to 1 in 1,000,000, the H-ion concentration of the perfusing fluid being kept constant. The contraction, whether produced on perfused strips of ventricle, perfused pieces of arteries or arterial rings, could be effectively abolished by adrenaline. This forms a very convenient method of showing that in the rabbit and dog adrenaline has a definite vaso-dilator effect, which is independent of the changes that it may induce in the heart muscle.

Experiment. Strip of rabbit's ventricle perfused through left coronary artery with non-oxygenated Ringer's fluid at a pressure of 80 cm. of water; temperature 36.5°C ., pH 7.4.

Drops per minute: 43, 44, 43, 44, 44. Perfusion changed to Ringer's with 1 : 1,000,000 histamine: 43, 31, 23, 17, 16, 13, 11, 12, 12, 10, 12, 11, 12. Injection into cannula of 0.1 c.c. adrenaline 1 : 1,000,000, 12, 16, 20, 21, 17, 14, 12, 11, 10, 11, 10, 11. Injection of 0.1 c.c. adrenaline 1 : 100,000, 27, 34, 36, 35, 22, 17, 15, 14, 15, 11, 13, 10, 11, 10.

The smallest doses of adrenaline which under these conditions were active always produced vaso-dilatation. We failed to observe the pre-

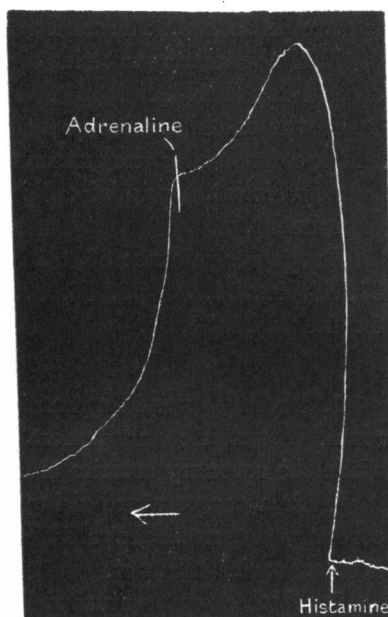


Fig. 5. Effect of histamine (1 : 200,000) upon the coronary rings of the ox; temperature 37.5°C .; three rings are used in a chain. The inside diameter of each ring was at room temperature 2.3 mm., at 37.5°C . 1.5 mm., after addition of histamine 0.5 mm. The effect of histamine was antagonised by addition of adrenaline (1 : 400,000). Reduction $\frac{1}{2}$.

liminary vaso-constriction described by Brodie and Cullis(11) in their experiments upon the perfused beating heart.

In the absence of oxygen the ventricular strips did not contract nor did they exhibit the tonic contracture described by Hammouda and Kinoshita(12). The increased rate of perfusion was therefore due purely to vaso-dilatation. The same results were observed in perfusion of pieces of rabbits' coronary arteries and upon rings of coronary arteries of the ox and dog (Fig. 5).

In the cat histamine produces vaso-dilatation of the perfused strips which corroborates the experiments of Gunn(13).

Experiment. Strip of cat's ventricle; conditions same as in above experiment.

Drops per minute: 36, 35, 35, 35. Histamine, Ringer 1 : 2,500,000: 37, 44, 52, 54, 56, 56, 56, 57. Normal Ringer: 57, 56, 55, 49; after 5 minutes 36, 35, 35.

CONCLUSIONS.

1. Freshly excised systemic arteries of ox, dog and man (carotid, renal, mesenteric and femoral) are at room temperature contracted, while the coronary arteries are completely relaxed.

With a temperature rising from 27° C. to 38° C. the systemic and coronary arteries behave differently: the systemic arteries relax while the coronaries contract.

2. With a temperature rising from 44° C. to 60° C. the coronary and systemic arteries behave similarly, showing a heat paralysis at 48°-50° C. and a heat contracture at 60°-61° C.

3. Isolated systemic rings are suitable for the study of the reversed effect of adrenaline after administration of ergotoxin. The reversal phenomenon is observed only on the smaller ramifications of arteries; in the larger arteries ergotoxin abolishes the constrictor effect of adrenaline but fails to produce a reversal.

4. Ergotoxin does not abolish the dialator effect of adrenaline upon coronary arteries.

5. Histamine contracts the coronary arteries of the ox, rabbit and man and dilates the blood vessels of a perfused strip of cat's ventricle.

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