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THE EFFECT OF THE CARDIAC CONTRACTION UPON THE CORONARY FLOW.

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In spite of the extensive researches made during recent years, some of the most fundamental questions concerning the coronary circulation still remain a field of considerable debate. The question whether the blood supply to the heart muscle is maximal during the period of systole or during the period of diastole seems to be the centre of most violent and uncompromising exchanges of opinion.

A comprehensive review of the literature on the coronary circulation was recently made by Condorelli [1932]. Amongst other problems, the author deals in a purely objective and unbiased way with the different opinions about the extent to which the cardiac contraction may affect the coronary flow. Condorelli concludes that the blood supply to the left ventricle during the period of systole is but little affected by the systolic rise of the aortic blood-pressure. A second monograph on the same subject by Hochrein [1932] is chiefly devoted to a restatement of the author's own opinions and to an attempt to prove that the maximal blood supply to the heart occurs, as in any other organ, during the period of systole. This conclusion is supported by references to the author's former publications. No new facts are provided, and the criticism of his experiments which was made in communications from this laboratory [Anrep, Davis and Volhard, 1931; Davis, Littler and Volhard, 1931] is left unanswered although it is mentioned. We refrain from any polemical discussion of this problem, as we prefer to subject the question to a still further experimental test.

If the coronary artery were suddenly and completely blocked for a short time during some definite period of the cardiac cycle, the effect of this block on the blood supply to the heart muscle would depend on whether the clamping period coincided with the period of maximal or of minimal blood flow through the artery. If the blood flow through the coronary artery were entirely uniform throughout the cardiac cycle, repeated short periods of clamping would always have the same effect upon the blood flow, and it would be immaterial whether these periods of clamping fell within the systole or the diastole. So long as the blood flow through the coronary artery is not uniform, however, and so long as periods of larger and smaller flows stand in some definite relation to the cardiac cycle, clamping of the coronary artery which coincided with the periods of reduced flow would produce a small diminution of the flow through the artery, while clamping which coincided with periods of large flow would produce a large diminution. If at some definite phase of the cardiac cycle the flow is at a standstill, clamping of the artery which exactly coincided with this phase should produce no change in the blood flow whatever. By gradually shifting the period of clamping so as to make it fall within different stages of the cardiac cycle, it should be possible to determine at which stage the clamping produces the minimal effect and thus to decide whether the blood supply to the heart is smaller during systole or during diastole.

If a glass tube is provided at each end with a rotating tap, the periods of closing and opening of which could be made to coincide or to alternate, the effect of closing these taps upon the flow of liquid through the tube would be maximal in the case of alternate closing; and if the closure of one tap were to coincide exactly with the opening of the other, the flow would be reduced to zero. Approximately similar conditions should hold for the heart, except that in this case we deal not with a rigid tube but with blood vessels which have certain elastic properties. In this respect one could compare the effect with that produced by turning two taps which are placed at the ends of a rubber tube. In the case of alternate closure of the taps, the rubber tube would be distended when the distal tap was closed and the proximal tap opened. When the proximal tap was closed and the distal one was opened, the rubber tube would empty itself to an extent determined by its elasticity. Therefore the flow of liquid would be considerably reduced but not completely stopped.

A constant effect of periodical clamping of an artery can only be hoped for if the clamping always takes place during some definite period of the cardiac cycle, and if the length of each clamping period is maintained constant. The most definite results should be expected if the length of clamping is made equal to the length of the period of the minimal or of the maximal blood flow through the artery. The apparatus necessary for this purpose should therefore be constructed so as to allow the clamping

