THE CORONARY CIRCULATION IN THE ISOLATED HEART.

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The correct interpretation of experiments on coronary circulation in the whole animal presents so many difficulties that it is necessary to use simplified forms of technique, which will permit the experimental conditions to be controlled. Apart from the use of isolated coronary blood vessels, the isolated perfused heart and the heart-lung preparation would seem to satisfy the requirements. These two methods have been used by many workers, but not always with concordant results. Porter(1) found in the isolated heart that augmentation both in the strength and in the rate of the cardiac contractions increased the coronary flow; Langendorff(2) and Maas(3) that arrest of the heart diminished the flow. Schafer(4), and especially Wiggers(5), consider that the coronary flow depends intimately upon the massaging influence of the cardiac contraction. On the other hand, Sassa(6) found that acceleration of the heart due to warming the perfusion fluid was accompanied by a considerable diminution in the coronary flow, while acceleration produced by means of heating the sino-auricular node caused a slight augmentation of the flow.

Experiments performed on the heart-lung preparation by Markwalder and Starling(7), Nakagawa(8), Hilton and Eichholtz(9) and Anrep and Segall(10) show that neither driving of the heart at different rates, nor strengthening of the cardiac contraction produced by increasing the stroke output have any appreciable effect upon the minute outflow from the coronary sinus; acceleration of the heart produced by raising the temperature of the blood from 33° to 40° slightly reduces the flow. In the denervated heart-lung preparation, therefore, the arterial blood-pressure is the only mechanical factor which determines the rate of flow through the coronary vessels.

Observations with regard to the action of adrenaline and stimulation of the sympathetic nerve upon the coronary circulation are equally contradictory. Schafer found no effect. Maas, Sassa, Kravkov(11)

observed a vasodilation. Brodie and Cullis(12) observed a vasoconstriction with small doses of adrenaline and a vasodilation with larger doses, whilst Wiggers observed in the resting heart a pure vasoconstriction. On the other hand, all workers who used the heart-lung preparation or isolated rings of coronary arteries (Langendorff(13), Pal(14), de Bonis and Sussanna(15), Campbell(16), Barbour(17), Cruickshank and Subba Rau(18)), found adrenaline to cause a pure vasodilation.

The experiments on the coronary circulation referred to above have been performed on the hearts of cat, dog, sheep, rabbit and ox. It is possible that adrenaline has a different effect in different species of animals, but the contradictory results of the experiments on mammalian hearts cannot be explained in this way, since several workers performed their experiments on the same type of animal.

At the suggestion of Dr G. V. Anrep we have reinvestigated the problem of the coronary circulation in the isolated perfused heart.

Method. One of the main sources of error in experiments upon the perfused hearts arises, as pointed out by Schafer and by Wiggers, from a part of the perfusion fluid leaking through the aortic valves into the left ventricle, so that all the fluid flowing from the heart does not pass through the coronary vessels. Wiggers finds that the magnitude of the leak bears no relation to the coronary flow and that it is necessary to obviate the leak either by inserting the perfusion cannulæ directly into the coronary arteries or by draining the left ventricle. Wiggers points out another possible source of error, namely, the right ventricle by more vigorous contractions may increase the outflow from the heart as it empties its cavity. Ätzler(19) and Sassa, to obviate this error, registered the inflow of the fluid into the coronary blood vessels, while Wiggers and Kravkov worked with arrested hearts. The error can also be eliminated by draining the right ventricle either by means of a tube introduced through the auricle or directly through the wall of the ventricle, the pulmonary veins and artery being in both cases ligatured. Our experiments (63 in number) were performed on isolated rabbits' hearts, which were perfused through the aorta, or through the coronary arteries. In the first case the left ventricle was drained and we found in confirmation of Wiggers that the leak may vary considerably, in our experiments from 8 to 55 p.c. of the total outflow. The coronary flow was collected from the right auricle and ventricle, so that both these were empty of fluid. Two perfusion fluids were used, (*a*) oxygenated carbonate-buffered Ringer's fluid, and (*b*) oxygenated borate-buffered

Ringer's fluid (modified Mines' solutions(20)), the second solution being used to maintain the H-ion concentration of the perfusion fluid constant throughout the experiment, and to avoid precipitation of calcium which usually occurs in ordinary Ringer's fluid. Provided the H-ion concentration of the borate-buffered Ringer is maintained within normal limits, it has no detrimental effect upon the isolated heart, no difference in the contractions of the heart, in the coronary outflow or length of survival of the heart being observed.

