A NOTE ON SOME FACTORS WHICH DETERMINE THE BLOOD-FLOW THROUGH THE CORONARY CIRCULATION.

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Various methods have been employed for the investigation of the coronary circulation. Bohr and Henriquez(1) judged of the amount of blood flowing through these vessels by comparing the total outflow through the aorta and the pulmonary artery respectively in a heart fed for a few minutes with defibrinated blood. Brodie and Cullis(2), as well as Wiggers(3), employed excised hearts perfused with Ringer's fluid. Langendorff(4) and Cow(5) examined the behaviour of strips of the coronary artery immersed in Ringer's fluid. Meyer(6) determined the outflow from a cannula placed in one of the superficial coronary veins. Of the methods so far adopted it seems to us that the best is that devised by Morawitz(7). This observer catheterises the coronary sinus in the living heart. For this purpose he has had constructed a double-walled cannula with a bulbous extremity which enters easily the coronary sinus. Just behind the bulbous end is a hole communicating with the outer chamber of the cannula. Over this hole is a ring of rubber membrane. Fluid can be forced through a side tube into the outer chamber so as to distend the rubber ring. The cannula is inserted through the right auricular appendix, escape of fluid being prevented by tying the tip of the appendix tightly round the stem of the cannula. The introduction of the cannula into the coronary sinus presents no difficulty, and its end can be felt and seen as it enters the thin-walled sinus. When it has been introduced the rubber ring is distended, thus fixing the cannula firmly in the mouth of the coronary sinus. The other end of the cannula has attached to it a tube which passes through the right thoracic wall. From this tube the blood drops either into a measuring cylinder or on to some volume counter. Of course it is necessary to prevent coagulation of the blood by the injection

of hirudin. When applied to the heart *in situ* this method of Morawitz enables conclusions to be drawn as to the influence of different factors on the blood-flow through the heart muscle. An analysis of these changes is not however easy, since it is difficult to dissociate the direct effects of a drug, *e.g.* adrenalin, on the blood vessels and the indirect effect it may produce by rise of blood-pressure or alteration of other conditions of the heart. It seemed to us that this method was admirably adapted for investigating the coronary circulation in the heart lung preparation employed in this laboratory, in which complete control can be exercised over the arterial pressure, the venous pressure, the venous inflow and the temperature of the heart. Prof. Morawitz very kindly placed at our disposal several coronary sinus cannulæ made to his instructions by his mechanic.

Methods. All our experiments were carried out on medium sized dogs, varying from 6 to 10 kilos in weight. These were anæsthetised as usual with morphia and A.C.E. mixture and a heart lung preparation made as detailed in Knowlton and Starling's paper(8). The side branch from the arterial cannula was connected with a mercurial manometer, the excursions of which were recorded on a kymograph. The total outflow from the venous end of the apparatus, *i.e.*, the output of the heart minus the blood flowing through the coronary arteries, was measured in some cases by a syphon Stromuhr(9). In other cases it was allowed to flow into a graduated cylinder and the time taken to collect 25 or 50 c.c. determined by means of a stop-watch. When the heart lung preparation had been made, a Morawitz cannula was introduced into the coronary sinus. The blood flowing through the cannula was received into a beaker and returned to the venous reservoir every few minutes. The coronary outflow was determined by receiving the blood into a measuring cylinder and finding the time in seconds required to collect 10 or 25 c.c. When we wished to intermit the observations for a time, the tube from the coronary cannula was connected with a side branch of the tube leading from the venous reservoir to the superior vena cava, so that the coronary blood could take its normal course into the right auricle. The presence of the cannula in the coronary sinus seemed to cause little or no disturbance of the heart's action, and the heart continued to beat normally and to maintain normal blood-pressure and normal outflow for two to four hours, which was as long as was necessary to make the series of observations in any given experiment. In some cases the rubber ring occluded partially or completely the opening of the posterior cardiac

vein into the sinus. The result was the production of a infarct limited to the ventricular and auricular walls in the immediate neighbourhood of the opening of this vein.

1. *The relation of the outflow from the coronary cannula to the total flow through the coronary arteries.*

