THE REGULATION OF THE HEART BEAT. By S. W. PATTERSON, H. PIPER and E. H. STARLING.

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The employment of the heart lung preparation has enabled us to study and analyse much more completely than was formerly the case the mechanical performance of the mammalian heart and to obtain clearer ideas of its capacity for work and its power of adapting its work to the mechanical conditions imposed upon it. We have learned that while the inflow is maintained constant, the output from the left ventricle is unaltered by rate of heart beat or by the resistance presented by arterial pressure, and on the other hand, that within wide limits the heart is able to increase its output in direct proportion to the inflow. The study of the respiratory exchanges of the heart lung preparation has shown that the metabolism of the heart increases or diminishes in proportion to the mechanical demands made upon this organ, so that the chemical sources of energy are drawn upon in proportion to its requirements. It is difficult to imagine a more perfectly regulated machine than the heart. In the experiments here described we have endeavoured to determine some underlying principle on which the heart's power of self-regulation may depend, or some elementary property of the tissues making up the heart from which the varied behaviour of the heart under different circumstances can be directly deduced.

In our preparation the heart is free from all nervous control. The question arises whether we can refer to one or a few elementary qualities of the muscular tissue the whole behaviour of the heart, under stress or light work, when efficient or failing, when stimulated or depressed by drug or nerve. The solution of this question can only be arrived at by accurate analysis of the mechanical phenomena of the heart beat under rigorous control of all its conditions. The results of such an analysis, which has occupied us for the last two years, are presented in the following pages. In order to lend interest to the dry facts, curves, and measurements of time and pressure, which we have to record, we propose

to reverse the usual order of a physiological communication and to begin by giving the general conclusions to which our experiments have led us. We shall then give the facts on which these conclusions are based, and shall endeavour to show that they are consistent with and confirmatory of the principles which we lay down.

The behaviour of the heart must be the sum of the behaviour of the muscle fibres of which it is composed. In considering the behaviour of contracting muscle, the original conception of Weber is of great assistance,—the conception according to which the muscle during contraction changes into a body with other elastic properties. In the words of A. V. Hill, "excitation causes a setting up of a new state in muscle. At and after this moment the muscle is simply a new elastic body of changed elastic properties and possessing potential energy which can be turned into work, if we desire, but which otherwise will degenerate in a few hundredths of a second into heat." Under the conditions of an ordinary physiological experiment a contracted muscle loaded only by a light lever is shorter than the non-contracted, but can be stretched to the length of the latter by a certain weight, when it will be in a condition of tension. This tension is often regarded as the measure of the power exerted by the muscle when it passes from the resting to the contracted state. Under normal circumstances, *i.e.* in their natural position in the body, muscles may possess any length between extreme contraction and extreme elongation, whether they are in a resting or in an excited condition. The relaxed muscle however requires only a minimal force to extend it to the maximum length possible under normal (*i.e.* the body) conditions, so that it is usual to speak of the different lengths of a contracted and uncontracted muscle, the lengths being in this case those which are impressed on the muscle by a minimal load.

The investigation of the maximum mechanical energy set free in the contraction of a muscle under different conditions of excitation was carried out by Blix (1), who arrived at the important result that this amount was a function of the length of the muscle fibres during the period of contractile stress set up by the excitation. The maximum energy which could be set free by a contracting muscle was measured by the isometric method. We have drawn Fig. 1 to represent the results of one such experiment. In this figure the ordinates represent the initial length of the muscle measured from above, and the abscissæ, the tension developed when the muscle passed into a state of contraction. He found that with increase in the length of the muscle, the tension developed also increased to the degree of maximal extension possible in

its natural relationships in the body. To stretch the muscle beyond this length required an ever-increasing initial tension. The contractile stress set up on passing to the excited state increased for a time with increasing initial tension and then diminished, so that the lines in the figure tend to approach one another. Heidenhain had already shown that the heat production in muscle was a function of the contractile stress it developed, and Frank (2), in his summary of the work on the development of heat in muscular activity, concludes that the essential determining factor is not the tension but the length of the muscle

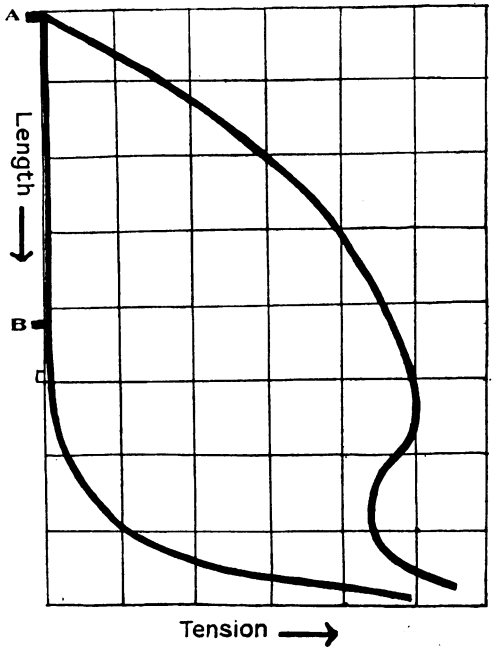

Fig. 1. Curve showing the relation of tension, initial length, and energy evolved in isometric twitch. (Drawn from the results of one of Blix's experiments. *Skand. Arch. f. Physiol.* v, Tab. VI, Fig. 4.)
A = Condition of maximum shortening.
B = Position of maximum length of muscle in the body.

during its state of activity. He states "if we take the length of the muscle as the independent variable, all relationships of heat production to the changes of mechanical state in the muscle can be represented with extraordinary facility." This conclusion has received powerful confirmation lately by the work of A. V. Hill (3). He shows, in confirmation of Blix, that the shortening of muscle diminishes the heat

production in so far as the chemically active surfaces are diminished, while lengthening the muscle increases the chemically active surfaces. The longer the muscle therefore (within physiological limits) the greater the amount of chemical energy, heat production, and tension set up when the muscle passes from the resting to the active condition[1].

These results can be transferred unreservedly to heart muscle, making only certain modifications that are necessitated by the anatomical arrangements in this organ. In the first place when the heart muscle is unloaded, *i.e.* when the heart is empty, the length of the relaxed

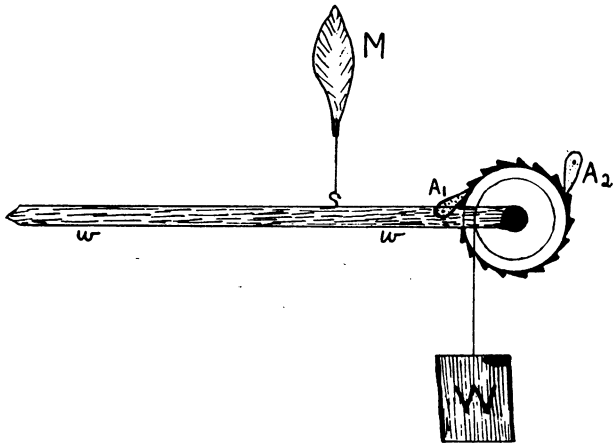

Fig. 2. The muscle *M* after contraction is extended simply by the weight of the lever *w*. When it begins to contract, the arm on the lever catches in the ratchet wheel so that the weight *W* is drawn up, *W* being supported by the arm A_2, so that the muscle after excitation cannot raise the weight *W* until its tension is equal to that of the weight. As soon as it has completed its contraction and begins to relax, the weight *W* is taken off it (cf. closure of aortic valves) and it is then extended by the small weight of the lever (pressure of inflowing blood). It is evident that the length of the muscle before it begins to contract depends on the weight of the lever, *i.e.* on the diastolic load. The extent to which it will contract depends on the tension aroused in it when it contracts and the amount of the weight *W* which it has to overcome.

muscle is the same as that of the contracted muscle (apart from slight shifting of the mutual position of the muscle fibres produced by rotation of this organ on its axis). According to the state of filling of the heart, the length of the "resting" muscle may be anything between that of maximal dilatation or lengthening and maximal contraction.

[1] It seems probable that the evolution of energy in the form of heat continues to increase with increasing length considerably beyond the length which is the optimum for the development of tension.

Another point of difference refers to the question of load. Under the conditions of ordinary physiological experiments, a skeletal muscle is loaded with a certain weight which it raises when it contracts and which extends the muscle when the latter relaxes. In the heart the extending load on the muscle is much less than the load during contraction. The extending load is represented by the diastolic intracardiac pressure and is dependent on the inflow. The load against which the muscle has to contract is represented by the pressure in the aorta. Until the tension exerted by the heart muscle rises to a height greater than that corresponding to this pressure, the contraction of the heart is isometric, and the muscle fibres can undergo no change in length. These conditions, as Henderson (4) has pointed out, can be imitated on

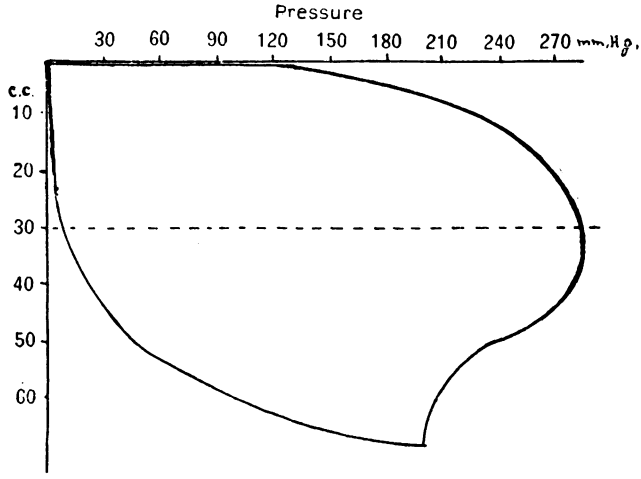

Fig. 3. See text. The abscissæ represent pressure in mm. Hg. and the ordinates measured from above the capacity of the ventricles.

a skeletal muscle by attaching to it weights arranged somewhat after the fashion of an "Arbeitssammler," as in the diagram (Fig. 2).

In the heart we have no means of measuring directly either the length or the tension of the muscle fibres, but on the length of the muscle fibres depends the capacity or volume of the heart, while the tension of the muscle fibres determines the intracardiac pressure. If we assume a linear relationship between capacity of heart and length of muscle fibre and between intracardiac pressure and tension of muscle fibre, we can in the muscle extensibility diagram replace length of fibre by heart volume, and tension of muscle fibre by intracardiac pressure

under the two conditions of rest and activity. If we do this, we must remember that the linear relationship even if it holds in the contracted heart, must be more and more departed from as the heart becomes distended and its shape more globular (cf. note in last paper (5)).

Taking these facts into consideration, we may draw a diagram for the heart, expressing the relation between volume and pressure, and interpret these relationships in terms of length and tension. The diagram (Fig. 3) is copied from Frank's (6) diagram representing the results of his measurements on the ventricle of the frog. We have however placed numbers which would in our opinion approximately represent the relation of the capacity of the left ventricle to its diastolic and systolic pressures in a healthy dog's heart weighing about 70 gms. The two lines representing extensibility, or the state of tension for different lengths of the contracted and uncontracted fibres respectively, are represented in the diagram as finally meeting, as they do in the diagram for skeletal muscle. The exact position of this point is however of little practical importance, since the heart would fail long before the diastolic tension was equal to the tension produced by contraction. During this contraction the ventricle has normally to shut the auriculo-ventricular valves and get up a pressure greater than that in the aorta. With increasing load the auriculo-ventricular valves finally become incompetent, and the heart remains permanently distended, with each contraction marked simply as a small wave on its surface. In this condition of extreme distension, as has been already shown, the tension of the muscle fibres would become more and more ineffective in producing a rise of intracardiac pressure.

So far our analysis of the mechanical condition of the heart's contraction does not differ essentially from Frank's classical exposition of the mechanical events affecting contraction of the frog's heart (7). In this work, however, Frank was dealing with a contractile tissue which had long periods of diastole, so that it had reached a static condition before the beginning of systole, and he found that the energy set free in the excited condition (as measured by the tension set up) was proportional to the initial, *i.e.* diastolic, tension on the muscle. But in this case it is not easy to decide whether the determining factor is really the initial tension or the initial length of the muscle fibres. Rohde (8), from a study of the perfused mammalian heart and a comparison of its isometric contractions and gaseous exchanges under varying conditions of initial and final tension, has come to the conclusion that in the heart, as in the skeletal muscle, there is a certain volume of

the heart at which the greatest development of energy will occur when the heart enters into a state of contraction, whether isometric or isotonic. This optimum volume would correspond to what Blix calls the natural length of the skeletal muscle. As a result of his experiments he makes the same change in Frank's formula for the contraction of the heart that the latter authority had already made for the connection between heat production and other mechanical conditions of skeletal muscle, namely, in place of initial tension he speaks of initial length of fibre or initial volume of the heart. Blix' statement for voluntary muscle could therefore be applied directly to the contracting heart. The proof that this replacement of initial tension by initial length is justified, is not however clear from Rohde's results, but we find the conclusion fully justified in the light of our experiments.

In the mammalian heart we are dealing with an organ which is contracting rapidly and rhythmically, such contraction being a necessary condition for the preservation of its functional activity. The condition of the heart therefore as to both tension and length of its muscle fibres is altering continuously during diastole from one beat to the next.