The composition of the borate-acetate solution used was as follows: boric acid 0·031 p.c.; sodium acetate 0·068 p.c.; $CaCl_2$ 0·021 p.c.; KCl 0·04 p.c.; NaCl 0·84 p.c.

The measurement of the coronary flow was made either by collecting the fluid in a cylinder graduated to 0·1 c.c. or by the graphic method employed by Brodie and Cullis; in some experiments this was checked by Ätzler's method of registering the coronary inflow. The perfusion pressure varied between 50 and 110 cm. of water. Records of the heart beat were taken in every experiment. The coronary outflow was studied in hearts beating naturally, in artificially driven hearts, in hearts with ventricular fibrillation, and in arrested hearts, the effect of adrenaline being tested in each case.

(*a*) *The effect of adrenaline in the naturally beating heart.* Brodie and Cullis found that small doses of adrenaline diminished the outflow; while larger doses caused a diminution which was followed by a prolonged augmentation, the latter phase predominating over the former with an increase in the dose. Two explanations of the temporary diminution in the coronary flow were considered: (1) that it is due to the augmentations of the contraction and to the acceleration of the heart, which produce a compression of the capillaries and thus increase the resistance to the flow until this effect is overcome by the proper dilatory action of adrenaline; (2) that adrenaline itself in small doses causes constriction, and in larger doses dilation. Brodie and Cullis reject the first explanation on the ground that the diminution of flow begins a few seconds before the augmentation of the cardiac contraction. On the whole our experiments confirm those of Brodie and Cullis, excepting only in respect to the time relations between the onset of diminution in flow and of augmentation of the heart beat. To determine the time relations between the changes in the cardiac contraction and the coronary flow we used two methods, one exactly similar to that of Brodie and Cullis, in which the heart was placed horizontally, and another in which the heart was suspended vertically. The results obtained

with these two methods were different. With the horizontally placed heart we obtained exactly the same time relations as Brodie and Cullis, but with the second method we found that the temporary phase of decreased flow either began simultaneously with the augmented contraction or followed it after an interval of a few beats.

Fig. 1 represents an average effect of a medium dose of adrenaline. Very small doses of adrenaline had in the case of the vertically suspended heart, either no effect or a pure diminution in the outflow, in which case an augmentation of the cardiac contraction or an acceleration were also present.

The difference of these results is due to the greater sensitivity of the recording system with the vertically placed heart; when the heart is lying on its side its contractions have to increase considerably before the increase gets registered, since the heart does not lift itself up with each beat and does not exercise a sufficient pull on the lever.

In several experiments the same heart was experimented upon both in the horizontal and vertical positions and we consistently found the results in the first case to be exactly as described by Brodie and Cullis, whilst in the second they were similar to that shown in Fig. 1[1].

The beginning of the augmentation of flow occurs in most cases at the time when the maximum increase in the contractions starts to fall off. The augmentation of the flow lasts for a very considerable length of time, and if all the experiments are taken into consideration it becomes clear that the increased coronary flow bears no relation to the increase in the cardiac contractions.

(*b*) *Effect of increasing the heart rate and of ventricular fibrillation upon the coronary flow.* The acceleration of the heart beat when produced either by warming the perfusion fluid or by heating the sino-auricular node is complicated in the first case by the effect of temperature upon the coronary blood vessels and in the second case by a possible stimulation of the nerves running within the region of the sinus. In our experiments the heart rate was changed by stimulation of the left auricular appendix with rhythmic induction shocks. We found no augmentation of the coronary flow even with considerable acceleration of the heart. In some experiments there was a small and transitory acceleration with the commencement of driving; however, within a few seconds the

[1] In the beginning of their research Brodie and Cullis also used a vertically suspended heart and in these experiments the beginning of the diminution of the flow was definitely later (so far as is possible to judge from their Fig. 1) than the commencement of the increase in the beat.