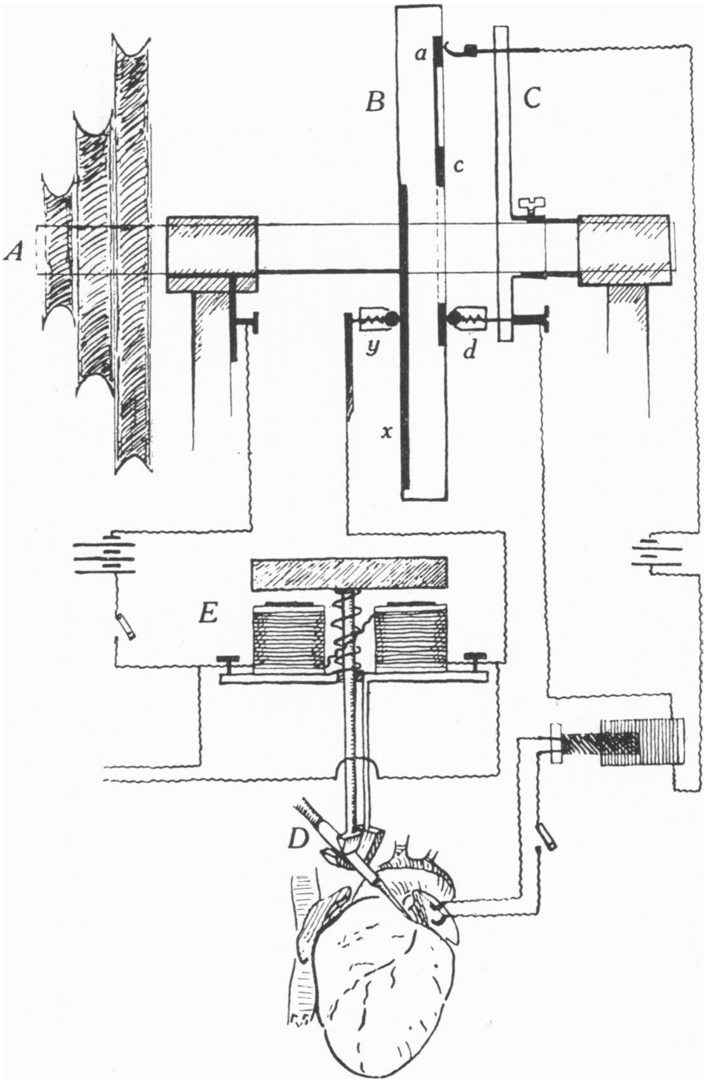

Fig. 1. The clamping apparatus. *A* are pulleys for driving the apparatus. *B* is an ebonite disk carrying a spring contact *a* for the "driving circuit" and a brass plate contact *x* for the "clamping circuit." The arm *C* is stationary and is insulated from the shaft; it can be fixed in any position in relation to the rotating disk, so that the moment at which the single induction shocks affect the heart can be changed; *c* is a brass circle which is in constant contact with the spring ball *d*. The brass plate *x* forms a sector of 180° of the disk close to the shaft and 36° at the periphery; the spring ball contact *y* is fixed on a swing arm which can be adjusted in any desired position so as to activate the clamping circuit for any duration between 0·1 and 0·5 of a revolution of the disk. *E* is the electromagnet and *D* the plunger-like extension of its armature which clamps a short piece of rubber tubing connected with the coronary cannula.

to be made at any desired phase of the cardiac cycle and to be continued for any desired length of time. We are greatly indebted to the instrument maker of the University, Mr F. W. King, for the construction of an apparatus which fulfilled these requirements (see Fig. 1). The important feature of the apparatus is that it can activate two independent electric circuits in such a way that the moment of activation of either of them and the duration of the activation of one can be altered at will. One circuit is connected with a pair of electrodes placed on the auricle or ventricle of the heart. Through these electrodes, by means of single induction shocks, the heart is driven to beat at a constant rate between 100 and 160 beats per minute. The contact for this circuit is made between a wire fixed on the rotating ebonite disk of the apparatus and a stationary spring contact. The second circuit is used to activate an electromagnet, by means of which the actual blocking of the coronary blood flow is effected. One of the contacts for this circuit is made out of a brass plate of a special shape and is fixed to the same rotating disk. The second contact for this circuit can be placed in such a position relative to the rotating disk that it can be made to slide over the brass plate contact for any desired fraction of the disk, cutting through sectors from 36 to 180°. On setting the disk in rotation, the clamping circuit can thus be activated for any length of time between one-tenth and one-half of the period of rotation. The position of the driving contact can be shifted round the whole disk, and thus the beginning of the activation of the clamping circuit can be made to coincide with the activation of the driving circuit, or can be made to follow it at any time within the period of revolution of the disk. In this manner the clamping of the coronary artery can be made to occur during any phase of the cardiac cycle and to continue from 0·1 to 0·5 of the cycle length.

