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THE CORONARY CIRCULATION IN THE ISOLATED PERFUSED HEART.

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The experiments described in the present communication have been performed on isolated hearts of the cat and the rabbit. The object of the research was to study in detail the factors governing the coronary circulation in the isolated heart, and to analyse by means of the hot-wire anemometer the action of various coronary vaso-dilator and vaso-constrictor substances.

The hot-wire method for measuring blood flows has already proved its value, but so far it has been used mainly in experiments on the heart-lung preparation and only for the registration of the blood flow through single large branches of the coronary arteries. The effects of the cardiac contraction and of various drugs upon the circulation through a single perfused branch are not necessarily the same as their action on the entire coronary system when the whole of it is perfused from a common source. In the first case the perfused branch is left in close connection (through arteriole and capillary anastomoses) with those coronary arteries which continue to receive their blood supply from the aorta. In the second case no such collateral connections can vitiate the observations, since the entire coronary system is perfused under identical conditions and the entry of blood into the perfused area from extraneous sources is prevented.

Our experiments are similar to those of Langendorff [1900] who also worked on the isolated heart but used the pressure changes in the coronary cannula as a measure of the coronary perfusion. Langendorff perfused the heart through a cannula introduced into the aorta, a method which is open to considerable criticism. Moreover, his recording system was one of low vibration frequency, so that the results he obtained cannot be accepted without being verified by more modern methods.

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Recently Hochrein and co-workers [1930 and 1931] severely criticized the use of the hot-wire method for blood-flow measurements. They maintain that the hot-wire anemometer is no more suitable for measuring rapid changes of blood flow than a mercury manometer is for measuring rapid changes in pressure. This criticism has been subjected to a detailed analysis by Davis, Littler and Volhard [in Press] who have shown it to be without foundation.

METHOD.

The isolated heart was perfused with oxygenated Ringer solution (NaCl 0·92; KCl 0·042; $CaCl_2$ 0·024; $NaHCO_3$ 0·024 p.c.) through a cannula devised by one of us [see Rössler, 1928]. This cannula has the following advantages. It allows the perfusion fluid to enter only the coronary arteries, it prevents leaks through the aortic valves, and moreover it is not tied to the coronary artery itself. Thus there is no risk of kinking of an artery against the nozzle of the cannula or narrowing of the bore of the artery by the cannula. The filling of the heart through the Thebesian channels was prevented by draining the ventricles of all fluid; leakage was therefore negligible. The reservoir holding the perfusion fluid was stoppered by a hot-wire container 4 mm. in diameter. The deflections of the string galvanometer were proportional to the flow of fluid up to about 35 c.c. a min., so that up to this limit the records obtained needed no correction except for the lag of the hot wire. This lag was of the same order as in the experiments of previous workers, namely about 0·02 sec. The volume of air above the fluid in the reservoir was kept very small and as constant as possible, the reservoir being refilled at short intervals. The perfusion pressure was kept constant at 0·5 cm. H_2O. The connections between the reservoir and the cannula were made of rigid tubes. On the way to the heart the fluid passed through a short metal spiral for the purpose of warming. Great care had to be taken to avoid the formation of gas bubbles in this spiral, since the presence of even small bubbles renders the hot-wire registration valueless. For this reason the perfusion fluid, before being introduced into the reservoir, was saturated with oxygen at a temperature not below 39° C. After oxygenation of the perfusion fluid its hydrogen ion concentration was adjusted to *p*H 7·6 by addition of phosphate buffers. The fluid escaping from the heart was measured either by means of a syphon recorder devised by one of us [see Rössler, 1926] or by the method of Brodie and Cullis [1911]. The first method was used to measure outflow quantitatively, while the second was used to measure the changes taking place in the average outflow. Both methods provided us with continuous registration of the coronary circulation, and in addition we obtained the detailed analysis given by the hot-wire anemometer.

The pressure changes taking place in the coronary arteries were registered by means of a sensitive optical manometer which was inserted immediately above the orifice of the coronary cannula. The vibration frequency of the membranes used varied in different experiments between 90 and 120. Thus the manometer was quite adequate for its purpose. In every experiment, at frequent intervals, the base lines of the hot wire and of the membrane manometer were verified. In both cases the base line signifies the position of the recording system after the coronary flow has been stopped. In this condition the hot wire registers a zero flow while the membrane manometer registers a maximum pressure, *i.e.* the pressure in the reservoir containing the perfusion fluid.

The registration of the movements of the heart was made as represented in Fig. 1. A light metal rod attached to the apex of the heart (*A*) was carried over a fulcrum to an ebonite wheel. Each contraction of the heart caused the wheel to move in the direction

of the arrow. By the connection (*H*) these movements were transmitted to a small mirror (*M*) reflecting a beam of light into the slot of the photographic camera. In all experiments the movements of the heart were registered with a magnification of nine times. The connections between the heart and the mirror registering its movements were rigid and free play was negligible. Although this method reproduced fairly accurately the time relations between systole and diastole, it is obvious that, like any other method of registering the movements of the beating heart, it could only give an approximate idea of the strength of the contraction.