Although this fact makes the analysis of the experimental results more difficult, the results are instructive, since they enable us to dissociate tension from length as factors in determining the energy evolved at each contraction. In Frank's experiments on the frog's heart the initial length was proportional to the initial tension, so that the augmentation of energy set free on contraction might have been due either to the increased tension or to the increased length. In our experiments we have found that it is length rather than tension which determines the energy of contraction,—a result which might be expected from what we know as to the influence of length on the evolution of energy in skeletal muscles. The proof that it is length rather than tension which determines the contraction of the heart is to be found in a study of the changes which occur at the beginning of diastole. If we take a heart which is contracting vigorously and in which the state of contraction passes off rapidly, with a small inflow we may find that it practically empties itself during systole and then rapidly relaxes. In this case the inflow during diastole is, so to speak, only just sufficient to follow up the relaxing ventricle and the pressure in the ventricle remains approximately zero up to the beginning of the next systole. We may now double the inflow without making it excessive for the heart, so that at the end of diastole the heart, although containing twice as much blood as previously, cannot be regarded as actively stretched by the

latter, and the initial pressure at which the heart begins to contract is still indistinguishable from zero. The heart however is fuller than before, its capacity may be doubled although its initial tension is not measurably altered. In this case we find that the tension developed by the contracting ventricle is increased in proportion to the increased filling of the heart.

We thus find no constant connection between the diastolic tension and the succeeding contraction, though as a rule these two quantities will be altered together. But we do find a direct proportion between the diastolic volume of the heart (*i.e.* the length of its muscle fibres) and the energy set free in the following systole.

The law of the heart is therefore the same as that of skeletal muscle, namely that the mechanical energy set free on passage from the resting to the contracted state depends on the area of "chemically active surfaces," *i.e.* on the length of the muscle fibres. This simple formula serves to "explain" the whole behaviour of the isolated mammalian heart,—its movements, powers of adaptation to varying demands made upon it, its behaviour in fatigue and under the influence of its nerves or chemical agencies, such as acid ions or adrenalin.

Let us take two examples. The left ventricle is putting out 600 c.c. of blood per min. against a mean arterial pressure of 80 mm. Hg. The mean arterial pressure is then raised suddenly to 140 mm. Hg. On measuring the total output it is found to be 600 c.c. as before. The heart continues to put out as much blood as it receives, though, as shown by Evans, at a greater expenditure of chemical energy. If we trace out the events occurring at each beat, the mechanism of adaptation is evident. At 80 mm. Hg. pressure the heart at each systole is developing just enough energy to put out say 8 c.c. of blood against a resistance which may vary from 65 mm. Hg. at the beginning of the outflow to 100 mm. Hg. towards the end. The arterial resistance is then suddenly increased, so that it needs a pressure of 110 mm. Hg. to force any blood through it and a mean pressure of 140 mm. Hg. in the aorta to keep up a flow through it at the rate of 600 c.c. per minute. The next heart beat gets up enough pressure to force some blood into the aorta and distend it up to 100 mm. Hg.,—let us say 3 c.c. Here the outflow stops. At the beginning of the next systole there is therefore 5 c.c. of blood more in the left ventricle than at the beginning of any preceding diastole. But the venous inflow is still proceeding steadily at 600 c.c. per minute or 8 c.c. per beat. At the beginning of the next systole the heart therefore contains its original residual blood, *plus* 5 c.c. residual blood from the

last contraction, *plus* 8 c.c. which have entered it during diastole. The muscle fibres are therefore longer than before by an amount corresponding to the 5 c.c. extra capacity of the ventricle, and therefore when they enter into the contracted condition, more energy is set free and the tension exerted by the muscle fibres is greater. We may assume that they get up enough tension to drive out blood against a pressure of 130 mm. Hg. The outflow of blood into the aorta through the resistance goes on until the pressure rises to 130 mm. Hg. and then ceases. Let us assume that 6 c.c. of blood are driven out. At the beginning of the next systole the heart therefore contains residual blood, 5 c.c. + 2 c.c. + 8 c.c. It is still more distended than before, the muscle fibres are longer, and more energy is set free on contraction. This may be enough to drive out the whole 8 c.c., which are entering it steadily during diastole, against a mean arterial pressure of 140 mm. Hg. If not, the process of increasing dilatation goes on until the energy of the contracting fibres is just sufficient. The heart then continues to beat at this increased volume and to maintain the original outflow against the greatly raised arterial pressure.

Similar reasoning serves to explain the automatic adaptation of the heart to increased inflow. The energy set free at each contraction of the heart is a simple function of the length of the fibres composing its muscular wall. It is evident that the same reasoning applies to the explanation of the almost instantaneous adaptation of the heart to artificially induced lesions of the valves or to artificial stenosis of the aorta. The output of the heart is a function of its filling, the energy of its contraction depends on the state of dilatation of the heart's cavities.

The meaning of tone and fatigue. Like any other living tissue the heart is unable to keep up a high degree of work for long periods of time, it needs opportunity for recuperation, it shows fatigue. In a skeletal muscle contracting isometrically, fatigue is shown by the fact that, starting at a given length, the change from the relaxed to the contracted state is attended with a smaller production of tension than was the case when the muscle was fresh. We may assume that the liberation of chemical substances responsible for the tension change becomes less either from diminution of their concentration within the cell or deficient building up between each contraction. Or we may regard the chief factor in fatigue as due to some retardation in the diffusion away or neutralisation of the active substances, so that the same concentration at the active surface causes smaller changes of potential and of surface energy. But the relation between the length of the muscle fibre and the tension set up at its

contraction remains as before. If the muscle fibre with an initial length of 2 cms. displayed a tension of 50 gms., and when elongated to 3 cms. a tension of 80 gms., a state of moderate fatigue might depress these two figures respectively to 30 gms. and 50 gms. The energy set free in contraction would still be a function of the length of the muscle fibre. In the same way, if the heart wall at a certain condition of filling, produces on contraction a tension equal to 100 mm. Hg., and when it is tired can only raise the intracardiac pressure to 80 mm. Hg., it is merely necessary to lengthen the fibre, *i.e.* to increase the filling of the heart, in order to obtain once more at contraction a tension of 100 mm. Hg. This means that a tired heart *must* dilate in order to carry on the same work as the fresh heart, and we know that this condition actually occurs. If by increasing the supply of blood or oxygen to the tissue, or by diminishing the load, we give the muscular fibre of the heart wall an opportunity to recover, the heart may once more return to its normal size, the evolution of energy per unit length of the muscle fibre at each contraction becoming the same as before. We get here a clue to the meaning of the term *tonus* or *tone* of the heart muscle. This term is constantly employed both in physiological and pathological literature, but it has hitherto been very difficult to obtain a clear conception of what was really meant by the word. When, on opening the chest, the heart is found to be dilated, it is often said to be "lacking in tone," and on the other hand, if the heart is found small and evidently emptying itself completely during systole and dilating only slightly during diastole, its tone is said to be increased. But the state of dilatation of the heart may be merely a question of the amount of blood entering it from the veins. A contracted heart may be in a bad condition and a dilated heart may be in a good condition. It is evident from what we have said above that the word *tone* is properly employed as synonymous with physiological condition or fitness of the muscle fibre, and its measure is the energy set free per unit length of muscle fibre at each contraction of the heart. A good heart, *i.e.* one with a good tone, will carry on a large circulation against a high arterial pressure and nearly empty itself at each contraction, while a heart with a defective tone, as is the case when it is tired, can carry on the same circulation but only when its fibres at the beginning of contraction are much longer, *i.e.* when the heart is dilated. In the latter case the output of blood will be the same as in the former, but both the systolic and the diastolic volumes of the heart will be increased.

Fatigue of the heart may go on to heart failure. This occurs when the dilatation, which is the mechanical result of unchanging inflow and

failing outflow and is the automatic means of regulating outflow to inflow, proceeds to such an extent that the tension of the muscle fibres becomes increasingly inadequate in producing rise of intracardiac pressure. The mechanical disadvantage, at which in the dilated spherical heart the skein of muscle fibres must act, finally smashes up the system and the circulation comes to an end.

The investigation of the mechanical conditions of contraction in skeletal muscle involves the measurements of its tension and length under alterations of initial and final load at different temperatures and with repetition of stimulus to the point of fatigue. To carry out the same analysis of the conditions determining the contraction of the heart we must in the first place measure the diastolic and systolic volumes of the heart and its output under varying conditions of inflow, arterial resistance, frequency of heart beat, temperature and fatigue. In the second place we must determine the tension or pressure in each of the heart cavities and during every phase of the heart's cycle under the same conditions.

The first part of the investigation, namely, the determination of the changes of volume of the heart under varying conditions, has been for the most part carried out by two of us at University College, while the investigation of the rapid changes in pressure occurring under the same conditions in the different heart cavities, was carried out in the Physiological Institute of Professor Rubner, in the University of Berlin. Shortly before beginning our work in Berlin, we heard from Dr Hermann Straub that he had been investigating a similar problem and by somewhat similar methods at Munich. He very kindly sent us a copy of his paper on the subject, which has since appeared in the *Archiv für klin. Medizin* (9). Although the conclusions to which we have arrived differ somewhat from those of Straub, we found the knowledge of his results of considerable value. In his paper he gives the same description of the reaction of the heart to increased arterial pressure as that given by Frank for the frog's heart, namely, as a reaction to initial tension (Anfangsspannung), an explanation which we regard as true only in so far as the initial tension determines initial length. His account of the reaction to increased inflow is less satisfactory, but this may probably be ascribed to his inability, working single-handed, to control all the conditions of a complicated experiment which in our case required the united efforts of three workers.

Methods. All the experiments were carried out on the heart lung preparation on dogs varying from 4 to 8 kilos. The arrangement of the heart lung preparation was the same as that described in the paper by

Patterson and Starling(5). For the measurement of the changes occurring in the volume of the heart at each contraction, we employed a glass cardiometer similar to that used by Henderson. The mouth of the cardiometer was covered with a rubber membrane in which a hole was burnt of such a diameter that when the cardiometer was placed round the heart, the rubber membrane rested in the auriculo-ventricular groove without exerting too great a pressure on the organ, but at the same time effecting an air-tight closure of the cardiometer. If the membrane were too loose, the error was shown by leakage of the apparatus. If the membrane were too tight, it caused a rise of pressure in the venous manometer attached to the inferior vena cava and might at the same time diminish the output from the heart. It was thus possible to adjust the hole in the membrane until it was of a proper size. Many different methods, including the soap bubble method employed by Hermann Straub(10), were tried for recording the changes in the volume of the air in the cardiometer accompanying each beat of the heart. The problem of registering rapid changes in volume is perhaps the hardest task which can be thrown on the graphic method. We finally adopted as the best instrument the large Albrecht piston recorder, already used by Heer(11) in his experiments. This consists of a brass cylinder of about 50 c.c. capacity, in which moves a very light ebonite piston with no lubricant. (We found the piston moved somewhat more easily if the inside of the cylinder and the outside of the piston were polished with graphite powder.) Some of our tracings of heart volume were made by means of a lever in the ordinary manner, so that the ordinate was the arc of a circle. In most cases, however, in consequence of the difficulty of measuring the time intervals under these conditions, we abandoned the lever and recorded the movements of the piston directly by means of a paper writing point attached to a long light aluminium rod, which was connected below to the piston and was attached above to an isotonically weighted lever, and was maintained vertical by allowing it to move up and down in the groove of a jewelled pulley. The rapidity of the response of this apparatus was sufficient to ensure an accurate reproduction of volume changes of air in the cardiometer on the tracing of the piston recorder. The vibration frequency of the system,—cardiometer, tube and piston recorder—was about 20 per second, but oscillations set up in the apparatus were very speedily damped and no trace of such oscillations are to be seen on our tracings.

A more serious danger in the use of the instrument is its sensitiveness to slight alterations of friction between the piston and cylinder. A small

particle of dust falling on the instrument, or any deviation of the piston from the vertical, might be seen to impede the free movement of the piston and make it stick in the cylinder. This danger was more marked with small movements of the piston. In most of our experiments however we were able to assure ourselves by a comparison of the total output of the two ventricles, as determined by the cardiometer tracing, and the total output, as directly measured by receiving the blood flowing through the apparatus into a graduated cylinder, that the apparatus was really giving a correct representation of the volume changes of the heart.

In all experiments we measured the pressure at the opening of the inferior vena cava into the right auricle by means of a water manometer, the pressure in the innominate artery by means of a mercurial manometer, and the strength of the arterial resistance by a manometer connected with the air chamber outside the thin rubber tube forming the resistance. The output of the left ventricle (*i.e.* the total output *minus* the coronary

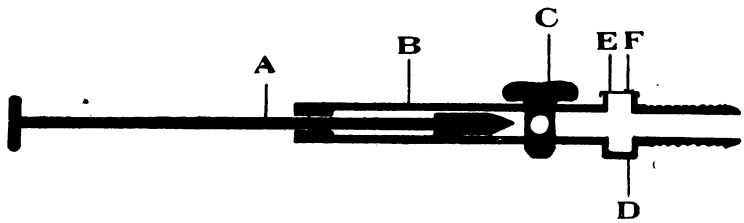

Fig. 4. Diagram to show construction of Piper's trocar manometer. See text.

flow) was measured by releasing the T-tube connected with the venous side of the apparatus and clamping the tube flowing into the spiral[1], so that all the blood coming to the apparatus flowed into a graduated cylinder. The time taken to collect 50 or 100 c.c. of blood in this way was measured by means of a stop-watch. The temperature of the blood supplying the heart was measured by a thermometer in the cannula leading from the venous reservoir to the superior vena cava. In some cases the left auricle was also connected by means of a cannula filled with hirudin solution with a water manometer.

For the measurement of the rapid changes of pressure occurring in each of the heart cavities,—auricles and ventricles, and in the aorta,—at each beat of the heart, we made use of the methods already employed by one of us (Piper) (12) for determining the form of the ventricular, auricular and arterial pressure variations under a variety of conditions

[1] See the illustration in the paper by Patterson and Starling. This *Journ.* XLVIII. p. 357. 1914.

in the whole animal. The only satisfactory method for recording the very rapid changes of pressure which occur in the heart, is the optical method first employed by Frank for this purpose. The method used by us is a modification and simplification of Frank's methods and is similar to that already employed by Straub (13). It is important that the moving mass in such an instrument should be as small as possible and the vibration frequency of the instrument as rapid as possible. The instrument we used consisted of a tube *B* 6 cms. long and 3·5 mm. bore, in which a stilet *A* fitted so that it could slide easily up and down. 3·2 cms. from the lower end is a tap *C* bored out so that in one position it permits the free movement of the stilet, and in the other absolutely closes the tube. Underneath the tap the trocar is widened out so as to form a small cylinder or tambour at right angles to the axis of the trocar. One end of this drum *D* is closed, over the other end is tightly stretched a thick rubber membrane *E*. This membrane forms a manometer, being slightly bulged out with every rise of pressure. The movements, which are extremely small, are rendered visible and recorded by attaching to the lower edge of the membrane a small mirror *F*, 1 mm. in diameter. By this mirror an image of a Nernst filament is thrown on to a slit behind which sensitive paper is moved along by means of a kymograph. It is found that the movements of this slit of light are proportional to the changes of pressure in the tambour.