The clamping was made by an electromagnet, the armature of which was connected with a plunger which could slide into a little groove. The electromagnet was strong enough to lift a weight of 2 kg. and to clamp a thin-walled rubber tube connected with a water pressure of 500 mm. Hg. The excursions of the electromagnet did not exceed 4 mm. and the clamping was extremely rapid. The registration of the clamping was made by means of a small electromagnetic signal connected with the clamping circuit. In order to determine the rapidity of the clamping and the accuracy of its registration by the signal, the following tests were made. A reservoir containing water was placed at a suitable height and connected by means of a metal tube to a cannula, the nozzle of which was provided with a short piece of thin rubber tubing. This rubber tube was placed in the groove under the plunger of the electromagnet, and the flow of water through the tube was measured before and during periods of clamping. The disk bearing the contact was set in rotation at some definite rate, and the length of each individual clamping of the tube was changed between the measurements of the flow by one-tenth of a revolution of the apparatus. Even under the best conditions one would hardly expect that, with each prolongation of the clamping time by one-tenth, the flow would diminish by exactly 10 p.c. The apparatus, however, worked quite satisfactorily, as can be seen from the following example. The free flow of water through the tube was 55 c.c. per min. The clamping contact was set in rotation at 150 revolutions per min., and the length of each clamping was increased by one-tenth of a revolution from 0·1 to 0·5, an increase of 0·04 sec. each time. The corresponding diminutions of the flow with each increase of the length of clamping were 9·0, 19·0, 29·0, 39·5 and 49·0 p.c.

Hot-wire registration of the outflow of water from the reservoir, or of the outflow from the cannula beyond the place of clamping, showed that the clamping was extremely rapid, the flow being arrested within 0·02 sec. The signal which was used for the registration of the clamping was found to work quite synchronously with the electromagnet. This was ascertained by simultaneously photographing on a roll-paper camera the movement of the armature of the electromagnet and the movement of the signal.

The blood flow through the coronary artery.

For the success of the experiments, it was imperative to have an accurate measurement of the minute flow through the coronary artery, and an exact knowledge of the phase of the cardiac cycle during which the clamping of the blood supply took place. The cardiac cycle was registered by means of a Wiggers optical manometer (vibration frequency 130–150 per sec.) which was inserted through the left subclavian artery into the aorta, when the experiment was made on the whole animal. In some experiments this was supplemented by an electrocardiogram, for which direct leads were taken from the ventricle. All our observations were made on the circumflex branch of the left coronary artery. The experiments were made on dogs weighing 8–12 kg., anæsthetized with chloralose or sodium luminal. In the whole animal, heparine was used to prevent coagulation. The chest of the experimental animal was opened through a midsternal incision, and artificial respiration was carried out by an

"Ideal" respiratory pump. The coronary artery was either perfused from a reservoir containing blood, which was placed at a suitable height above the animal, or from the aorta of the animal through a connection leading from the subclavian artery to a cannula which was inserted into the peripheral end of the coronary artery. The perfusion from the reservoir (constant pressure perfusion) could be switched over to the perfusion from the aorta (autoperfusion with the pulsatile pressure) by turning a tap with a large bore (Fig. 2). All connections between the perfusion source, whether aorta or reservoir, and the cannula were rigid. The few end-to-end glass connections were made with very inelastic thick pressure tubing. These precautions were especially necessary in the case of the autoperfusion, since otherwise the transmission of the pulse pressure from the aorta to the coronary artery might have been delayed and the cardiac systole would not have coincided with the rise of the blood-pressure in the artery. In consequence of this, the maximal pressure in the coronary artery would have been shifted somewhat towards the diastole. On many occasions we measured simultaneously the blood-pressure in the aorta and in the coronary cannula, and proved to our satisfaction that the rigidity of the apparatus was sufficient to prevent such a displacement. The blood flow through the artery was recorded by means of a small Stolnicov stromuhr of about 10 c.c. capacity. The time taken for a flow of 5 c.c. was measured with an accuracy of half a second, which means that with an average blood flow of 20–25 c.c. per min. the measurements were accurate to about 0·2 c.c.

