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THE CORONARY CIRCULATION.

III. The dependence of changes in the coronary blood flow on cardiac and local vascular factors.

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The study of the blood supply to the heart muscle presents certain difficulties which are not encountered in similar investigations on most organs. Plethysmographic methods, which are helpful in investigations upon the blood supply to many organs, are useless in the case of the coronary circulation. In experiments on the whole animal in which the coronary blood flow is measured by collecting the blood which emerges from a cut cardiac vein, or from the coronary sinus, the results are always open to criticism because of the great difficulty of controlling the arterial blood-pressure and the output of the heart. On account of the extreme dependence of the coronary blood flow on the aortic blood-pressure, it is necessary (probably more necessary here than in the case of any other organ) to use various devices which permit of a perfect control of all the mechanical factors of the circulation. It is therefore not surprising that most physiological and pharmacological studies of the coronary circulation have been made on the isolated perfused heart, or on the heart-lung preparation. The object of this communication is to show that even the degree of control which is obtainable in these preparations is in many cases insufficient, and that an augmentation or diminution of the coronary blood flow under the influence of some physical or chemical agents does not necessarily indicate, as in the case of most organs, a respective vaso-dilator or vaso-constrictor reaction. In other words, records of the outflow per minute from a coronary vein, or of the inflow per minute into a coronary artery, are often misleading without further analysis, even under conditions of a uniform blood-pressure. The principle of the necessary analysis has been described before (1, 2); it is based on the application of the hot-wire anemometer. It has been shown in previous experiments (3, 4) that the circulation in a perfused coronary artery depends largely on the heart beat, that when the strength of the contraction is increased by any means whatever the diminution of the

coronary blood flow during each systole becomes more conspicuous, and that in extreme cases there may be a regurgitation of blood into the arterial system. Therefore, at a constant coronary pressure, the blood flow per minute is smaller the stronger the contraction of the heart. The effect of changes of heart rate on the coronary blood flow is determined by the relative duration and by the strength of systole.

Various physical and chemical agents which affect the coronary blood vessels usually also affect the heart muscle and, since the experimenter has no means of controlling the strength of the heart beat, he must at least have some method of measuring it, so as to be able to analyse the mechanism by which any change in the coronary blood flow is produced—whether it is due to the action of the agent on the heart muscle or on the coronary blood vessels or both, and in the latter case to what extent each of the two factors is responsible. In order to demonstrate the dependence of the changes in the coronary blood flow on the cardiac and local vascular factors, a comparison was made between the action of four substances, two of which have a predominantly vascular effect, while the other two are known to have a considerable effect on the heart muscle, and also some effect on the coronary blood vessels. The first two substances were (*a*) amyl nitrite, which conspicuously increases the coronary blood flow, and (*b*) pituitary extract, which diminishes the coronary blood flow; in small doses these drugs are not known to have any direct effect on the heart muscle. The other two substances were (*c*) adrenaline, which considerably strengthens the heart beat, and (*d*) carbon dioxide, which weakens it. As regards their action on the coronary blood flow, opinions are divided about the action of adrenaline, but carbon dioxide is generally considered to increase the coronary blood flow.

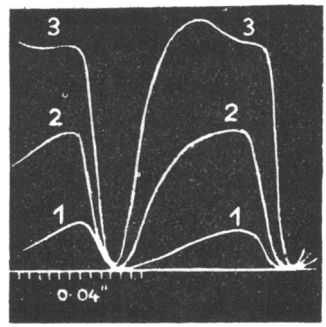

Fig. 1. Superimposed corrected hot-wire records of the inflow of blood into the left coronary artery. Heart-lung preparation. All the mechanical conditions of the circulation and the heart rate were maintained constant. The mean aortic blood-pressure and the perfusion pressure were kept at 100 mm. Hg.

1. After injection of 0·1 c.c. of B.D.H. pituitary extract into the blood perfusing the coronary artery.
2. Normal record.
3. After injection of 1 c.c. of saline solution saturated with amyl nitrite.