To use the apparatus a purse string suture is put round a spot on the anterior surface of the right or left ventricle. The open end of the manometer with the stilet pushed to the end is then plunged through the wall of the heart in the middle of the ring of suture. The two ends of the purse string suture are then tied tightly so as to lie in one of the grooves with which the lower end of the trocar is provided. The action of the heart is not disturbed at all by this procedure. The stilet is then withdrawn and blood follows. It comes out of the free end of the tube, displacing all air bubbles in the apparatus. The tap is then turned, and we have then a manometer of extremely high efficiency connected directly with the cavity of one of the ventricles. A thinner membrane is generally employed for taking similar changes of pressure in the right ventricle than for the left ventricle. Similar thin membranes were used for recording the pressures in the auricles, the cannula in this case being tied into one of the auricular appendages. In all our experiments the pressure was registered simultaneously in two chambers of the heart, generally right auricle and ventricle or left auricle and ventricle. In a few cases the pressure was measured simultaneously in the left ventricle

and in the aorta, and in one experiment the pressures were registered simultaneously in the right ventricle and in the pulmonary artery, a T cannula being introduced into the latter. At the end of the experiment the manometers used were calibrated by determining the extent of the excursion of the spot of light under given variations of pressure. The cannulæ were fixed rigidly in position by iron bars and clamps attached to each side of the table. It is evident that the slightest shifting of either of the manometers would cause an alteration of the zero point and render it difficult, if not impossible, to compare two tracings following one another, taken under different circumstances. In order to carry out such comparisons we adopted two methods. In the first place in the majority of experiments tracings of two successive observations were taken on the same piece of sensitive paper, the drum being allowed to revolve once (first observation), and then when the conditions were changed, it was allowed to revolve a second time, so that no shifting of the paper could occur. As an additional safeguard against any possible shifting of the apparatus or of the manometers we arranged in all our later experiments to have a third spot of light recorded on the tracing. This spot was reflected from a mirror on a rod firmly attached to the same clamps which were holding the manometers in position. If in two successive records on the same length of paper the second record of the fixed spot was identical with the first record, we could be certain that no shifting had occurred in any part of our apparatus. By this means we were able to get accurate records of the rapid pressure changes in the heart cavities and aorta under every condition of inflow up to the maximal, of arterial resistance up to the maximal, at rates varying from 60 to 240 per minute, under stimulation of the vagus, under the action of carbon dioxide and adrenalin, and in every case the pressure in the inferior cava, the output, the average arterial pressure maintained, and the temperature at which the heart was contracting.

In order to correlate these results with those obtained on the volume of the heart by the use of the cardiometer, it was necessary to carry out some experiments in which the volume and pressure changes were recorded simultaneously. For this purpose a method was devised by one of us (Piper).

Our methods of registering rapid changes of pressure are now fairly perfect. But the same cannot be said for our methods of registering rapid changes in volume. We therefore adopted the plan of converting the volume change into a pressure change. A brass cardiometer (*C*) was made with an oval slot in the side wall connecting with the wide orifice

into which the heart (*H*) was inserted (see Fig. 5). Both the mouth of the cardiometer and the adjoining oval orifice were surrounded with a lip over which a rubber membrane could be tied. A brass flanged circular ring (*R*) of the same diameter as the circumference of the mouth of the cardiometer was also made. Over this ring a rubber membrane was stretched, and an oval hole burnt in it of a proper size to fit closely over the auriculo-ventricular junction. The ring was then pushed over the ventricles, until the rubber membrane rested in the auriculo-ventricular groove.

A purse string suture was then loosely inserted in the anterior surface of the cavity which it was desired to investigate. The mano-

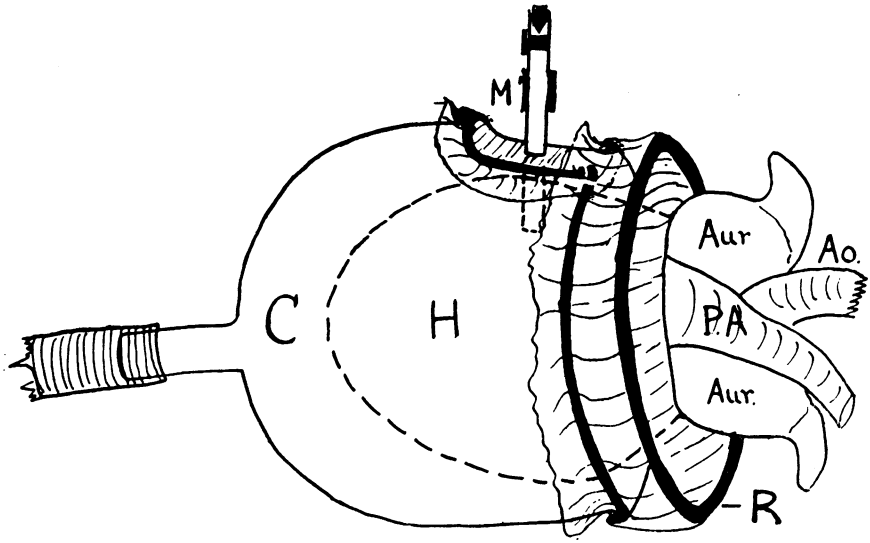

Fig. 5. See text.

meter *M* with trocar was pushed through a rubber membrane which was then securely tied round the stem of the manometer. The trocar was then plunged into the heart and tied in by means of the purse string suture. The cardiometer was now passed over the heart, so that the manometer projected through the slot. The rubber membrane on the manometer was then tied tightly by means of a wire passed round the groove surrounding the slot, so that this was closed and made air-tight. Finally the edges of the rubber membrane affixed to the ring were pulled over the cardiometer, and secured by a copper wire in the groove surrounding the edge of the cardiometer.

The tube at the end of the cardiometer was then connected by thick rubber tubing with a large rubber tambour 12 cms. in diameter. It was found by trial that 50 c.c. of air could be forced into this tambour and produce a rise of pressure amounting to only 20 mm. H_2O. The smaller oscillations of volume, such as would occur as the result of the heart beat, would produce a change of pressure in the manometer of two or three mms. H_2O. To record these small changes of pressure a side tube led from the big tambour to a small glass funnel about 1 cm. in diameter, over the mouth of which a thin rubber membrane was stretched fairly tightly. This membrane formed an efficient manometer for the measurement of the small changes of pressure occurring in the big tambour at each heart beat. The changes of pressure were proportional to the changes of volume and could be recorded optically by means of a tiny mirror attached to the edge of the rubber membrane. In our actual experiments, in our endeavour to avoid any possible hindrance to the action of the heart by changes of pressure in the big tambour, the membrane was stretched a little too loosely, so that the oscillations of our optical cardiometer, as registered on the tracings, were only small. They present also secondary oscillations probably due to the system,—air *plus* rubber membrane closing the large tambour. This could probably be avoided by a slight modification of the apparatus. Since they did not prevent a comparison of the changes of volume with the changes of pressure nor render difficult the reading of the volume curves, we did not trouble to find means of getting rid of them.

I. The reaction of the heart to varying arterial resistance.

It has been shown that the heart is able to put out a constant amount of blood with very wide variations in the arterial pressure, provided only that the venous inflow is constant. Our first aim was to investigate the changes in the volume of the heart and in the pressures in its various cavities associated with variations in the arterial resistance, the venous inflow being kept constant at a low, medium or high level.

(*a*) *Volume changes of the heart.* These were determined cardiometrically according to the method already described. In Figs. 6 and 7 we show the effects of a sudden increase and diminution of the arterial resistance,—in Fig. 6 with a moderate inflow and an output at each beat of about 5·5 c.c., and in Fig. 7 with an output of about 10 c.c. Both tracings were taken from a dog of 5·15 kilos., with a heart

weighing 67 gms. The piston recorder was inverted, so that systole produced a movement of the lever in the upward direction. In Fig. 6 the pressure maintaining the artificial arterial resistance was altered from

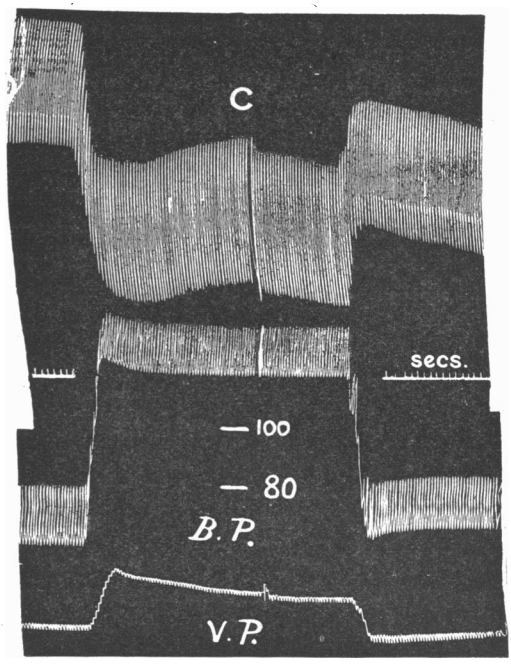

Fig. 6. Effects of rise of arterial resistance on the volume of the heart. (Curves in Figs. 6 to 11 to be read from left to right.)

C, cardiometer tracing; B.P., arterial pressure; V.P., venous pressure. The data of the experiment are as follows:

T.	A.R.	B.P.	V.P.	Rate in 10″	O.P. in 10″
35° C.	40	68	65	22	74
35	103	128	90	22	—
35	42	75	55	22	—

In this, as in all other shortened protocols of the experiments,

T = temperature of blood flowing into the heart.

A.R. = the artificial resistance, as measured by the pressure in the air space surrounding the thin rubber tube in mm. Hg.

B.P. = the arterial blood-pressure as measured by a mercurial manometer connected with the side branch of the cannula in the innominate artery in mm. Hg.

V.P. = the pressure in the inferior vena cava close to the heart, measured in mm. H_2O.

Rate = number of beats in 10 seconds.

O.P. = output in c.c. per 10 seconds, as measured on the peripheral side of the artificial resistance.

40 to 108, then it dropped to 104, and then was suddenly lowered to 42. The mean arterial pressure as measured in the innominate artery was 75 mm. Hg., with a resistance of 42, and 128 mm. Hg. with a resistance

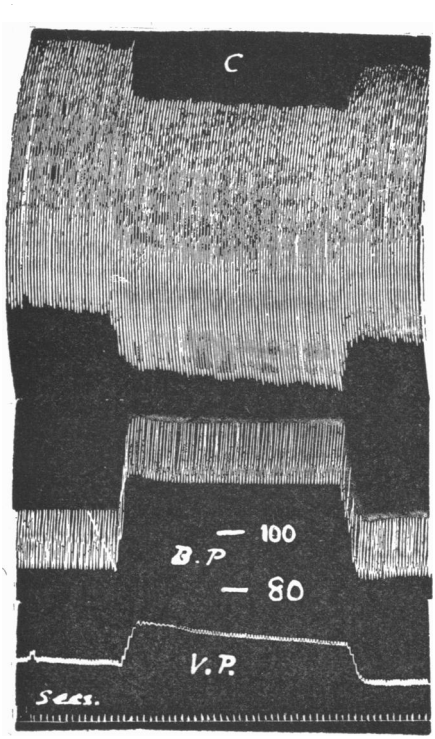

Fig. 7.

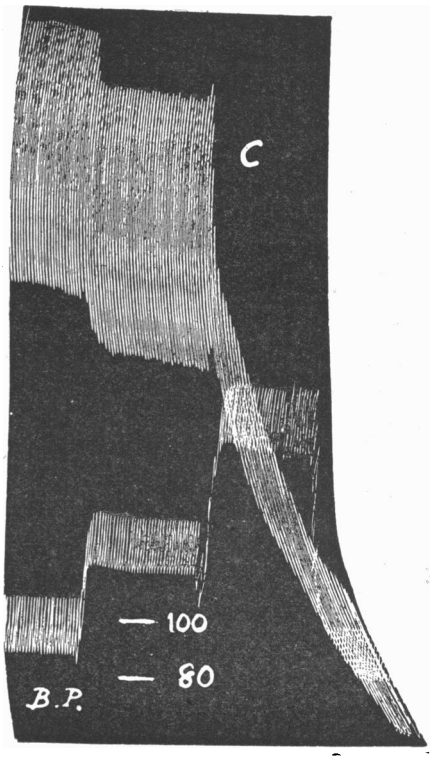

Fig. 8.

Fig. 7. Effect of increased arterial pressure on the volume changes of the heart with a large inflow (154 c.c. per 10″).

T.	A.R.	B.P.	V.P.	Rate	O.P. 10″	O.P. per beat calc.	O.P. per beat observed
35° C.	60	98	125	23	154	6·7	10
35	100	128	145	23	—	—	10
35	60	95	120	23	—	—	10·25

Fig. 8. Continuation of same experiment as Figs. 6 and 7, showing volume changes of the heart with a big inflow when the arterial pressure was raised to a height too great for the capacity of the heart.

T.	A.R.	B.P.	V.P.	Rate	O.P. 10″	O.P. per beat calc.	O.P. per beat observed
35° C.	60	95	120	23	154	6·7	9·5
35	96	126	145	23	—	—	9·5
35	144	170	200	23	—	—	9·0

of 103. The pressure in the inferior vena cava was 90 mm. H_2O at 128 and 55 mm. H_2O at 42.