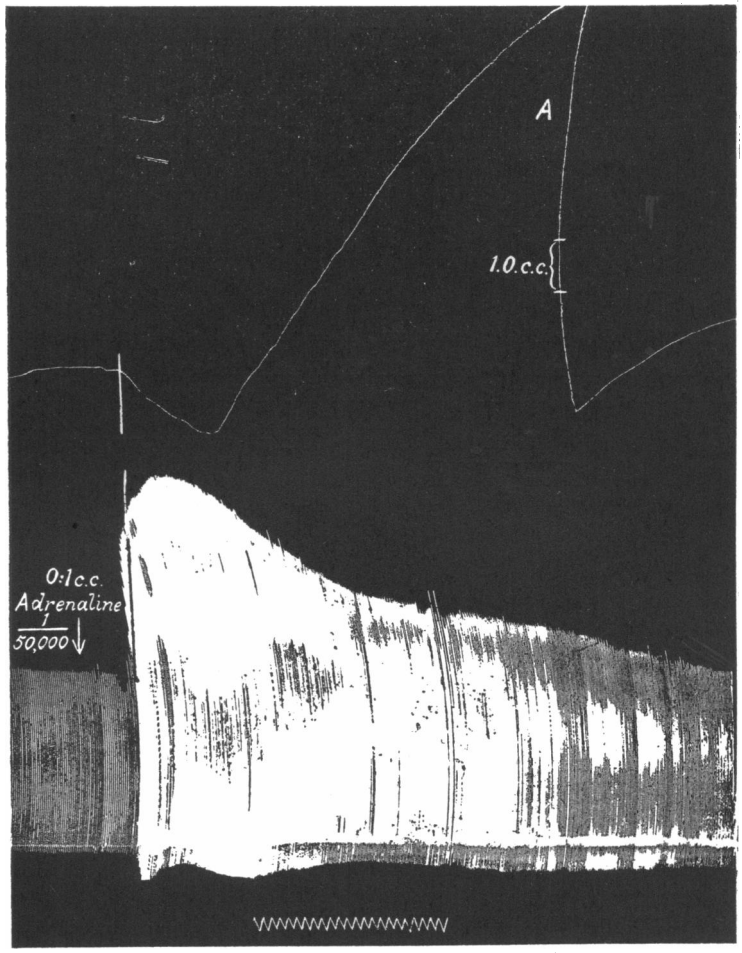

Fig. 1. Effect of 0·1 c.c. of 1 : 50,000 adrenaline upon the heart beat and the coronary outflow. The heart is suspended in a vertical position; systole is registered in all tracings by an upward movement of the lever. The coronary flow (8 c.c. per minute before injection of adrenaline) was registered by the method of Brodie and Cullis. The temporary diminution in the coronary flow is synchronous with strengthening of the heart beat. At *A* the lever of the recording apparatus was lowered. The tracing should be read from left to right. Time in this and the rest of the tracings is recorded in 5 seconds.

flow returned to its initial magnitude or sometimes fell even below it (Table I).

Injection of adrenaline into a heart which is driven at a constant rate produces a transitory diminution followed by an augmentation of the coronary flow; the changes are comparable with those observed in hearts beating at their spontaneous rhythm. It thus becomes evident that the augmentation of the coronary outflow cannot be explained by the acceleration of the heart beat, in driven hearts, since adrenaline fails to cause any such acceleration provided of course that the artificial heart rate is above the maximum effect of adrenaline on the heart beating spontaneously.

TABLE I. Effect of heart rate upon the coronary outflow per minute.

(The heart rate was changed by application of rhythmic induction shocks to the left auricular appendix. The artificial rate was maintained in each case for not less than 5 minutes.)

	Heart rate		Coronary flow c.c. per min.	
	Before	After	Before	After
Exp. 1	64	110	6·4	6·4
	66	120	7·0	6·8
	60	180	7·0	6·2
Exp. 2	52	80	5·0	5·0
	52	100	5·0	4·8
	50	180	6·0	4·8
Exp. 3	40	85	3·2	3·4
	40	100	3·6	3·4
	40	130	3·4	3·0

The experiments given in the above table show that in confirmation of observations on the heart-lung preparation, acceleration of the heart beat within wide limits has no effect upon the minute flow through the coronary blood vessels. If, however, the acceleration is excessive, the coronary flow tends to diminish.