The respective coronary blood flows were 0·09 c.c., 0·37 c.c. and 0·85 c.c. per cardiac cycle. The heart rate in this and all the following tracings was controlled by rhythmic stimulation of the right auricle.

An anaylsis of the effect of amyl nitrite and of pituitary extract is

shown in Fig. 1, in which a normal hot-wire record is also given for comparison. It can be seen that in the three records there is a complete arrest of the coronary blood flow during the period of systole. During the period of diastole the blood flow is increased by amyl nitrite and decreased by pituitary extract.

Fig. 2 is an original record taken before and after administration of pituitary extract.

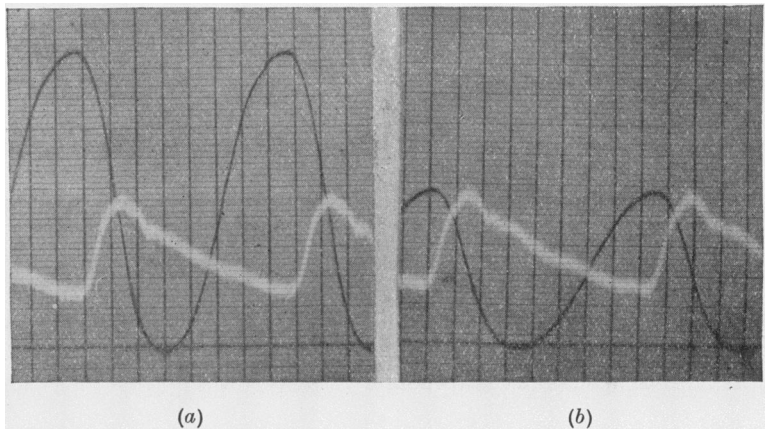

Fig. 2. Original hot-wire records and optical registration of the aortic blood-pressure: (*a*) normal record; (*b*) 15th and 16th heart beat after injection of 0·1 c.c. of pituitary extract into the perfused left coronary artery. The coronary blood flows per cycle were 0·66 c.c. and 0·32 c.c. respectively. Time in this and all the following tracings 0·04 sec.

The shift of the level of the diastolic part of the record may be taken to represent the most accurate measure at present possible of the changes in the resistance of the coronary system, *i.e.* vaso-dilation or vaso-constriction. The rate at which the coronary blood vessels are refilled, after having been emptied by the preceding contraction of the heart, is greater when they are dilated. In the case of considerable dilation, the refilling is so rapid that the maximum rate of inflow of blood takes place in the first part of diastole, and the true diastolic level of the record is only reached later. In the case of small doses of amyl nitrite and of pituitary extract the changes in the coronary blood flow, as recorded by measuring the inflow of blood per minute, are proportional to the shift of the diastolic part of the hot-wire record. In some experiments amyl nitrite in large doses had a strengthening effect on the heart itself, as can be seen from Fig. 3. In this case the cardiac contraction was not

sufficiently strong to stop the inflow of blood into the perfused coronary artery. On administration of amyl nitrite the diastolic level of the

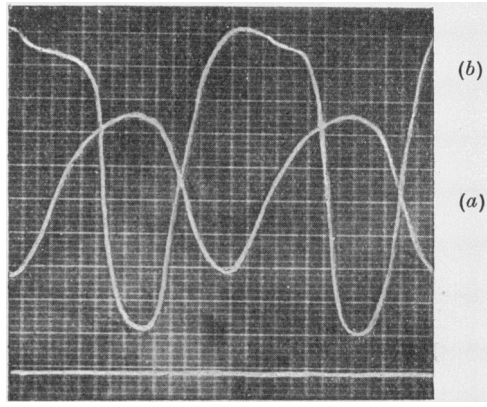

Fig. 3. Original hot-wire records: (*a*) normal; (*b*) after injection of 1 c.c. of saline saturated with amyl nitrite. The coronary perfusion pressure was 100 mm. and the mean aortic blood-pressure 75 mm. Hg. Both records were taken on the same film, the time-marker being removed during the second exposure.

coronary inflow was shifted in the upward direction, and at the same time the diminution of the blood flow during systole became more pronounced. These changes in the hot-wire record indicate the occurrence of the usual (with amyl nitrite) dilation of the blood vessels, and also a more forcible compression of the blood vessels during systole. It is difficult to decide whether this strengthening of the contraction is due to a direct effect of amyl nitrite on the heart muscle itself, or indirectly to a more vigorous coronary circulation following the administration of the drug. This effect was observed in a few cases only.