The preparation of the heart itself was made according to the usual routine. At the end of each experiment methylene blue was injected into the coronary cannula in order to make sure that every part of the heart was uniformly perfused and that no perfusion fluid had penetrated into the cavities of the ventricles directly from the cannula. The drugs used were in every case dissolved in 1 c.c. of the Ringer fluid, the *p*H of which was readjusted just before the injection. The injections were made into the coronary cannula immediately above the heart.

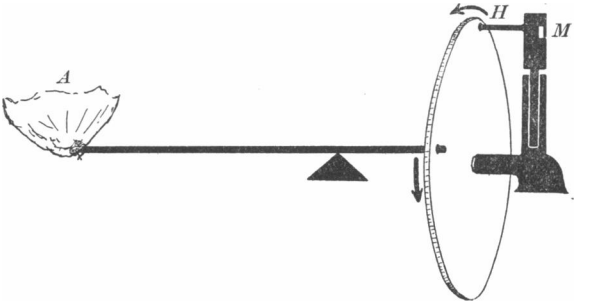

Fig. 1. Apparatus for optical registration of the heart beat.

The effect of systole upon the coronary circulation.

As a result of measurements of pressure changes taking place in the aortic cannula perfusing the heart, Langendorff arrived at conclusions which may be summarized as follows: (*a*) during the isometric period of contraction, the inflow of blood into the vessels is facilitated and the outflow from the coronary sinus is made possible; (*b*) during the ejection phase, the inflow is impeded while the outflow is increased; (*c*) during the diastole, the inflow is facilitated, but there is no outflow on account of the filling of the blood vessels; (*d*) during the auricular systole, the inflow is increased, but there is no outflow owing to the closure of the coronary sinus. Anrep and Häusler [1928 and 1929] and Häusler [1929], working partly on the whole animal but chiefly on the heart-lung preparation, registered the blood flow in the perfused coronary artery by means of the hot-wire anemometer. They failed to observe any effect of the auricular contraction upon the inflow of blood. Neither did they notice an increase in flow during the period of isometric contraction. They regard the systole of the ventricles as a factor which does not

facilitate the coronary inflow at any stage of its development. The systole acts only as a resistance to the inflow, and this resistance increases as the contraction of the heart becomes stronger. In the case of very strong contractions, a certain amount of blood is regurgitated from the coronary vessels into the perfusing system. During diastole, starting from the dicrotic notch, the emptied coronary system gradually begins to fill up and the inflow reaches a maximum at some period of diastole. The inflow of blood remains at this maximum until the next ventricular contraction sets in. The rate at which the inflow is re-established after systole does not bear any relation to the rate of relaxation of the heart. The refilling of the blood vessels is always slower than the relaxation because the inflowing blood has to overcome the tone of the blood vessels and the viscous properties of the heart muscle. The smaller these two factors are, the more rapid is the refilling.

Hochrein and his co-workers registered the blood flow through the perfused left coronary artery in the whole animal. For this purpose they used simultaneously Broemser's tachograph and the hot-wire anemometer. These observers state that it is impossible to discover an exact relation between the changes taking place in the coronary blood flow and the various phases of the cardiac cycle. Usually they find that the maximum flow occurs during systole; but even in the same experiment and under precisely the same conditions the maximum may shift from the beginning to the end of the systole or even into the diastole. Hochrein regards the contraction of the heart as a factor facilitating the blood flow through the perfused coronary artery. So far as we understand the description of his experiments, the entire length of the connection between the perfusion reservoir and the coronary artery was made of rubber tubing. The introduction of a length of 50 cm. of rubber tubing between two sensitive recording apparatus like Broemser's tachograph and the hot wire is incompatible with accuracy. This probably explains the fact that the two recording apparatus never worked synchronously. The hot wire used in these experiments was of a very low sensitivity and had an enormous lag. Moreover, the records both of the tachograph and of the hot wire show such a quantity of vibrations that in our opinion it is difficult to draw any conclusions at all from the published tracings. Neither calibration nor correction of the records was attempted. In most tracings the base line is not indicated.