While changes in the heart rate have no effect upon the coronary flow, ventricular fibrillation causes a definite augmentation of the flow. Fibrillation was produced in our experiments by stimulation of the ventricle with a strong faradic current. When ventricular fibrillation is produced early in the experiment the heart fibrillates in a state of nearly complete diastole; the coronary outflow is always in these cases augmented (Exp. 4). This observation confirms the experiments of Maas and of Hilton and Eichholtz on the dog's heart.

Exp. 4. Rabbit's heart perfused with borate Ringer, *p*H 7·4, temp. 38° C., heart rate 50–60 beats per minute. Coronary flow in c.c. per minute, 5·4, 5·4, 5·4. Strong faradic current is applied for 10 seconds to the left ventricle; both ventricles continue to fibrillate

after the removal of the current; the coronary flow augments to 5·6, 7·0, 8·6, 8·8, 8·4, 8·4 c.c. per minute.

The increased coronary flow lasts so long as the fibrillation continues. In cases when the ventricles spontaneously recover from fibrillation the coronary flow diminishes to its previous level.

At the end of an experiment when the ventricles are contracting with diminished strength or stop altogether, a short faradic stimulation will also send the heart into fibrillation; this will not, however, bring about a relaxation of the ventricles which fibrillate in a semi-contracted state. In this case fibrillation does not cause any increase in the coronary flow.

The experiments on fibrillation show that the coordinated contractions of the heart do not exercise a greater massaging action upon the coronary blood vessels than does fibrillation.

Injections of adrenaline into a fibrillating heart causes a definite augmentation of the coronary flow (Exp. 5).

Exp. 5. Rabbit's heart perfused with carbonate Ringer solution. Perfusion pressure 100 cm. of water, temp. 36° C. Before the injection of adrenaline the coronary outflow was 8·8–9·0 c.c. per minute and the heart rate 50 beats per minute.

After injection of 0·2 c.c. of 1 : 40,000 (readings every 30 seconds):

C. flow in c.c. per min.	7·0	12·0	13·4	13·4	13·0	12·6	11·8	11·6	10·0	9·4	9·0	8·8
H. rate per min.	80	86	74	74	70	62	62	52	46	46	46	46

The ventricles are now set into fibrillation by a short faradisation, the coronary flow augments from 8·8 to 10·2 c.c. per minute at which level it stays for 5 minutes. The same dose of adrenaline is now injected. The ventricles now fibrillate much more vigorously and the coronary flow increases about 20 seconds later.

C. flow in c.c. per min.	10·2	12·4	14·4	14·4	14	13·2	12·6	11·8	11·0	10·8	10·4

Two outstanding details in the action of adrenaline upon a fibrillating heart should be mentioned; the first is the complete absence of the preliminary period of diminution of the coronary flow which is of nearly constant occurrence in the rhythmically beating ventricle; the second is the almost equal latent period for the dilation to take place in both the rhythmically beating and the fibrillating ventricle. It seems to us that if adrenaline has a true constrictor action which brings about the preliminary diminution in the flow then this constriction should occur in the fibrillating ventricle. The preliminary diminution is more satisfactorily explained by increased resistance to the flow owing to the more vigorous systole compressing the intramuscular coronary blood vessels.

This explanation is strengthened by a few experiments in which the

fibrillation of the ventricle stopped spontaneously after adrenaline had been injected (Exps. 6 and 7).

Exp. 6. Rabbit's heart perfused with borate Ringer's fluid; the coronary outflow is registered every 20 seconds; perfusion pressure = 85 cm. H_2O; the coronary flow is steady for 5 minutes at 5·4 c.c. per minute. The ventricles are now set into fibrillation by a short faradisation; the coronary flow during fibrillation of the ventricles augments to 6·4 c.c. per minute. Injection of 0·2 c.c. of adrenaline 1 : 40,000 increases the coronary flow to 6·4, 7·4, 9·8 c.c. per minute. At this stage the auricles begin to beat at 60 and both ventricles beat feebly at 40 beats per minute, the coronary flow falling to 9·6, 9·0, 8·2 c.c. per minute. The ventricles are again caused to fibrillate after the end of the faradisation; the coronary flow is 7·6, 7·4, 7·0 c.c. per minute in consecutive periods of 20 seconds. Two minutes later fibrillation is still present and the coronary flow is 6·2 c.c. per minute.