It will be seen that the course of events corresponds exactly to the theoretical case described in the introduction to this paper. On raising the arterial resistance from 40 to 103 the systolic volume increases, *i.e.* the heart does not empty itself so effectively as before. The diastolic volume therefore increases as well, and this increase of systolic and diastolic volume proceeds for eight beats. The heart then takes up a new level in which its systolic volume is practically identical with its previous diastolic volume, and at this level it continues to empty itself as effectively as before. The output, as measured by the cardiometer excursion, is in fact somewhat increased, namely, from 4·6 to 5 c.c. On dropping the arterial resistance again from 103 to 42, the arterial pressure drops and the volume of the heart undergoes an inverse change. Over a series of seven beats it empties itself more effectively before taking up a level which is nearly constant. It does not in this case return precisely to its previous volume but remains somewhat dilated. Fig. 7 shows the same mode of adaptation of the heart to changing arterial resistance when the inflow and output are considerably larger,—10 c.c. per beat. The arterial resistance was raised from 60 to 100, then dropped again to 60. The corresponding arterial pressures were 98, 128, and 95 mm. Hg., and the pressures in the inferior cava, 125, 145, and 120 mm. H_2O. The heart rate was 23 in ten seconds. Here again the heart reacts to a rise of arterial pressure by an increase in its mean volume, taking about five beats to change from one volume to the other. This behaviour of the heart to alterations of arterial resistance is of constant occurrence and shows that the reaction of the heart to alterations in arterial resistance is always accompanied by changes in its mean volume, and that the adaptation to a rise of pressure is effected by the heart dilating until its muscle fibres are of such a length that at their contraction they produce sufficient tension to overcome the increased resistance.

It is evident that this power of adaptation must have its limit, and the limit will be reached when the dilatation of the heart proceeds to such an extent that the muscle fibres work at too great a mechanical disadvantage in producing a rise of intracardiac pressure. This failure of the heart can occur either with a small or a large inflow, only the failure will occur at a lower arterial resistance with a large than with a small inflow. In Fig. 8 we get the effect of failure of the heart with a large inflow, corresponding to about 10 c.c. per beat when the pressure

was raised from 96 to 144, a pressure which the heart easily overcame when the inflow was lower. It will be seen that the heart loses ground with each beat, so that it finally contains at the end of systole two or three times as much as it did at the lower pressure. In order to save the heart the arterial resistance was quickly lowered before the dilatation had reached its maximum.

In considering the causation of the gradual changes in the mean volume of the heart we have to take into account not only the mechanical conditions of inflow and arterial resistance but also the physiological state of the heart muscle. This latter will tend to deteriorate steadily during the course of an experiment, and the more rapidly the greater the demands made on the functional capacity of the heart. But this physiological condition—what we have previously defined as *tone*—is itself largely dependent on the supply of oxygen, and possibly food material, to the heart muscle by means of the coronary circulation, which in its turn undergoes alterations in consequence of changes in the mechanical conditions of the heart. As has been shown previously (14), the coronary flow is markedly influenced by the arterial pressure and may for instance be more than doubled by a rise of arterial pressure from 60 to 120 mm. Hg. Added to this mechanical influence we have the effect of metabolites, produced by the heart muscle itself and formed in large quantities when the heart is inadequately supplied with oxygen or subjected to an undue strain. This influence of mechanical conditions on the coronary circulation affects indirectly the physiological state of the heart muscle. Thus, a rise of arterial pressure from 60 to 120 mm. Hg., will at first cause a dilatation of the heart as already described, until the muscle fibres take up a new length at which they can do the work required by them. But at the higher pressure there is a marked increase in the blood supply to the heart muscle. The improved nourishment of the muscle causes an improvement in its physiological condition, and this improvement shows itself by an increase of the tension set up at each degree of contraction in the muscle fibre and therefore a diminution in the length of the muscle fibre necessary to produce a certain tension. We therefore find that the primary dilatation of the heart is followed by a slow recovery, as shown by a diminution of its mean volume. The reverse is also true. When the arterial resistance is suddenly diminished, the heart empties itself more completely and beat by beat returns to a smaller mean pressure. But now the blood supply to the muscle is also diminished and the heart begins to lose ground, so that the primary rapid diminution of volume

is succeeded by a slow dilatation. These conditions are illustrated in Fig. 9, showing the effect of a series of changes of pressure, first in the upward and then in the downward direction. With an arterial resistance of 116 and an arterial pressure of 144 mm. Hg. there is a well marked recovery from the primary dilatation, which then gives place to a slow secondary dilatation, which we may regard as part of the gradual diminution of the functional capacity of the heart muscle which proceeds

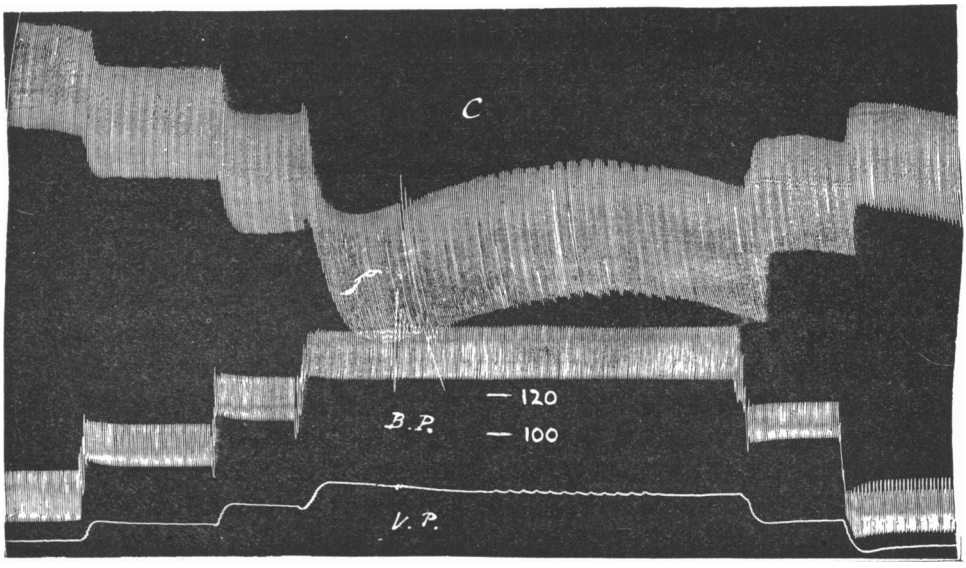

Fig. 9. Effect of raising and lowering the arterial resistance on the volume and output of the ventricles.

T.	A.R.	B.P.	V.P.	Rate	O.P. 10″	O.P. per beat calc.	O.P. per beat observed
35° C.	40	70	85	23	110	4·8	6·0
35	66	95	105	—	—	—	6·75
35	98	118	120	—	—	—	6·75
35	116	142	138	—	—	—	7·0
35	70	105	103	—	—,	—	6·0
35	28	58	75	—	—	—	5·75

during the whole survival period of the heart, and more rapidly with inadequate coronary flow. It is this diminution in functional capacity which is responsible for the fact that on lowering the artificial resistance at the end of the tracing first to 70 and then to 28, the volume of the heart does not return to the same level as it had at the beginning of the tracing with an arterial resistance of 40 and 66. This two-fold effect of

a rise or fall of arterial pressure was described by Anrep (15) as an attempt of the heart to return to its proper volume. The factors we have just mentioned give a more satisfactory explanation of the phenomenon.

It may have been noticed that in some of these curves the excursion at each beat, *i.e.* the output at each beat as measured by the cardiometer, is somewhat larger at the higher pressure than at the lower. This is due to the fact that the increased flow through the coronary vessels is

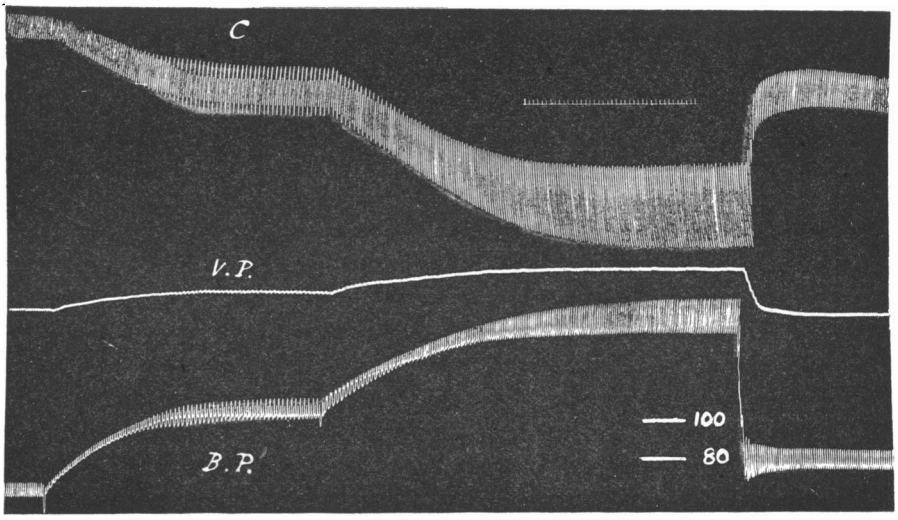

Fig. 10. Marked influence of changes in coronary circulation on the total output of the ventricles with high arterial pressures.

T.	A.R.	B.P.	V.P.	Rate	O.P. 10″	O.P. per beat calc.	O P. per beat observed
35° C.	40	60	27	22	26	1·2	1·75
35	90	100	47	—	—	—	2·25
35	140	152	75	—	0	0	{2·5 / 4·5}
35	56	80	35	—	—	—	2·0

added to the ordinary inflow and outflow of the heart. With a small inflow and a high arterial resistance, the greater part of the outflow may pass through the coronary arteries. This summation of ordinary inflow and coronary inflow is well illustrated in the experiment of which a record is given in Fig. 10. In this case we are dealing with a minimal inflow, only 160 c.c. per minute. On raising the arterial resistance from 40 to 90 the arterial pressure rises very slowly, and there is at the same

time a slow increase in the volume of the heart. So small an amount of blood was coming into the heart between each two beats that it did not put out enough to raise the arterial pressure quickly. The output, as measured on the diastolic side of the peripheral resistance, fell therefore to 0, and the blood leaving the heart went chiefly through the coronary vessels, and what was left over was expended in distending the arterial tubes. The arterial resistance was then raised to 140. We notice in the tracing the same slow increase in heart beat. The arterial pressure rose also slowly and then attained a constant level, but there was *no output* as measured on the distal side of the peripheral resistance. Judging from this alone we might have said that the heart was putting out no blood, but a glance at the cardiometer tracing shows us that the output of the heart was double what it had been at the beginning of the experiment. The whole of the blood which it put out was however passing through the coronary vessels, distending the aorta at each beat and leaking rapidly away from this through the coronary vessels, so that none was left over to pass through the peripheral resistance. In this experiment we were dealing with an exaggeratedly small inflow and with an exaggeratedly large arterial pressure, but it serves to illustrate the important changes occurring in the coronary circulation with alterations in the mechanical conditions of the heart beat, and a possible source of confusion when we compare cardiometer records of output with the output as measured by the flow of blood through the arteries and veins of the systemic circulation. The smaller the inflow of blood and the larger the arterial resistance, the more will the output, as measured by the cardiometer, exceed the output as measured directly by the flow through the arterial resistance.

(*b*) *The effect of variations in the arterial resistance on the volume changes of the heart at each beat.* The course of the volume curve at each beat may be studied by taking cardiometer tracings on a rapidly moving drum. In Fig. 11 we give a series of such tracings taken from one experiment which may be considered as typical. The details of the conditions under which each curve was taken are given in the accompanying table.

In the tracings from 1 to 4 the arterial pressure was raised by steps from 84 to 190 mm. Hg., the inflow being maintained constant at a considerable height, namely, about 720 c.c. per minute. In curves 5 to 7 the arterial pressure was reduced again by steps to 46 mm. Hg. On examining first the systole we see that in each case it can be divided into three parts. The first part is represented by a quick

descent, corresponding to a rapid outflow of blood from the ventricles. In the second part the outflow becomes much smaller or even stops,—corresponding to the velocity minimum in the pulse curve recorded by Frank. The third part varies in the different tracings. With a low arterial pressure the outflow becomes more rapid again at a point which probably corresponds to a falling arterial pressure and the descent of the so-called systolic plateau. As the pressure is raised two changes are noticed in the form of the curve. The first part of the curve alters in slope, so that the diminution of volume is more rapid at 140 mm. Hg. arterial pressure than at 84 arterial pressure. The chief

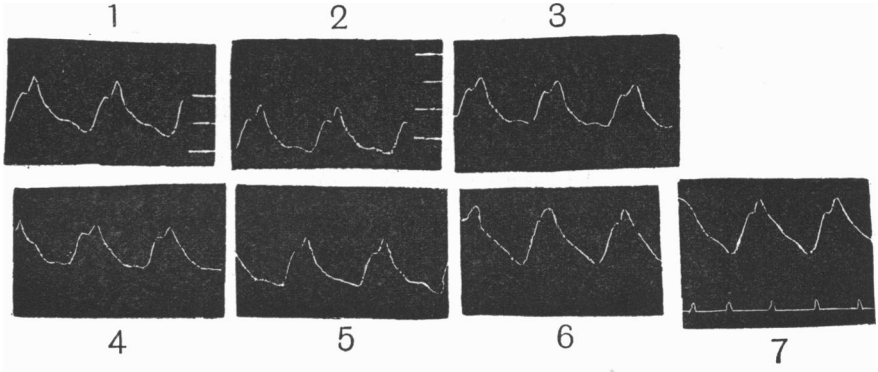

Fig. 11. Cardiometer tracings on a rapidly moving drum, showing influence of varying arterial pressure.

