Regulation of Ventricular Contraction
Influence of Cardiac Sympathetic and Vagal Nerve Stimulation on Atrial and Ventricular Dynamics

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The vigor with which the ventricle contracts and propels blood through the tissues of the organism is central to the problem of circulatory regulation. It is to be supposed that a clearer understanding of those influences which modify the ventricle’s contraction and a systemization of the observed phenomena will have some integrative value and confer a greater degree of predictability in the analysis of circulatory adaptation to changing states.

The effect of stimulating the cardiac sympathetic and vagus nerves on the performance characteristics of the heart will be the subject of this communication. Preliminary reports of this work have appeared elsewhere.1-4

Methods

Mongrel dogs of both sexes, weighing an average of 18 Kg., were used; they were premedicated with morphine sulfate intramuscularly and given a mixture of chloralose and urethane intravenously.5 Pressures were measured in the right and left atria, pulmonary artery, left ventricle and aorta with Statham strain gages; heart rate was measured either with a Waters or Gilford cardiograph. Total aortic blood flow was metered with the Potter electroturbinometer.6 All values were simultaneously recorded on an 8-channel Sanborn direct writing oscillograph. An initial dose of 75 mg. heparin was injected intravenously followed by 10 mg. each hour thereafter. Intermittent positive pressure breathing was maintained by a Starling pump after thoracotomy and tracheal intubation. An end-expiratory pressure of about 4 cm. H2O was usually maintained by inserting the expiratory line an appropriate depth into a water bottle, so as to prevent the tendency to arterial desaturation when the lungs are allowed to collapse completely during expiration.

A left thoracotomy in the fourth or fifth interspace was then performed. Cannulae and tygon tubing were placed so as to permit the recording of aortic flow7 with a side arm from the aortic tubing supplying the head, either through the brachiocephalic or the common carotid arteries. The brachiocephalic and left subclavian arteries were ligated at their point of origin from the aortic arch. In this manner, aortic flow, i.e., the output of the left ventricle minus coronary flow, was continuously recorded. Care was taken to avoid injury to nerves during the dissection.

In those experiments in which left stellate ganglion stimulation was to be employed, all rami to this ganglion were sectioned and the ganglion placed in a bipolar electrode. Less frequently, a unipolar Kubicek electrode8 was applied to the common ansa subclavia. Vagal stimulation, when used, was applied to the distal cut end of either vagus nerve by means of a bipolar electrode. The impulse duration used in stimulating the stellate, ansa, or vagus was 3 to 10 msec. The voltage and frequency were determined by the particular experimental objectives. A Grass impulse generator was used.

Heart rate was controlled in all the experiments, except where otherwise specified, by bipolar stimulation of either the right or left atrium with a Grass impulse generator. The rate was chosen by preliminary observations with the anticipated experimental intervention, such as stellate stimulation. The atrium was then paced throughout the course of the experiment just above the highest rate thereby induced.

When either right-sided stellactomy, crushing of the sino-atrial node or surgically induced atrioventricular block was required, these procedures were done through a right thoracotomy as the initial step in the preparation; the thoracotomy was then closed. High cervical vagotomy was done in some experiments.

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The term “ventricular function curve” will be indicated by the abbreviation V.F.C. In each instance, this abbreviation will be accompanied by a subscript to indicate whether the curve is the plot of mean left atrial pressure against left ventricular stroke work (V.F.C.L.A) or left ventricular end-diastolic pressure against left ventricular stroke work (V.F.C.L.V). Stroke work
was calculated as previously described. The actual changes in stroke work induced by any given experimental intervention were at least as great as those shown in the data presented below. Had the stroke work been calculated using stroke volume X mean systolic aortic pressure (instead of mean aortic pressure) or as advocated by Chapman et al., the changes induced would in each instance have been greater than those shown below. Similarly, the absence of coronary flow from the cardiac output measurement diminishes the extent of the observed changes. The ventricular function curves were obtained by stepwise infusion of previous mixed blood (from donor dogs) from a reservoir connected to a femoral vein. In some experiments, changes in the length of a segment of left ventricular myocardium were also recorded simultaneously with ventricular diastolic pressure.

Results

Fifty-two experiments were performed to ascertain the hemodynamic consequences of sympathetic or parasympathetic stimulation for the heart.