Morawitz was of the opinion that by his method the whole of the coronary blood was conducted outside the heart, so that in determining the outflow from the cannula one was determining the total blood supply to the cardiac muscle. It must be remembered that the large posterior cardiac vein opens into the coronary sinus close to its orifice, so that if the cannula is introduced some way into the coronary sinus it may miss the vein altogether. In other cases the vein may be partially obstructed, and it is doubtful which side of the obstruction the blood will flow into the coronary sinus. Besides this large vein there are some small cardiac veins opening into the right auricle, and the veins of Thebesius which open directly into the right ventricle. The outflow therefore could not represent the whole of the coronary flow, although we imagined that it would represent all but a very small fraction. It was necessary however to make certain of this point. The question was therefore investigated by one of us with Dr Evans, and the experiments have been described more fully in another paper(10). The result was to show that a very considerable proportion of the blood passing through the heart is not collected through the coronary cannula but passes by other ways into the right auricle. The exact proportion varied in different experiments. The outflow from the coronary cannula was always greater than half the total flow through the heart muscle and was generally less than two-thirds. On the average we may say that three-fifths of the coronary blood is collected by the coronary cannula and about two-fifths is missed by this method. In dealing with the influence of various factors on the coronary circulation it is therefore essential to know whether these two fractions of the coronary circulation are altered proportionally or whether the flow through the coronary sinus may be altered independently of the flow through the other channels into the right side of the heart.

In order to decide this question the heart of another dog was fed through the aorta and coronary arteries from an ordinary heart lung preparation, by means of a side branch running off from the arterial cannula close to its connection with the innominate artery. Cannulæ were inserted into the pulmonary artery and into the coronary sinus of

the fed heart, the former giving the total flow through the coronary vessels, minus that through the coronary sinus, while the latter gave the flow through the coronary sinus only. The arterial blood-pressure in the heart lung preparation was kept at 80 mm. Hg, and the temperature varied between 34·8 and 36·4 C. It will be seen from the following figures that the ratio of the blood passing by the cannula in the coronary sinus to the blood collected by the cannula in the pulmonary artery was approximately constant throughout the experiment, although considerable alterations were produced in the total flow, first by the injection of adrenalin, and secondly by the induction of asphyxia.

TABLE I.

Time, mins.	Temperature	Outflow, coronary sinus, c.c. per min.	Outflow, pulmonary artery, c.c. per min.	Ratio of pulmonary outflow to sinus flow
0	34·0	21·4	11·9	·56
3	34·8	20·7	11·9	·57
9	36·0	23·5	11·9	·51
11	36·4	21·3	11·9	·55
13	Adrenalin administered.			
15	36·4	34·5	21·6	·62
17	36·2	45·5	23·2	·51
20	36·0	36·6	23·3	·64
21	Asphyxia begun.			
23	35·5	34·5	21·5	·62
25	36·0	37·0	24·3	·66
27	36·0	43·7	28·3	·65
30	36·0	89·5	60·0	·67
31	35·7	111·0	66·5	·60
32	Circulation fails.			

We thus see that although in this experiment the total circulation through the heart varied from 32 to 177 c.c. in a minute, the ratio of the blood flowing through the sinus to the blood flowing through the other vessels of the heart varied only between ·51 and ·67, and if we take the mean of the ratio during the different periods, the difference is still smaller.

We may then take the flow through the cannula as accounting for at least three-fifths of the total flow through the heart and as showing variations under different conditions, which apply equally to the other coronary vessels whose blood is not being collected.

2. *The influence of the arterial pressure on the coronary circulation.*

The coronary flow is extremely susceptible to changes in the arterial pressure. In a number of experiments which had previously been carried out in this laboratory the arterial pressure had been purposely left low in order to spare the heart, as we imagined, as much as possible. The experimental results which follow show that under these circumstances the blood-flow through the heart muscle was very small and in fact insufficient for its needs. We therefore advise that in all cases where this heart lung preparation is made use of, the arterial resistance should be adjusted so as to maintain an average pressure of 90 mm. Hg in the innominate artery. The results obtained in various experiments on hearts of different sizes are shown in the following tables.

TABLE II.

In all the experiments the temperature was kept between 34° C. and 36° C.

EXP. I.

Time, mins.	Arterial B.-P., mm. Hg	Coronary sinus output, c.c. per min.
0	75	12
7	75	11
12	115	26
14	140	40
18	72	9
21	110	18

EXP. II.

Time, mins.	Arterial B.-P., mm. Hg	Coronary sinus output, c.c. per min.
0	110	31
5	110	27
6	140	67
8	140	64
11	110	32
15	110	30
19	80	19
23	50	9
26	50	10
29	110	39

EXP. III.

Time, mins.	Arterial B.-P., mm. Hg	Systemic output, c.c. per min.	Coronary sinus output, c.c. per min.	Calculated total coronary output	Calculated total output of heart
0	94	280	36	60	340
8	32	319	15	25	344
14	58	306	23	38	334
18	77	306	35	58	364
21	96	254	63	105	359
23	116	223	96	160	383
26	77	278	41	68	346
29	77	—	45	72	—

EXP. IV.