Our own experiments on the isolated heart confirm Anrep's observations. The inflow of fluid into the coronary arteries was found to be diminished or stopped during the ventricular contraction. We have never

observed an increased flow during systole. Neither could we confirm Langendorff's observation that the auricular contraction and the beginning of the ventricular systole facilitate the coronary inflow. Examples of records illustrating our observations are given in Fig. 2. Record A of this figure shows a case of a strongly beating heart, the contractions of which were powerful enough to stop the coronary inflow, in spite of the perfusion pressure being 80 cm. Hg. Record B was obtained after an interval of 30 min. when the heart beat had weakened

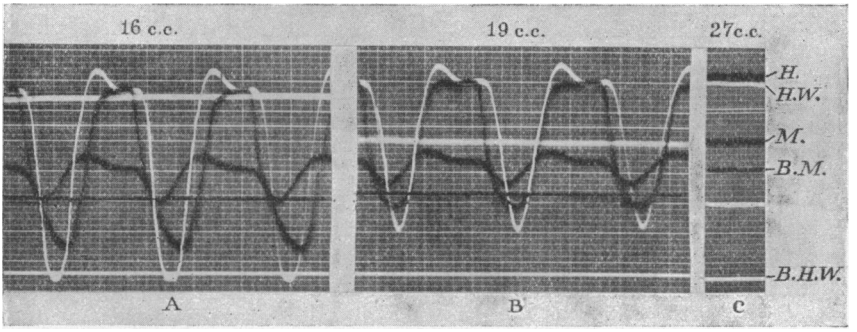

Fig. 2. Effect of systole on the coronary circulation in the isolated cat's heart. The white line *B.H.W.* at the bottom of the record is the base line for the hot wire. The white line *H.W.* showing the deflections is the hot-wire record. The horizontal black line *B.M.* is the base line for the coronary pressure. The black line *M* showing the smaller deflections is the record of the coronary pressure. The black line *H* showing the larger deflections is the optical registration of the heart beat. The upper horizontal white line is the record of the volume flow, obtained by the method of Brodie and Cullis. This line should be disregarded in all tracings, as the flows are given in every case in c.c. per min.; a drop of this line denotes an increase in flow. The time in all tracings is 0·04 sec. All tracings are to be read from left to right. It must be remembered that the coronary pressure and the hot-wire tracing reach their respective base lines when the coronary flow is zero. A deflection upwards means in both cases an augmentation, and a deflection downwards a diminution of the coronary inflow. In C the base line of the manometer is shifted upwards by 4 mm.

somewhat. The coronary inflow was nevertheless considerably reduced during systole but not altogether stopped. Tracing C was taken 1 min. after B when the heart spontaneously started fibrillating. The records obtained by the hot wire are duplicated by the excursions of the optical manometer which shows in A a complete return of the pressure in the coronary arteries to the zero position, denoting a temporary cessation of the coronary inflow; in B the pressure does not reach its base line during systole, showing that some flow took place during the period of contraction. During fibrillation in C the inflow is steady at the level at which

it has been during the second half of diastole while the heart was contracting; this is shown by the hot wire as well as by the pressure registration. In Fig. 2 the hot-wire record is not corrected, which accounts for the fact that the arrest of the flow as registered by the manometer occurs about 0·03 sec. before it is registered by the hot wire. This discrepancy disappears after the necessary correction has been made. The extent of the correction can be seen from the next figure.

Hochrein, in criticizing the use of the hot-wire anemometer for registration of the coronary inflow, states that it registers events with a lag which is as great as 0·1 sec., that it cannot be used for recording changes of flow which are more rapid than about two per second and that it gives records which are completely distorted. The observation of Anrep and Häusler that the inflow into the perfused artery is stopped

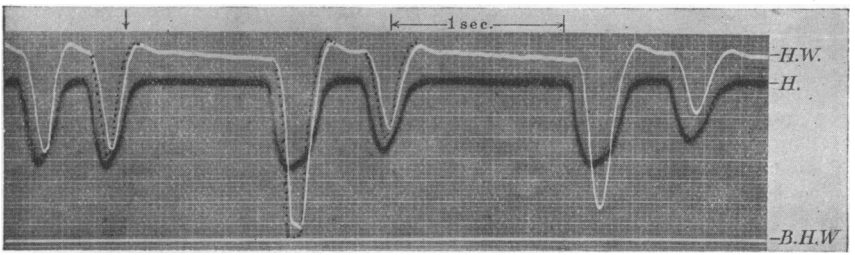

Fig. 3. *H.W.* is the hot-wire record; *H* is the record of the heart beat; *B.H.W.* is the base line for the hot wire. At the arrow the rhythmic stimulation of the auricles was discontinued. The correction of the hot-wire record is shown by the dotted lines.

