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THE RELATION BETWEEN AMPLITUDE OF CONTRACTION AND RATE OF RHYTHM IN THE MAMMALIAN VENTRICLE. (INCLUDING INTERPRETATION OF THE APPARENT INDIRECT ACTION OF THE VAGUS ON AMPLITUDE OF VENTRICULAR CONTRACTION.)[1]

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Part I.

The apparent indirect action of the vagus on the amplitude of ventricular contraction.

Introductory.

The question whether the ventricle of the mammalian heart receives inhibitory fibres from the vagus nerve has produced much conflicting evidence. It is a well-established fact, that, after complete dissociation between auricle and ventricle has been produced by crushing or cutting of the A.-V. bundle [Krehl and Romberg, 1892; Hering, 1905; Erlanger, 1909], stimulation of the vagus nerve has no effect on the rhythm of the ventricle or on the strength of its contractions. Injection of vago-mimetic drugs, however, still produces, in the rabbit, a slight slowing, suggesting a weak negative chronotropic action of the vagus on the ventricle itself [Krehl and Romberg, 1892; Cullis and Tribe, 1913], though the distribution of the fibres concerned is unknown.

With regard to the inotropic action of the vagus on the ventricle the evidence is conflicting. Cullis and Tribe showed that, in the perfused intact heart *in situ*, stimulation of the vagus nerve or injection of vago-mimetic drugs slowed the heart rhythm, and at the same time decreased the strength of contraction of both auricle and ventricle. When the bundle was cut the effects on the ventricle of stimulating the nerve and of injection of drugs were abolished, except for the slight slowing

[1] This work was carried out during the tenure of the Gilchrist Studentship of Newnham College, and the Michael Foster Studentship of the University of Cambridge.

produced by relatively large doses. More recent work by Drury [1923] and Rothberger and Scherf [1930] on the whole animal (dog) has shown that, if the ventricular rate is maintained constant by rhythmic shocks throughout, vagus stimulation does not influence the strength of the ventricular contractions. Cullis and Tribe, finding that the vagus or vago-mimetic drugs only affected the strength of contraction of the ventricle when the latter was connected to the auricle by the A.-V. bundle, concluded that "normally, the vagus exerts its effect on the ventricle, only indirectly, through its action on the auricular rhythm." The present experiments were carried out in an attempt to determine what the nature of this "indirect" action might be.

Methods.

The experiments were performed, with one exception, on the hearts of rabbits. In the one exception a cat's heart was used. The animals were killed by a blow on the head and the hearts, after removal from the body, were perfused with a modified Ringer's solution by means of a cannula tied into the aorta. The cannula carried a thermometer, and the solution entered by a side tube. The perfusion pressure, which was about 1 metre of saline, was maintained from a Mariotte's bottle, suspended at a suitable height. From the Mariotte's bottle the solution passed to a glass tower where oxygen was continuously bubbled through it, and thence to a glass coil immersed in a water bath. The coil was connected by rubber tubing to the side tube of the cannula. The temperature in the water bath was regulated so that the thermometer in the cannula registered 36–38° C.

The composition of the Ringer's solution was as follows: NaCl 0·85 p.c., Na_2HPO_4 0·06 p.c., KCl 0·042 p.c., dextrose 0·1 p.c., $CaCl_2$ 0·024 p.c. The *p*H was adjusted to 7·5 by the addition of HCl, comparison being made with a standard buffer solution, using phenol red as indicator. The water used in making up the solution was distilled in a porcelain still. Great difficulty was experienced initially as, although the auricles beat quite vigorously, the ventricles contracted only very feebly or not at all. This was found to be due to the presence in the distilled water of a high concentration of CO_2. If the water, after condensation, was thoroughly boiled and allowed to cool before use the hearts beat very well. It was found later that this precaution of using boiled water for the solution was only necessary at the beginning of an experiment. When the heart was once beating vigorously, solution containing CO_2 could be used without having any deleterious effect. The reason for this effect of CO_2

is not understood, but it would seem to be specific and not due to its acid properties, as the reaction of the solution was always controlled.

The drug used in most of the experiments was arecoline, though acetylcholine was occasionally used. The latter is not very satisfactory in these experiments, however, as its effect is too transient. The arecoline was obtained as the crystalline bromide and made up in a 0·1 p.c. solution. This was diluted with Ringer's solution to 0·001 p.c. for each experiment. The usual dose was 0·1 c.c. to 0·5 c.c. of this diluted solution, injected with a syringe into the rubber tubing leading to the cannula.

The contractions of the left auricle and left ventricle were recorded by means of light straw levers carrying Bayliss writing points. The levers were held in brass bearings, and the vibration frequency of each was increased by a small rubber band which resisted the raising of the lever. The heart was suspended vertically from the cannula, and the apex of the left ventricle was fixed by a ligature to a metal rod. One lever was attached to a point near the base of the ventricle by a silk thread sewn through the epicardium, the other to the left auricular wall in the same way. By this method of attachment the use of pulleys for the ventricular record is avoided, and the risk of distortion of the record by movements (swinging, etc.) of the whole heart is greatly diminished. It has the further advantage, of special importance in these experiments, that the shortening of the ventricular muscle is recorded, uncomplicated by the pull of the auricular contraction.

