

ON THE RELATION OF THE VOLUME OF THE CORONARY CIRCULATION TO THE FREQUENCY AND FORCE OF THE VENTRICULAR CONTRACTION IN THE ISOLATED HEART OF THE CAT.

BY G. B. MAGRATH AND H. KENNEDY.

(From the Laboratory of Physiology in the Harvard Medical School.)

PLATES II AND III.

In the experiments recorded in this paper, the heart of the cat was kept beating by passing defibrinated cat's blood from the aorta through the coronary vessels into the right auricle and ventricle, whence it escaped through a cannula in the pulmonary artery. The blood thus transfused through the coronary vessels into the right heart flowed from the tube in the pulmonary artery in drops, as a rule. The volume of the transfused blood was measured by counting the drops. The volume could be increased or diminished at will by increasing or diminishing the pressure of the blood at the mouths of the coronary arteries. A Hürthle membrane manometer, connected with the left ventricle by a tube passed through the left auricular appendix and mitral valve, measured the force and frequency of ventricular contraction, the left ventricle and the connecting tubes being filled with normal saline solution. The experiments were performed in a warm chamber at a sufficiently constant temperature.

The results of the investigation show that the force of ventricular contraction is immediately affected by a change in the amount of blood supplied to the cardiac muscle, the ventricle beating with more force if the volume of the coronary circulation is increased, and with less force if it is diminished; and this holds true within wide, but, as yet, not accurately determined limits. The frequency of ventricular contraction, on the contrary, is largely independent of the blood supply to the cardiac muscle, and may remain almost unchanged

even while the force of contraction, in consequence of lessening the supply of blood, is much reduced. We noted also that the left ventricle of the isolated cat's heart, working with a constant load of a very few millimetres of mercury, will develop a high intracardiac pressure on a surprisingly small coronary circulation.

Certain other facts of interest were incidentally observed. The distension of the left auricle and ventricle lessened the coronary flow. The fibrillary contractions occasionally present sometimes gave place to wholly normal beats, one heart, we especially remember, showing strong fibrillary contractions during forty-five minutes and then falling into regular, normal contractions, which continued for more than an hour. The heart appears to add little, if any, fibrin to the blood.

Interesting also is the observation that a heart, from which the blood supply had been almost entirely cut off, began to group its contractions in a kind of "staircase" form. As the circulation through the cardiac muscle was restored, the individual groups in the intracardiac pressure curve grew longer and longer, until they gradually merged into an unbroken series of normal contractions.

It was remarked, further, that the amount of blood passing through the veins of Thebesius into the left heart was usually but a few drops per minute.

All these various observations will be discussed after the methods employed by us have been more fully described.

METHOD.

The method employed in our researches required a warm chamber; a blood-supply apparatus; a drop counter, for recording the number of drops flowing through the coronary vessels; and a membrane manometer, for recording the intraventricular pressure.

The warm chamber.—The warm chamber was made of "window sash," and was 200 cm. long, 80 cm. wide, and 150 cm. high, giving a contents of 2.4 cubic metres. Access to the chamber was afforded by two tightly closing doors, hinged above, which together formed the lower two-thirds of the front of the chamber. When the doors were raised, the entire length of the chamber was exposed, provid-

ing abundant room for arranging apparatus and for cleaning. The chamber stood upon a table, the top of which was made almost entirely of sheet copper. This sheet formed the roof of a copper tank, 150 cm. long, 60 cm. wide, and 15 cm. deep, partly filled with water. Thus the table was merely a support for the copper water-tank and the glass chamber over it. The water was put into the tank through an opening in the top, after which the opening was closed with a cork, perforated by a perpendicular glass tube, 15 mm. in diameter, which ran through the roof of the warm chamber and served to let out the steam when the water was heated. Thirty-two centimetres above the floor of the chamber this escape pipe was furnished with a short side branch, through which a part of the hot watery vapor passed into the warm chamber and kept the air moist.

The tank was heated by four Bunsen burners placed beneath it. It was our habit to light the Bunsen burners about an hour and a half before the animal was ready to be put in the chamber. At the end of that time, the temperature of the chamber having risen to about 37° C., the animal was placed as far as possible from the doors, one door was tightly closed, and the other was let down until it rested against the back of the observer in charge of the manometers, who stood with the upper half of his body inside the chamber. The temperature of the chamber remained sufficiently constant for our purposes, the large contents, namely, 2.4 cubic metres, and the large heating surface, 9000 square centimetres, keeping it so, in spite of the partial opening of one of the doors. The temperature was measured by a thermometer, the bulb of which hung in the middle of the chamber about 20 cm. above the animal. Many control readings were taken from a thermometer placed in the thorax. In the course of 27 experiments the thermometer was read about 500 times. The fluctuations during the period of observation were rarely over 0.5° C., an amount too small to constitute a serious source of error. In fact, our position in respect of temperature errors was not a difficult one, for our time of observation was made up of three brief, consecutive periods: the first, recording the force and frequency of ventricular contraction with a known volume of coronary circulation; the second,

with that volume altered in one direction or the other; and the third, with the coronary circulation restored, as near as might be, to the volume of the first period. All these periods together lasted but three or four minutes, sometimes less, and the temperature could vary but little during this short time.

Blood-supply apparatus.—The blood was contained in a glass tube, 14 cm. long, 3 cm. wide, of 50 cb. cm. contents, drawn out slightly at one end, and closed at the other with a rubber stopper. The drawn out or lower end connected, through a light brass stopcock, with the aortic cannula. The rubber stopper, closing the upper end, was perforated by two glass tubes. The first of these led through a stopcock to the filling reservoir, of the same dimensions as the blood reservoir but open at its upper end. The second of the tubes perforating the stopper of the blood reservoir was a short T, the side branch of which opened, through a stopcock, to the atmosphere, while the direct tube led, through a stopcock, to the pressure bottle.