The above experiments show that the main effect of these two drugs is to shift the level of the diastolic part of the hot-wire record, which conforms with the predominantly vascular nature of their action. Conditions are however not often as simple as these. When the agent used has a greater effect on the heart muscle, it becomes increasingly difficult to determine its effect on the coronary blood vessels. I believe that a great number of controversial statements concerning the action of such potent cardiac drugs as adrenaline and strophanthin are due to these difficulties. Almost within a month, strophanthin has been claimed to be a coronary vaso-constrictor and a coronary vaso-dilator substance. As regards adrenaline, some observers deny that it has any effect on

the coronary circulation, others ascribe to it purely vaso-constrictor properties, others regard it as a coronary vaso-constrictor substance in small doses and a vaso-dilator substance in large doses, and still others ascribe to it vaso-dilator properties only (5). These conflicting results are due to the fact that the blood flow per minute through the coronary system has been taken as a measure of coronary vaso-dilation or of vaso-constriction. In the action of adrenaline there are at least three factors which have to be considered. The net result on the coronary blood flow is the algebraic summation of the effects of the change in heart rate, the change in strength of contraction, and the vascular changes proper. The first factor can be eliminated because the heart rate can be controlled by the experimenter. The extent of the effect on the coronary circulation of the change in the strength of the beat and of local vascular phenomena must however be determined by analysis on the same lines as that which was applied in the case of amyl nitrite and pituitary extract.

The following is an example of such an analysis of the effect of adrenaline on the inflow of blood into the perfused left coronary artery in the heart-lung preparation. The coronary artery was perfused with a pressure at which the contraction of the heart was able to stop the coronary circulation during each systole. The hot-wire record of this period is shown in Fig. 4 (*a*). Adrenaline was then injected into the

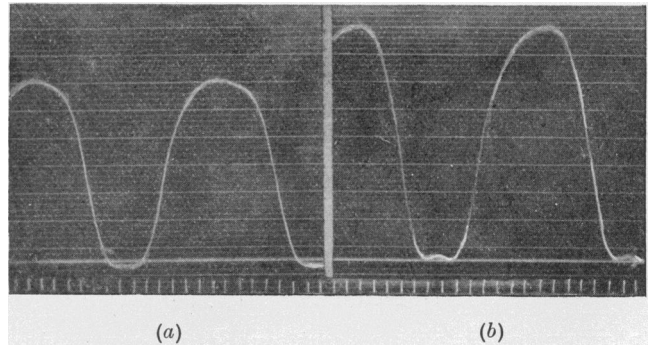

Fig. 4. Original hot-wire records: (*a*) before, (*b*) after injection of 0·4 c.c. of 1 : 50,000 solution of adrenaline chloride into the left coronary artery. The mean aortic and the perfusion pressures were 100 mm. Hg. Coronary blood flow per cycle 0·52 c.c. and 0·72 c.c. in (*a*) and (*b*) respectively.

perfused artery; the corresponding hot-wire record in Fig. 4 (*b*) shows that the effect is somewhat like that produced by amyl nitrite but smaller.

The observation was repeated under conditions in which the cardiac contraction was not strong enough to stop the inflow into the coronary artery. This weakening of the contraction was obtained by lowering the aortic blood-pressure to about 30 mm. of mercury below the perfusion pressure. After the injection the coronary blood flow at first diminished. The hot-wire record of Fig. 5 shows that this diminution