In order to avoid distension of the left ventricle by perfusion fluid leaking through the aortic valves, a glass tube was passed into the cavity of the ventricle through a small slit made in its apex, and tied in position. Any fluid tending to collect in the ventricle was thus drained away.

Results.

Effects of vago-mimetic drugs. The object of the first experiments was to repeat the experiment of Cullis and Tribe. The effects of varying doses of arecoline on the heart with A.-V. bundle intact were first recorded. The bundle was then cut and the procedure repeated. Fig. 1 gives a typical example of the records obtained.

It will be noticed that in record *a*, taken before cutting the bundle, the injection of 0·001 mg. of arecoline is followed by a slowing of the heart rhythm, accompanied by a diminution in the amplitude of the auricular and the ventricular contractions. A curious point is the rise of the base line, which is particularly noticeable in the ventricular tracing. The reason for this rise is not clearly understood, but in any case it is

unconnected with the diminution in the amplitude of the contractions, as it occurs after the bundle is cut, when no such diminution is seen.

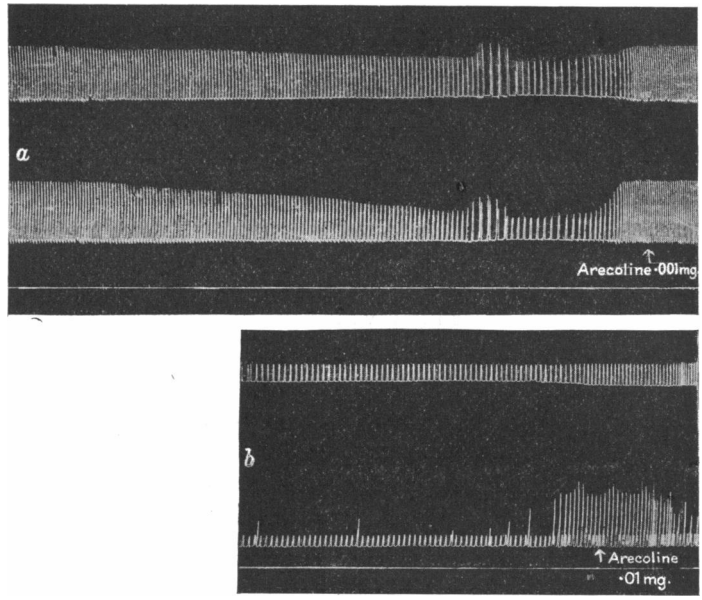

Fig. 1. *Exp.* 3. xii. 29. Read from right to left. In both *a* and *b* the upper tracing is the ventricular record, the lower that of auricle followed by ventricle. *a*. Intact heart. *b*. After cutting the bundle.

Further, when another method of registration, which will be described later, is used, this rise of the base line does not occur, while the diminution in the size of the ventricular contractions is still observed. It will be noticed that premature contractions are followed by greatly enlarged ventricular beats. The significance of this will be considered later.

Record *b* shows the effect of arecoline after section of the A.-V. bundle. The dose, 0·01 mg., is sufficient to inhibit the auricular contractions almost completely, while the ventricular rate is slightly diminished. A close scrutiny reveals a very slight decrease in the height of the ventricular record, but this decrease is very much smaller than that observed before cutting the A.-V. bundle. The results just described, which are typical of many obtained, are identical with those of Cullis and Tribe, except for one small difference. Cullis and Tribe never obtained a diminution in amplitude of the ventricular contractions when vagomimetic drugs were injected after section of the A.-V. bundle. In the

present experiments this diminution was only obtained with large doses of arecoline. Normal doses had no such effect. Cullis and Tribe's conclusion still holds, therefore, for normal doses, while for large doses we may qualify it by adding that arecoline affects the size of the ventricular contractions greatly when the A.-V. bundle is intact, and slightly when the ventricle is no longer in connection with the auricle. With regard to the nature of this "indirect" action, it might be supposed that the diminution in the size of the ventricular contractions was due to a change in the impulse passing by the A.-V. bundle from auricle to ventricle. If that were the case the phenomenon would present a clear exception to the "All or None" law. Such a supposition, however, is unnecessary, as a much simpler explanation is at hand. Close inspection of the records of the present series of experiments shows that the ventricular contractions only decreased in size after injection of arecoline when the heart rhythm was slowed, which suggested that the change of rate is in some way responsible for the change in the size of the contractions. This is supported by the fact that the idio-ventricular rhythm which obtains after section of the A.-V. bundle is only slightly influenced by arecoline, and that in the ventricle isolated in this manner the size of the beat remained unchanged by any dose of arecoline which did not affect the rate. It is evident that if the diminution in the amplitude of the ventricular contractions, which follows injection of arecoline when the bundle is intact, is simply due to the slowing of the rhythm, then a similar diminution should occur when the rhythm is slowed by any other means.