Dog 4·6 kilos; heart 52 gms. Cardiometer writing vertically; systole downwards. Venous supply maintained constant and arterial resistance varied.

	A.R.	B.P.	V.P.	O.P.	Pulse rate
1.	60	84	45	115	26·5
2.	80	110	62	115	26·5
3.	110	140	80	111	26·5
4.	150	190	110	108	26·5
5.	70	106	60	115	26·0
6.	18	50	50	116	26·0
7.	0	46	45	118	26·0

At the side of curves (1) and (2) is given the calibration of the recorder, each division corresponding to an output of 5 c.c.

effect of the rise of the arterial pressure is however on the third part of the curve. In the curves taken with pressures of 140 and 190 mm. Hg. there is practically no further fall in the third part of the curve, so that this part of the curve runs parallel with the abscissa. This behaviour of the curve can only be interpreted by assuming that at this period of the ventricular contraction practically no blood is leaving the ventricles.

The flattened systolic curve is still more marked when the inflow of blood is small. When observed with a small inflow and a small arterial pressure it may mean that the ventricles actually empty themselves at each contraction, so that the period of outflow of blood from the ventricles necessarily comes to an end before the contraction of the muscle gives place to diastolic relaxation. This cannot however be the explanation of the flat top observed under the conditions in which the curves in Fig. 11 were taken. From our study of the volume changes, as recorded on a slowly moving drum, we know that the heart has been continually expanding as the arterial resistance was raised, so that at the end of the contraction in the fourth curve the heart contained more blood than at the end of diastole in the first curve. With these high arterial pressures therefore the greater part of the outflow may occur during the beginning of the ventricular systole. During the latter part of the curve the ventricular muscle has maintained a tension which so nearly approximates to that in the aorta that practically no outflow of blood occurs. There seems therefore to be some justification for the old idea that the latter portion of the systole of the ventricles represents a "Verharrungszeit" or "rückständige Kontraktion" in which the ventricle remained contracted without forcing out any blood. This time, as described by Landois, Moens, and others (16), was however supposed to be due to the complete emptying of the ventricle and not, as we see here, to a simple holding up of aortic pressure. It must certainly be quite uneconomical and probably is only obtainable under such artificial conditions as those ruling in our experiments, where we can control factors independently which under normal circumstances of the body vary together. The change in the slope of the first part of the systole which accompanies increased arterial resistance, may be due either to a more rapid development of tension by the contracting muscle fibres, or to the fact that the dilatation of the heart which we have seen to accompany increased arterial resistance, has, so to speak, taken up the slack, so that the contraction of the muscle has a more immediate influence in raising the intra-ventricular pressure.

The diastolic part of the curve, during which the ventricles are being filled, does not present many features worthy of note. The amount of blood flowing in at each systole was the same throughout the experiment. The only difference between the filling of the heart at the high and the low pressure lies in the fact that the venous pressure, and therefore the distending force, is greater when the arterial pressure is high than when it is low. This is probably responsible for the slightly

increased steepness of slope in curve No. 4 as compared with curve No. 1. In each case the increased rapidity of inflow with increased volume of the ventricles, due to contraction of the auricles and emptying of their contents into the ventricles, is well marked.

(*c*) *Pressure changes accompanying the reaction of the heart to variations in arterial pressure.* Whereas the diastolic filling of the heart determines the subsequent contraction, the pressure changes in the heart, as the result of the contraction, are responsible for the changes in volume that we have just studied. We therefore investigated the influence of alterations in the arterial resistance on the pressures in the different cavities of the heart, in each experiment making two simultaneous determinations, namely, (1) the left ventricular pressure with cardiometer tracing, (2) simultaneous records of pressure in the left ventricle and aorta, (3) simultaneous records of pressure in the left ventricle and left auricle, (4) simultaneous records of pressure in right ventricle and right auricle.

In the same experiment we investigated the influence of varied filling of the heart as well as of variations in rate as brought about by stimulation of the vagus or by differences of temperature. The influence of these various conditions on the form of the endocardiac pressure curves in the various cavities of the heart, we shall deal with more fully in a subsequent paper. Here we wish to draw attention merely to the experimental data which throw light on the questions raised in the introduction to this paper.

The influence of changes in the arterial pressure on the volume of the two ventricles and on the pressure in the left ventricle is shown in Figs. 12 and 13. In Fig. 12 the pressure was raised from 68 to 128, the inflow being maintained constant at about 900 c.c. per minute. The tracings at the two different pressures were taken on the same piece of paper so as to allow of an accurate comparison of the tracings under the two sets of conditions. In Fig. 13 the first tracing was taken with an arterial pressure of 132, and the second one with an arterial pressure of 52. It will be noticed that in each case the cardiometer readings show the changes of volume with rise in arterial pressure which have already been described. Both systolic and diastolic volumes increase with rise of pressure and diminish with fall of arterial pressure. In comparing the curves of intra-ventricular pressure, the first thing to note is that, as we should expect, the ventricular pressure rises higher when the arterial resistance is raised. The most interesting point is perhaps however the difference in slope of the rising part of

the curve, the pressure increasing more rapidly when the arterial pressure is high than when it is low. Thus in Fig. 13 the ventricle took ·037 second to raise the pressure in its interior 100 mm. Hg. at 130 mm. Hg. arterial pressure. On reducing the arterial pressure to 52 mm. Hg., the same rise of endocardiac pressure was not accomplished under ·074 second. This alteration in the rapidity of rise of pressure is evidently associated with the change in the steepness of the systolic part of the cardiometer tracing, which is also evident in the cardiometer curves photographically registered in Figs. 12 and 13. It is difficult to decide

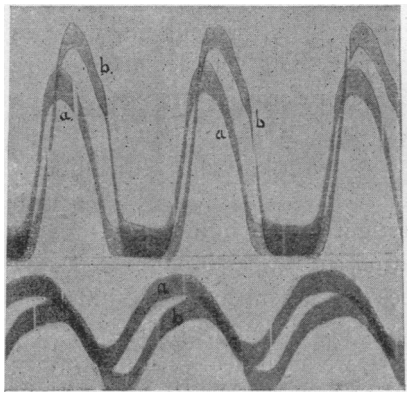

Fig. 12

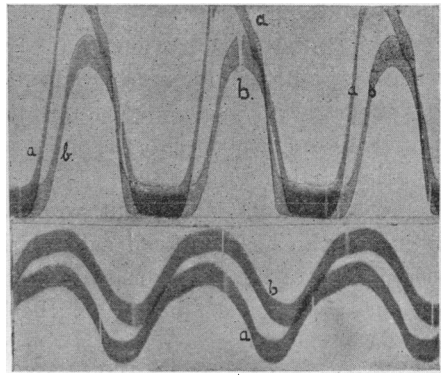

Fig. 13

Fig. 12. Pressure in left ventricle and of volume of the two ventricles. Curve to be read from right to left.

Dog 6·5 kilos; heart 70 gms.

	T.	B.P.	V.P.	O.P.	Rate	Maximum endo-cardiac pressure mm. Hg.	Time to get up 100 mm. Hg.
a.	37° C.	68	88	153	25·5	133	0·083″
b.	36·8	128	110	153	26	174	0·047

Fig. 13. Same experiment as Fig. 12. Read from right to left.

	T.	B.P.	V.P.	O.P.	Rate	Maximum endo-cardiac pressure mm. Hg.	Time to get up 100 mm. Hg.
a.	36·8° C.	132	128	153	26	178	0·037″
b.	36·7	52	86	153	26	126	0·074

whether this should be interpreted as a more rapid setting up of tensile stress in the contracting muscle fibre, or as the simple mechanical result of the stretching of the heart muscle and therefore less slack to be taken up at the beginning of contraction. We are inclined to ascribe greater probability to the former of these two explanations.

Still more important as regards the mechanical effect of the ven-

tricular contraction in driving blood out into the aorta is the influence of the rise of pressure on the duration of the curve. The duration of the ventricular contraction may be measured by determining the time between the beginning of the rise and the point at which the aortic valves close. In every case increased arterial resistance caused an increase in the duration of the period of contractile stress of the heart. This is quite evident in Figs. 12 and 13 but is still more marked in Fig. 14, where the difference of arterial pressure between the two tracings is greater. In Fig. 12 the duration of the ventricular contraction with an arterial pressure of 68 mm. Hg. was ·1835″ or 48·5 % and

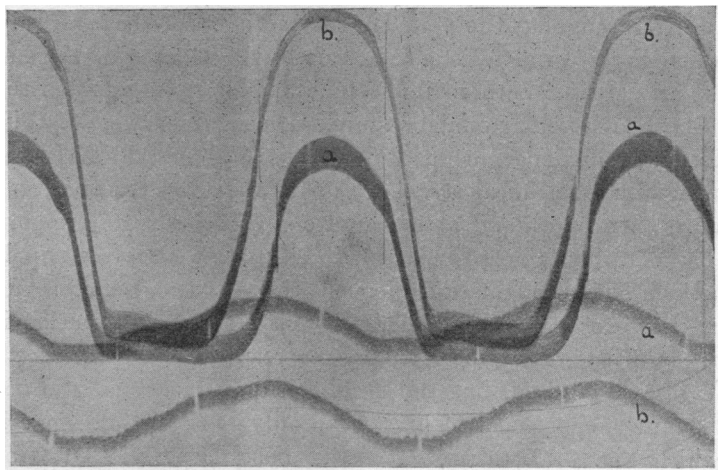

Fig. 14. Simultaneous record of left ventricular pressure and ventricular volume. Read from right to left.

Dog 9·5 kilos (pregnant); heart 49 gms.

	T.	B.P.	V.P.	O.P.	Rate
a.	36·2° C.	68	34	88	21·5
b.	36·2	166	66	88	20·5

During the isometric period the time of equal rise of pressure in *b* and *a* is in the proportion of 5 to 9.

at 128 mm. Hg. ·19″ or 50 % of total cycle. In Fig. 14 the relative durations of the ventricular contractions at 68 and 166 mm. Hg. were ·224″ or 46 % and ·262 or 54 % respectively. In the case of skeletal muscle it has been shown that hindrance to shortening applied during the period of rise of contractile stress increases the total metabolism of the muscle, as judged by its heat production, and also the tension set up in the muscle or the mechanical effect of its contraction. If the extending

force is applied to the muscle at the end of this short period, it has no influence on the metabolic processes of the muscle. The heart muscle appears to differ from voluntary muscle, *e.g.* the skeletal muscle of the frog, essentially in the time relations of the excitatory process.

The chemical change at the surface of the ultimate fibrils, which is responsible for the production of the contractile stress, is not limited to two or three hundredths of a second, as in skeletal muscle, but lasts throughout the whole of the contraction, *i.e.* nearly as long as the mechanical response. The amount of energy set free therefore during each contraction of the ventricles will be determined not merely by the initial length of the fibres composing its walls, but by the length of these fibres throughout the period of contraction. We have already seen that when the arterial resistance is raised, the volume of the heart is permanently greater both in its systolic and diastolic position than its volume with a lower arterial pressure. During the whole of this time therefore the influence of length of muscle fibre will be potent in increasing the mechanical stress set up in the muscle. It is, so far as we know, a new fact, and at any rate one of considerable importance, that this condition increases not only the contractile stress set up during contraction, but also the duration of the excitatory state. As the arterial pressure is raised therefore, we get a marked alteration in the relative durations of systole and diastole respectively. The rhythm of the heart is unaltered, but the systole is prolonged and the diastole correspondingly shortened. This is especially marked in the experiment from which Fig. 14 is taken, where the diastolic period on raising the blood-pressure from 68 to 166 mm. Hg. is diminished by 20 %, namely from ·261″ to ·223″.

There is another feature in the diastolic part of the curve to which we would particularly draw attention. It will be noted that the fall of pressure occurs about as rapidly as the rise, the closure of the aortic valves being probably indicated by the thinning out of the descending part of the curve near its commencement. The pressure falls then rapidly to the zero line and then in most cases rises gradually but very slightly during diastole. (In certain cases the pressure may remain at approximately zero during the greater part of diastole.) In both these tracings the pressure at the end of diastole is approximately the same at the high arterial pressure as at the low arterial pressure. This signifies that the only difference in the condition of the ventricular muscle at the beginning of the systole is one of length and not of tension. The initial tension of the heart muscle is approximately the same under the two

sets of conditions, though a reference to the cardiometer curves below the endocardiac pressure curves shows that there is a considerable difference in the diastolic volume of the heart and therefore in the length of the muscle fibres. This constancy of initial tension with varying arterial resistance is of course not invariably found. If the inflow is larger or the heart more dilated to start with, or the rise of arterial pressure excessive, we get a marked difference in the diastolic pressure with difference in initial filling, and in fact we shall expect the diastolic tension to increase with diastolic filling. But cases such as those recorded in Figs. 12 and 13 are of special importance since they enable us to differentiate between changes in tension and changes in length as factors determining the amount of energy set free in the contraction of the heart muscle. We see from these tracings that an invariable condition of increased contractile stress is increased initial length of the muscle fibre. This may be accompanied or brought about by increase in the initial tension of the muscle fibre, but the two conditions are not invariably connected, and we shall find later other cases in which length varying without changes in tension has brought about its proper effect on the strength of contraction of a muscle.

Fig. 14 furnishes an example in which diastolic tension and diastolic length varied together. The change in arterial pressure was here considerable, namely, from 68 mm. Hg. to 166 mm. Hg. We observe the same changes in the systolic part of the curve which we have already recorded—rise of maximum pressure, rise of point of opening of aortic valves, increased steepness of rise of pressure, increased duration of contraction. In the diastolic part of the curve however there is a well marked difference between the two tracings, the diastolic pressure or initial tension at the beginning of systole being considerably higher at the high arterial pressure than at the low arterial pressure.