or diminished during systole is considered by Hochrein to be an error due to the considerable lag and displacement with which the hot-wire anemometer registers changes in flow. According to Hochrein, the flow is diminished during diastole and increased during systole. If Hochrein's statements were correct and Anrep's as well as our own observations are due to such a displacement, this displacement must distort the records enough to shift the events taking place during systole and make them appear in diastole and *vice versa*. This is the only reasoning by which our observations could be explained from Hochrein's point of view. However, if such were the case, a displacement of this kind could happen only as a chance coincidence when the diastole and the systole were approximately equal in length, that is only at a definite heart rate. In actual fact we find that, whatever the heart rate may be, the diminution of the coronary inflow always takes place during systole. We consider that this is conclusively proved by Fig. 3, which shows a

sudden change of the heart rate following the discontinuation of an artificial rhythmic stimulation of the auricle. The length of the cardiac cycle during the artificial rhythm was 0·44 sec. On switching off the electric stimulation, the ventricular contractions became irregular, the successive cycles being 1·1, 0·6, 1·22, 0·56 sec. respectively. In spite of these considerable differences in the length of cycles, and therefore in the relative durations of the respective systole and diastole, we find that in every case it is during the systole that the coronary flow is diminished. It seems impossible to explain records of this type by a lag or by an inaccuracy of the recording system. These observations lead us to the same conclusion as was reached by Davis, Littler and Volhard, who worked on the whole animal and on the heart-lung preparation, and who succeeded in obtaining records of the coronary inflow in hearts beating at the rate of two to five beats a minute. We agree with these observers that Hochrein's hot-wire technique has not been subjected to a sufficiently rigid control.

New method of heart perfusion.

In experiments with coronary perfusion, whether they are made on the whole animal or on the heart-lung preparation or on the isolated heart, the perfusion is usually carried out from a reservoir which is placed at a suitable height and which is connected with the coronary cannula by a system of tubes. This arrangement presents several disadvantages, specially if used in conjunction with a hot-wire anemometer. The friction of the perfusion fluid in the tubes, the ease with which gas bubbles form in these tubes, the necessity of making all connections perfectly rigid are all possible sources of trouble. Furthermore it is necessary to use rather large quantities of the perfusion fluid to fill up the whole system. In order to ensure that our hot-wire records are not affected by any of these possible errors, the new method of heart perfusion shown in Fig. 4 was devised. The Dewar flask *B*, 25 to 100 c.c. in capacity, is filled through the tap *C* with warm oxygenated blood or Ringer fluid. The temperature of the fluid in the flask remains steady during the period of observation. The reservoir *A*, 3 to 5 litres in capacity, is an oxygen pressure chamber. It is connected with an oxygen cylinder and filled with gas at any desired pressure. The hot-wire container is placed between the two reservoirs, and the lower opening of the Dewar flask is connected with the coronary cannula. Since the two reservoirs *A* and *B* have a capacity of 5 litres

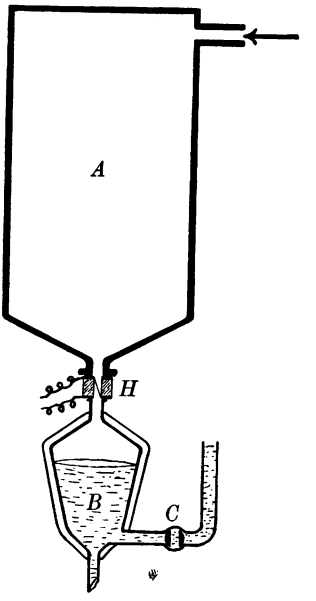

Fig. 4. Apparatus used for hot-wire registration of the coronary circulation in isolated hearts. (Explanation in text

and 50 c.c. respectively, a complete emptying of the reservoir *B* leads to a diminution of the perfusion pressure of not more than 1 p.c. The only precaution that has to be taken with this apparatus is that no oxygen must be allowed to enter the coronary arteries. This method of perfusion obviously eliminates all the above-mentioned disadvantages of perfusion with the usual technique. We also find that hearts perfused in this manner beat considerably better than under other conditions. This is probably due to the higher oxygen tension in the perfusion fluid. The hot-wire records of the coronary inflow obtained with this modified technique were found to be similar in every detail to those obtained with the usual perfusion method. It is therefore clear that, so long as all the possible sources of error are eliminated, the perfusion of the heart through the usual long system of tubes gives accurate registration.

Coronary regurgitation.

On perfusing large branches of coronary arteries, Anrep and Häusler noticed that, when the cardiac contraction is very strong in comparison with the perfusion pressure, a certain amount of blood emerges during systole from the artery and flows back into the perfusion reservoir. The stronger the heart beat the more conspicuous is the regurgitation. Anrep's observations show that in this connection it is immaterial through what channels the perfused area has been filled during the diastole, whether it is from the perfusion reservoir or through various anastomoses from the aorta. The increase of the compressing force in the case of a strong contraction is so rapid that the blood which entered the blood vessels during the preceding diastole has not time to be completely pressed out into the veins. Some of it is thrown back against the perfusion pressure and the arteries thus perform during a strong contraction a rôle similar to that of coronary veins.

It is of interest to find that Drury and Smith [1924] noticed the systolic arrest of the forward flow and the regurgitation by direct microscopic observations of the coronary arteries of the tortoise. Their observations are all the more important, since they were performed on coronary blood vessels which were supplied with blood in the normal way from the aorta.