To fill the blood reservoir, all the stopcocks were closed and the defibrinated blood was poured into the filling reservoir. The stopcock leading to the atmosphere and then the stopcock leading to the filling reservoir were now opened and the blood filled the blood reservoir. The last-mentioned cocks were closed again, and those leading respectively to the aortic cannula and the pressure bottle were opened. The contents of the blood reservoir and its communicating tubes, namely, the aortic cannula, the aorta and the main coronary arteries, stood now under a constant pressure nearly that of the pressure bottle.

The pressure was made by joining the pressure bottle with a thick-walled rubber tube to a water bottle, suspended from the ceiling of the operating room. The water bottle could be raised or lowered and fixed at any height. It was so arranged that the level of the water within remained the same, whatever the height of the bottle. This constant level was maintained by an outflow tube in the shape of an L. The branch of the outflow tube rose to a height of about 15 cm. above the level of the floor of the bottle, and then turned to be continued downward into a sink. At the turn it was provided with an upright tube, open to the atmosphere, to prevent siphonage. The

direct limb of the outflow tube of the water bottle was connected with the pressure bottle in the warm chamber. The water flowed continuously into the water bottle through the neck, and, passing through the tubulure, rose in the upright branch and turned down into the sink. A small part, however, found its way down the pressure tube to the pressure bottle. The pressure bottle being very large—its capacity was 5000 cb. cm.—and the volume of the coronary circulation very small, it could be used several hours without requiring to be emptied. With this apparatus the pressure at the mouth of the coronary arteries could be kept sufficiently constant at any desired level, or rapidly and easily changed simply by raising or lowering the water bottle. The flow through the coronary arteries could thus be varied within wide limits.

The pressure at the mouth of the coronary arteries was recorded by a mercury manometer connected with a cannula passed into the innominate artery at its origin from the aortic arch. In some experiments the manometer was furnished with a writing style. The curves thus secured (see Plate II, and Figs. 2 and 3, Plate III) bear witness to the uniformity of pressure at various levels and the ease with which the pressure is modified. The mercury manometer is also useful in determining whether a failure in the coronary circulation is due to lack of pressure or to an obstruction in the blood-vessels.

The drop counter.—The drop counter consisted of a glass tube, 165 mm. in length and of 4.5 mm. lumen, one end of which was tied in the pulmonary artery, just above the semilunar valves. The other end projected over the cat's left shoulder, and was usually somewhat lower than the heart, so that, when full, it acted as a weak siphon and favored the flow of blood. The same tube was used in every experiment. The blood dropped out of this tube on a triangular piece of thin aluminium about 17 mm. long and 14 mm. wide at the base, placed about 4 cm. below the outlet of the tube. The aluminium, which was so bent that the blood could not collect upon it, but ran off into a porcelain dish beneath, was fastened to the lever of an ordinary Marey tambour. From this ran a rubber tube to a small and very sensitive recording tambour, covered with very thin rubber, and

carrying a very light straw lever, which made a sufficiently large excursion for each drop that fell on the aluminium plate.

In a number of experiments the drop counter was not used, the drops being counted by an assistant, in periods of 15 or 30 seconds each. Another assistant marked the periods on the smoked paper by closing the circuit of a writing electro-magnet. An example of this marking is seen in Fig. 1, Plate III.

It will be remembered that the experiments we are discussing consist in comparing the frequency and the force of contraction in two or three consecutive short periods, while the conditions under which the heart is working remain the same, except that the volume of the coronary circulation is made to vary by varying the pressure at the mouths of the coronary arteries. The volume of the coronary circulation is estimated by counting the drops from the outflow tube. A difference in the size of the drops would, therefore, constitute a source of error. We must, then, consider the possible causes of such a difference. It might be thought that the size of the drops would vary with the quickness of flow, the more frequent drops being smaller than the less frequent ones. In this case we should expect that a given number of drops escaping from the outflow tube at a slow rate would differ in volume from an equal number escaping at a rapid rate. But the volume does not differ. On the contrary, the slow and the rapid drops are of approximately equal volume, as the following experiment shows.

Experiment, February 13, 1896.—Giving the volume of 100 drops of blood discharged at a slow and at a rapid rate, the variation in rate being produced by varying the pressure of the blood at the mouths of the coronary arteries, the temperature remaining unchanged.

Coronary Pressure.	Coronary Flow.	Volume of Coronary Flow.
18 mm. Hg.	100 drops.	8.25 cc.
18	100	9.00
18	100	8.75
60	100	8.25
62	100	8.00
62	100	8.25

It is seen at first glance that the volume of 100 drops is approximately the same at a coronary pressure of 18 and of 62 mm. Hg, in other words, with a slow and with a rapid flow. The difference in coronary pressure (44 mm. Hg) in this experiment is as great, lacking 1 mm., as in any experiment presented in this paper. It seems fair to conclude, then, that the difference in rate of flow, which in this experiment failed to influence the volume of an equal number of escaping drops, must, in the remaining experiments, likewise have failed to influence their volume.

This same experiment disposes of another speculative objection, namely, the possibility that strong contractions of the right ventricle dislodge larger drops from the outflow tube than weak contractions. Were this criticism sound, we should have a greater volume per 100 drops at a high coronary pressure than at a low pressure, for a rapid coronary circulation in consequence of a high aortic pressure causes the ventricles to beat more forcibly. But the measurements of February 13 demonstrate that the size of the drops is approximately the same, in spite of the inevitable difference in force of contraction entailed by a difference in coronary flow corresponding to a rise from 18 to 62 mm. Hg.