0	60	160	66	110	270
3	80	85	106	175	260
5	100	70	150	250	320
6	100	55	147	245	300
8	80	75	108	180	255
10	60	125	75	125	250
12	40	150	45	75	225
14	20	155	24	40	195
16	60	105	84	140	245

From the above tables it will be seen that the increase in the coronary flow caused by raising the arterial pressure may give rise to an appreciable modification of the total outflow from the aorta. The outflow from the aorta in fact does not represent the total output of the heart. We must add to this outflow the coronary flow. If the total outflow from the aorta, or the ventricular output, is small, the coronary flow may form a very considerable fraction of the total ventricular output. In the last two columns of the tables from Exps. III and IV we therefore give the probable total coronary flow[1] obtained by multiplying the flow from the coronary cannula by $\frac{5}{3}$, and the total cardiac output obtained by adding this figure to the output directly measured on the venous side of the arterial resistance, *i.e.*, the amount of blood which flows through this resistance into the venous reservoir. It will be seen that we can never speak of any relationship between the total output of the heart and the total coronary outflow. If the heart is in good condition its total output depends entirely on the venous pressure, *i.e.*, on the amount of blood available to fill it during diastole, and the pressure at which this filling takes place. The coronary flow on the other hand is independent of the total cardiac output and depends solely on the pressure obtaining at the root of the aorta. Of course in the whole animal the pressure in the aorta will be largely determined by the venous filling of the heart, and venous filling and arterial pressure will therefore alter more or less together. But there may be wide divergences between these two conditions, since the chief factor in the arterial pressure is the amount of resistance which the blood has to overcome in the arterioles. In Exp. III, taken from a small dog, the total coronary flow, even under high arterial pressure, was not equal to the amount of blood flowing through the systemic resistance, though even here the total coronary flow was 160 in the minute, while the amount of blood left over to pass through the peripheral resistance was only 223 c.c. per minute. On the other hand in Exp. IV, in which the heart was large and the venous inflow for so large a heart relatively small, the total coronary flow, even at a pressure of 60 mm. Hg, was not ever below one half the total output from the left ventricle, while under a pressure of 100 mm. Hg the total coronary flow rose to 250, while the flow of blood through the peripheral systemic resistance only amounted to 70 c.c. per minute. A comparison of the figures showing the systemic output, *i.e.*, the amount of blood which is forced through

[1] It is remarkable in Exp. III how constant this total is under different pressures; much more so than the output as measured by the flow through the peripheral resistance.

the artificial resistance, with the total output in the last column, as calculated by adding systemic output and total coronary flow together, will show what a considerable fallacy can arise if we take the output through the systemic resistance as really representing the chief work of the heart. In this case the heart was mainly employed in driving blood through its own vessels. It must be noted that the figures obtained from the coronary flow in this case were exceptionally high, but a reference to the paper (10) already published by one of us with Dr Evans will show that figures of 100 c.c. per minute frequently occur even in medium sized hearts.

3. *The influence of chemical factors on the coronary circulation.*

We have used the method described above to determine the influence of alterations in the composition of the blood, such as that produced by injection of adrenalin, by administration of carbon dioxide, and by asphyxia, on the coronary circulation.

(*a*) *Effect of adrenalin.* The effect of adrenalin on the coronary circulation has already been often investigated. Most authors have found a dilator effect of adrenalin, *e.g.*, Cow, Langendorff, Morawitz, Meyer. According to Brodie and Cullis a very minute dose of adrenalin causes a decreased coronary flow for 80 secs., followed by an increase, and with a still smaller dose constriction only was produced. In our experiments we have observed only a dilator effect of adrenalin. However small the dose, if we obtained any effect at all, it was one of dilatation and quickening of the blood-flow through the coronary sinus. Thus a dose of adrenalin 1 in 100,000 gave rise to the following alteration in the coronary circulation.

Before the injection 10 c.c. passed in the following times:

Secs.:—12·8, 13·8.

After the injection the coronary flow as measured by the time requisite to collect 10 c.c. was as follows:

Secs.:—8·8, 8·8, 8·6, 8·2, 8·2, 10.

The readings are taken at minute intervals.

With large doses the effect was more marked, as shown in the following experiment.

Output in c.c. per minute by coronary sinus.

75	*100	115	124	124	124	77	
72	*100	120	120	110	*124	103	120

An injection of 1 or 2 c.c. of 1 in 10,000 adrenalin was given at the asterisk.

The same effect is seen in Table I.

(*b*) *Effect of carbon dioxide.* The effects of carbon dioxide on the circulation through the coronary vessels were tested by attaching a large balloon containing a known mixture of this gas with air and oxygen, and the inlet side of the bellows used for artificial respiration. In every case we found that the effect of carbon dioxide on the coronary vessels was the same as that shown by Bayliss(11) and other observers in other blood vessels of the body, and the same as its effect on the heart itself, namely, one of relaxation or dilatation. The following table gives the results of an experiment of this character in which a mixture of carbon dioxide, containing about 12 % of the gas, was administered.

