ON THE CORONARY CIRCULATION IN THE HEART-LUNG PREPARATION.

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In an investigation by Markwalder and Starling(1) on the factors which influence the blood flow through the coronary arteries, it was shown that in the increase of blood flow through the heart muscle which accompanies increased activity of the heart, three factors were involved. These were (1) rise of the arterial blood-pressure, (2) stimulation of the sympathetic nerve, or the presence of adrenalin in the blood, (3) the production of metabolites by the heart muscle, when for any reason its supply of oxygen falls short of its requirements. Carbonic acid and lactic acid had an influence in the same direction but were not capable of producing anything like the dilatation of the coronary vessels which could be brought about by these unknown metabolites. These facts were also observed by Morawitz and Zahn(2), working on the heart *in situ*.

A rise of arterial pressure is not, however, the only factor which may necessitate increased effort on the part of the heart muscle. The consumption of oxygen by the heart is increased under all conditions which evoke increased mechanical work. Under the conditions of the heart-lung preparation it is possible to increase the inflow and the output of the heart without altering in any way the arterial blood-pressure, although the work of the heart muscle and the dilatation of the heart, and therewith the chemical changes, are largely increased. It was shown, moreover, by Evans(3) that the oxygen usage of the heart—the resistance being kept constant—is nearly constant per beat, so that the consumption of oxygen per minute is almost proportional to the number of beats. The heart requires more oxygen therefore when its rhythm is increased by artificial stimulation, by rise of temperature, or by removing any tonic action of the vagus. It seemed interesting to enquire how far these conditions influenced the flow through the coronary arteries, and whether, in fact, the automatic regulation of the coronary circulation is so perfect that it reacts by an increase to any factor which raises the oxygen consumption of the heart muscle. At Prof. Starling's suggestion I have

therefore undertaken the investigation of these questions. I have also made some experiments on the influence of pericardial effusion, or rather of the presence of fluid in the pericardial sac, on the flow through the coronary circulation.

Methods. Most of the experiments were carried out on medium sized dogs. These were anæsthetised with morphia and C.E. mixture and were then given an intravenous dose of chloralose, ·1 gm. per kilo. A heart-lung preparation was made as described in Knowlton and Starling's paper(4) and in subsequent papers from this Institute. The arterial pressure was measured by a mercurial manometer which was connected with the side branch from the arterial cannula. From the venous end of the apparatus the blood was allowed to flow into a graduated cylinder, and the time taken to collect 50 c.c. determined by means of a stop-watch. This amount was the arterial output, *i.e.* the output of the heart minus the blood flowing through the coronary arteries. The coronary outflow was measured by collecting the blood through a Morawitz cannula(5) introduced into the coronary sinus, and the time taken to collect 10 c.c. was noted. The blood flowing through the cannula was returned to the venous reservoir every few minutes, but it was necessary to circulate fresh amounts of blood to remove the effect of vaso-dilator metabolites. In each experiment it was found necessary to use blood from another dog, or in some cases from two dogs. The blood was defibrinated.

In order to investigate the influence of the pericardial fluid on the coronary circulation, de Barenne's(6) heart-lung preparation with empty beating right heart was used. After Starling's heart-lung preparation was made, a small incision was made in the pericardium just above the pulmonary artery, into which a T-shaped cannula was inserted. One branch of the T cannula was connected with the rubber tube to the venous reservoir, which was raised to the height of a column of blood of 50 cm. The third branch of the cannula was stopped by a rubber cork with a thermometer. The blood flowing into the pulmonary artery reaches the left side of the heart through the lung, so that the right heart receives only the whole blood through the coronary vessels. This blood was collected through a cannula inserted in the superior vena cava, and the time required to collect 25 c.c. was taken. The scheme of this circulation will be seen in de Barenne's paper(7). The opening made in the pericardium was then sewn up to prevent leakage of the fluid injected into the pericardial cavity.

In the tables the c.c. of blood are given to the nearest whole number.

The influence of the venous inflow on the coronary circulation. The venous inflow is regulated to any desired extent by adjusting the screw clip on the tube passing from the venous reservoir to the superior vena cava. Since increase in venous inflow tends to raise the blood-pressure, the latter was kept constant by adjusting the arterial resistance. The temperature was also kept constant. The effect of varying the inflow, and thereby the filling of the heart, on the output from the coronary sinus was as follows:

TABLE I. Arterial pressure 90 mm. Hg. Temp. 32° C.

Exp. 1. Bitch, 10·8 kilos.