Hochrein regards the whole phenomenon of regurgitation as the result of an experimental error. Since according to this observer the coronary inflow is maximal during systole, he explains the regurgitation by a direct transmission of the aortic pulse wave through anastomoses into the perfused artery, and not by an active expulsion of blood which filled the perfused area during the preceding diastole. However, in our experiments on the isolated perfused heart, the regurgitation could be observed with the greatest ease. In this case the explanation given by Hochrein cannot apply, because the entire coronary system was per-

fused under identical conditions while the ventricular cavities were kept empty of all fluid. Regurgitation always accompanies a strong contraction, but is especially obvious after injection of some cardiac stimulant such as adrenaline or ephedrine. The lower the perfusion pressure the more easily regurgitation is obtained, but in many experiments we observed it with a perfusion pressure of 100 cm. of H_2O and over. The introduction into the perfusion system of a valve which would permit only a forward flow abolishes the systolic back rush of fluid. The behaviour of the coronary pressure during regurgitation will be described below.

The overshoot.

In the blood-perfused coronary artery of a heart-lung preparation or of a whole animal, the refilling of the coronary blood vessels during diastole is usually slow, the maximal flow being reached only late in diastole. The higher the tone of the blood vessels, the more slowly they are refilled. In Ringer-perfused isolated hearts the refilling is considerably more rapid. In fact it frequently happens that the blood vessels show the smallest resistance to the inflow of fluid immediately after the relaxation of the heart, when they have just been partially emptied by the preceding contraction. Obviously the greater the emptying of the blood vessels, in other words the stronger the contraction of the heart, the greater is the likelihood of this overshoot (see Fig. 5 C and D). Therefore in the isolated perfused heart we find that, in the presence of a systolic regurgitation, the overshoot becomes more conspicuous. Anrep and Häusler have noticed only small overshoots, and these usually towards the end of an experiment or after administration of vaso-dilator substances. Since the overshoot is a purely passive phenomenon which is determined by mechanical factors, it would be incorrect to judge the state of tone of the coronary blood vessels in the perfused heart by the rate of inflow of fluid during the first part of the diastole. It would also be incorrect to do so in the blood-perfused coronary artery of the heart-lung preparation or of the whole animal, but in this case it is because the refilling of the blood vessels is rather slow on account of their tone. It is only by the inflow when it has reached a steady rate that one can judge the state of vaso-constriction or vaso-dilation of the coronary blood vessels. In the first part of the diastole the inflow is either excessively rapid or too slow.

The possibility of the occurrence of what we call the overshoot has been considered already by Porter [1898], who used the idea for the elaboration of his massaging theory of coronary circulation.

The combination of factors affecting the circulation in the isolated heart.

It can be seen from the above description that the coronary circulation in the isolated heart presents a rather complicated picture. During a simple cardiac cycle several changes follow one another with rapid succession, and the volume of fluid passing through the coronary blood vessels is of course determined by the algebraic summation of all these changes. The consideration of these factors is of especial importance in the investigation of the vaso-motor effects of various pharmacological and physiological agents. When faced with the complex series of events taking place in the coronary circulation, it is difficult to see for instance how the vaso-motor action of a drug can be ascertained by simply measuring the amounts of fluid entering or leaving the coronary blood vessels of a perfused heart, unless the vaso-motor effect is very pronounced. The amount of fluid passing through the coronary system per unit of time at a constant perfusion pressure will be determined by the state of the coronary blood vessels on the one hand and by the effect of the cardiac contraction upon the coronary circulation on the other. This is especially the case when drugs are used, since most of the drugs which affect the coronary blood vessels also exert some action upon the heart muscle. These actions may interfere with each other, the vaso-dilator effect for example becoming completely masked or unduly augmented by the cardiac effect. As the following examples show, measurements of volume-flows may in many cases give rise to misleading conclusions, specially in the study of the effect of drugs with weak action or of small concentrations of powerful drugs. In Fig. 5, A and B show the effect of an acute weakening of the heart muscle. As a result of this, the small overshoot disappeared, the systolic restriction of the flow diminished considerably, the coronary circulation increased from 14 c.c. to 21 c.c. a minute, but no vaso-dilation can be detected, for the level of the hot-wire record at the end of diastole in A and during diastole in B is the same. C and D show the effect of a small dose of adrenaline. In the case of weakly beating hearts such a dose changes the flow as it is in B to that in A; that is, the volume flow diminishes on account of a more conspicuous systolic restriction, but shows no sign of a real vaso-motor effect. In strongly beating hearts as in C, the addition of adrenaline brings about still stronger contractions which cause a regurgitation of fluid and an overshoot. During the period of regurgitation, the coronary pressure increases above the base line, showing that the pressure at the orifice of the coronary arteries becomes greater than the perfusion

pressure. The pressure again reaches its base line when the forward coronary flow becomes re-established. The hot-wire tracing in these curves is not corrected, and there is therefore a small discrepancy between the beginning of the forward flow as recorded by the hot wire and by the manometer. After correction of the hot-wire record, the two records coincide. The fact that we deal with regurgitation in the systolic deflection of the hot wire is proved by the behaviour of the coronary pressure and by the fact that this deflection, as has already been mentioned, disappears when a valve is introduced in the perfusion system. Vaso-motor changes are absent as shown by the hot wire, the deflection of which reaches the same level late in diastole in C and D. This is further confirmed by