In Fig. 15 we give simultaneous records of the ventricular pressure as measured in the left ventricle and of the aortic pressure under two conditions, namely, at an arterial pressure of 78 and at an arterial pressure of 156, with a large inflow and output, namely, over 1300 c.c. per minute. The aortic pressure curve at the low pressures resembles closely that given by Frank for the normal animal and presents a well marked dicrotic elevation, followed by two or three oscillations. The rise in the curve immediately preceding the opening of the aortic valves is probably due to a reflected wave from the artificial arterial resistance. The great difference in level between the curves at high and low arterial pressures respectively is due to the fact that the diastolic pressure could

not sink below the minimum represented by our artificial resistance. We observe in the systolic part of the intraventricular curve the same increased steepness of slope as with the higher pressure, to which attention has already been called. We would call attention especially however to the diastolic part of the curve. Here it will be noticed that although blood is flowing into the ventricles during the whole of diastole, the pressure does not rise, the inflow of blood evidently being not more than sufficient to follow up the relaxation of the ventricle. This is the case even with the big inflow of 1300 c.c. per minute. There

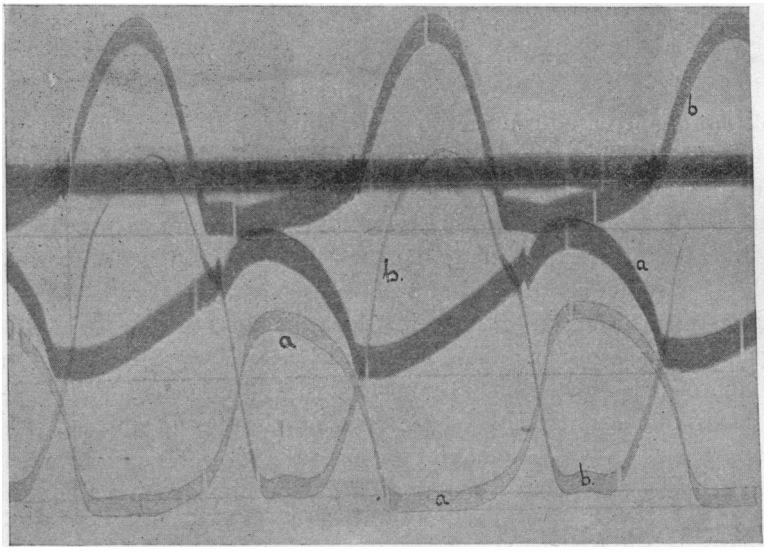

Fig. 15. × ⅔. Simultaneous record of pressures in left subclavian artery and in left ventricle. Read from right to left.

70 mm. ventricular manometer = 200 mm. Hg.

82 mm. subclavian manometer = 200 mm. Hg.[1]

Dog 8·5 kilos; heart 85 gms.

	T.	B.P.	V.P.	O.P.	Rate	Max. vent. press.	Time to raise pressure 60 mm. Hg.
a.	35·3° C.	78	32	223	22	109	0·050″
b.	35·3	156	40	223	22	198	0·036

is however a difference of initial tension in the ventricular cavities at the beginning of systole, the tension being higher with the higher arterial resistance. The contraction of the ventricle also lasts longer

[1] The calibration here and elsewhere refers to the original tracings, and not to the figures as reduced.

with the higher arterial resistance, and the change in diastolic tension seems to be conditioned more by the inadequate relaxation at the high pressure as compared with the relaxation at the low pressure. It must be borne in mind that the volume of the heart would be considerably bigger at the high pressure than at the low pressure.

II. The reaction of the heart to varying inflow.

Within wide limits the output of the heart is determined by and equal to the inflow into the right auricle. A heart of 50 gms. in good condition puts out as much blood as it receives, whether this be 200 or 2000 c.c. in the minute. We have investigated the changes in the volume of the ventricles and the changes in the pressure within the ventricles which accompany this reaction of the heart to alterations in venous inflow.

Changes in the volume of the heart. The effect of alterations in venous inflow on the systolic and diastolic volumes of the ventricles is shown in Fig. 16, where the cardiometer record taken on a slowly moving drum is compared with the arterial pressure and with the venous pressure. In the first part of this tracing the heart was beating regularly and put out 86 c.c. of blood every ten seconds against an arterial pressure of 124 mm. Hg. The venous inflow was now increased and the output of the heart, as measured on the other side of the arterial resistance, rose to 140 in 10 seconds. The outflow per beat, obtained by measuring the flow through the artificial arterial resistance, was 3·9 c.c. in the first case and 6·4 c.c. in the second case. A direct measurement of the cardiometer curves gave 5·75 c.c. and 8 c.c. respectively, but this would include also the amount of blood flowing through the coronary circulation, which at this high arterial pressure would be considerable. It will be seen that the heart adapts itself to the increased inflow in almost precisely the same fashion as it adapts itself to increased arterial resistance. The heart has naturally to set up a greater pressure in its cavities in order to drive out a larger amount of blood against the same arterial resistance as before. Theoretically one might imagine that the heart, being increased in size during diastole by the greater inflow of blood, might react so perfectly that the increased contractile stress set up as the result of the lengthening of the fibres would be sufficient to empty out the whole of the surplus blood it had received, so that the heart would go on beating with a larger excursion

at each beat and a greater diastolic volume but with the same systolic volume as before. This condition however we have never met, though we would admit the possibility of its occurrence in a heart with high physiological efficiency. In every case we have found that the result of increasing the inflow is to increase the systolic as well as the diastolic volume, even when care is taken by adjustment of the artificial resist-

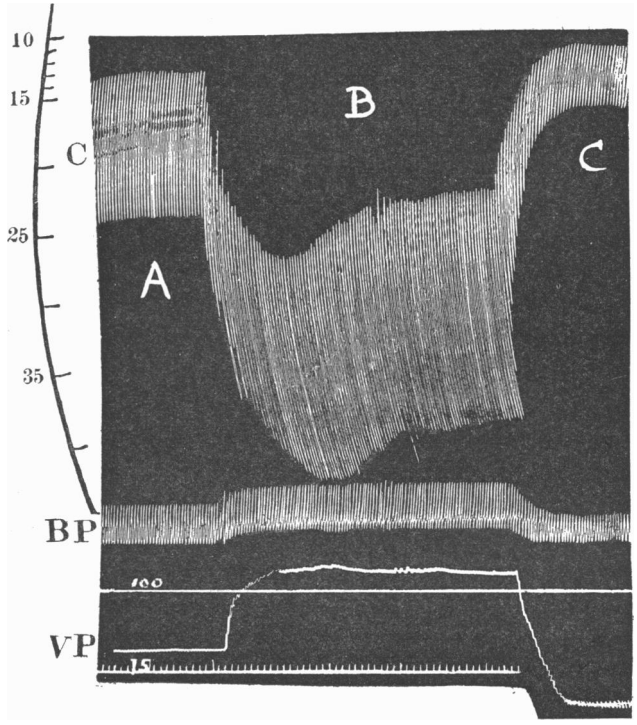

Fig. 16. Effect of alteration in venous supply on volume of heart. Read from left to right.

Dog 5·15 kilos; heart 67 gms.

	A.R.	B.P.	V.P.	Rate	O.P.	O.P. per beat calc.	O.P. per beat observed
A.	100	124	95	22	86	3·9	5·7
B.	100	130	145	22	140	6·4	8·0
C.	100	122	55	22	33	1·5	2·5

ance to keep the mean pressure in the aorta constant. Even under this condition, although the pressure in the aorta at the end of diastole will be lower, the pressure at the end of systole will be higher than when the output per beat is smaller, and it seems probable that in order to keep

the systolic volume constant, we should have to diminish the arterial resistance to such an extent that the maximum systolic pressure in the aorta remained the same as before. We thus get with increased inflow increase in volume of the heart, which in the curve represented in Fig. 16 proceeds for 24 beats. We now get partial recovery of heart volume, the causation of which has already been discussed, so that finally the heart takes up a volume which oscillates between a constant systolic and constant diastolic volume, both of which are greater than the corresponding volumes with a smaller inflow. On now reducing again the inflow to 33 c.c. per 10 seconds a reversed change takes place. Each heart beat is smaller, and finally the heart settles down to a new state, in which each ventricle is putting out 2·5 c.c. of blood per beat and both systolic and diastolic volumes are smaller than they were at the beginning of the experiment with a larger inflow of 86 c.c. per 10 seconds. It will be seen that the pressure in the inferior vena cava rises and falls with the venous inflow. The significance of these changes has been discussed in a previous paper. We would here only observe that these changes in venous pressure must not be taken as necessarily implying corresponding increase or diminution in the diastolic pressure in the ventricles, *i.e.* in the initial tension in the ventricular cavities at the beginning of systole. A greater flow from the superior cava into the right ventricle must involve a greater head of pressure in the former, even if the pressure in the right ventricle is 0. Moreover the inflow into the veins from the reservoir is continuous. The inflow into the ventricle occurs only during the intervals between its contractions. Any lengthening induration of the contracted state, and corresponding shortening of diastole, will therefore raise the average pressure as measured in the inferior vena cava, even though the ventricles relax so quickly as to allow a practically free inflow of blood into them during the diastolic period. The initial tension on the ventricular fibres must therefore be determined directly before we can attempt to dissociate the influence of the two factors on the process of contraction.

The volume changes at each contraction with varying venous inflow. In Fig. 17 we give a series of cardiometer tracings taken at a fast rate of the drum under varying conditions of inflow, the arterial resistance being kept constant, so that increasing inflow caused a moderate increase in the mean arterial pressure. The temperature was maintained constant, so that the rate did not vary. In successive steps the inflow, as measured by the output from the peripheral side of the resistance, was increased from 40 c.c. to 250 c.c. in 10 seconds. The

amplitude of the curves naturally increases with increasing output, and this greater amplitude of excursion must mean a greater average steepness both of the diastolic and systolic parts of the curve. It is evidently quite impossible to speak of a uniform shape of the curves or even of a part of the curve, as Henderson has done(4). Such a uniformity could only exist if the rate of the heart beat were accurately adjusted to the rate at which the blood is flowing into and being expelled from the heart. The systolic part of the curve with the lower inflow (up to 143 c.c. per 10 seconds) shows the division into three phases, which have already been discussed in describing the effect of change in arterial resistance. As the heart becomes fuller and its output at systole greater, these divisions disappear, and the descent of the curve, which signalises the expulsion of blood, becomes uniform. The diastolic part of the curve shows the rapid increase in volume due to the inflow of blood under the venous pressure at the root of the vena cava. This venous pressure varied from 20 mm. H_2O up to 210 mm. H_2O. In all cases the effect of the auricular systole is well marked on the diastolic upstroke. With the moderate inflow the effect of the auricular systole on the curve is probably exaggerated by the auricular muscles pulling on the ventricular wall and so causing some shifting of the elastic diaphragm closing the cardiometer. This on the curve would give an impression of a check in the rate at which the heart was being filled. With the high inflow and output of 238 and 250, the heart was reaching its limit of distensibility towards the end of diastole. This is shown by the fact

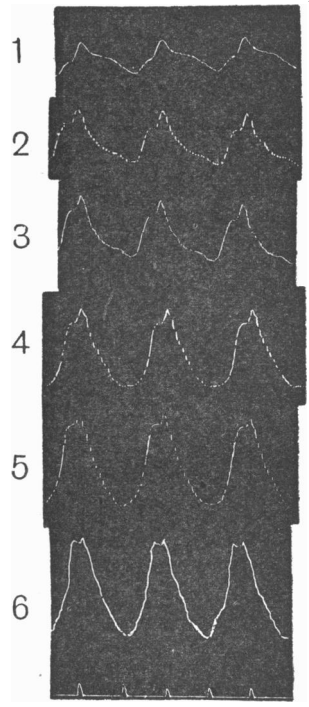

Fig. 17. Cardiometer tracings from the ventricles with varying inflow. Systole caused a movement downwards. Curves to be read from left to right. The tracings were taken under the following conditions.

Time marking = $\frac{1}{5}$".

	T.	B.P.	V.P.	O.P.
1.	34·4° C.	88	20	40
2.	—	88	65	111
3.	—	88	75	143
4.	—	100	115	196
5.	—	104	145	238
6.	—	110	210	250

that a rise of venous pressure from 145 to 210 only caused an increased output of 12 c.c. in the 10 seconds, whereas a rise from 75 to 115 mm. H_2O in curves 3 and 4 caused an increased output of 53 c.c. There is in consequence an almost flat top to the curve just before the auricular systole occurs. This flat top would correspond to the period of diastasis described by Henderson(4). As pointed out by Straub(10), it cannot be regarded as a normal feature in the volume curve of the ventricles but occurs only when the inflow during diastole, either in consequence of rapidity of inflow or slowing of the rate of the heart, is so great that

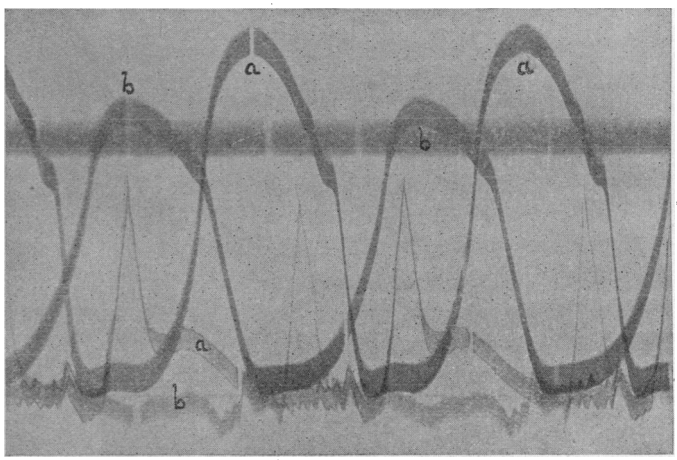

Fig. 18. $\times \frac{3}{4}$. Simultaneous tracings of pressures in left ventricle and left auricle taken with varying venous inflow. Read from right to left.