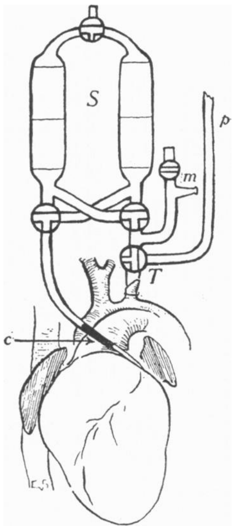

Fig. 2 shows the arrangement of the apparatus. *p* is the connection with the perfusion reservoir containing blood, *m* is the optical manometer, *S* the stromuhr, *c* the place of clamping by the electromagnet, and *T* is a tap by means of which the perfusion of the coronary artery with the constant pressure can be changed to the autoperfusion with the pulsatile aortic pressure. The apparatus is rigid and its taps have a bore of 4 mm. in diameter.

On the way to the coronary artery, and immediately preceding the cannula which was introduced into it, the blood was made to pass through a short piece of thin-walled rubber tubing, the internal diameter of which was 3 mm., while the length of the free part of the rubber tube was equal to 3–4 mm. The rubber tube was placed in a groove underneath the plunger of the electromagnet which, when periodically activated, clamped the tube in the middle of its free part. The plunger was 2 mm. wide, so that the displacement of fluid in the tube during the clamping was extremely small (about 0·01 c.c.).

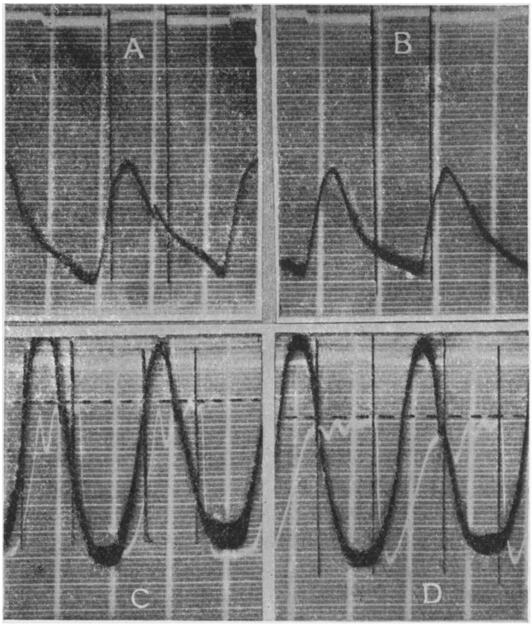

Fig. 3. A and B show the registration of the exact moment and the duration of the coronary clamping in relation to the cardiac cycle. Records of the aortic blood-pressure; the top line is the signal recording the clamping by an upward movement. In A the clamping starts during systole and extends slightly into the diastole; in B it starts in diastole and ends soon after the beginning of systole. Records C and D show a similar experiment, together with a hot-wire registration of the inflow of blood into the perfused coronary artery. The interrupted straight line across the records is the base line for the hot wire. With increase of the blood flow, the shadow of the string moves downwards. The vibrations of the hot-wire record are caused by the impacts of the electromagnet. For other explanations see text. All the tracings in this paper should be read from left to right. Time in 0·2 sec. The time lines in these tracings run somewhat obliquely because of an instrumental error; they are nevertheless accurate.