The criticism we have just answered has lurking within it the idea that the number of drops is, in some way, related to the number of heart beats. We have not found this to be the case. On the contrary, we shall show, when we come to discuss fully the outcome of our researches, that great changes may be made in the number of drops of outflow, with little and sometimes no change in the frequency of contraction.

Further information regarding the volume of the outflow drops is given by the record of the drop counter, which, as may be seen most clearly in Fig. 2, Plate III, records equal excursions for drops at slow and rapid rate of flow, and during strong and weak ventricular contractions.* Blood drops of unequal volume, being of unequal weight, would have caused unequal excursions of the drop-counting lever.

* An apparent exception to this statement is seen in Fig. 3, Plate III, in which the excursions are not everywhere equal, but the inequality is here due to unequal friction of the delicate lever of the recording tambour on the smoked paper. If the degree of friction is carefully regulated, the uniformity seen in Fig. 2 will be secured, *i. e.*, positive evidence of equality.

The membrane manometer.—The membrane manometer employed to record the pressure in the left ventricle was essentially that devised by Hürthle. The chamber was covered with thin rubber membrane. The writing lever rose 17 mm. above the atmospheric pressure line, when the pressure within the chamber was raised from zero to 100 mm. Hg. The manometer was usually placed on or near the level of the heart, the difference between the two levels probably never exceeding 4 cm. The tube connecting the manometer with the ventricle was about 15 cm. long and had 3 mm. lumen. It was passed through the left auricular appendix and mitral valve, the appendix being tied about it some distance from the circumflex branch of the left coronary artery.

The isolation of the heart.—The cats are put in a box, etherized until motionless, placed on a Czermak holder, tracheotomized, and, still under ether, bled from the left carotid artery until respiration ceases. The sternum, with the contiguous cartilages, are now rapidly removed, thus exposing the heart and the great vessels, and the left subclavian and innominate arteries, the superior vena cava, the right azygos vein, the inferior vena cava, and the aorta, beyond the origin of the left subclavian artery, ligated in the order named. Cannulas are now placed in the innominate artery and the aorta, and the outflow tube tied into the pulmonary artery just above the semilunar valves. The innominate cannula should be provided with a stopcock. These various operations occupy but a few moments, and are usually finished before the heart has entirely ceased to beat. The dead cat is now put in the warm chamber, and the aortic cannula coupled to the blood reservoir, already filled with the cat's blood, which, meantime, has been whipped, filtered through glass wool, and kept near its normal temperature in the warm chamber. The filling of the aortic cannula is best accomplished by allowing the blood to flow through it into the aorta and out again by the innominate cannula. This device expels the small clots that sometimes form above the semilunar valves and drives out the air bubbles as well, a matter of much importance, for embolism by blood clots or air bubbles is apparently the most frequent and dangerous of the causes which work against the survival of the

heart. As soon as the clots and air bubbles are out, the stopcock of the innominate cannula, and the stopcocks leading from the blood reservoir to the atmosphere and the filling reservoir, are closed, and the stopcock from the blood reservoir to the pressure bottle opened. The heart swells as its arteries are filled, and in a moment a dark venous stream is seen to flow out of the pulmonary artery, the heart, as a rule, beginning to beat in a vigorous and regular fashion. The innominate cannula may now be connected with the mercurial manometer. It is well to begin the experiment with a coronary pressure of not more than 50 mm. Hg, for at first the blood runs more freely through the coronary vessels, often coming out for a short time too fast to be counted. In a few minutes the flow diminishes. The pressure may then be increased.

The failure of the heart to beat, and even the presence of fibrillary contractions, should not discourage the operator, provided the circulation through the coronary vessels is fairly good. Strong fibrillary contractions may continue half an hour or more and still give place to good, coordinated beats. If the blood refuses to flow, even at a pressure of say 70 mm. Hg, a search should be made for blood clots at the mouths of the coronary arteries. Sometimes air emboli cause the failure. Usually in such a case the ramus descendens will be seen to be filled with air. Yet we have observed even such hearts begin to beat.

The left side of the heart is sometimes considerably distended. This distension has always, so far as we remember, lessened the coronary flow, a fact to which we shall presently return. The distension of which we speak may, of course, be the result of leakage through an incompetent semilunar valve. In that case the mercury manometer usually falls slowly. If the tube leading from the left ventricle is now opened, blood will escape from it, while the mercury manometer goes speedily down to atmospheric pressure. Almost always, however, the semilunar valves are intact. The mercury then remains stationary, when the tube from the left ventricle is opened, and the flow from the tube after the first moment is at the rate of a few drops per minute, which indicates that the distension of the left ventricle is the result of the gradual inflow from the veins of Thebesius. We

have invariably found that the quantity of blood thus escaping into the left side of the heart is too small to constitute a source of error in these experiments. We shall come back to this in the discussion of our observations.

Oxygenation of blood.—The oxygenation of the blood is best performed by shaking it in a beaker in the warm chamber. We made many trials to determine whether it was not better oxygenated by a stream of pure oxygen gas, but the decision was in favor of shaking. Perfect oxygenation grows apparently more and more difficult as the experiment continues.

The formation of *fibrin* in the blood gave very little trouble. After the contents of the cardiac vessels and the great arteries used in the method have been thoroughly washed out with defibrinated blood, and this is usually accomplished by the first 50 cc. transfused, filtration of the blood which has passed through the cardiac muscle is rarely necessary.