Dog 10·5 kilos; heart 84 gms.

85 mm. ventricular manometer = 200 mm. Hg.

42 mm. auricular manometer = 200 mm. H_2O.

	T.	B.P.	V.P.	O.P.
a.	34·6° C.	100	25	338
b.	34·6	100	13	108

In *a* a rise of pressure of 80 mm. Hg. occupied ·041″; in *b* the same rise of pressure occupied ·061″.

the ventricle attains its limit of distensibility under the maximum venous pressure possible under the circumstances of the experiment before the onset of the next beat.

The effect of varying inflow on the pressure changes in the heart. If the mean arterial pressure is maintained constant while the inflow is increased, the output of the left ventricle is increased in proportion. The

arterial resistance must therefore be diminished with increased inflow, and the arterial blood-pressure will show larger oscillations, the systolic pressure being increased, while the diastolic pressure is diminished.

In Fig. 18 we give curves of two observations taken one immediately after the other on the same paper without altering the position of the manometers. In the first record (*a*) the mean arterial pressure was 100 mm. Hg. and the output was 338 c.c. in 10 seconds—over two litres a minute. The heart was fairly large—84 gms.—and in excellent condition, as shown by the fact that the pressure in the inferior vena cava with this large inflow was only 25 mm. H_2O. The inflow was then reduced so that the output fell to 108 c.c. in 10 seconds, the arterial pressure being maintained at the same level as before, by increasing the arterial resistance. The pressure in the inferior vena cava fell to 13 mm. H_2O. The pressures were taken in the left ventricle and the left auricle. The first point we would draw attention to is the fact that the initial tension on the ventricular muscle at the commencement of contraction with the large output is the same or even a fraction lower than with the smaller output. It will be seen also that the auricular pressure, measured with a much more sensitive manometer directly after the auricular systole, falls to the same level when the heart has to expel 338 c.c. of blood per 10 secs. as when it has to expel only 108 c.c. per 10 secs. There is thus no difference in the initial tension on the muscle fibres of the ventricle to evoke any corresponding difference in the evolution of energy in the contracting muscle. But the difference in response of the ventricle in the two cases is marked. In the contraction with the larger inflow the rate of rise of pressure is more rapid and the maximum pressure produced is higher. In curve *a* the heart takes ·041 sec. to raise the pressure to 80 mm. Hg. In curve *b* the ventricle takes ·061 sec. to raise the pressure to the same extent. We do not observe here the great prolongation of the contracted condition which we noticed with the rise of arterial pressure, but this, as we have seen, is a question of the length of the muscle fibres, *i.e.* the volume of the heart, during the continuance of the contracted state.

Fig. 19 shows still more strikingly the absence of relation between the energy of the ventricular contraction and the initial tension on its muscle fibres. It has been already pointed out in a previous paper that with increasing venous inflow there is at first hardly any rise of pressure in the inferior vena cava. It only becomes marked as the heart is approaching its limits of distensibility. So long as the pressure in the inferior vena cava remains low, diastolic pressure in the ventricle will

depend essentially on the rate of relaxation of the ventricular muscle rather than on slight variations in the pressure in the inferior vena cava. A slight change in the physiological condition of the heart muscle, which might alter this rate of relaxation, might therefore have a considerable influence on the actual diastolic pressure attained in the ventricle.

In the experiment from which curves in Fig. 19 were taken the heart had been fed for some time at an arterial pressure of only 75 mm. Hg. The pressure was then put up to 116, with an output of 102 c.c. per 10 secs., and the first curve was taken. The output was then diminished to 50 c.c. per 10 secs. It will be noticed that the diastolic pressure with the lower output is actually slightly higher than with the

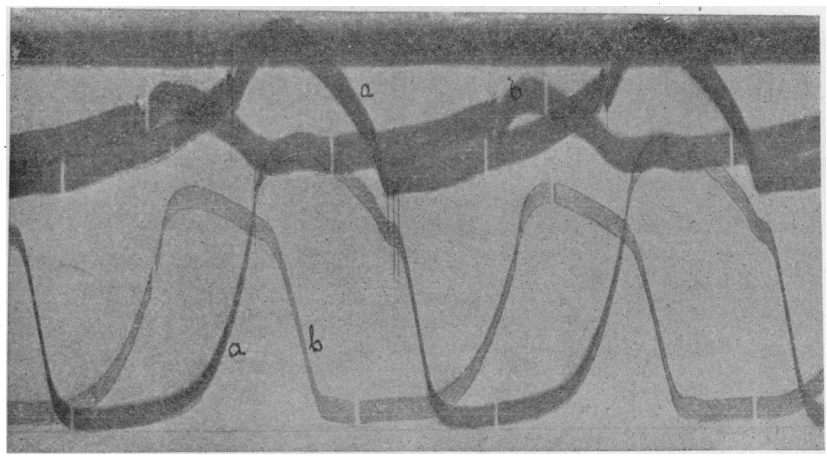

Fig. 19. $\times\frac{2}{3}$. Simultaneous tracings of pressure in the left subclavian stump and in left ventricle with varying venous filling. Read from right to left.
Dog 8·5 kilos; heart 85 gms.
70 mm. ventricular manometer = 200 mm. Hg.

	T.	B.P.	V.P.	O.P.	Rate
a.	34·4° C.	116	36	102	20
b.	34·4	116	14	50	20·5

larger output. The inferior vena cava pressure in the two cases was 36 and 14 mm. H_2O, so that the two tracings were taken within the limits at which the rate of relaxation of the heart is the determining factor for the diastolic pressure in the ventricle.

As soon as the alterations in venous inflow are attended with marked alterations in venous pressure, we observe a similar change in the diastolic pressure in the ventricles. Towards the end of an experiment, when the heart is dilating, any slight alteration in inflow causes a

corresponding change in the inferior vena cava pressure and in the diastolic pressure in the ventricles. In Fig. 20 we give two curves taken at different inflows and showing the pressure in the left ventricle and the volume of the two ventricles. The changes in the ventricular curve are similar to those described in Fig. 18, but for the fact that the diastolic pressure immediately before the commencement of systole is slightly higher in the curve with a larger inflow. In these cases the output varied between 55 c.c. and 180 c.c. in the 10 seconds. The pressure in

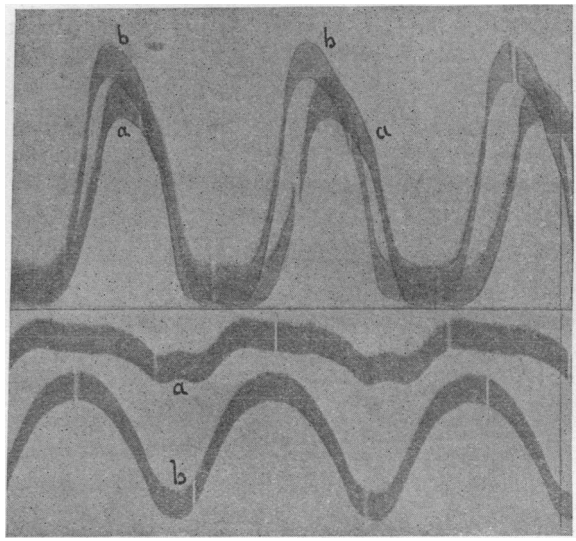

Fig. 20. $\times \frac{3}{4}$. Simultaneous tracings of pressure in left ventricle and volume of the two ventricles, with varying inflow. Read from right to left.
Dog 6·5 kilos, heart 70 gms.
54 mm. ventricular manometer = 200 mm. Hg.

	T.	B.P.	V.P.	O.P.	Rate
a.	36·2° C.	96	50	55	25
b.	36·7	94	106	180	25·5

the inferior vena cava varied between 50 and 106 mm. H_2O. A still bigger effect is shown in Fig. 21, where in a small heart of 49 gms. the output was altered from 172 to 54 c.c. in 10 secs., with a corresponding fall in venous pressure from 100 to 22 mm. H_2O. In the curves represented in Figs. 20 and 21, the cardiometer tracings show the changes which we have found to occur invariably with alterations in venous inflow. We thus find that in the reaction of the heart to increased venous inflow, as in its reaction to increased arterial resistance, the only

factor which constantly varies with the response of the ventricles is the volume of the heart, *i.e.* the length of its muscle fibres, and we are therefore justified in ascribing the increased energy of the heart's contraction under conditions of increased pressure or increased inflow to alterations in the length of the muscle fibres at the beginning of and

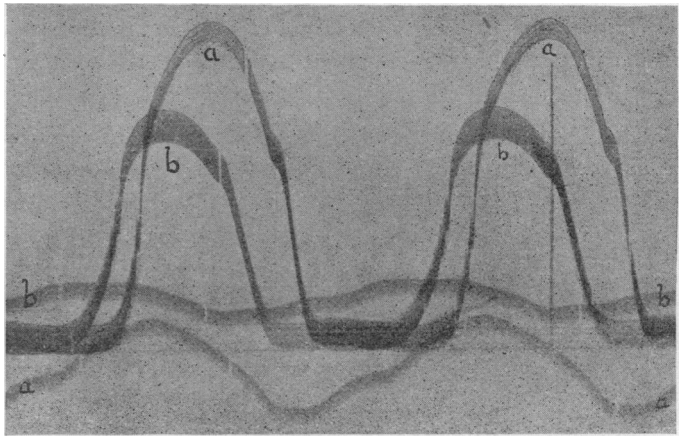

Fig. 21. As Fig. 20. Dog 9·5 kilos (pregnant); heart 49 gms.

	T.	B.P.	V.P.	O.P.	Rate
a.	36·2° C.	90	100	172	20·5
b.	35·8	90	22	54	19·5

during their state of excitation, and not to changes in the tension on the fibres, which, as we have seen, may or may not be present at the same time.

III. The influence of rate.

In our preparation the rhythm of the heart is determined entirely by the local condition of the heart muscle and is a function simply of the temperature of the pace maker. Its average rate at the temperature of the body, 37° C., is about 160 per minute as compared with the normal rate in the intact animal of 70 to 90 per minute. We can reduce its rate by stimulation of the vagus nerves or by cooling the blood with which it is supplied, or by administration of carbon dioxide by the lungs. We can increase its rate by raising the temperature, by stimulation of its sympathetic supply, or by administration of adrenalin. We propose here to deal with the influence of two of these factors, namely stimulation of the vagus and cooling, both of which will diminish its natural rate.

Of the two the influence of the vagus may be regarded as having the more significance, since it is by the influence of the tonic impulses descending this nerve that the heart rate in the intact animal is kept at its normal level.

The influence of the vagus. The general effect of stimulation of the vagus on the volume of the heart is well known. As the heart slows, it becomes larger owing to the greater time allowed for the inflow of blood. When it contracts it therefore puts out more blood. The slowing of the heart leads to a lowering of the diastolic pressure. In the heart lung preparation the diastolic pressure is set by the arterial resistance. Below this point the blood-pressure can only fall by the leakage of blood from the arterial side of the system through the coronary vessels. The systolic pressure will therefore be greater when the heart is slowed

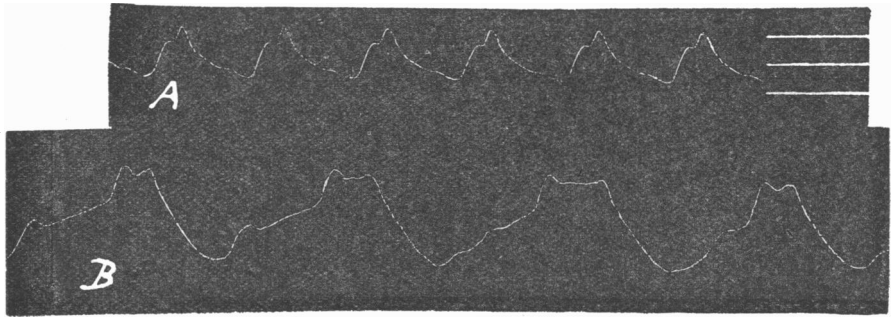

Fig. 22. Cardiometer tracings of dog's heart in heart lung preparation. Read from left to right. Systole caused a movement of the lever downwards.

	T.	B.P.	V.P.	O.P.	Rate
a. Normal tracing	35° C.	80	75	124	26
b. Left vagus stimulated	35	?	200—220	106	12·5

To the right of *a* is placed the calibration of the cardiometer, the space between two horizontal lines corresponding to an output of 5 c.c.

than when beating at its normal rate, since the output of blood at each beat is increased.

The effect of vagus slowing and the variations in cardiac volume accompanying each beat are shown in Fig. 22. In this experiment, by stimulation of the left vagus, the heart was slowed from a rate of 26 in 10 secs. to one of 12·5 in 10 secs., the conditions of inflow remaining constant. The output fell from 124 c.c. to 106 c.c. in 10 secs., and there was therefore a considerable rise in the pressure in the inferior cava, namely from 75 to 220 mm. H_2O. At this point the distensibility of the

heart, or at any rate of its right side, must have been approaching its limits, and we therefore find that the diastolic part of the curve shows the flat top towards the end, the causation of which we have already discussed. (The small elevations on the curve are due to the contractions of the auricles which under the influence of the vagus were beating independently of the ventricles.) The duration of the contraction was approximately the same under vagus stimulation as it had been before, the slowing being dependent on a prolongation of the diastolic period or period of filling.