Effects of cooling the S.-A. *node.* A series of experiments was, therefore, performed in which the heart rate was decreased by cooling of the S.A. node. The preparation was set up as before, and the cooling was effected by means of a piece of narrow lead pipe through which iced water flowed. The pipe was bent sharply at one point, and the outer surface of the bend was brought into contact with the region of the S.-A. node, thus producing localized cooling. Fig. 2 *a* shows a typical example of the result of slowing the rhythm by this method; *b* and *c* show the effect of two different doses of arecoline for comparison. In *c* a 2–1 block was produced by the drug, the ventricular rhythm thus slowing to about the same degree as that produced by cooling in *a*, and it will be seen that the diminution in the size of the ventricular contractions is practically the same in the two cases.

Effects of drugs at constant rhythms. Such results give very strong support to the hypothesis that the slowing of the rhythm is the deter-

mining factor in the action of arecoline on the size of the ventricular contractions in the intact heart. It now remained to be determined

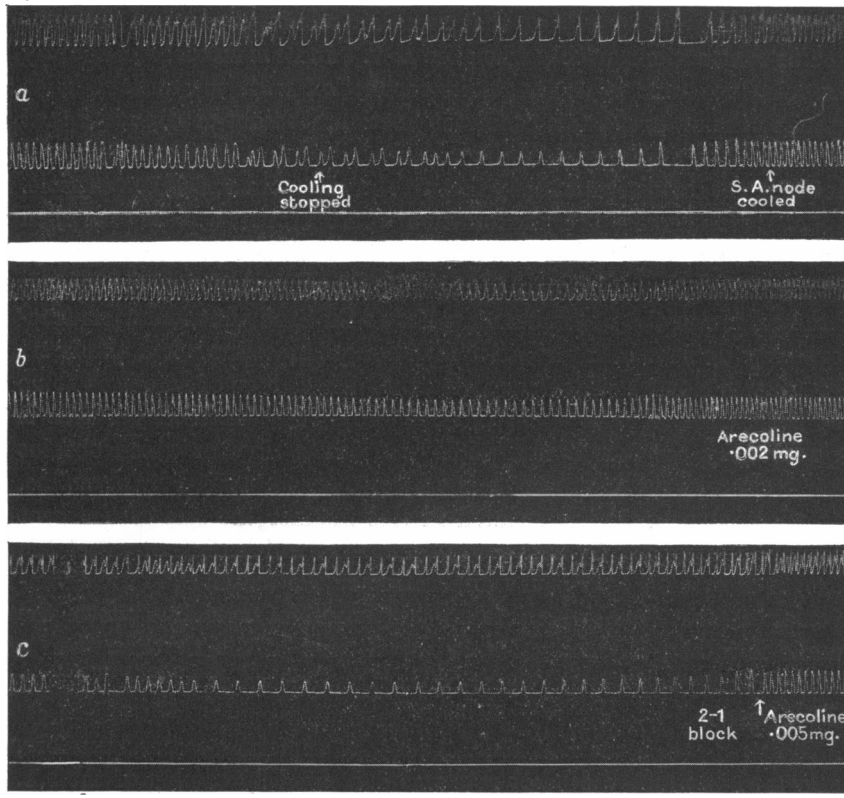

Fig. 2. *Exp.* 13. xii. 29. Read from right to left. In *a*, *b* and *c* upper tracing represents auricular followed by ventricular contractions. Lower tracing ventricular contractions only. *a*. S.-A. node cooled between points indicated by arrows. *b*. 0·002 mg. arecoline injected shortly before beginning of record. *c*. 0·005 mg. arecoline injected shortly before beginning of record. Arrow indicates beginning of 2–1 block.

whether the size of ventricular contractions would be unaffected by arecoline when the heart rate was maintained artificially constant. The heart was, therefore, stimulated rhythmically by electrodes placed on the right auricle. The rhythmic shocks were produced by means of a rotary contact breaker placed in the primary circuit of an induction coil. Fig. 3 shows the results of such an experiment, and includes a record of slowing by cooling for comparison.

Fig. 3 *a* shows the usual result of cooling the S.-A. node: *b* shows the

effect of injecting a small dose of arecoline while the heart was being driven at constant rate. The dose 0·002 mg. is one which, with spontaneous