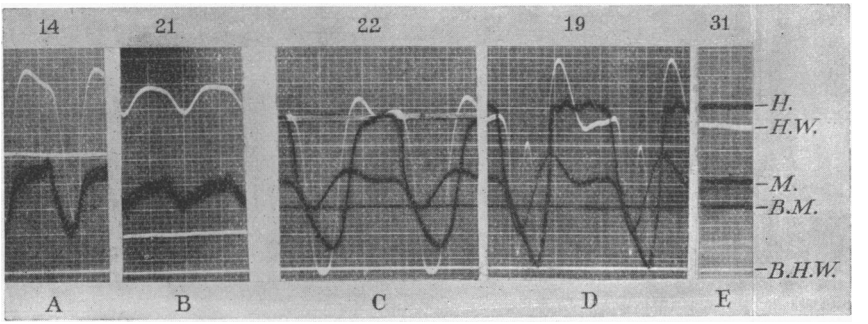

Fig. 5. A and B show the effect, on the coronary flow, of an acute weakening of the heart. C and D show the effect of strengthening of the heart beat after administration of a small dose of adrenaline. E was taken 20 sec. after D and shows the effect of ventricular fibrillation. The lettering is the same as in Fig. 1. The volume flows are given in c.c. per min. (Further explanation in text.)

record E which was taken during fibrillation initiated by a brief faradic current. In this record the hot wire shows a steady deflection within a millimetre of the height reached during the end of diastole in the two preceding tracings. It was ascertained that even this small displacement was only apparent and was due to a shift of the zero position of the hot wire. As regards the volume flow in this particular experiment it was 22 c.c. in C, 19 c.c. in D and 31 c.c. in E. The change in flow observed after administration of adrenaline, in doses which do not exert a vaso-motor effect, depends on the balance between the regurgitation and the overshoot. At first one and then the other may predominate, so that the volume flow may show a decrease followed by an increase or *vice versa*. The marked augmentation of the flow in E is the usual effect of fibrillation, and is due to the disappearance of the systolic restrictions.

Fig. 6 shows a number of records obtained on four different hearts. A shows the result of the administration of 0·01 mg. of histamine to the cat's heart, causing a pure vaso-dilation and an augmentation of flow. B indicates the effect of 0·02 mg. of histamine on the rabbit, causing a pure vaso-constriction and a diminution of flow. The same result is obtained by administration of pitressin to both the cat and the rabbit. C illustrates the effect of administration to the cat of 20 c.c. of Ringer solution *p*H 6, together with 0·01 mg. of histamine. The considerable increase in flow is in this case obviously due to two causes, namely to

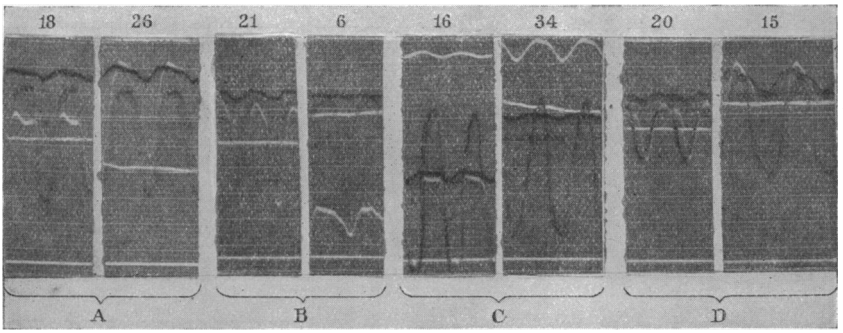

Fig. 6. This shows how the effect of a vaso-motor substance may be distorted by its simultaneous action on the heart muscle. A, effect of histamine 0·01 mg.; cat's heart. B, effect of histamine 0·01 mg.; rabbit's heart. C, effect of histamine 0·01 mg. with a simultaneous weakening of the heart; cat's heart. D, effect of histamine 0·01 mg. with a simultaneous strengthening of the heart; cat's heart. The volume flows are given in c.c. per min. In A from top downwards the lines indicate: manometer, heart, hot wire, flow recorder, base line of the hot wire. The records are easy to follow in the other tracings except that the white line at the top of the first segment of C is the flow recorder. The hot wire is the lower white line which is partially covered by the registration of the heart beat. In the second segment of C the hot-wire registration is at the top. In C and D the base line of the manometer is also given.