It is evident that under such conditions as those under which Fig. 22 was taken there must be a considerable rise of diastolic pressure in the right ventricle, and probably also in the left

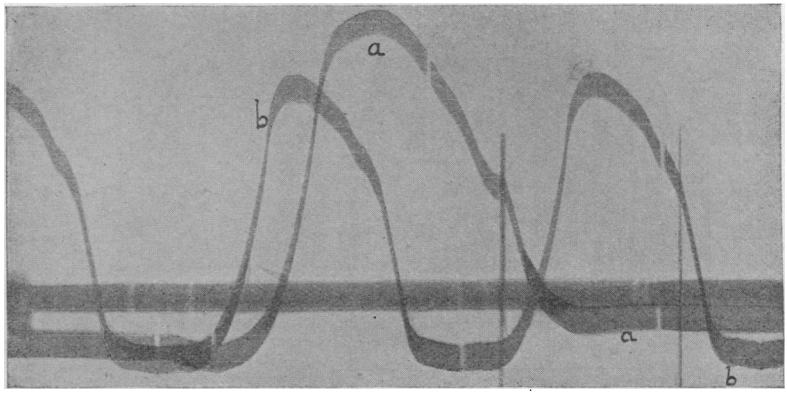

Fig. 23. × ⅔. Pressure curve from left ventricle. Read from right to left.
Dog 8·5 kilos; heart 66 gms.
88 mm. ventricular manometer = 200 mm. Hg.

		T.	B.P.	V.P.	O.P.
a.	Left vagus stimulated	35° C.	?	220	?
b.	Normal tracing	35	90	60	100

ventricle, though it must be remembered that the diastolic supply of blood to the left ventricle depends on the contraction of the right ventricle and is not unlimited, as is the case on the right side of the heart which is connected directly with the inexhaustible venous reservoir. Such a rise of diastolic pressure is given in the curves in Fig. 23, where the pressure in the left ventricle is taken first with stimulation of the left vagus, which gave rise to extreme slowing, and secondly when the heart is beating freely. The pressure in the inferior vena cava rose from 60 to 220 mm. H_2O, and it will be seen that when the ventricle starts

to give its single beat in curve *a*, the pressure in the left ventricle is 7 mm. above the base line, corresponding to a pressure of about 16 mm. Hg. After the beat the pressure sinks to the zero line and then gradually rises again. Since, as we know, the volume of the heart must have been considerably greater under vagus stimulation than when beating at its normal rhythm, we might expect the rise of pressure in the ventricles to be more rapid under vagus stimulation than with the normal beat. As a matter of fact the reverse is the case. The rise of pressure is somewhat slower and the rise of the curve after the opening of the aortic valves is no more rapid than in the normal tracing, although the maximum height to which the pressure rises is considerably greater.

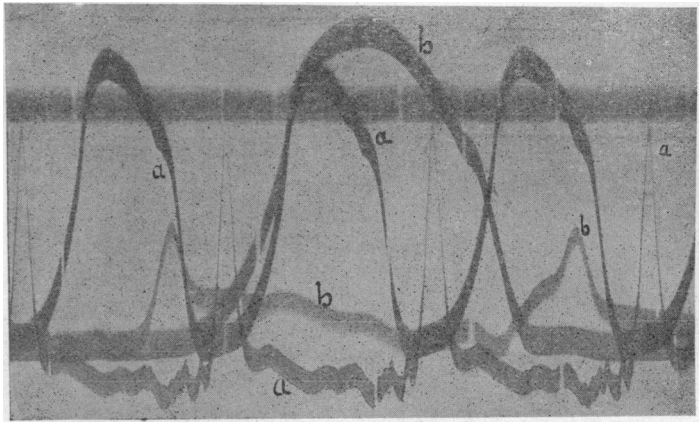

Fig. 24. $\times \frac{3}{4}$. Simultaneous pressure tracings taken in the left ventricle and in the left auricle. Dog 10·5 kilos; heart 84 gms.
85 mm. ventricular manometer = 200 mm. Hg.
42 mm. auricular manometer 200 mm. H_2O.

	T.	B.P.	V.P.	O.P.
a. Normal tracing	35° C.	100	16	139
b. Left vagus stimulated	35	100	50—60	?

The prolongation of the duration of contraction seems to indicate that length of fibre is still effective in increasing the amount of energy set free during the contraction, and the duration of the excitatory state, but the slow rate of rise of the pressure shows that the effect of the vagus is not confined to altering the rhythm, as determined by the pace maker, but is a direct one on the processes of the ventricular muscle itself. The process of relaxation is seen to occur at the same rate as in the normal contraction.

In Fig. 24 we have a similar tracing, in which the pressure in the left auricles is also measured. Here the pressure in the left ventricle comes down to the base line and only rises slightly above it as the effect of auricular systole. In this case the pressure in the inferior vena cava only rose from 16 to 50 mm. H_2O during stimulation of the vagus. The process of relaxation is somewhat slower in the vagus beat than in the normal beat. The vagus would thus seem here to slow all the processes occurring in the ventricular muscle though not to abolish the fundamental relation between length of muscle fibre and amount of energy evoked during contraction.

In the experiment from which Fig. 25 was taken the effect of the vagus was to produce a more moderate slowing of the heart, namely,

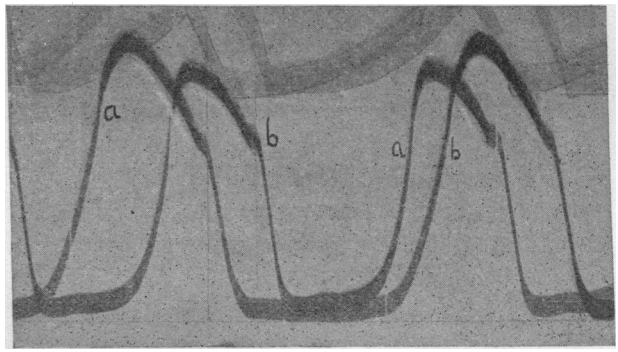

Fig. 25. $\times \frac{2}{3}$. **Simultaneous pressure tracings in left ventricle and in subclavian artery. Read from right to left. (Note. The mirror on the subclavian manometer was obscured, so that the tracings from this are hazy.)**

Dog 8·5 kilos; heart 85 gms.

70 mm. ventricular manometer = 200 mm. Hg.

		T.	B.P.	V.P.	O.P.	Rate	Max. press.
a.	Left vagus stim.	36° C.	114	50—140	?	16·5	150
b.	Normal tracing	36	114	28	189	24	134

Rise of pressure of 90 mm. Hg. in *a* took ·046″ and in *b* ·040″.

from 24 to 16·5 in ten seconds. The pressure in the veins entering the right side of the heart rose from 28 to a height varying between 50 and 140 mm. H_2O. In this experiment we were recording also the pressure in the aorta, and the larger rise of pressure accompanying the vagus beats was evidence of the greater outflow from the left ventricle at each beat and therefore of the greater filling of these cavities. In spite of this greater filling it will be seen that the diastolic pressure under vagus stimulation falls to a lower level than during the normal beat. The rate

of rise of pressure was only slightly slowed, but the rate of fall of pressure was somewhat more definitely slowed. The effect of the vagus on the ventricle is therefore to prolong diastole without a corresponding rise in diastolic pressure, so that the inflow of blood into the ventricles is facilitated. It slows the rate of rise of pressure but still allows the heart to respond to its filling by increased duration of contraction, and thus produces a contraction which seems more adapted to driving the mass of viscous blood into the aorta against resistance than the short sharp beat of the unbridled heart of the heart lung preparation.

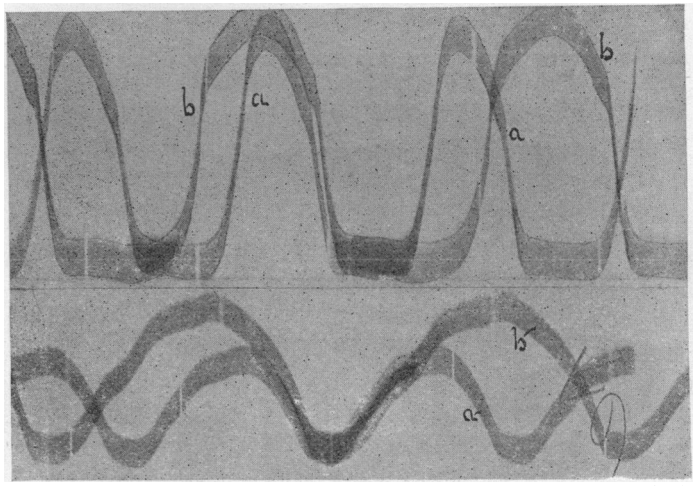

Fig. 26. Simultaneous records of pressure in left ventricle and volume of both ventricles. Read from right to left.

Dog 6·5 kilos; heart 70 gms.

	T.	B.P.	V.P.	O.P.	Rate	Max. press. mm. Hg.
a.	36·8° C.	100	104	153	25·5	150
b.	31	100	114	153	16·5	160

A study of the pressure conditions ruling in the heart during the different phases of the heart's cycle tend therefore to support the views which are commonly held as to the sparing influence of the vagus on the heart.

The influence of temperature. It has been shown (Markwalder and Starling (17)) that alteration of the rate of the heart by changes of temperature, keeping the venous inflow constant, causes no alteration in the total output of the heart, though the falling rate induced by diminution of temperature is attended by a rise of venous pressure as measured in

the inferior vena cava. Thus in one experiment with a rate of heart beat of 156 per minute at 39° C., the outflow was 650 c.c. and the venous pressure was 38 mm. H_2O; with a rate of 72 and a temperature of 28°·2 C. the output was 652 c.c. per minute and the venous pressure 110 mm. H_2O. On inspection, the heart, as it cools, though filling more at each diastole, seems to empty itself as effectively, or rather more so, at the lower as at the higher temperature. The influence of a moderate fall of temperature, namely from about 37° to 31° C., and from 34°·3 to 30° C. is shown in Figs. 26 and 27. In Fig. 26 the pressure in the left ventricle was taken simultaneously with the record of the volume of the two ventricles. The rate of beat dropped from 25·5 in ten seconds to 16·5 in ten seconds. Both records gave evidence of an improvement in the physiological state of the heart muscle, which we have taken to be synonymous with tone. These cardiometer curves show that whereas the diastolic volume was equal in the two cases, the systolic volume is diminished proportionately to the diminution in the number of heart beats, so that the heart empties itself more completely at each contraction. With this moderate difference of rate there was only a slight increase in the venous pressure in the vessels entering the right side of the heart, namely from 104 to 114 mm. H_2O. The output remains steady at 153 c.c. per ten seconds. The diastolic pressure in the left ventricle is seen to be identical at both rates. The rate of rise as well as the rate of fall of pressure is slightly greater in the cooled than in the warm heart. The main difference between the two conditions is the prolongation of the excitatory state and the prolongation of the diastolic state. In consequence of this prolongation of the process of contraction the heart is able to send out the increased amount of blood which has entered it during diastole with hardly any increase in its maximum pressure.

A similar story is told by the curves given in Fig. 27, taken from an experiment in which the aortic pressure was registered simultaneously with the pressure in the left ventricle. Here we have diastolic pressure identical at the two temperatures, the rate of rise and the rate of fall of pressure also practically identical, the only change being in the duration of the contracted state and of the relaxed state. If the cooling of the heart is carried further to 28° or even 26° C., this slowing of the processes operative in the heart muscle increases to such a degree that both rise and fall of the pressure curve are markedly slowed. Within the limits employed in the two experiments recorded, it would seem that the effect of lowering the temperature is purely beneficial in economising

the energies of the heart muscle. The same conclusion may be drawn from Evans' observations on the efficiency of the heart muscle and the relation of its total metabolism to the mechanical work which it performs at various temperatures. It must be remembered however that the mammalian heart is not merely able to carry out a constant amount of work but is always ready to respond in moments of stress or danger to an enormous increase in the demands made upon it. We have already seen (Patterson and Starling (5)) that the maximum amount of blood which can be put out by the heart is a function of its rate. Moreover a cooled heart cannot respond to the action of adrenalin in the manner that a heart will at the normal body temperature. In the intact

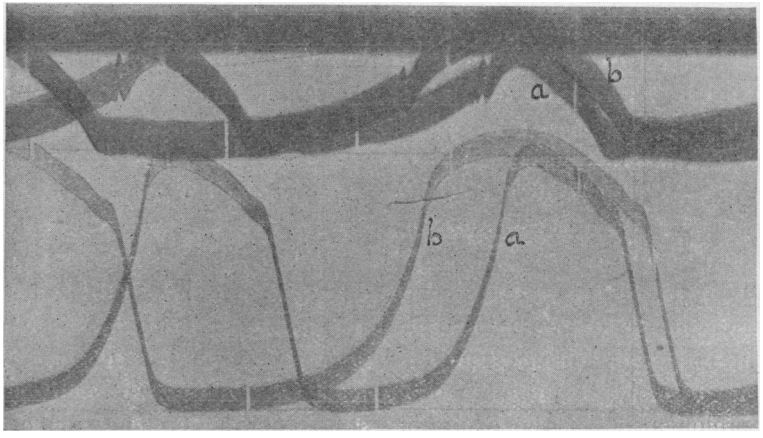

Fig. 27. Simultaneous records of pressure in left ventricle and in subclavian artery, to show influence of cooling. (Owing to parallax the arterial record is shifted about 1·5 mm. to the left of the ventricular record.) Read from right to left.

	T.	B.P.	V.P.	O.P.	Rate	Max. press. mm. Hg.
a.	34·3° C.	120	20	109	21	120
b.	30	120	26	109	14	132

animal therefore, the sparing effect, which in the heart lung preparation we can produce by cooling the organ, is produced by the constant tonic influence exercised by the vagus centre.

Finally it should be mentioned that the cooled heart differs in no respect from the warm heart in its reaction to changes in venous inflow or changes in arterial pressure. Every increase in either of these factors gives an increased diastolic volume of the heart and increased mechanical response at contraction. With a moderate increase in inflow

or arterial resistance, the diastolic pressure in the ventricles may be unaltered. If the increase in size during diastole becomes excessive, such an increase can only be produced by an active stretching of the ventricular wall, and we then find that the diastolic pressure, and therefore the initial tension on the muscle fibres at the commencement of contraction, is increased at the same time as the cardiac volume. In every case therefore the reaction of the heart muscle seems to be determined by the length of its constituent fibres at the moment of activity. Changes in initial tension are merely incidental to changes in length.

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