Stellate Ganglion Stimulation

Effects on Cardiac Output and Atrial and Arterial Pressures

Supramaximal stimulation of the isolated left stellate ganglion produced the type of changes shown in figures 1A and B. Heart rate was held constant throughout by left atrial excitation. The prompt elevation of systolic, mean and diastolic aortic pressures after the onset of stimulation was accompanied by a fall in left and right atrial pressures. Pulmonary artery pressure was not consistently affected, but usually changed little. Uniformly, however, there was a widening of the PA-LA pressure difference with the observed increase in flow in each of the experiments in which such observations were made. The response to stellate stimulation was inhibited by ganglionic blockade with tetraethylammonium chloride. An observation of interest was that, as found by Shipley and Gregg, left stellate ganglion stimulation sometimes did not cause an appreciable change in heart rate. In such animals, observations on myocardial contractility were made with and without a controlled heart rate and the results were the same. In some experiments, the elevation

\[ A: \text{L.A.} = \text{mean atrial pressure; } \text{Ao.} = \text{aortic pressure; } \text{R.A.} = \text{mean right atrial pressure; } \text{P.A.} = \text{mean pulmonary artery pressure; } \text{A.F.} = \text{total aortic flow. Line at bottom right = interval of 1 minute. Chart speed is } 0.5 \text{ mm./sec. During the interval between the arrows at top of first channel, the isolated left stellate ganglion was stimulated at 6 volts, 4/sec. with a 5 msec. impulse duration. Heart rate was maintained at } 150/\text{min. throughout by atrial pacing. The rami to the right stellate ganglion were cut and both vagi sectioned in the neck. } B: \text{P.R. = pulse rate. Other symbols as in figure 1A. Stimulation of left stellate ganglion at signal in first panel, 3.5 volts, 5/sec. 5 msec. Stimulus stopped at end of first panel. Second panel is 2.4 minutes after first panel. Third panel, 1.3 minutes after second panel, shows effect of the intravenous injection of 5.0 gamma of norepinephrine base at signal in third panel. Fourth panel is 2.6 minutes after third panel. Heart rate held constant by atrial pacing. Chart speed is } 2.5 \text{ mm./sec. Dog weight = 21.0 Kg.} \]
Effects of Graded Stellate Ganglion Stimulation on Cardiac Output, External Stroke Work and the Position of the Ventricular Function Curve (V.F.C.LA)

An examination was made of the effects of applying frequency-graded stimulation to the left stellate ganglion on cardiac output, stroke volume and external stroke work. From these data, ventricular function curves (V.F.C.LA) were then constructed.

Figure 2A (left) demonstrates the type of response obtained. Each time the stimulus frequency (with supramaximal voltage) was increased from zero up through 4 per second, the fall in left and right atrial pressures and the rise in aortic pressure was accompanied by an increased cardiac output and, since heart rate was held constant, by a proportional increase in stroke volume. The calculated external ventricular stroke work thus rose with each increase in stimulus frequency while atrial pressure fell. The same type of result was also obtained when the stimulus voltage was varied from zero to the level of maximal response while the stimulation frequency was held constant.

At the end of the series of observations shown in the left panel of figure 2, stellate stimulation was stopped and an interval of 6 minutes allowed to pass during which period each of the hemodynamic values returned to control levels. An infusion of approximately 100 ml. of blood was then made. This resulted in a modest elevation of atrial and arterial pressures, cardiac output, stroke volume and stroke work, as can be seen by comparing the first segment of the left panel of figure 2 (before infusion) with the first segment of the right panel (after 1 infusion). The same series of frequency graded stimuli were then once again applied with the results seen in the right panel of figure 2. This sequence of interventions was repeated until 6 sets of 6 points each were obtained. Heart rate was held constant throughout.

The plot of mean left atrial pressure versus left ventricular stroke work (V.F.C.LA) resulting from these data is shown in figure 3 (left). The number adjacent to each curve indicates the stimulus frequency. Worthy of note was the magnitude of change in the ventricular work produced at a given mean left atrial pressure under the influence of left stellate stimulation, especially since only a portion of the cardiac sympathetic nerves were stimulated. The effects of left stellate ganglion stimulation on right ventricular function (V.F.C.RA) were similar to the effects observed on the left. One hour and fifteen minutes after the completion of the experiment shown in figure 3 (left), the entire experiment was repeated with similar results (fig. 3, right).