Time in mins.	Systemic output c.c. per min.	Coronary sinus output c.c. per min.	Heart beats per min.	Calculated total coronary output c.c. per min.
0	254	30	108	50
5	500	34	114	56
7	116	28	108	47
9	600	34	114	57
12	852	35	120	58
	Exp. 2. Bitch, 9 kilos. Temp. 35° C.			
0	146	36	132	60
5	233	38	132	63
8	750	40	138	67

The total coronary output was calculated on the assumption that the measured flow from the coronary sinus was three-fifths of the total according to Markwalder and Starling(1). The total output of the heart is the sum of the systematic output and the calculated total coronary output, and this represents the venous inflow.

The experiments show that the effect of the venous inflow on the coronary circulation is very slight, as stated by Starling(1). There is no proportionality between the inflow and the coronary output, although the latter is slightly raised by the increase of the former. The total heart output, 909·5 and 817·0 in each experiment, was the optimum in order to keep the pressure constant in the apparatus used. It is possible that the slight increase observed may be accounted for by greater pulse pressure with bigger inflow. In the experiments it was the mean arterial pressure that was maintained constant. A greater inflow would therefore mean a higher systolic pressure and a lower diastolic pressure, and the slightly increased coronary flow may be due to the rise in systolic pressure.

The influence of temperature on the coronary circulation. The effect of change in the temperature of the circulating blood with constant arterial pressure and constant venous inflow is given in Table II. In this case the coronary blood collected was not returned to the reservoir in

the first series of experiments, but was kept in the thermostat so that any effect of metabolites was removed.

TABLE II. Arterial pressure 90 mm. Hg. Venous inflow constant.

Time in mins.	Temp. C.	Heart beats	Coronary sinus output c.c. per min.	Systemic output c.c. per min.
		Exp. 1. Bitch, 7 kilos.		
0	39	192	29	185
4	37	168	32	185
8	35	144	38	174
12	33	132	43	174
15	31	120	43	177
20	29	102	37	177
27	27	84	32	173
34	25	66	31	—
		Exp. 2. Dog, 7·5 kilos.		
0	40	180	26	118
10	38	150	28	119
27	34	126	29	—
32	29	84	33	110
40	28	72	36	97
47	26	60	34	97
51	25	54	31	—
56	24	42	27	—
		Exp. 3. Bitch, 8 kilos.		
—	38	192	27	178
—	35	144	36	—
—	31	120	43	—
—	29	96	37	—

When the temperature is lowered, the number of the heart beats is decreased, while the coronary flow is increased at a certain lower temperature. The temperature at which the coronary outflow reaches its optimum varies in different hearts. Although this optimum temperature was from 29° to 31° C. in most cases, in some instances it was 34° and 25° C. The greater coronary outflow at a lower temperature, described by Markwalder and Starling, was thus partly confirmed. Their assumption is that the dilatation at low temperatures may be due to a slowing of the process of oxidation, so that the partly oxidised metabolites may escape from the cells and exercise a dilating influence on the coronary vessels. But it is difficult on this explanation to see why the process should stop short at about 31° C., and further cooling be attended by a falling off of coronary flow. It may be that we have here a resultant effect depending partly on production of metabolites, partly on a direct influence of temperature on the calibre of the coronary vessels. At any rate the coronary circulation is not directly proportional to the oxygen usage of the heart muscle.

It is stated by Starling and his co-workers that the output of the heart is practically independent of the temperature within wide limits, and in the above experiments, therefore, the systemic output was sometimes measured. The venous inflow given in Table II was calculated by adding to the systemic output the mean value of the calculated coronary outflow.

The influence of the rate of heart beat on the coronary circulation. In endeavouring to interpret the above experiments it was necessary to eliminate the direct action of temperature on the coronary circulation from the indirect one which might be brought about mechanically by the alteration in the rate and amplitude of heart beat also induced by temperature alterations. Accordingly an endeavour was made to alter the rate of heart beat while maintaining the temperature constant.

In order to get tachycardia the sino-auricular node was stimulated by means of single induction shocks. Any fall of the arterial pressure caused by the stimulation was prevented by adjustment of the arterial resistance, the mean arterial pressure being maintained constant. Before and during the stimulation, the temperature, the venous inflow and the pressure were the same. The following table shows the effect of tachycardia on the coronary circulation.

TABLE III. Effect of acceleration of heart beat.

Weight of dog. Kilos.	Systemic output c.c. per min.	Arterial pressure mm. Hg.	Temp.	Heart beats		Coronary output c.c. per min.		Secs. of stim.
				Before	During	Before	During	
11·0	306	90	30	102	132	50	50	24
,,	,,	,,	29	84	132	51	51	23
,,	,,	,,	28	84	132	47	48	21
,,	,,	95	35	126	132	54	54	16
10·0	312	90	28	84	120	45	45	13
11·0	375	,,	33	120	168	34	34	17
,,	,,	,,	31	104	168	36	36	—
9·0	480	90	37	156	186	33	33	8
10·5	320	,,	31	84	138	64	63	9
9·5	282	95	31	96	162	69	67	9
,,	,,	,,	,,	,,	,,	69	68	—

Thus acceleration of the heart beat has little, if any, influence on the coronary output. Morawitz and Zahn(2) found that the tachycardia caused by warming the sino-auricular node diminishes the coronary outflow, but in their experiments the diminution of the coronary output was accompanied and was probably caused by a fall of arterial pressure. In Table III it will be seen that when the node was stimulated for a short period, the coronary outflow was slightly decreased, but when the time

of stimulation was longer, the outflow was the same before and during the stimulation. In conclusion it may be said that tachycardia itself has no influence on the coronary circulation, which is thus apparently independent of the rate of the heart beat.