The effect of adrenaline in this experiment was not changed by the onset of the cardiac contractions. In other experiments in which the contraction started with more vigour the effect was to diminish the coronary outflow (Exp. 7).

Exp. 7. Rabbit's heart perfused with borate Ringer's fluid; perfusion pressure = 60 cm.; coronary flow = 4·8 c.c. per minute. Ventricular fibrillation is induced by a short faradisation; the coronary flow augments to 5·1, 5·6, 6·4 c.c. per minute. Fibrillation stopped spontaneously and the coronary flow dropped to 4·0, 4·4, 4·5, 4·6 c.c. Ventricular fibrillation is induced for a second time and after the coronary flow reached a steady level of 6·6–7·0 c.c. per minute 0·2 c.c. of 1 : 40,000 adrenaline is injected.

Coronary flow in c.c. per min.: 7·0, 8·6, 9·4, 8·8, 8·4, 8·4, 7·6. The ventricles continue to fibrillate the whole time. After an interval of 10 minutes another 0·2 c.c. of adrenaline is injected. Coronary flow in c.c. per min.: 6·6, 8·4, 9·2, the ventricles suddenly recover from fibrillation and beat forcibly at the rate of 75 per minute; the coronary flow abruptly diminishes to 6·0, 5·6, 4·8 c.c. per minute and reaches after an interval of 5 minutes 3·6–4 c.c. a minute.

Injection of adrenaline in the later stages of the experiment, whether into the fibrillating or the beating heart, never produces the same degree of augmentation in the flow as while the heart is fresh.

The doses of adrenaline necessary to produce acceleration and especially augmentation of the contractions are much smaller than those which cause a dilation of the coronary blood vessels. In experiment with very small doses it can be clearly seen that the heart does respond with vigorous contractions and beats faster, but only a pure diminution of the flow can be observed which is not followed by an increase and which coincides with the period of strong cardiac contractions.

(*c*) *Effect of arresting of the heart in diastole and in systole.* The heart was arrested by the following methods: (1) removal of oxygen; (2) perfusion with oxygenated or unoxygenated 0·9 p.c. NaCl of the same H-ion concentration (Wigger's method); (3) perfusion with Ca-free Ringer; (4) perfusion with Ringer solution containing strophanthin

1 : 30,000 for 10–15 minutes; (5) perfusion with Ringer containing cyanides.

To that we may add a few experiments in which there was observed a spontaneous cessation of contractions. In the case of removal of oxygen or injection of sodium cyanide we observed a quick increase in the coronary flow, thus confirming the observations of Hilton and Eichholtz. With oxygen-free solutions a progressive weakening of the contractions was caused.

Administration of Ca-free Ringer, strophanthin and oxygenated saline had no immediate effect upon the coronary flow, but after 5–10 minutes when the heart became arrested in diastole the coronary flow was always considerably increased. Fig. 2 shows a case in which the