TABLE III.

Time	Arterial B.-P.	Systemic output	Coronary output	Pulse rate
0	80	190	43	92
2	CO_2 (about 12 %) administered.			
3	80	150	41	98
4	80	85	43	88
5	70	60	43	88
7	66	50	54	88
8	66	55	62	82
9	66	20	75	76
10	65	10	89	—
11	Administration of CO_2 discontinued.			
12	48	10	85	80
13	78	240	120	82
14	78	210	100	104
15	78	270	67	104
16	78	230	54	92
17	78	240	47	88
18	78	240	44	100

The heart dilated, the systemic output diminished continuously, and the blood-pressure, as measured at the beginning of the innominate artery, fell considerably until it was too low to force any blood through the arterial resistance. The administration of the gas was then discontinued, its place being taken by ordinary air. The heart rapidly recovered, emptying itself of the excess of blood which had accumulated in its cavity. With the failure of the heart the coronary flow steadily increased, and was at its highest just after the heart had begun to recover and had raised the arterial blood-pressure to the height ruling at the beginning of the experiment.

(*c*) *Effect of asphyxia.* Still more marked than the influence of carbon dioxide is the effect produced by the total products which

accumulate in the blood during asphyxia. In the following experiment (Table IV) the coronary output was increased, when the heart was

TABLE IV.

Time, mins.	Temperature	Arterial B.-P.	Coronary output
0	35·8	110	33
2	35·8	110	33
3	Respiration stopped.		
5	35·0	110	37
8	34·8	105	40
10	34·9	105	58
12	34·9	105	67
14	34·8	92	75
16	34·8	80	79
17	Heart irregular.		
18	Delirium cordis.		

asphyxiated, from 33 at an arterial pressure of 110 mm. Hg to 79 at an arterial pressure of 80 mm. Hg. This was in a small heart. A still more marked effect is shown in the experiment given on p. 278 (Table I) where the blood-flow from the coronary sinus rose from a normal of 21·4 c.c. per minute to 111 c.c. per minute just before the circulation failed. In this action of asphyxial blood other metabolites than carbon dioxide must play an important part. In fact, we may say that whenever the heart is failing, the circulation through its vessels is increased, and this increase may be marked even when the aeration of the blood is well carried out so that no opportunity is allowed for the accumulation of carbon dioxide in this fluid. It is probably on account of the accumulation of non-volatile metabolites in the blood that the coronary flow tends to increase steadily in the course of a long experiment, and for the same reason a temporary large flow may be observed at the very beginning of the experiment as a result of the partial asphyxiation of the cardiac tissue which may take place when the circulation is being changed from natural conditions to those appertaining to the heart lung preparation. Indeed so marked is this influence of metabolites that we should be inclined to ascribe the action of adrenalin to this factor were it not for the observations of other workers on the influence of this substance on isolated coronary vessels. The injection of adrenalin, as Evans has shown, enormously increases the metabolism of the heart muscle and causes the blood flowing through the heart muscle to be much more venous than under normal circumstances. The production of other

metabolites must therefore be increased in the same proportion and must play their part in bringing about the dilatation of the coronary vessels produced by administration of adrenalin.

This effect of metabolites was also observed by Morawitz, who was struck with the increased flow from the coronary sinus which he obtained after injecting into the animal the blood collected from the coronary sinus. Under these conditions it would seem that the heart muscle during its contraction produces special substances which act as specific vaso-dilators for the coronary vessels.

Conclusions.

1. Morawitz's method of catheterising the coronary sinus can be applied with ease to the heart lung preparation.

2. The blood which can be collected in this way from the coronary sinus amounts to about three-fifths of the total blood flowing through the heart wall.

3. Variations in the coronary sinus flow are accompanied by similar variations in the flow through the other vessels of the heart, so that the results obtained from the flow through the sinus may be extended to apply to the total circulation through the heart wall.

4. The coronary circulation is intimately dependent on the arterial pressure. Hence it is necessary in an excised heart to maintain a normal arterial pressure if the heart muscle is to be properly supplied with blood.

5. In confirmation of other workers we find that adrenalin causes dilatation of the coronary vessels. We have not been able to detect evidence of constriction with small doses.

6. Increased tension of carbon dioxide in the blood causes dilatation of the coronary vessels associated with dilatation of the heart.

7. The most potent agent in causing dilatation of the coronary vessels is non-volatile metabolites produced by the heart muscle. By this means a local mechanism is supplied by which the heart muscle will increase the circulation through itself whenever increased demands are made on its functional capacity. In asphyxia the circulation through the heart is at its maximum just before the heart fails altogether.

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