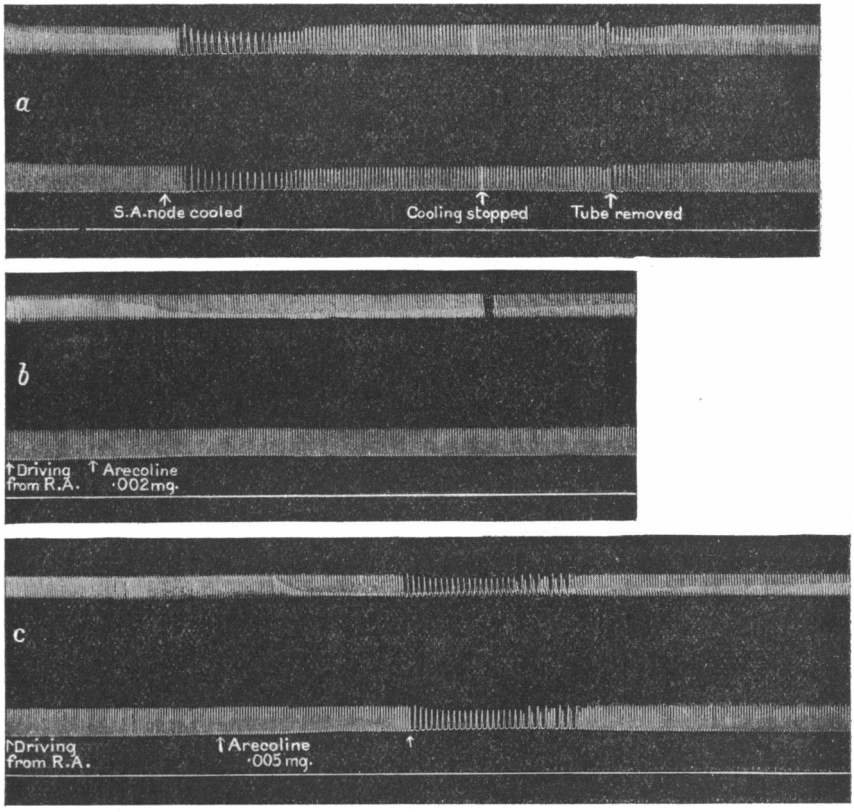

Fig. 3. *Exp.* 11. ii. 30. Read from left to right. In *a*, *b* and *c*. Upper tracing represents auricular followed by ventricular contractions. Auricular contractions are smaller than ventricular, but their height can be seen as the upper edge of the denser portion of the tracing. Lower tracing is that of ventricular contractions only. *a*. Cooling of S.-A. node. Auricular tracing disappears owing to substitution of nodal for sinus rhythm. *b*. Heart driven at constant rate. Injection of 0·002 mg. arecoline at arrow. *c*. Heart driven at constant rate. Injection of 0·005 mg. arecoline at first arrow. Second arrow indicates appearance of 2–1 block.

rhythm, would produce a marked slowing, with weakening of the ventricular contraction. In this case the strength of contraction is unaffected. Record *c* provides especially clear evidence on the point under discussion. The dose was a large one, 0·005 mg., which almost abolished the auricular contractions at one point. Later, when the auricular beats were re-

covering, the effect on the A.-V. conducting system became evident, and a 2–1 block was produced. The amplitude of the ventricular contractions, which till then had remained unchanged, immediately diminished in size, and this reduction of amplitude persisted as long as the 2–1 block was maintained. The period of block was followed by a short phase in which an occasional beat was dropped. After this the block disappeared completely, a ventricular contraction following each auricular one, and with this resumption of the original rhythm by the ventricle, the contractions returned to their normal size.

Effects of varying an artificial rhythm. It seems clear from these observations that arecoline is unable to exert its negative inotropic effect on the ventricle when the bundle is intact, unless, at the same time, it is able to diminish the heart rate. It might still be argued, however, that the auricle affects the ventricle in some way other than by change of rhythm when arecoline is injected, though this is unlikely in view of the last experiments described (Fig. 3). In order to eliminate this possibility, a few experiments were performed, in which the bundle was cut and the ventricle driven at varying speeds without the administration of any drug. Fig. 4, which is an example of the results obtained, is a record taken from a cat's heart. The heart showed a spontaneous block and, as the left ventricle was beating feebly, the record was taken from the right ventricle, which contracted vigorously and responded well to artificial stimulation. The rotary contact breaker mentioned above was used, and the rate of stimulation was varied by changing the resistance in series with the motor driving the contact breaker.

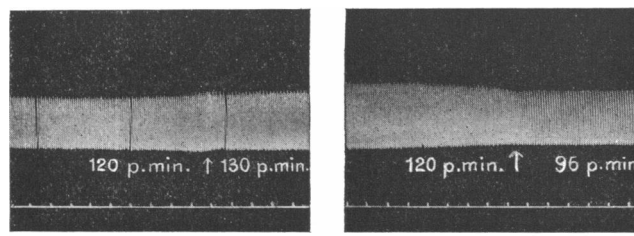

Fig. 4. *Exp.* 23. i. 30. Read from right to left. Ventricle of cat driven at various rates. *a*. Acceleration from 96 to 120 per min. *b*. Retardation from 130 to 120 per min.

Fig. 4 *a* shows the result of changing the rate of stimulation from 96 to 120 per min., namely, a definite increase in the size of the contractions. The change is gradual, as the motor took a little time to attain

the new speed. Fig. 4 *b* shows the change in the reverse direction, from 130 to 120 per min., the result being a diminution in the size of the contractions. It will be noticed that the size of the contractions at 130 per min. in record *b* is smaller than that at 120 per min. in record *a*. This is probably a fatigue effect, since, when the rate was increased from 120 to 130 per min., there was an increase in the size of the contractions at first, but this gave way to a gradual diminution. It seems probable that the heart could not maintain such a vigorous contraction at this high rate when depending only on the oxygen dissolved in the Ringer's solution. When the stimulation rate was reduced again to 96 per min. the contractions gradually regained their original size corresponding to this rate.

It is possible, therefore, to vary the size of the ventricular contraction by changing the rhythm, when this is being produced artificially, in exactly the same way as when the ventricle is receiving its stimuli from the auricle by way of the A.-V. bundle. Experiments with perfused ventricular strips, to be described later, confirm this.