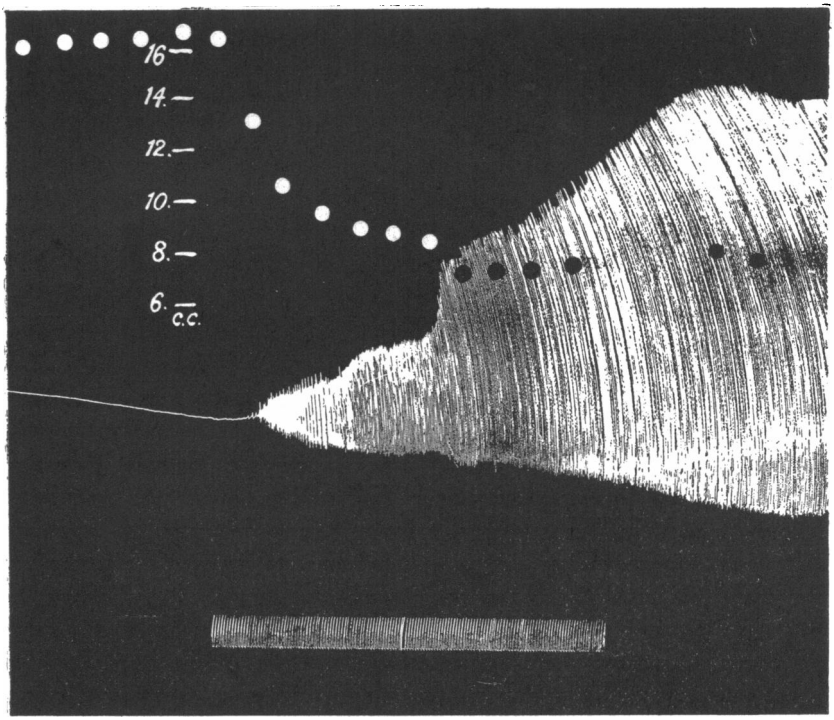

Fig. 2. Effect of diastolic arrest of the heart upon the coronary outflow. The heart is perfused with oxygenated saline of *p*H 7·4. The coronary outflow is shown by the black and white dots. The tracing should be read from right to left.

heart was arrested in diastole by perfusion with oxygenated saline, in this instance the coronary flow being doubled.

When the heart is arrested in systole whether this is preceded by ventricular fibrillation or not, the coronary flow is greatly diminished. This is illustrated in Fig. 3. The heart was being perfused with non-oxygenated Ringer solution and consequently the coronary flow was

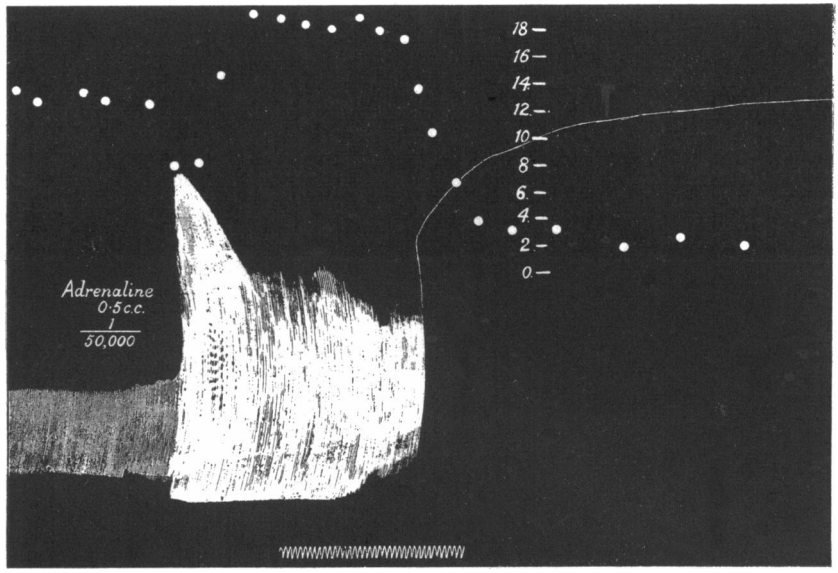

Fig. 3. Effect of adrenaline and of systolic arrest of the heart upon the coronary outflow (white dots). The tracing should be read from left to right.

large. A large dose of adrenaline was then injected, which as usual at first decreased and then increased considerably the coronary flow. Suddenly the heart went into a systolic contraction which was preceded by violent ventricular fibrillation; it contracted definitely beyond the maximum height of contraction in the first phase of the action of adrenaline. Simultaneously with this arrest in systole the coronary flow diminished from over 18 c.c. to about 3 c.c. per minute. We had several more cases in which the heart assumed such a prolonged systolic contraction, either for no obvious reason or after a large dose of adrenaline; in every case the coronary flow greatly diminished: on the other hand, if the heart was arrested in diastole the coronary flow increased.