considerable vaso-dilation, which is shown by the rise of the diastolic level of the hot-wire record, and to a weakening of the heart which is shown by the diminished effect of systole. Tracing D presents a special interest. It shows the effect of the administration of a small dose of adrenaline together with histamine. In this case, in spite of the obvious vaso-dilation, the coronary flow diminished owing to increased systolic restrictions. Thus we see that the effect of vaso-dilation may be greatly augmented by a coincident weakening of the heart, leading to an excessively large increase in volume flow or conversely, in the case of strengthened contraction, a diminution of flow may take place in spite

of a considerable vaso-dilation. These examples show how difficult it is to make conclusions regarding the nature of various drugs with very weak effect from measurements of volume flows without a more detailed analysis as given by the hot-wire anemometer.

How very involved and complicated the action of a drug can be is shown by the effect of a strong dose of adrenaline, see Fig. 7. A rabbit's heart perfused at 80 c.c. H_2O pressure was made to fibrillate in section A of Fig. 7. The hot-wire deflection shows a straight line, the height of which depends on the degree of relaxation of the coronary blood vessels. In B the heart spontaneously resumed its beat. The height of the hot-wire deflection in the second half of diastole is equal to that observed during the preceding period of fibrillation. The coronary pressure is also the same in both curves. Between B and C 0·3 c.c. of 1 : 40,000 adrenaline (Parke, Davis tabloids) was injected, and soon the heart beat became stronger. The seventh beat produced a complete restriction of the flow during systole and a somewhat increased overshoot. Regurgitation begins from the ninth beat, and this is accompanied by an increased overshoot. Both are seen to grow with every successive contraction, until in D they reach a maximum. The blood vessels are not yet however dilated, as is again shown by the fact that the hot-wire deflection at the very end of each diastole is not higher than in C and B and in A during fibrillation. In D, during periods of regurgitation, the coronary blood-pressure is higher than the perfusion pressure, as can be seen from the fact that it crosses the base line. Only in E do the blood vessels show a considerable dilation, the presystolic level of the hot-wire deflection being considerably higher than before. The regurgitation is, however, still considerable. In F the regurgitation begins to diminish but not the vaso-dilation, in fact the presystolic level of the hot-wire record is even somewhat higher than in F. During all this time the heart rate was controlled at 150 beats per min. In G the artificial rhythm was discontinued, the heart beating now at 94 beats. The regurgitation, which had disappeared during the artificial rhythm, is also absent in G. Simultaneously with the disappearance of the regurgitation, the coronary pressure during systole becomes equal to the perfusion pressure, showing that only an arrest of flow is taking place. The diastolic level of the flow denotes that the considerable dilatation persists. This is further confirmed by sending the ventricle once more into fibrillation as in H. In this last section of Fig. 7, the fibrillation level of the deflection is equal to the presystolic level in G. The debated problem whether the coronary dilatation is due to a direct vaso-motor action of the drug or appears only