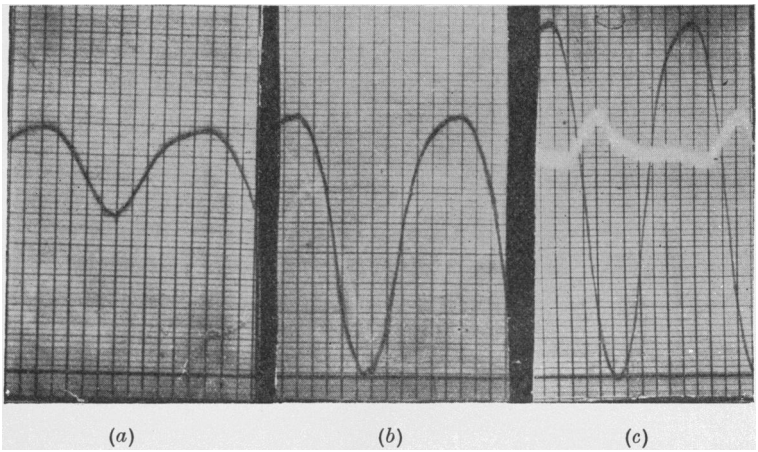

Fig. 5. (*a*) Normal record. (*b*) The 7th end, (*c*) the 30th heart beat after injection of 0·4 c.c. of a 1 : 50,000 solution of adrenaline. Mean aortic blood-pressure 70 mm., perfusion pressure 100 mm. Hg. Coronary blood flows per cycle 0·85 c.c., 0·60 c.c. and 0·98 c.c. in (*a*), (*b*) and (*c*) respectively. The optical manometer recording the aortic blood-pressure was screened off in (*a*) and (*b*).

is due to a more pronounced restriction of the coronary circulation by the strengthened contraction of the heart. At this stage the diastolic level of the inflow of blood is not much affected. But later vaso-dilation takes place as can be seen by the upward shift of the diastolic portion of the record. These observations make it evident that, although the dilation of the coronary blood vessels in the case of adrenaline may be considerable, the blood flow may be smaller than before; only a certain degree of vaso-dilation will overcome the antagonistic effect of the stronger contraction and augment the coronary blood flow. The effect of adrenaline is often complicated by the development of a back-thrust of blood into the arterial system, as happens when the contraction of the heart is very vigorous (3). When this regurgitation of blood occurs, it constitutes another factor counterbalancing the vaso-dilator effect of the drug. During the action of adrenaline two antagonistic factors are

thus at play: (*a*) the direct vaso-dilator effect, and (*b*) the indirect effects which are due to changes of the heart beat. It is therefore not possible to predict with certainty whether the coronary blood flow will be increased or decreased, even in those experiments in which the heart rate is controlled. It is known that an increase in the coronary blood flow is produced by considerably larger doses of adrenaline than those which are necessary to affect the strength of the heart beat. It is therefore not surprising that many observers who experimented on the isolated heart report a diminution of the coronary blood flow in the case of small doses of adrenaline. This diminution, however, is not due to vaso-constriction but to an increased "vaso-compression" (Fig. 6).

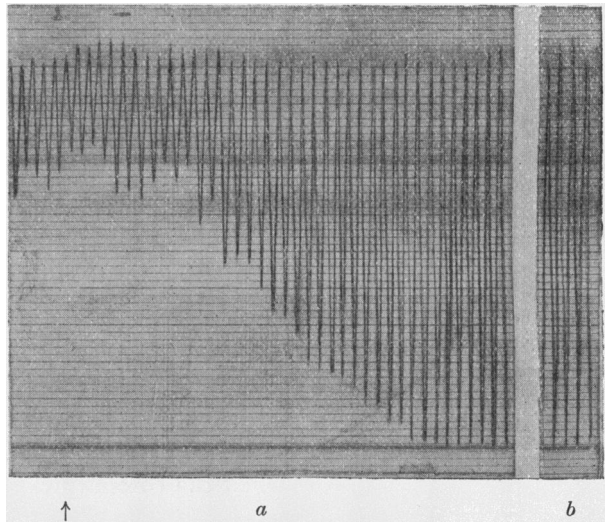

Fig. 6. (*a*) Effect of injection of 0·1 c.c. of 1 : 50,000 adrenaline (at the arrow). (*b*) 30 seconds later. The coronary blood flow was 27·4 c.c. before and 15·6 c.c. after the injection of adrenaline. Plate moving at reduced speed.