The heart was driven to beat at a constant rate throughout a whole experiment. Several consecutive measurements of the free blood flow through the coronary artery were made. The clamping circuit was then switched in, and the blood-flow measurements were repeated. In order to know the exact time within the cardiac cycle during which the clamping took place, the aortic blood-pressure was recorded photographically, together with the movement of the electromagnetic signal. As said before, in some experiments this was supplemented by an electrocardiogram. An example of an actual record is given in Fig. 3 A and B. In the first the clamping starts during systole and extends somewhat into the diastole. In the second it starts during diastole and extends into the next systole. The relative position of the clamping period within the cycle was then changed by adjusting the moment at which the driving induction shock was sent into the heart. Measurements of the blood flow were repeated with every new change of the clamping. In between each change the clamping was stopped, and the free flow through the coronary artery was again determined. Usually the procedure was such that three or four measurements of the free flow were interimposed between two or three measurements during the periods of clamping. In some experiments with perfusion of the artery with a constant pressure, a hot-wire registration of the inflow of blood into the artery was also made. An example of such a record is given in Fig. 3 C and D, which was obtained from an experiment on the whole animal. In the first record the clamping starts a little after the onset of systole and extends slightly into the diastole. In the second it starts at the dicrotic notch and continues during a long stretch of diastole. The hot-wire record, although distorted by the vibrations caused by the electromagnet, shows that the systolic diminution of the blood flow develops considerably more rapidly in Fig. 3 C than in Fig. 3 D. In the first case the diminution is started by the systole and accentuated by the clamping of the artery. In the second the diminution is due to the systole alone; the clamping begins at the moment of the minimal blood flow and only serves to prolong this diminution.

Hochrein states that in the whole animal, when the coronary artery is perfused at a constant pressure, the maximal blood flow occurs during systole, which would imply that during systole the heart muscle opposes the minimal resistance to the blood flow. Since, during normal pulsatile aortic perfusion of the artery, the maximal pressure in the coronary artery is synchronous with the maximal pressure in the aorta, one would expect in the whole animal a most vigorous systolic perfusion of the heart. This is the reverse of what we find in the heart-lung preparation [Anrep and Häusler, 1928, 1929] and in the isolated perfused heart [Rössler and Pascual, 1932]. But Hochrein considers that the conditions of the circulation in the heart-lung preparation are so abnormal that the coronary circulation may be entirely changed. Without going into this question any further, we should like to say that it is difficult to under-stand why a coronary artery, which is perfused at a constant pressure from an outside source, should behave in such a strikingly different manner in the heart-lung preparation and in the whole animal. In our previous experiments we found no such difference. Whether in the heart-lung preparation or in the isolated heart or in the whole animal, the perfused coronary artery had invariably a minimal blood flow during systole

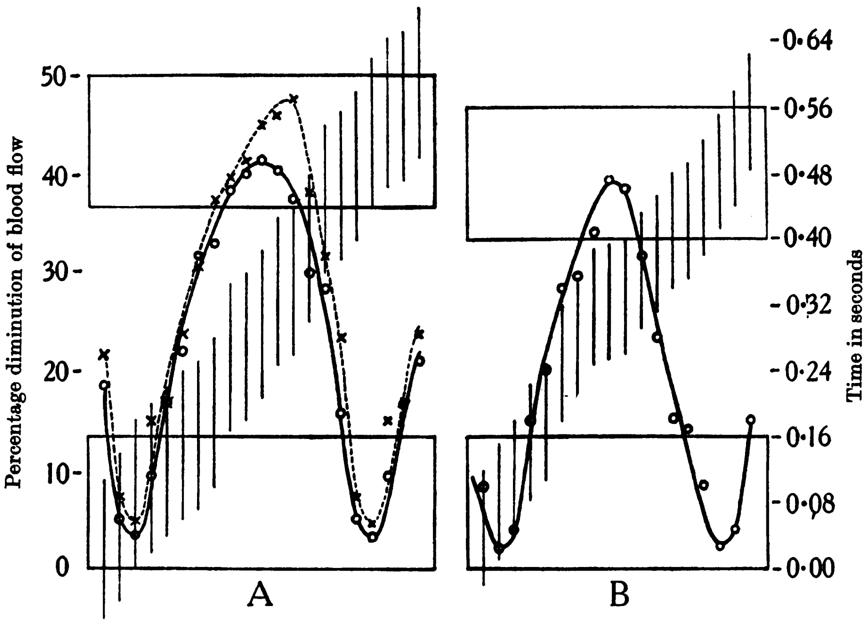

Fig. 4. Percentage diminution of the minute blood flow through the left circumflex coronary artery during short periodical clampings of the artery at various phases of the cardiac cycle. The diagram should be read from below upwards. The two rectangles at the bottom and at the top represent the duration of the systole, and the space between them represents the duration of the diastole. The ascending row of straight lines shows the duration of the clamping and its position within the cycle. A is from an experiment on the heart-lung preparation; B is from an experiment on the whole animal. The dotted line with crosses shows the result of clamping during a constant pressure perfusion; the continuous line with circles shows the result during autoperfusion.

and a maximal during the second half of diastole. However, since the objection has been made, we decided to perform our experiments on the whole animal and to compare the results with those obtained on the heart-lung preparation. The result of two experiments is given in Fig. 4. The left-hand side of the figure shows the effect of clamping of the coronary artery at different periods of the cardiac cycle in a heart-lung preparation, the right-hand side shows the results obtained on the whole animal.