Finally, before passing to the discussion of results, we may add that the flow through the coronary arteries usually diminishes when the experiment is prolonged over an hour. Some temporary acceleration may then be gained by raising the coronary pressure, but often the highest pressure that the semilunar valves will safely bear fails to restore the rapid flow which marked the earlier stages of the experiment. It is obvious that many causes may contribute to bring about the increased resistance to the passage of the blood. Alterations in the physical properties of the blood, the increasing difficulty of its proper oxygenation, physical changes in the tunica intima of the arteries owing to disturbed nutrition, and constriction of the vessels are some of these. That narrowing of the vessels does actually take place in organs submitted to artificial circulation was long ago observed by Sadler (10), Genersich (3) and Heger (5), and referred to local asphyctic constriction. But we cannot discuss this question here.

DISCUSSION OF RESULTS.

A number of the facts which it is the object of this paper to point out are illustrated by Plate II, the graphic record of the following experiment.

EXPERIMENT 9, MARCH 20, 1896.

The heart of a cat weighing 3012 grammes was kept alive by feeding it with defibrinated cat's blood, after the manner described under "Method," page 20. The curves reproduced in Plate II were taken shortly after the isolation of the heart. The temperature remained throughout the experiment at about 37° C., the variation being certainly not more than 0.5° C. The heart weighed 15.5 grammes. The upper curve (curve 1) in Plate II was drawn by a mercury manometer connected with the innominate artery at its origin; it gives the "coronary pressure," *i. e.*, the pressure in the aorta at the mouth of the coronary artery; curve 2 gives the pressure in the left ventricle; curve 3 the time in seconds; and curve 4 shows the volume of the coronary circulation, each elevation in the curve recording the outflow of one drop from the tube in the pulmonary artery (100 drops = 8.3 cc.); the horizontal line in this same curve 4 is the atmospheric pressure for the mercury manometer (curve 1). The numerical values of the curves are presented in Table I.

TABLE I.
Giving the Numerical Values of the Curves in Plate II.

Time in Periods of 15 secs.	Coronary Pressure at the close of each 15 secs.	Coronary Flow during each 15 secs.	Maximum Intraventricular Pressure at the close of each 15 secs.	Number of Contractions during each 15 secs.
1-15 secs.	90 mm. Hg.	14 drops.	53 mm. Hg.	28
15-30	90	12	53	28
30-45	64	10	47	28
45-60	54	6	41	28
60-75	52	5	36	28
75-90	52	5	35	28
90-105	52	4	32	28
105-120	52	4	30	27
120-135	52	5	28	28
135-150	52	4	24	27
150-165	60	5	21	27
165-180	80	10	18	27
180-195	88	14	22	27
195-210	88	16	25	27
210-225	88	16	32	27
225-240	88	16	38	28
240-255	88	16	52.5	28

Force and frequency of ventricular contraction.—Examining Plate II the reader will perhaps notice first the regularity of the curves; the steadiness with which the pressure in the aorta is maintained at the desired level; the ease with which it is lowered and then restored to its former plane; the absolute command of the volume of the coronary circulation; the way in which the number of drops flowing out of the pulmonary artery follows the rise and fall in coronary pressure; and the smooth, uniform action of the isolated, surviving heart—facts which create confidence in the method. Soon, however, the beautiful dip and rise of the intraventricular pressure curve will claim attention. The intraventricular pressure is seen to sink as the outflow from the pulmonary artery (curve 4) diminishes, and to rise again as the outflow recovers its former volume. The force of the ventricular contraction wanes as the supply of blood to the ventricular muscle lessens, and increases again with the increase of the food supply. Nor does the force of contraction follow tardily the changes in the food supply. The two go hand-in-hand. They are almost perfectly synchronous. A glance at the curves of Plates II and III shows that the rise and fall in the volume of the coronary circulation immediately alter the force of contraction.

The importance of this observation is, in our opinion, very considerable. It would seem *a priori* probable that an organ, charged with a task on the proper performance of which life itself depends, would have within itself a reserve of instantly available power that should make it independent of very temporary alterations in its food supply. This, however, is not the case. There is no such immediately available reserve. The force of cardiac contraction is most closely dependent on the quantity of blood supplied to the cardiac muscle.

This result is in entire accord with Porter's (9) observation of the lowering in force of contraction that follows the closure of a very large branch of the left coronary artery in the dog.

The frequency of contraction is little impaired by even great reductions in the food supply. In the example before us (Plate II) the volume of the coronary circulation was reduced 71 per cent; the frequency of contraction fell but 4 per cent, while the force fell 67

per cent. On restoring the coronary pressure to about its former level, the volume of the coronary circulation increased 75 per cent, causing a rise of only 4 per cent in frequency, but of 67 per cent in force of contraction.

An examination of the remaining experiments in which the intraventricular pressure was measured gives further weight to the view already presented. Table II (p. 26) contains the percentage variations in coronary pressure, coronary flow, intraventricular pressure, and frequency of contraction for twelve experiments, conducted at a constant temperature of about 37° C., according to the method already described. On the left-hand side the consequences of diminishing the volume of the coronary circulation are shown; on the right side, the consequences of restoring the volume to about its former level. The percentages are secured by dividing the fall or rise in coronary pressure, the number of drops per 30 secs., the intraventricular pressure, and the number of contractions per 30 secs. by respectively the coronary pressure, the number of drops, the intraventricular pressure, and the number of contractions observed before the coronary pressure was first changed. Thus, taking Experiment 9, page 23, as an example, the number of drops flowing from the coronary artery fell, when the coronary pressure was reduced, from 14 to 4 per 15 secs., a difference of 10, which is 71 per cent of 14, the rate of flow before lowering the pressure. The result of lowering the pressure was, therefore, a fall of 71 per cent in the volume of the coronary circulation, and this figure is accordingly set down in its proper place in Table II.