A point which is important for later discussion must be mentioned here. It is evident in all curves in which there is an abrupt slowing of the heart-rate, that the beat following the first prolonged pause is enlarged, and that this is then followed by a descending staircase of beats, until the small size of beat, typical of the slower rate, is reached. The change from slow to fast rate is usually more gradual, but where an abrupt change occurs, as in Fig. 2 *c*, where a 2–1 block gives way to the normal A.-V. sequence, it is evident that the beat following the first short pause is diminished, and is followed by an ascending staircase of beats.

Demonstration of effect in tension records. From the results of the experiments so far described it must be concluded that, in the isolated perfused rabbit's heart in which the contractions are recorded by means of levers, the so-called indirect effect of vago-mimetic drugs on the size of the ventricular contractions is due to the slowing of the rhythm produced by the action of the drug on the pacemaker of the heart. Experiments with levers, however, are always open to criticism on the ground that distortion of the records may occur, owing to the natural vibration frequency of the levers being too low. In the case of a rapidly beating rabbit's heart it is essential that the recording system have a high natural frequency, and it might well be argued that, in the experiments above described, the excursions of the lever give a true record of the size of the contractions only when the rate is slow, the larger excursions at higher rates of beating being due to overthrow of the lever.

In order to eliminate such an objection the experiments were repeated, using a high-frequency system for recording the tension changes in the ventricular muscle.

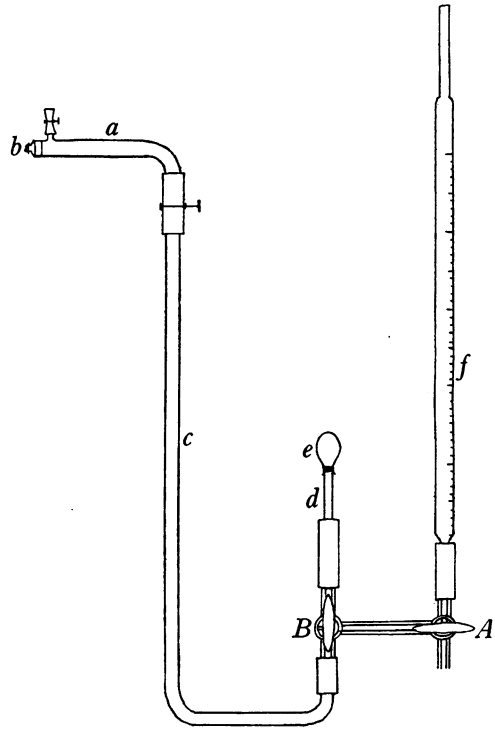

Fig. 5. Diagram of apparatus for recording intraventricular pressure. *a*, brass tube carrying membrane; *b*, rubber membrane with mirror attached radially; *c*, connecting tube of lead piping; *d*, brass tube to which balloon *e* is attached; *f*, 5 c.c. pipette containing liquid paraffin for filling balloon; *A* and *B*, 3-way (T) taps.

Fig. 5 is a diagrammatic representation of the apparatus used. It consisted essentially of a balloon, filled with fluid which was introduced into the cavity of the left ventricle, and connected by tubes filled with fluid to a tightly stretched rubber membrane. A mirror attached to the membrane reflected a beam of light into a moving paper camera. Difficulty was experienced at first in the choice of a suitable balloon. Small thin rubber balloons were tried but, unless these were blown to extreme tightness, the contraction of the ventricle caused the top of the balloon to bulge into the auricular cavity. In the process of this bulging a large amount of distortion of the record could occur. A tightly stretched rubber balloon has two disadvantages, the first that it bursts very easily,

and the second that the initial pressure is so high that the ordinary glass taps cannot stand it, and leakages occur. It was decided, therefore, to use an inextensible balloon, and for this purpose the gall bladder of a small cat served very well. The bladder was removed from the animal and washed out with saline. It was then bound firmly to a small piece of brass tube, and stored in saline, covered with a layer of toluene to keep it sterile. When in use the bladder was filled with liquid paraffin. Saline is unsuitable as it diffuses through the walls of the bladder when this is subjected to pressure. The perfusion apparatus was the same as that used in the experiments already described. The bladder was introduced through a small slit in the apex of the left ventricle, this being done as follows. The bladder and brass tube were filled with paraffin by means of a fine glass pipette, care being taken to exclude all air bubbles. The 5 c.c. pipette (Fig. 5, *f*) was also filled with paraffin and placed in position. The taps *A* and *B* were then turned so that the paraffin flowed from the pipette and filled the tubes and the rubber connection for the brass tube carrying the bladder. The brass tube was then inserted into the rubber connection, care again being taken to avoid the entrance of air bubbles. The paraffin was then sucked back into the pipette, and the balloon, which was quite flexible, was thus inverted into the brass tube. The end of the tube could now easily be inserted into the ventricle, and was tied firmly in place. Finally, by blowing from the end of the pipette, the bladder was everted into the ventricular cavity, and filled to any desired extent. It was then connected with the membrane by turning the tap *B*.