The V.F.C.LA was shifted to the left by
Figure 3
In the left panel are curves showing the relation between mean left atrial pressure and left ventricular stroke work during control period (0) and during stimulation of isolated left stellate ganglion at 0.2, 0.5, 1.0, 2.0 and 4.0 per second, using 7 volts and an impulse duration 10 msec. Kami to right stellate ganglion and both vagi sectioned. Heart rate held constant at 150/min. by atrial pacing. One hour and 15 minutes later the experiment was repeated; the resulting curves are shown in the right panel.

Figure 4
Effect of Stellate Ganglion Stimulation or the Continuous Infusion of Norepinephrine on the Ventricular Function Curve (V.F.C.LV)

In the course of these and other experiments, high speed tracings of undamped pulse contours were obtained several hundred times in 59 experiments in which left stellate ganglion stimulation was done while the heart was held at the same rate by atrial stimulation. The fall in left atrial pressure during stellate stimulation was consistently accompanied by a lowering of left ventricular end-diastolic pressure. The more rapid development of tension, the more rapid myocardial shortening, the augmented aortic pressure, the shorter duration of ejection and the more rapid relaxation were consistent and noteworthy. Changes of the type observed can be seen in figure 6 (lower).

In 8 of the 19 function curve experiments described above (under stellate stimulation), left ventricular end-diastolic pressure, as well as mean left atrial pressure, were recorded before and during left stellate ganglion stimulation. Resolution of the diastolic ventricular pressure was increased by recording ventricular pressure only from zero to 40 cm.H2O. The type of tracings obtained is shown in figure 6. In all 8 such experiments (fig. 4, left), a shift of the ventricular function curve to the left was observed when either mean left atrial pressure (V.F.C.LA) or left ventricular end-diastolic pressure (V.F.C.LV) was plotted against stroke work; the mean left atrial pressure fell more than the end-diastolic value at any given level of stroke work. The extent of the difference between
the fall in mean atrial and end-diastolic pressures depended upon whether the ventricle was on a relatively steep or relatively flat portion of the function curve.

Five additional experiments were done in which the effect of norepinephrine on ventricular function (V.F.C.LV and V.F.C.LA) was examined. The results were directly comparable to those obtained with stellate stimulation (fig. 4, right).

Influence of Stellate Ganglion Stimulation on the Relation between Ventricular Myocardial Segment Length and Stroke Work

The lack of a change in the relation between ventricular end-diastolic pressure and myocardial segment length during stellate stimulation as previously described indicated that, under such stimulation, the ventricle contracts more forcefully from any given fiber length as well as from any given ventricular end-diastolic pressure. Figure 5 shows (left) the relation between left ventricular end-diastolic pressure and stroke work, (middle) the relation between left ventricular end-diastolic pressure and myocardial segment length, and (right) the work produced from any given myocardial segment length before and during sympathetic stimulation. In 8 such experiments, it was observed that the ventricle contracts more forcefully from any given myocardial segment length as well as from any given end-diastolic pressure during stellate stimulation. An example of a more vigorous ventricular contraction from a shorter end-diastolic fiber length as well as from a lower pressure can be seen in figure 6 (lower).

More complete systolic emptying from any given end-diastolic pressure or length during stellate ganglion stimulation is implicit in the results described above; i.e., stellate stimulation induced the delivery of a substantially greater stroke volume as well as stroke work from any given left ventricular end-diastolic segment length or pressure.

Effect of Stellate Stimulation on the Ventricular Stroke Work Produced per Systolic Second (Ventricular Power)

The shortening of systole (fig. 6) observed during stellate stimulation while the ventricle produced an increased work from any given end-diastolic pressure (fig. 4, left) indicated a greater increase in stroke power than in stroke work. In that experiment, during stellate stimulation the shortened duration of ventricular systole from any given end-diastolic pressure was such that the increase in power was an average of 25 per cent greater than the increase in work. A similar effect was produced by the administration of norepinephrine (fig. 4, right). In that experiment, during norepinephrine infusion the shortened duration of ventricular systole from any given end-diastolic pressure was such that the increase in power was an average of 33 per cent greater than the increase in work. The increase in stroke work produced during stellate stimulation or norepinephrine infusion was consistently ac-
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Figure 5

Data for the curves shown in first, second and third panels were obtained simultaneously. First panel shows the relation between left ventricular end-diastolic pressure and stroke work before (solid circles) and during (open circles) stellate ganglion stimulation. Second panel shows relation between left ventricular end-diastolic pressure and change in end-diastolic myocardial segment length before (solid circles) and during (open circles) stellate stimulation. Third panel shows relation between changes in end-diastolic myocardial segment length and left ventricular stroke work before (solid circles) and during (open circles) stellate stimulation. Heart rate held constant at 171/min. by atrial pacing. Bilateral cervical vagotomy; right stellate ganglion intact.