The figure should be read from below upwards. The width of the two rectangles at the bottom and at the top of each side of the figure represents the average length of systole, while the distance between the rectangles represents the length of diastole. The gradually ascending row of straight lines shows the duration and the position of the clamping of the coronary artery in relation to the cardiac cycle. The part of the lines which lies within the rectangles shows the length of clamping which fell within the systole, and the parts lying between the rectangles within the diastole. In the experiment on the heart-lung preparation, two sets of measurements were made with each new changed position of the clamping, one while the coronary artery was perfused from a reservoir at a constant pressure of 110 mm. Hg, and the other during autoperfusion from the aorta of the same preparation. (The average systolic pressure was 160 and the average diastolic pressure was 100 mm. Hg.) The percentage diminution of the coronary blood flow is shown in the case of the constant pressure perfusion by crosses (dotted line) and in the case of the autoperfusion by circles (continuous line). It can be seen that, with the gradual encroachment of the clamping on the diastole, the effect of it on the blood flow increases. Clamping of the artery during diastole has a conspicuously greater effect than a similar clamping during systole. The clamping during the second half of the diastole has a somewhat greater effect than the clamping during the beginning of the diastole. Fig. 4B shows that there is no difference between the behaviour of the heart in a heart-lung preparation and in the whole animal. The effect of the coronary clamping was found to be in both cases the same in character and magnitude.

In some experiments on the whole animal the clamping of the coronary blood flow at various periods of the cardiac cycle was made during constant pressure perfusion as well as during autoperfusion from the aorta. In other words, the experiment was done exactly in the same way as the one on the heart-lung preparation, the results of which are given in Fig. 4A. The results were the same in the two cases. A large number of observations was made by us on many animals and all cases gave the same results, except that the extent of the effect differed from one animal to another. The greatest diminution of the coronary blood flow during diastolic clamping, which occupied about one-half of the diastole, was 54 p.c. The smallest effect was 28 p.c. Systolic clamping had in some experiments almost no effect on the coronary blood flow, and in others it slightly reduced the flow, usually by not more than about 5 p.c.; only in one experiment was the diminution of the flow as great as 10 p.c. We found no difference in the result after section of the cervical vagi. From a consideration of these experiments the conclusion seems to be unavoidable that the blood flow through the coronary artery is maximal during diastole and minimal during systole. It also seems obvious that in this respect there is no fundamental difference between the heart-lung preparation and the whole animal and that, disregarding minor points, the circulatory conditions in the perfused and in the autoperfused artery are comparable.

THE BLOOD-PRESSURE IN THE CORONARY ARTERY.

Further evidence in favour of this conclusion was obtained by measurements of the blood-pressure in the coronary artery between the place of clamping and the heart. If, during the periods of the systolic clamping, there is little or no inflow of blood into the heart, then the pressure in the cannula, from the beginning of the clamping until the time when the next diastole sets in, must remain approximately at the level at which it was during the moment of clamping. On the other hand, if during the diastolic clamping there is no restriction of the blood flow into the heart muscle, the pressure in the coronary cannula should progressively fall during the whole period of clamping. In order to test this, the coronary cannula was provided with a wide side branch, which was connected to a high-frequency optical manometer. The stromuhr was omitted, so that the whole preparation consisted in the establishment of a communication between the aorta and the coronary cannula. This connection was made entirely rigid except for the 3–4 mm. length of the rubber tube under the plunger of the electromagnet. Thus during the clamping the pressure was measured in the peripheral end of the coronary artery. The cannula carrying the side tube was introduced, as in the blood-flow experiments, into the circumflex branch of the left coronary artery. The heart was driven at a constant rate and the blood-pressure in the artery was recorded during the periods of clamping at various phases of the cardiac cycle. Fig. 5 shows the effect of a purely systolic and of a purely diastolic clamping. The records speak for themselves. During the systolic clamping, not only is there no fall but there is a definite rise of the pressure in the artery; during the diastolic clamping there is a precipitate and conspicuous fall. This effect is equally well marked in an artery which is perfused at a constant pressure and in one which is perfused by the pulsatile aortic pressure. The rise of pressure during systolic clamping was not observed in all experiments. In many cases, instead of rising, the pressure remained steady at the level at which it was when the clamping took place. It fell abruptly only with the onset of the diastole. In other experiments there was a small fall of pressure during the systolic clamping. This fall, however, was negligible as compared with the huge drop of pressure observed during the diastolic clamping, when the pressure