We have now to deal with the contradictory observations concerning the action of adrenaline on the beating heart and on the arrested heart. Those authors who worked on the beating rabbit's heart found

that adrenaline caused vasodilation; most of those who worked on the arrested heart found a diminution in the coronary flow which was explained by vasoconstriction. However, Elliott(20), perfusing quiescent pieces of the cat's heart, found that adrenaline caused a vasodilation; Kravkov found also a vasodilation in the rabbit's heart which was arrested by strophanthin; no precautions were taken, however, to obviate the leak through the aortic valves. Wiggers and Campbell observed a diminution of the outflow which they ascribed to vasoconstriction.

As shown in Fig. 2 a diastolic arrest of the heart is accompanied by a considerable increase in the coronary flow. In this experiment the arrest of the heart was produced by substituting the Ringer fluid by saline both oxygenated and both of *p*H 7·4. In the cases when the diastolic arrest comes on spontaneously without any modification of the perfusion fluid the sequence of events is exactly the same. However, in none of the cases the coronary flow remains at its new high value

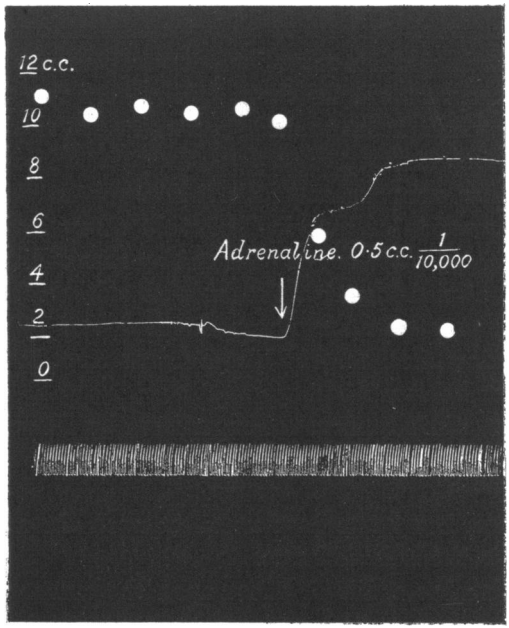

Fig. 4. Effect of adrenaline upon the coronary flow on the arrested heart (white dots). The curve shows the contracture of the heart muscle. The tracing should be read from left to right.

for more than 2–5 minutes; the flow soon begins very gradually to diminish, this period of diminution continues in different hearts for about 15–30 minutes when the flow reaches a minimum. In every case it can be noticed that simultaneously with the diminution of the flow the state of the heart muscle changes also. The heart gradually and spontaneously enters into a state of contraction which finally brings about a greater shortening of the muscle fibres than that observed in the strongest contractions of the beating heart. We are not in a position to say whether this contracture is due to a quickly developing rigor or a real tonic contraction. Adrenaline accelerates the development of this contracture, a case which is illustrated by Fig. 4. In this experiment the heart arrested spontaneously; before the arrest the coronary flow varied between 5 and 6 c.c. per minute after the arrest it augmented to 11 c.c.; an injection of adrenaline was followed by a contracture of the muscle and a simultaneous diminution in the outflow to about 2 c.c. per minute. If adrenaline is injected soon after the arrest of the heart and in not large doses, an acceleration of the flow can be sometimes observed; in most cases, however, it is diminished. Fig. 5 shows the effect of six successive injections, each followed by a diminution of the outflow. From the second injection onwards the muscle relaxes after the effect of adrenaline has worn off, the coronary flow correspondingly increases.

While the whole heart when arrested reacts to adrenaline by a diminution in the outflow it is easy to show that this diminution is not due to an active compression of the blood vessels, but rather to an increased compression of the capillaries. If a few incisions are made in the muscle so as not to cut any larger branches of the coronaries and the perfusion carried through the arterial side, adrenaline shows a definite dilator effect which is not counterbalanced by the contraction of the surrounding muscles. The blood vessels react in this case in the same manner as isolated rings.

These observations confirm the experiment by Elliott, who worked on strips of cat's heart.

Conclusions.

1. Changes in heart rate have no effect upon the magnitude of the coronary flow in the isolated heart.

2. Adrenaline has a dilator effect upon the coronary blood vessels of the rabbit.

3. The preliminary diminution of the coronary flow is due to mechanical factors; it coincides with the period of maximal contractions of the heart.