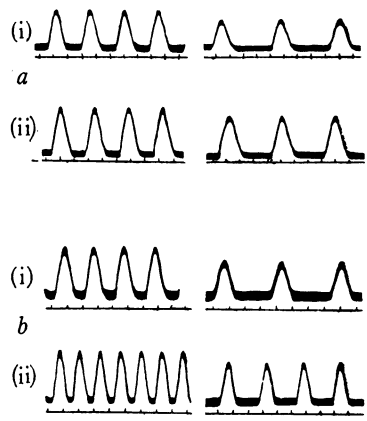

Fig. 6. Read from left to right. Sample curves taken from two experiments. *a*. From *Exp.* 3. v. 30. *b*. From *Exp.* 6. v. 30. *a* (i). On left, heart beating at normal rhythm. On right, during cooling of S.-A. node. *a* (ii). On left, heart beating at normal rhythm. On right, after injection of 0·001 mg. arecoline. *b* (i). On left, heart beating at normal rhythm. On right, after injection of 0·002 mg. arecoline. *b* (ii). On left, heart driven at constant rhythm. On right, after injection of 0·003 mg. arecoline. A 2–1 block has appeared and ventricular rate is halved.

The observations repeated with this method of recording were: cooling of the S.-A. node, simple injection of arecoline, and injection of arecoline while the heart was being driven at constant rate. Fig. 6 shows a series of records, taken from two experiments, illustrating the three methods of slowing.

It is evident from these records that the decreased size of ventricular contraction produced by slowing of the heart rhythm is not an apparent one, due to defects in the recording apparatus, but a real one, as it still persists in records taken with an apparatus in which all possibility of overthrow is eliminated. The rise of the base line during the action of arecoline, so evident in the records taken with the levers, is entirely absent in these records, and may be taken to be an artefact peculiar to the method of registration.

Conclusions from Part I.

The conclusions to be drawn from the experiments described in Part I of this paper may be summarized as follows:

The results of other workers, which show that vago-mimetic drugs such as arecoline, in small doses, only influence the size of the ventricular contraction when the A.-V. bundle is intact, have been confirmed. It has further been shown that this decrease in amplitude is a real one, and is not produced by imperfect methods of registration.

That the effect is only observed when the ventricle is connected with the auricle is due to the fact that, in this case, the heart rhythm is greatly slowed by the drugs in question, whereas the idio-ventricular rhythm, which sets in after bundle section, is only affected to a very small degree.

The theory that it is the slowing of the rhythm which determines the diminished size of the ventricular contractions is supported by the facts that the drug does not affect the ventricle when the heart rate is kept constant by rhythmic auricular stimulation, and that when the dose is large enough to produce heart block, the slowing of the ventricular rhythm which results produces a diminution in the size of the contractions. Further, a slowing of the rhythm produced by cooling of the S.-A. node produces effects on the ventricle identical with those observed after injection of arecoline.

That the inotropic effect is truly secondary to the chronotropic effect, and does not depend on some obscure auricular influence, is shown by the fact that it can be produced in the isolated ventricle when this is stimulated artificially and the rate of stimulation is varied.

PART II.

THE RELATION BETWEEN AMPLITUDE OF CONTRACTION AND RATE OF RHYTHM.

The relation between the rate of beating and size of contraction which has been described in Part I is not the generally accepted one. For the mammalian heart, at least, it is usually stated that the contractions are more vigorous at slow rates than at fast ones, the customary explanation being that at the slow rates the muscle has more time for recovery between beats. The fact that the relation so stated is the exact opposite of that described in Part I of this paper must be due to differences in experimental method. There appear to be two methods of experiment in which increased amplitude with slowing of the rhythm would be observed. The first is that in which the whole animal is employed, and the heart is left *in situ*. Slowing of the rhythm, produced, for example, by cooling of the S.-A. node, will allow increased time for filling of the ventricles during diastole with consequent greater length of ventricular fibres at the beginning of systole. The second method uses the isolated perfused heart, in which slowing of the rhythm is produced by cooling of the perfusion fluid. In this way, not only is the pacemaker cooled, thus slowing the rhythm, but the ventricular muscle is also cooled. Cooling of the heart muscle is known to produce larger contractions, even when the heart rate is kept constant.

To account for the smaller contractions at slower rates, observed in the present series of experiments, two possibilities offer themselves. A simple and easily tested hypothesis is based on Wiggers' theory of fractionate contractions. It is quite conceivable that, at slow rates, the impulse would travel more slowly, so that fewer muscular fractions would be in action at any one moment, and the records would show curves which were smaller in height, but proportionately greater in duration, than those found at high rates. The other possibility is that the phenomenon is a property of the cardiac muscle itself.

(1) The former hypothesis was tested first. If it were correct, then the duration of a contraction should always show a distinct increase at the slower rates. The measurements were made on the optical records which had been taken on fast moving paper (see Fig. 6). In many cases the decrease of amplitudes with decrease of rate was accompanied by no increase in duration. In a few cases the duration showed a slight increase under these conditions; but this was never great enough to

account for decrease of amplitude by slowing of transmission, and in many cases, notably those in which arecoline was used, the slight increase of duration persisted after return to the original rhythm and amplitude. It cannot, therefore, be connected with the slowing of rhythm and loss of amplitude, and is probably a fatigue effect due to the filling of the ventricular cavity with the tense bladder.