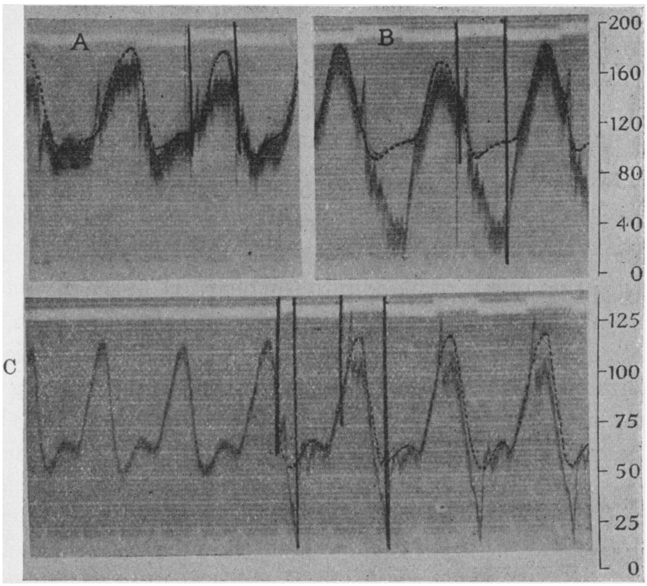

Fig. 5. The effect of clamping of the coronary artery upon the coronary blood-pressure. The top line is the signal recording the clamping; the dotted curves show the blood-pressure before the periodical clamping was begun. Tracings A and B are taken from the same experiment. In A, systolic clamping, in B, diastolic clamping. Tracing C, from another experiment, shows the beginning of a clamping period. The first clamping is very short and purely diastolic. The next clampings start during systole and involve a part of the diastole. Note that the drop of the blood-pressure occurs only during the diastolic part of the clamping. During the systolic clamping the blood-pressure in these two experiments shows a considerable rise.

may fall almost to zero. Only in one experiment was the fall of pressure during the systolic clamping rather considerable, but even here it was still very much smaller than that taking place during the diastolic clamping. In this case a particularly large auricular branch was found to leave the coronary artery just below the nozzle of the cannula.

The difference between the effect of systolic and diastolic clamping is even better observed when the driving of the heart is omitted. The heart is allowed to beat at its own rhythm, while the clamping is set to work at a rhythm which is slightly faster or slightly slower than the heart rate. The clamping thus gradually shifts with each heart beat from diastole more and more into the systole and then again into the diastole. In this