On glancing at the averages at the bottom of each column, it appears that the average fall and rise in coronary pressure, or driving pressure of the coronary blood, is practically equal, and that the average changes produced in the coronary circulation by lowering and raising the coronary pressure 41 or 42 per cent are also equal.

The average rise in intraventricular pressure and frequency of contraction is a little less than the average fall. This discrepancy does not mean that the recovery of force and frequency after the restoration of the coronary circulation to its former value is imperfect. Recovery within the wide limits used by us has always been complete,

even in the occasional instances in which the heart-beat became irregular, as illustrated in Fig. 3, Plate III. The lower averages for the rise of intraventricular pressure and frequency of contraction are due simply to the fact that a curve long enough to show full recovery could not always be written within the length of a Baltzer drum, and the use of a larger kymograph in the warm chamber would have been very inconvenient. Thus it happened more than once that the clock-work had to be stopped a half-minute or so before the curves had attained their former level. We would not give the impression that the recovery is slower than the fall. Careful examination of all the curves show that the heart responds quite as rapidly to a restoration as to a diminution of its blood supply.

TABLE II.

Comparison of Percentage Variation of Coronary Pressure, Coronary Flow, Intraventricular Pressure, and Frequency of Contraction.

Number of Experiment.	FALL.				RISE.			
	Coronary Pressure.	Coronary Flow.	Intra-vent. Pressure.	Frequency of Contraction.	Coronary Pressure.	Coronary Flow.	Intra-vent. Pressure.	Frequency of Contraction.
1	36 %	69 %	50 %	9 %	36 %	63 %	40 %	6 %
2	42	75	58	3	*
3	45	73	53	17	47	80	50	7
4	45	85	57	10	44	81	46	9
5	45	86	67	13	45	88	62	10
6	44	75	59	7	45	74	42	5
8	30	70	11	..	30	73	38	..
9	42	71	67	4	41	75	67	4
10	44	77	58	8	43	77	52	8
11	42	63	45	14	40	69	54	14
12	44	68	21	6	43	50	21	4
13	45	64	38	12	*
Average	42	73	49	9	41	73	47	7

* The rise of Exp. 2 and Exp. 13 has been omitted because the smoked surface employed for the curves of these experiments was used up before the heart had time to recover from the lessening in the volume of the coronary circulation.

The average reduction in intraventricular pressure is almost 50 per cent, but in frequency of contraction only 9 per cent, certainly a striking difference. In one experiment, indeed, the force of contraction fell 11 per cent and then rose 38 per cent, while the frequency

remained unchanged. This, however, must be regarded as exceptional, for the record in this case was made toward the end of a long series of experiments, after the heart had lost much of its sensitiveness to changes in its blood supply.

Special attention should, we think, be drawn to the experiment just mentioned, in which, in a heart which had long been under the experimenter's hands, a reduction of 70 per cent in the volume of the coronary circulation caused a fall of but 11 per cent in the force of contraction, and no fall whatever in the frequency of contraction. Those familiar with the literature concerning the closure of the coronary arteries in the dog will be interested in the bearing of this fact on Cohnheim and von Schulthess-Rechberg's observation, that ligation of the coronary arteries in the dog stops the heart more speedily and with greater certainty, when the operation is quickly done, than when a longer time elapses between the exposure of the heart and the interference with its blood supply.

Refilling the blood reservoir with blood has a favorable influence on the force of contraction, probably not to be explained as a reaction from an hypothetical depression caused by the very brief and inconsiderable fall in coronary pressure which refilling the reservoir entails. Cyon (2) long ago pointed out a similar phenomenon in the surviving heart of the frog. In a few moments after refilling, the heart reaches what may be termed an equilibrium, beating then with great uniformity. Fig. 2, Plate III, shows at the extreme left the rising intraventricular pressure immediately following a fresh charge of blood. Fig. 1 of the same plate illustrates the uniform action soon attained.

Distension of the heart.—Turning from the main objects of the investigation, namely, the relation between the volume of the coronary circulation and the force and frequency of ventricular contraction, to the phenomena incidentally observed, we shall deal first with the effect of distension of the cavities of the heart on the flow of blood through its walls. It not infrequently happens in the first five minutes after the feeding of the isolated heart begins that the left auricle and ventricle become distended with blood. The first thought would naturally be that the aortic valves were not perfectly tight, thus allow-

ing some of the blood kept at a high pressure in the aorta to enter and distend the ventricle. But insufficiency of the cat's aortic valves to a pressure of not more than 100 mm. Hg is rarely observed, and can easily be excluded by the device already mentioned on page 21.

A part, if not the whole, of the distending blood comes from the veins of Thebesius (13), as will be shown in the next paragraph. We wish first to point out that the distension of the cavities of the heart with blood always, so far as we remember, diminished the flow through the coronary vessels. The consequences of such distension are now making the subject of a special study, so that we shall no more than point out the probable importance of this observation to the pathology of the heart. It cannot be doubted that the pressure of the blood in the cardiac capillaries and veins is very low. As the distension of the heart witnessed in our experiments was sufficient to diminish the coronary flow, it is probable that the distension observed during excessive muscular effort, and in many pathological conditions likewise, diminishes the supply of blood to the heart muscle. The speedy consequence of such a falling off in the coronary circulation is a lowering of the force of contraction, and this lowering must still further reduce the amount of blood flowing through the stretched heart walls. It is not unlikely that many of the heart "failures" ascribed to "paralysis of the heart by over-distension" are in reality failures due to ischæmia of the heart. But it would be unwise to speak too decidedly on this question pending the results of the experiments now making.