The study of the atrial a wave in the heart block dog as above has the advantage of permitting observations on the consequences of atrial activity to be made without contiguous ventricular disturbances. With this background at hand, however, experiments on the heart with normally conducted impulses were undertaken. In addition to pressure measurements, recordings were also made of changes in myocardial segment length. Figure 6 (lower) shows one such record before and during stellate stimulation. Mild efferent vagal nerve stimulation was used so as to slow the heart to a rate of approximately that in the unanesthetized resting dog. This mild vagal activity was held as a constant background throughout the course of the experiment. The control tracing is at the left; that during stellate stimulation is at the right. Table 1 shows the values for each of the components analyzed. It is clear from these tracings that during stellate stimulation the atrial contraction produced a larger end-diastolic increment

Atrial Contractility during Stellate Ganglion Stimulation

Evidence indicating that the atrium as well as the ventricle contracts with more vigor during sympathetic stimulation is shown in figure 6. In the upper panel of figure 6 are left atrial, left ventricular diastolic and aortic pressure tracings from a dog in which atrioventricular block had been surgically induced. The atrium was paced at a constant rate. An increased amplitude of the atrial a wave contour was observed during stellate stimulation. It was also observed that the duration of atrial systole is shortened during stellate stimulation, suggesting that atrial as well as ventricular power is augmented by sympathetic stimulation. The same results were obtained after the intravenous administration of nor-epinephrine (fig. 6, middle). These findings indicate that sympathetic stimulation augments the vigor of atrial contraction.

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of both ventricular pressure and segment length. The greater rise in end-diastolic ventricular pressure can only be attributed to the more vigorous atrial contraction; the greater elongation of the myocardial segment is attributed not only to the more forceful atrial contraction but also to the lower position on the ventricle's pressure-length curve, brought about by the more complete systolic emptying in the previous beat. In some experiments, the increased atrial contraction was not apparent during sympathetic stimulation when the drop in ventricular and atrial pressure is pronounced. Under such circumstances, restoring the level of atrial and ventricular pressure by infusion revealed the stronger atrial contraction.

**Vagal Stimulation**

*Effect of Vagal Stimulation on the Relation between Mean Left Atrial Pressure and Left Ventricular Stroke Work (V.F.C.LA)*

Some of the hemodynamic consequences of vagal stimulation, while the heart rate is maintained constant by atrial pacing, are shown in figure 7 (left). Mean right and left atrial pressures rose while aortic pressure, cardiac output and stroke work fell. That the magnitude of the response was a function of the vagal impulse frequency used is shown in the data at the right in figure 7; the observed responses increased in a stepwise manner as the stimulation frequency was increased from 0 to 6 per second. It should be noted that the carotid sinus pressure was maintained constant throughout the course of this experiment in order to control the reflex sympathetic influences emanating from this area.

More complete experiments were then carried out in which the effect of vagal stimulation on the relation between mean left atrial pressure and left ventricular stroke work was examined over wide ranges. The results of 1 of the 9 such experiments performed are shown in figure 8. The curve describing the relation between mean left atrial pressure and stroke work (V.F.C.LA) is shifted to the right as a result of vagal stimulation; the extent of the observed shift is a function of the vagal...
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Impulse frequency applied. The same effect was observed on the right (V.F.C.RA).

Effect of Atropine

In 3 experiments, atropine was administered at the height of the response to vagal stimulation in order to block the cholinergic mechanism involved in the observed changes. One such experiment is shown in figure 9. After 3 control responses to vagal stimulation were obtained (A, B and C), 8.0 mg. of atropine sulfate were given intravenously during the plateau of the fourth response (at the arrow between D and D') while the stimulus was maintained. The effects of the sustained vagal stimulation were promptly abolished (D') and subsequent stimulation was without effect (E). Carotid sinus pressure was not controlled in this experiment and it is of interest to note the rebound from the initial drop in arterial pressure and initial pressure soon after the onset of each period of vagal stimulation. Such recoveries were not observed when the carotid pressure was held constant (fig. 7).