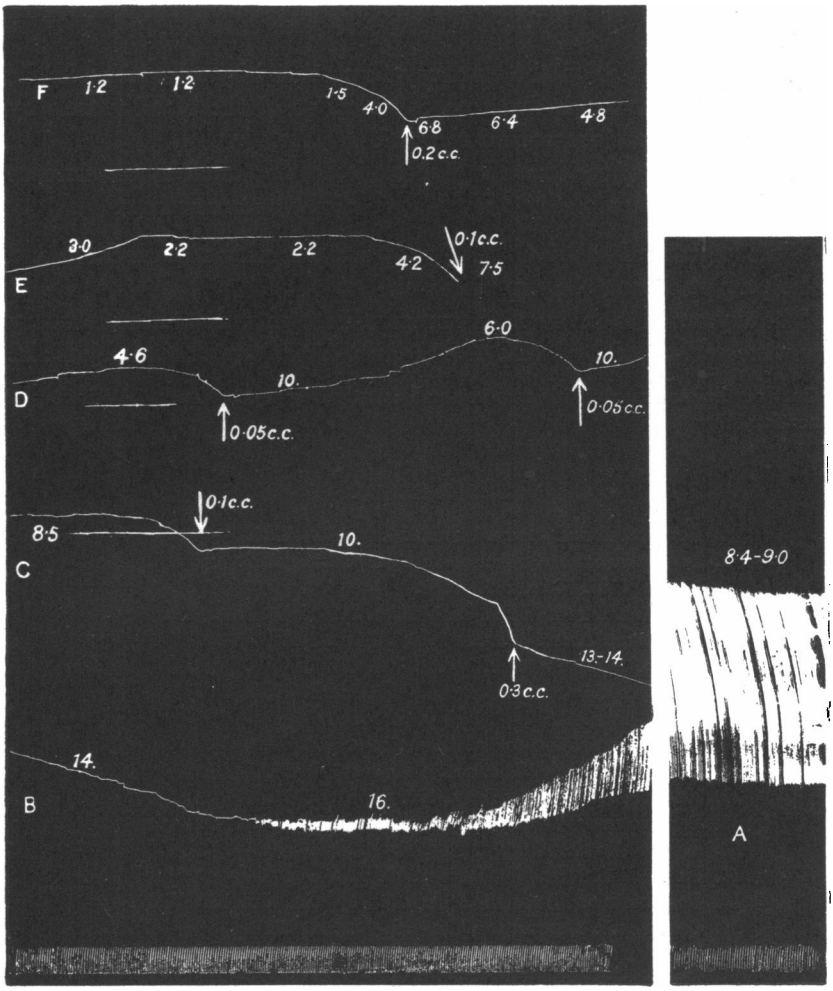

Fig. 5. The tracing should be read from right to left. *A*, normal heart beat and coronary flow; *B–F*, effect of six injections of adrenaline upon the arrested heart. Adrenaline (1 : 50,000) is injected at the arrows. The magnitude of the coronary flow is shown by the figures on the curve. Tracings *B–F* are continuations of one another. The four short horizontal lines indicate the height of the normal systolic contractions: it can be seen that the heart enters into a state of contracture which finally becomes more vigorous than the normal systole. The coronary flow progressively diminishes with increase of contracture. Each injection of adrenaline accentuates the contracture and the diminution of the coronary flow.

4. Fibrillation of the relaxed ventricle increases the coronary flow; the dilator effect of adrenaline can be also shown on the fibrillating heart.

5. The diminution in the coronary flow caused by adrenaline in the arrested rabbit's heart is due to a compression of the blood vessels by the muscle and not to vasoconstriction[1].

6. The arrest of the heart in diastole is accompanied by an increase and the arrest in systole by a diminution of the coronary flow.

We are grateful to Dr G. V. Anrep for directing this research and for helping us during the experiments.

The experiments on the plethysmographic registration of the coronary flow were performed by R. K. All the rest of the experiments by M. H.

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[1] Since these experiments were completed, one of us found that adrenaline considerably augments the coronary flow in rabbits' hearts which are arrested by arecoline; in this case however adrenaline fails to cause any contracture of the cardiac muscle.

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