In order to obtain slowing of the heart beat the peripheral end of the cut vagus nerve was stimulated with an alternating current. The consequent fall of arterial pressure was adjusted by raising the arterial resistance so that the pressure was maintained constant. The venous inflow and the temperature of the blood flowing to the heart were also kept constant before and during stimulation. The results are given in Table IV.

TABLE IV. Effect of slowing of heart beat.

The arterial pressure in each experiment was kept at 90 mm. Hg.

Weight of dog.		Systemic output c.c.	Heart beats		Coronary sinus		Secs. of
Kilos.	Temp.	per min.	Before	During	Before	During	stim.
10·8	33	270	126	30	21	21	27
8·7	34	204	120	40	20	20	17
„	„	„	„	31	20	19	20
9·0	37	500	156	23	28	29	12
„	38	481	162	55	29	33	5
7·4	36	178	168	51	23	22	11
10·0	35	125	126	60	30	30	18
„	„	„	„	„	30	32	17
8·0	30	190	108	50	23	24	12
„	„	„	108	65	24	25	9

It will be seen that the coronary outflow in most experiments was unaffected by the slowing of the heart produced by vagus stimulation, but occasionally there was a slight increase or decrease. At the beginning of stimulation the heart acts forcibly, takes up and drives on more blood, and if the outflow is calculated as that occurring during the first few beats it is sometimes found to be considerably increased. Notwithstanding that during the period of slowing as a whole, the circulation through the heart is retarded, there does not appear to be sufficient accumulation of metabolites to cause vaso-dilatation.

The influence of pericardial effusion. In investigating this point, de Barenne's method, namely, leading the blood from the venous reservoir directly into the pulmonary artery, was employed. The effects of pericardial effusion were imitated by allowing liquid paraffin at about 30° C. to flow into the pericardial sac. Considerable difficulty was met with in preventing leakage from the opening which had been previously made and sewn up for the purpose of inserting the cannula into the pulmonary artery. In the following experiment the leakage was, however, very slight.

TABLE V. Arterial pressure 80 mm. Hg. Venous inflow constant.

Bitch, 8·2 kilos. Weight of heart, 60 gms. Height of venous reservoir, 50 cm.

Time in secs.	Temp.	Heart beats per min.	Arterial output c.c. per min.	Coronary output c.c. per min.	Paraffin injected or withdrawn c.c.	Paraffin in cavity c.c.
0	32·5	133	191	32	0	0
10	„	123	171	32	+20	20
20	31·5	123	105	26	+20	40
25	„	63	Arterial pressure fell to 60 mm. Hg.		+20	60
28	29·0	100	103	42	−10	50
31	29·5	105	143	42	−10	40
35	30·5	117	150	43	−10	30
40	„	117	150	44	−10	20
45	„	„	„	44	−10	10
50	31·5	120	150	45	0	10
52	31·0	112	142	45	+20	30
55	„	113	125	43	+10	40
60	„	„	100	38	+10	50
63	„	99	14	33	+10	60

From these results it is seen that there may be a considerable amount of fluid in the pericardium, sufficiently to diminish materially the filling of the heart, without altering the flow through the coronary vessels. It was only with an extreme degree of distension of the pericardium when there was a positive pressure in this cavity that there was any falling off in the coronary flow, and this might be ascribed to a direct influence of the pressure on the coronary sinus. Apart from this direct influence, we may say that pericardial effusion does not influence the coronary circulation.

CONCLUSIONS.

The result of my experiments is to confine the factors influencing the blood flow through the heart muscle to those described by Markwalder and Starling. When we dissociate, as is possible in the heart-lung preparation, the factors which are normally involved in any increased effort of the heart, the beautiful automatic regulation of the coronary circulation in proportion to the needs of the heart muscle fails, and we find that under many conditions there may be wide variations in the oxygen consumption and oxygen needs of the heart muscle without any corresponding change in the coronary blood flow. It is especially interesting that the beat of the heart itself seems to be without effect on the coronary vessels, and that the coronary circulation is within wide limits almost independent of the temperature of the heart.

In conclusion I have to express my thanks to Prof. Starling for his guidance throughout the investigation, and my appreciation of Dr Anrep's assistance in the performance of some of the experiments.

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