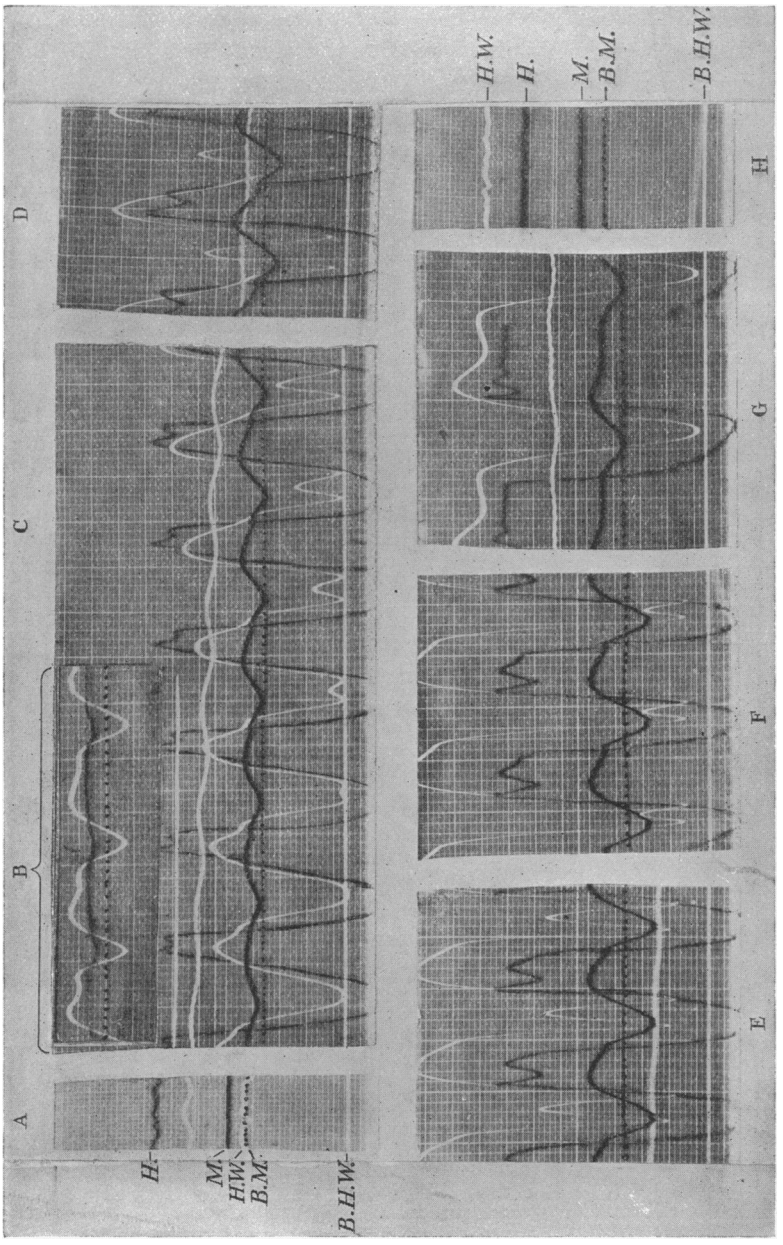

Fig. 7. The effect of a large dose of adrenaline. A, fibrillation before adrenaline. B, resumed beat before adrenaline. C, the seventh to thirteenth heart beat after injection of adrenaline. D, the seventeenth and eighteenth beat. E, 30 sec. after injection. F, 40 sec. after injection. G, 60 sec. after injection. H, fibrillation immediately after G. The dotted line is the base line of the coronary pressure. The rest of the lettering is the same as in Fig. 2. The horizontal white line across the records should not be confused with the hot-wire registration. It is made by the flow recorder. The volume flows per minute in the respective tracings from A to G were: 26, 22, 16, 17, 34, 38, 30 and 39 c.c.

as a secondary effect in response to an accumulation of metabolites is solved by Fig. 8, which was obtained in the same experiment as Fig. 7. The same dose of adrenaline was injected after the heart had stopped in diastole. The vaso-dilator effect is in this case nearly equal to that produced in the beating heart, which can be seen from the extent of the hot-wire deflection. The sequence of events following an injection of adrenaline is usually as described above. In several experiments, however, we noticed that the vaso-dilator effect of adrenaline made its

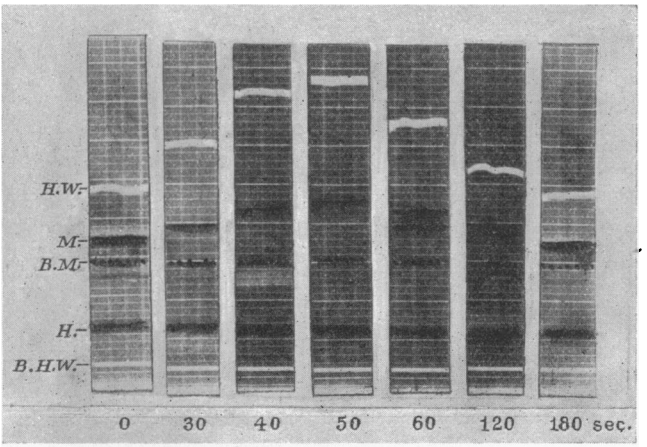

Fig. 8. The effect of adrenaline upon the cat's heart which is not beating. The same dose was used as in the preceding figure. The lettering is the same as in Fig. 2. The first section was taken before administration of the drug. The others were taken after administration at intervals indicated in the figure.

appearance somewhat before the strengthening of the heart beat. In these cases adrenaline causes at first an augmentation of the volume flow which is rapidly succeeded by a diminution, due to the stronger cardiac beat. The subsequent changes are the same as those described for Fig. 7.

We consider that the experiments described above are an example of the most complete analysis of the action of a drug which is possible by the hot-wire anemometer. Without such analysis it is extremely difficult to determine either the mode of action of drugs on the coronary circulation or the minimal dose which is required to produce an action.

SUMMARY.

1. The coronary circulation in the isolated perfused heart is analysed by means of the hot-wire anemometer; the chief peculiarities of this circulation are discussed.

2. A convenient method for optical registration of the heart beat and a new method of heart perfusion are described.

3. The statement of Hochrein and co-workers that the coronary flow in a perfused artery is maximal during systole is not supported by our experiments. The inflow is diminished by the contraction of the heart in proportion to its strength.

4. Certain peculiarities of the coronary circulation such as regurgitation and the overshoot are described and analysed.

5. Examples are given of the action of various drugs, and it is shown how the vaso-motor effect of a drug may be masked, accentuated or reversed by the action which the drug may simultaneously exercise on the heart beat.

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