An unlikely possibility still remained, namely, that at the slower rates the impulse might travel by a different path, and so alter the shape and size of the ventricular mechanogram. Rothberger and Scherf [1930] showed that a change in the point of application of artificial stimuli to the ventricle in the whole animal, changed both the electrocardiogram and the intra-ventricular pressure curve. To test this possibility, electrical records were taken[1]. The hearts were set up for perfusion in the usual way, and simultaneous records were taken of the electrocardiogram and the tension developed by the ventricular muscle, the latter by the balloon method already described. Slowing was produced by cooling of the S.-A. node, and by injection of acetylcholine. Arecoline is unsuitable for these observations, as it produces permanent changes in the form of the electrocardiogram, especially in the T-wave, which persist after the effect on the mechanogram has disappeared. Measurement of the records showed that, when slowing of the heart rate was produced by cooling the S.-A. node or injecting acetylcholine, with a corresponding diminution of amplitude, in many cases the electrocardiogram was unchanged. In some there was a slight alteration in the T-wave, but in no case was there any change in the initial *QRS* complex, which is determined by the spread of the excitatory process. These experiments rule out the possibility that the smaller contractions at slow rates are due to changes in the rate or the path of propagation of the impulse.

(2) It seemed probable, accordingly, that the phenomenon was due to a property of the cardiac muscle itself, and, to test this, experiments were carried out on perfused ventricular strips.

Rabbits' hearts were used as before. Strips of rabbits' ventricle have the advantage that they do not beat spontaneously, so that no difficulty was experienced in imposing artificial rhythms on them. Fig. 7 gives a diagrammatic representation of the apparatus used. The Ringer's solution was of the same composition as that used in the experiments on the whole heart, and the arrangements for oxygenating and warming it were the same as before. The cannula, a glass tube bent twice at right angles,

[1] I am much indebted to Dr A. N. Drury for his help in the taking of these records.

was drawn out into a nozzle, sufficiently fine for insertion into one of the coronary arteries through its opening out of the aorta. A silk ligature,

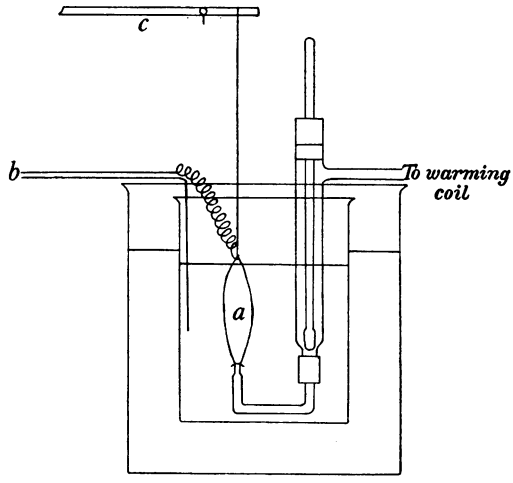

Fig. 7. Apparatus for perfusing isolated ventricular strips. *a*, strip of ventricular muscle; *b*, stimulating electrodes; *c*, recording lever (only part shown).

passed under the coronary artery with a curved needle, served to tie the nozzle of the cannula firmly in position. Strips of right ventricle were tried at first, as it was expected that they would survive better; but it was found that the left ventricle was preferable, probably owing to the fact that the left coronary artery is the larger, and allows a bigger flow of perfusion fluid. In any case, the flow was never large enough to maintain the temperature of the muscle much above room temperature. It was, therefore, necessary to immerse the strip in a bath of the Ringer's solution. This, in turn, was immersed in a beaker of water, warmed to the desired temperature by a micro-burner. The free end of the strip was attached by a silk thread to a lever, similar to those used in the first experiments on whole hearts. The strip was stimulated rhythmically, one of the electrodes dipping in the bath of Ringer's solution, and the other being attached to the upper free end of the strip. The latter electrode was made of fine wire and the lead from it was coiled, so that it was freely movable, and did not impede the movement of the strip. The rhythmic stimuli were produced by means of a rotary contact breaker, similar to that used in previous experiments, but having two rotating arms connected in parallel in the primary circuit of an induction coil. Either arm could thus complete the circuit, and they were so

adjusted that the rhythm of shocks, produced when both were in action, was halved by cutting one out. The initial rate of stimulation was controlled by a variable resistance included in series with the motor driving the contact breaker.

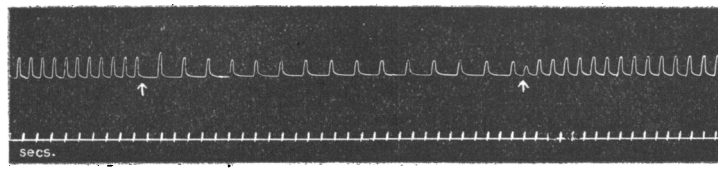

Fig. 8. *Exp.* 11. vi. 30. Read from left to right. Record obtained with perfused strip of left ventricle. Stimulated rhythmically at a rate of 50 per min. At first arrow rate of stimulation was halved. At second arrow it returned to normal.

Fig. 8 gives a typical example of the results obtained. It will be noticed that, when the rate of the stimulating shocks is halved, the beat after the first longer pause is enlarged, and that the following beats gradually decrease in size until a minimum is reached. When the original rhythm is resumed the beat following the first shorter interval is distinctly smaller, but the following beats at the more rapid rhythm gradually increase in size until they are as large as those initially produced at that rate. This series of events agrees in every detail with what is observed in the whole ventricle when the rhythm is slowed.