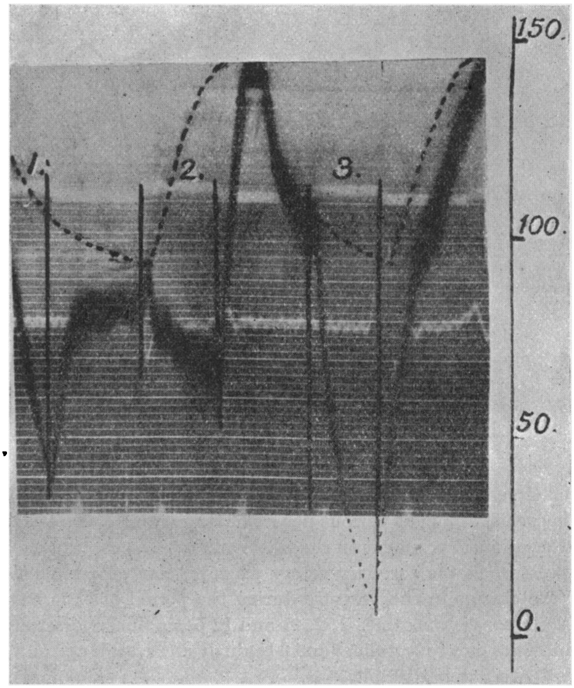

Fig. 6. Whole animal. The effect of two successive clampings of the coronary artery upon the coronary blood-pressure. The dotted curve is a retraced record of the aortic blood-pressure. (1) is the end of a clamping which was partly systolic and partly diastolic, (2) a systolic clamping, (3) a diastolic clamping. The dotted line continuing the drop of pressure in (3) is retraced from the 21st cycle following, in which an exactly similar relative position of the clamping took place and in which the camera was moved so as to include the low pressure levels. An E.C.G. (direct leads from the ventricle) was taken during this experiment. During the systolic clamping the blood-pressure fell by 16 mm. Hg; during the diastolic clamping it fell by 94 mm. Hg, almost reaching zero.

way one gets all the possible combinations in the time relations between the cardiac cycle and the clamping. It would be impossible to reproduce an original record of such an experiment on account of its length. Therefore we give only a small section of a record (see Fig. 6), in which a systolic clamping is followed by a diastolic clamping, and a diagram which is composed of retraced pressure records obtained in an experiment with autoperfusion on the whole animal (see Fig. 7). We would like again to stress the fact that experiments on the whole animal and on the heart-lung preparation with autoperfusion and with constant pressure perfusion gave the same results.

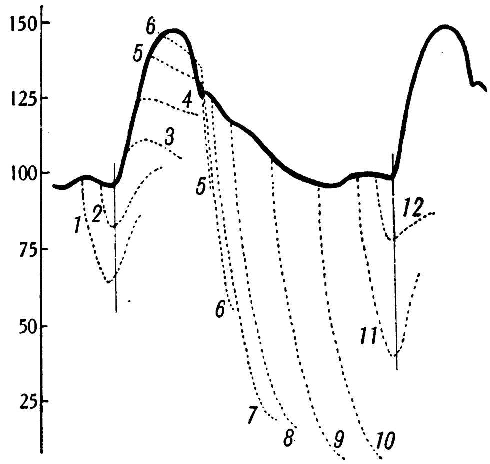

Fig. 7. Retraced superimposed records of changes in the blood-pressure in the coronary artery during its clamping at various phases of the cardiac cycle. All the records were obtained in the same experiment on the whole animal. The continuous curve represents the blood-pressure in the coronary artery when no clamping took place. The dotted lines show the change in the pressure during the period of clamping. The length of clamping in all cases is the same. 1, 2, 11 and 12 begin during diastole and end during systole; 3 and 4 are purely systolic; 5 and 6 begin during systole and end during diastole; 7, 8, 9 and 10 are purely diastolic.

Summary and conclusions.

In previous communications from this laboratory it has been shown, by means of hot-wire measurements of the inflow into the perfused left coronary artery, that the heart offers the greatest resistance to the blood flow during the period of systole. These experiments were repeated and no difference was found in this respect between the heart-lung preparation and the whole animal. In further experiments it was shown that, with small differences, the same holds true for a heart in which the coronary artery gets its blood supply from the aorta. The results of the experiments described in this communication lend further support to our former observations by showing that:

(1) Repeated obstructions of the coronary blood flow which occur in diastole conspicuously reduce the blood supply through the artery; on

the other hand, equal obstructions which occur during systole have almost no effect upon the blood flow. This result demonstrates that the blood supply to the heart during systole is negligible.

(2) Measurements of the blood-pressure between the place of clamping and the heart muscle show that during systolic clamping there is no change or sometimes even a rise of pressure in the coronary artery, while during diastolic clamping there is a precipitate fall of pressure. This result demonstrates that the heart muscle opposes the greatest resistance to the coronary blood supply during systole and the smallest resistance during diastole.

(3) These results were obtained in the heart-lung preparation and in the whole animal, in artificially perfused coronary arteries and in arteries which remained in connection with the aorta.

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