In the above experiments adrenaline was injected into the perfused coronary artery so that both the perfused blood vessels and the part of the heart muscle supplied by them were equally affected by the drug. On injecting adrenaline into the systemic circulation, that is on subjecting to the drug those coronary blood vessels which are left in connection with the aorta, no definite change in the hot-wire record can be noticed in the driven heart. In hearts, the rate of which is not controlled, the effect is similar to that produced by acceleration of the heart by means of stimulation with single induction shocks(4). In a few

experiments a strengthening of the contractions of the perfused area was observed.

Thus we see that changes of the cardiac contraction and of the state of the coronary blood vessels produced by adrenaline act as two antagonistic factors in their effect upon the coronary circulation. The augmentation of the coronary blood flow produced by administration of carbon dioxide is due to a co-operation of these factors. In the strongly beating heart in which the coronary blood flow is stopped during each systole carbon dioxide leads to an upward shift of the diastolic as well as of the systolic part of the hot-wire record. Thus the compression of the coronary blood vessels during systole becomes diminished, while during diastole the blood vessels become more rapidly filled and allow a larger amount of blood to flow through them on account of loss of tone. This effect can be seen in Fig. 7 in which hot-wire records obtained

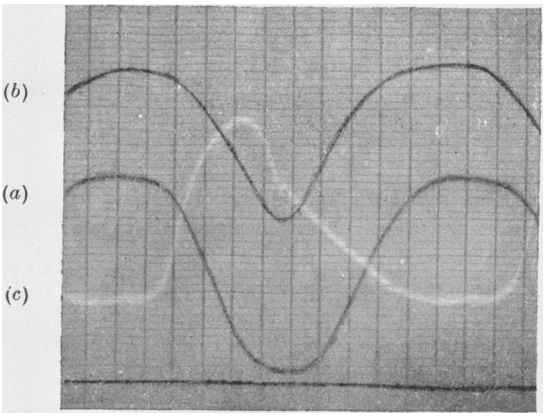

Fig. 7. (*a*) Normal record. (*b*) During the perfusion of the coronary artery with blood exposed to 7·5 p.c. CO_2. (*c*) Aortic blood-pressure. The mean aortic blood-pressure was 75 mm. and the perfusion pressure 100 mm. Hg. The coronary blood flow per cycle was 0·33 c.c. and 0·69 c.c. in (*a*) and (*b*) respectively; (*a*) is an original record, (*b*) is retraced from another plate.

before and during the action of carbon dioxide are superimposed. In this experiment blood, previously exposed to 7·5 p.c. carbon dioxide, was introduced into the perfusion reservoir and allowed to enter the left coronary artery. The mean aortic blood-pressure was maintained at 75 mm. and the perfusion pressure at 95 mm. of mercury.

The object of the experiments described in this communication has been not so much to study the action of various drugs upon the coronary

circulation as to find a method by means of which such a study could be made with a greater precision than it is possible by simply registering the inflow or outflow of blood per minute.

SUMMARY.

The hot-wire anemometer is employed for the purpose of studying the action of chemical and pharmacological agencies on the perfused coronary system of the working heart. The method gives more precise information about the cause of changes of the coronary circulation than it is possible to obtain by other methods. Various agencies may affect the blood flow through a perfused coronary artery either indirectly by modifying the heart beat or directly by altering the tone of the coronary blood vessels. These factors are in some instances antagonistic and in others additive. Examples of the application of the method are given, and it is shown that changes in the coronary circulation at a constant perfusion pressure do not necessarily indicate simply changes in the tone of the coronary system, and that in some instances the coronary circulation may diminish in spite of a considerable relaxation of the coronary blood vessels.

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REFERENCES.

1. Anrep and Downing. Journ. Sci. Inst. 3. p. 221. 1926.
2. Anrep, Cruickshank, Downing and Subba Rau. Heart, 14. p. 111. 1927.
3. Anrep and Häusler. This Journ. 65. p. 357. 1928.
4. Anrep and Häusler. Ibid. 67. p. 299. 1929.
5. Anrep. Physiol. Rev. 6. p. 596. 1926.