Veins of Thebesius.—It has already been said that a part of the blood sometimes found in the left heart after the beginning of the artificial coronary circulation comes out of the veins of Thebesius. The proof of this is that blood continues to flow into the left heart after every source except these veins has been shut off. The quantity thus entering the left auricle and ventricle is, however, very small; far too small to affect the method employed in this paper. The amount can be readily observed by draining the left heart by a tube passed through the left auricular appendix. Such a tube was in the ventricle throughout the experiment of February 26, in which the isolated heart beat 4 hours and 12 minutes. The flow was scarcely measureable. During

the experiment of February 28 not more than three drops per minute flowed from the cannula in the left ventricle, while the flow from the right side of the heart was from 40 to 145 drops per minute (3.3 cc. to 12 cc.), the pressure at the semilunar valves being made to vary from 36 to 68 mm. Hg. Similar observations were often made. It was noticed also, during the recording of intraventricular pressure, that when the left heart filled, the base line of the membrane manometer curve gradually diverged from the atmospheric pressure line. A base line that remains parallel to the atmospheric pressure line excludes any significant addition to the contents of the left ventricle. It will be seen that the curves of Plates II and III show this parallelism. It is hardly to be doubted that the flow into the left heart from the veins of Thebesius is somewhat greater during life than in the surviving heart, inasmuch as there is little doubt that the coronary circulation as a whole is larger during life.

The smallness of the blood supply on which a good intraventricular pressure and a regular beat can be kept up is surprising, even when the small load of the left ventricle (a few mm. Hg) is taken into account. Reference to Fig. 1, Plate III, will show that admirable contractions were secured with 40 drops per minute (about 3.3 cc.). In the experiment of March 13 fair contractions were seen with a coronary circulation of only 22 drops per minute (less than 2 cc.). This heart had been isolated a long time when the observation was made. The ordinary volume during our experiments ranged, for vigorous contractions, from 3.5 cc. to 13 cc. per minute.

Fibrin in the blood.—A noteworthy incident in the beautiful method of isolating the lungs and heart, devised by Ludwig and Stolnikow (11), and afterward employed by Pawlow (8) and others, is the freedom of the circulating blood from fibrin. One would suppose that blood driven through the rubber and glass tubing of the new Ludwig Stromuhr used by these observers would speedily clot, but it is found that the circulation through lungs, heart and Stromuhr goes on for several hours. Either the heart makes no fibrin factors, or, if made by the heart, they are destroyed, probably in the lungs. Such at least are the ideas at present entertained regarding the failure of the blood

to clot. With the wholly isolated heart shut off, as it is, from even the lungs, valuable information can be added to the observation of Ludwig and Stolnikow. We have repeatedly noticed that after 50 to 100 cc. of defibrinated blood had passed through the coronary vessels of the cat's heart, it was no longer necessary to filter the blood. The early filtrations were required because of the fibrin derived from the unwhipped contents of the cardiac vessels at the beginning of the experiments. Whether no fibrin factors are formed in the metabolism of the heart, or whether the amount so formed is too small to affect the circulation, cannot be stated without quantitative experiments, which, we are informed, will soon be published.

The "staircase" beats sometimes observed when the coronary circulation is very much reduced are illustrated by Fig. 3, Plate III. It is noteworthy that when the blood supply is restored, the entire "staircase" is, so to speak, lifted, each of the contractions being more forcible than before, but the group as a whole preserving the staircase character. Interesting, too, is the strong compensatory contraction following each dropped beat.

Fibrillary contractions.—The recovery of the cat's heart from fibrillary contractions has already been mentioned on another page. We return to the subject here in order to point out how irreconcilable our observations are with the view that fibrillary contractions are occasioned by mechanical injury of the heart. We have seen normal contractions give place to fibrillary contractions in consequence of disturbances in the coronary circulation, although the heart had meanwhile not been touched.

Our observations, finally, are also opposed to the idea that fibrillary contractions are necessarily fatal in the dog. We have more than once witnessed marked and long-continued fibrillations in the cat's heart yield to normal contractions, prolonged for many minutes, and we cannot admit that the heart of the cat is so fundamentally different from the heart of the dog that a disturbance frequently recovered from in the former should be always irrecoverably fatal in the latter. None of the investigators who assert that fibrillary contractions are necessarily fatal in the dog has published experiments in which the

resuscitation of the dog's heart after fibrillary contractions has been attempted by the only rational plan, namely, the re-establishment of the coronary circulation (12).

In conclusion, we desire to express our thanks for the advice and unstinted aid of Dr. W. T. Porter, at whose suggestion this work was done.

HISTORICAL NOTE.

The maintenance of the contractions of the heart by means of the artificial circulation of defibrinated blood through the coronary arteries was first accomplished by Martin and Applegarth (7) in their experiments on "The temperature limits of the vitality of the mammalian heart." The essential principle of their method has been adopted by all subsequent investigators, namely, Arnaud (1), Hédon and Gilis (4), Langendorff (6), Porter and ourselves. It is described by Martin and Applegarth as follows: All the branches of the aorta, except the coronary arteries, are ligated. The venæ cavæ are also ligated. In the aorta itself is placed a cannula, which is connected with a Mariotte's flask, raised a sufficient height above the organ. The defibrinated blood from the flask fills the connecting tubes, the aorta and the coronary arteries at a constant pressure, which, of course, is quite independent of the force and frequency of the heart beat. The blood taking the coronary circuit, on reaching the right auricle, proceeds to the corresponding ventricle, and from it through the lungs to the left auricle. This blood is, therefore, the only blood entering the cavities of the heart or passing through the lungs, unless there be some inefficiency of the aortic semilunar valves. That the cavities of the heart are not distended with more blood is found not to influence the normal character of its beat, which continues rhythmically and forcibly for three or four hours.