Another property, common to the whole ventricle and the strips, is observed when the slowing of the rhythm is long enough maintained. When the slowing persists for more than ten or fifteen beats, it is noticed that the size of the beats tends again to increase gradually from the minimum, though it does not attain the amplitude characteristic of the faster rate. This was found to be much more distinct in some whole hearts than in others, and the same was true of the strips. After a secondary increase of this kind the return to the faster rhythm produced beats which were supernormal as compared with those recorded before slowing took place. After a short period the beats returned to the original amplitude.

Discussion.

The phenomenon described could be most simply explained by assuming that the optimal rhythm for rabbit's ventricular muscle, that is, the rhythm at which the contractions are maximal, is a high one; in fact that it is of the same order as the natural sinus rhythm. A slowing of such a rhythm would then cause the contractions to become smaller.

An example of such a high optimal rhythm is described by Mines for the ventricles of certain elasmobranch hearts at temperatures between 20° C. and 25° C. The natural rhythm in this case was sub-optimal, as acceleration by artificial stimulation augmented the contractions. There is a striking difference, however, between the records obtained by Mines and those obtained in the present work on rabbits' hearts. In Mines' experiments the first beat at the higher rhythm is augmented, and is followed by an ascending staircase of beats, until the larger size characteristic of the faster rhythm is reached. When the artificial stimulation is stopped and the rhythm returns to normal the beats diminish abruptly to the smaller size without any intervening staircase. In the case of the mammalian ventricle, as has been already described, the first beat at an accelerated rhythm is always diminished, and is then followed by an ascending staircase of beats until the larger size of contraction is attained. On the other hand, when the rhythm changes from a high to a low one, the first beat at the slow rhythm is augmented and is then followed by a descending staircase until the smaller size of beat characteristic of the slow rhythm is reached. It seems, therefore, that there is some other factor at work in the mammalian ventricle which is the cause of these transition phenomena. The high rate of beating appears to exert a favourable influence on the contractility of the muscle, and to leave some "trace" behind it, which causes the first beat at the slow rhythm to be augmented. The augmented beat occurring after a premature contraction in the perfused heart could be explained in the same way. It is worth noting here that a premature contraction occurring during a phase of slow rhythm with the resultant small beats will cause the beat following it to be augmented to a size of the same order as that of the first beat at the slow rhythm. This is well seen in the ventricular record of Fig. 1 *a*.

The changes in amplitude which occur when the rhythm changes from a slow to a fast one do not fit in with a simple explanation based on an optimal rhythm hypothesis. If we were concerned with a simple case of a high optimal rhythm, the first beat at the higher rhythm should be enlarged, as in Mines' experiment. In fact it is conspicuously diminished, and is followed by an ascending staircase of beats. Here again it seems that the higher rate of beating exerts some favourable influence on the cardiac muscle.

It seems, therefore, that we cannot define these high rhythms as optimal for the rabbit's ventricular muscle in the generally accepted sense of the term. The large amplitudes observed at the high rhythms

appear to depend on a cumulative action of the contractions themselves. Such an action is very similar to that described by Bowditch from the frog's ventricle, and it must be concluded that we are dealing here with a form of Bowditch staircase. (Woodworth [1903] describes a similar beneficial action of rapid rhythms on the perfused ventricular apex of the dog. He ascribes the enlargement of the first contraction at a slowed rhythm to the combined effects of this cumulative action of the contractions and the prolonged pause.)

This explanation is admittedly inconclusive. Until more experimental results are available it is impossible to draw more definite conclusions. It is hoped that further experiments will make a more exact interpretation possible.

So far the relation between rate and size of contraction has only been discussed with regard to the ventricle. It will be observed, however, that in the experiments in which the S.-A. node was cooled the auricular contractions diminished in size when slowing took place. Great stress is not laid on these results, as it is very probable that a certain amount of overthrow occurred in the recording of the auricular contractions. However, a recent paper by H. Loos [1930] supports the idea that the relation does hold for the auricle. He finds that the size of auricular contraction in the rabbit's heart is affected more profoundly by vagus stimulation when the rhythm is allowed to slow, than when the rate is maintained constant by artificial stimulation. Loos' experiments were performed on whole rabbits, but the phenomenon was still observed when the venæ cavæ were clamped, so that it is not determined by factors relating to the filling of the auricle.

Summary.

1. Cullis and Tribe's observation, that vago-mimetic drugs only diminish the amplitude of contraction of the rabbit's ventricle when the A.-V. bundle is intact, is confirmed.

2. This action is shown to depend on the fact that the S.-A. nodal rhythm is slowed by the action of the drug, while the idio-ventricular rhythm which obtains after section of the A.-V. bundle is not affected, similar diminutions of amplitude being observed when the rhythm is slowed by other means.

3. A diminution is also obtained in the amplitude of contraction of perfused ventricular strips, stimulated artificially, when the rate of stimulation is diminished.

4. This relation between the amplitude of contraction and the rhythm is ascribed to a form of Bowditch staircase.

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