Arnaud, in 1891, apparently unaware that his observation had been anticipated by Martin and Applegarth, also revived the rabbit's heart by injecting defibrinated blood into the aorta.

Hédon and Gilis, the following year, performed the same experiment on a dog and on the heart of an executed man. They make no mention of previous experiments.

In a recent work on the isolated mammalian heart, Langendorff, after citing the experiments of Arnaud and of Hédon and Gilis, remarks in an appendix that he has purposely omitted any reference to Martin's work, because the method of Martin and his pupils has very little in common with his own. It is plain, however, that the distinguished physiologist of Rostock has seen only the earlier works of the Baltimore school. He nowhere mentions the investigations of Martin and Applegarth, and refers only to the previous researches of Martin and his associates, in which blood was supplied to the heart through the right auricle.*

The methods of Martin and Applegarth and of Langendorff are alike in the following fundamental points: (1) The heart muscle is fed by maintaining a constant pressure in the root of the aorta, and hence in the coronary arteries, the nutrition of the heart muscle being not directly dependent on the contractions of the heart. (2) The right ventricle receives no blood except the small quantity coming from the coronary veins. (3) The left ventricle works against a constant resistance. (4) The right ventricle in Langendorff's hearts works against practically no resistance. In the hearts of Martin and Applegarth the resistance can be little more, for the pulmonary circulation is reduced to the blood passing through the coronary vessels, and our own observations show that this quantity is but a few cubic centimetres per minute. (5) In both procedures, probably, the influence of the central nervous system is excluded, for we can hardly suppose that the brain and spinal cord remain functional after the total arrest of the circulation.

The method employed in the present investigation is also a modification of that used by Martin and Applegarth.

The first account of the intracardiac pressure in the isolated heart and the effect of changes in the volume of the coronary circulation on the force and frequency of the ventricular contraction was published by Porter in *The American Text-book of Physiology*, Philadelphia, 1896, p. 476, Fig. 125.

* Martin and Applegarth's work is indexed by the *Index Medicus*, but is omitted in the *Centralblatt für Physiologie*, the *Jahresbericht über die Fortschritte der Physiologie*, and Tigerstedt's *Lehrbuch der Physiologie des Kreislaufes*.

REFERENCES.

1. Arnaud (H.).—Expérience pour décider si le cœur et le centre respiratoire ayant cessé d'agir, sont irrévocablement morts. *Arch. de physiologie*, 1891, p. 396.
2. Cyon (E.).—Ueber den Einfluss der Temperaturänderungen auf Zahl, Dauer und Stärke der Herzschläge. *Arbeiten aus der physiol. Anstalt zu Leipzig*, 1866, p. 89.
3. Genersich.—Die Aufnahme der Lymphe durch die Sehnen und Fascien der Skelettmuskeln. *Berichte d. math.-physikal. Classe der Sächs. Gesellsch. d. Wissensch.*, 1870, p. 55.
4. Hédon (E.) and Gilis (P.).—Sur la reprise des contractions du cœur après arrêt complet de ses battements, sous l'influence d'une injection de sang dans les artères coronaires. *C. r. de la Soc. de biologie, Par.*, 1892, p. 760.
5. Heger (P.).—Expériences sur la circulation du sang dans les organes isolés. Thèse, Bruxelles, 1873, p. 21.
6. Langendorff (O.).—Untersuchungen am überlebenden Säugethierherzen. *Arch. f. d. ges. Physiol.*, lxi, 1895, p. 292.
7. Martin (H. N.) and Applegarth (E. C.).—On the Temperature Limits of the Vitality of the Mammalian Heart. *Studies from the Biological Laboratory of the Johns Hopkins University*, iv, 1890, pp. 275-285. Also *Memoirs from the Biological Laboratory of the Johns Hopkins University*, iii, Baltimore, 1895, p. 98.
8. Pawlow (J. P.).—Ueber den Einfluss des Vagus auf die Arbeit der linken Herzkammer. *Arch. für Physiologie*, 1887, p. 458.
9. Porter (W. T.).—Further Researches on the Closure of the Coronary Arteries. *The Journal of Experimental Medicine*, i, 1896, p. 49.
10. Sadler (W.).—Ueber den Blutstrom in den ruhenden, verkürzten und ermüdeten Muskeln des lebenden Thieres. *Arbeiten a. d. physiol. Anstalt zu Leipzig*, 1869, p. 100.
11. Stolnikow.—Die Aichung des Blutstromes in der Aorta des Hundes. *Arch. für Physiologie*, 1886, p. 10.
12. For the literature of this subject see Porter, *The Journal of Experimental Medicine*, i, 1896, p. 46 et seq.
13. Compare Gad's note on the *foramina Thebesii*, *Arch. für Physiologie*, 1886, p. 382.

DESCRIPTION OF PLATES II AND III.

Like curves have been given the same number in both plates and all figures.

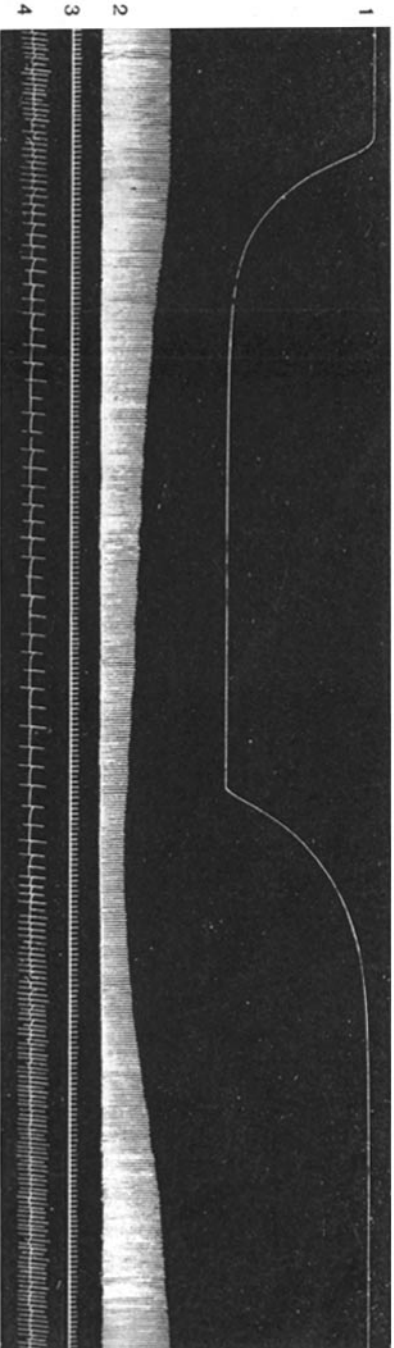
Curve 1 is everywhere the line drawn during the experiment by a mercury manometer connected with the root of the aorta. It indicates the blood pressure at the mouths of the coronary arteries.

Curve 2 is everywhere the intraventricular pressure curve, drawn by a Hürthle membrane manometer, connected with the left ventricle through the auricular appendix and mitral valve.

Curve 3 is time in seconds.

Curve 4 is the quantity of blood passing through the coronary vessels into the right side of the heart and thence out through a tube placed in the pulmonary artery. In Fig. 1, Plate III, the number of drops is given per 30 seconds, the number being respectively 20, 14, 5, 5 and 19 drops, and the periods of 30 seconds are registered by an electro-magnetic signal, while the drops are counted by an assistant. In the remaining figures of both plates the number of drops is registered automatically by the drop counter described on page 17. Each upward stroke in the curve records one drop. One hundred drops equal 8.3 cc. cat's blood. In Fig. 3, Plate III, and to a much less degree in Plate II, the friction of the writing point of the very sensitive recording tambour of the drop counter was too great, leading to irregularities in the height of the individual strokes. This difficulty is overcome in Fig. 2, Plate III.

Curve 5 is the atmospheric pressure for the mercury manometer (curve 1), drawn immediately after the experiment.



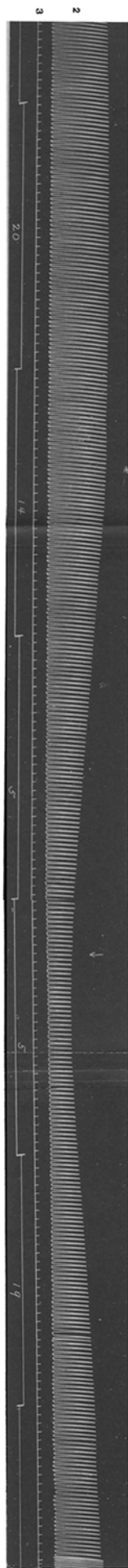


FIG. 1.

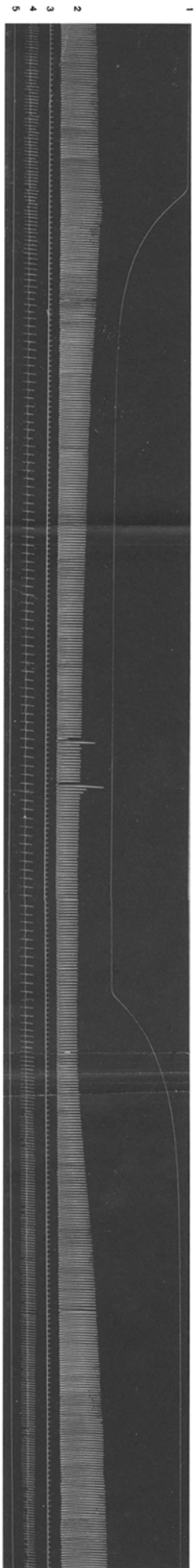


FIG. 2.

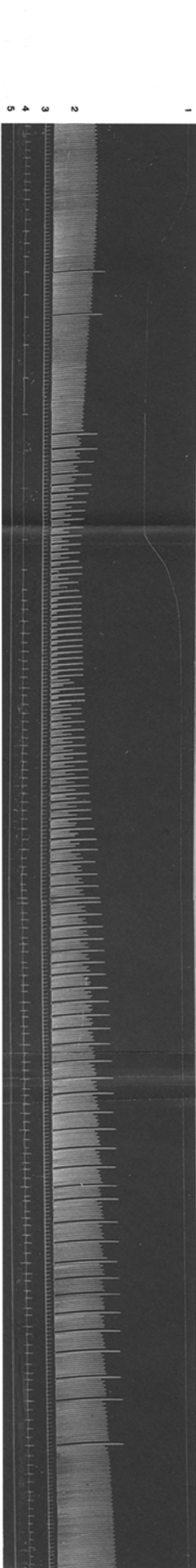


FIG. 3.