Difference Between V.F.C.LV and V.F.C.LA During Vagal Stimulation

At this point in the investigation, it was considered that the observed phenomena could be explained in 3 different ways: (1) that despite the lack of available anatomic evidence for vagal innervation of the ventricle,15,16 vagal stimulation can in some way influence the force of ventricular contraction from any given end-diastolic pressure; (2) that changes in mean left atrial pressure do not, during vagal stimulation, indicate similar directional changes in left ventricular end-diastolic pressure; (3) that changes in left ventricular myocardial extensibility during vagal stimulation could account for the observed phenomena. The latter possibility was satisfactorily eliminated in other experiments described elsewhere18 and the remaining experiments were therefore designed to differentiate between 1 and 2 above.

Four experiments were done in which data were gathered in such a manner as to make it possible to relate both mean left atrial pressure and left ventricular end-diastolic pressure to the stroke work of the left ventricle. The results of one such experiment are shown in figure 10. It was clear that no change in left ventricular contractility had taken place, i.e., the left ventricle produced as much work from any given end-diastolic pressure (V.F.C.LV) during vagal stimulation as without it (fig. 10, left). Mean aortic pressure ranged from 58 to 165 mm. Hg when the control values were obtained, from 54 to 158 mm. Hg while the vagus was stimulated. The relation between mean left atrial pressure and stroke work (V.F.C.LA) was shifted to the right (fig. 10, right) as observed in the previous experiments (fig. 8).

Effect of Vagal Stimulation on Atrial Contractility

In view of the above, it appeared worth while to make a direct and detailed re-
Table 1

<table>
<thead>
<tr>
<th>Duration of atrial systole, msec.†</th>
<th>Control</th>
<th>Stellate stimulation</th>
<th>Per cent change</th>
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</thead>
<tbody>
<tr>
<td>Duration of ventricular systole, msec.†</td>
<td>120</td>
<td>87</td>
<td>-28</td>
</tr>
<tr>
<td>Duration of ventricular diastole, msec.§</td>
<td>270</td>
<td>207</td>
<td>-23</td>
</tr>
<tr>
<td>Duration of ventricular diastole, msec.§</td>
<td>450</td>
<td>365</td>
<td>-26</td>
</tr>
<tr>
<td>Increment in I.V.E.D. (cm. H2O), produced by atrial systole</td>
<td>2.0</td>
<td>6.5</td>
<td>+225</td>
</tr>
<tr>
<td>Duration of isometric contraction, msec.**</td>
<td>105</td>
<td>55</td>
<td>-48</td>
</tr>
<tr>
<td>Relaxation time, msec.††</td>
<td>93</td>
<td>75</td>
<td>-19</td>
</tr>
</tbody>
</table>

*Heart rate constant at 116/min; (total cycle time = 520 msec.); analysis of tracing shown in figure 6 (lower)
†From beginning of increase in atrial pressure until beginning of rise in ventricular pressure.
‡From beginning of rise in ventricular pressure until aortic incisura.
§From beginning of aortic incisura to the rise in ventricular pressure.
||A-B interval: from beginning of rise in atrial pressure to lowest point of ventricular diastole pressure ("relaxation point").
**From beginning of rise in ventricular pressure until beginning of rise in aortic pressure.
††From aortic incisura until lowest point of ventricular diastolic pressure.

examination of the extent to which vagal stimulation can alter atrial contractility. This was done in hearts with and without heart block. Figure 11 (upper) shows the changes induced in the amplitude of the atrial pulse and the consequent changes in the contour of left ventricular diastolic pressure before, during and after distal vagal nerve stimulation. During stimulation, in late diastole, atrial pressure was higher and left ventricular pressure lower. In figure 11 (middle) the left panel (control) shows the individual atrial contractions that occur between each ventricular beat, the effect thereof on left ventricular diastolic pressure and the increased myocardial segment length that is induced. The right panel, a tracing taken during vagal stimulation, and with the atrium still being paced, shows the suppression of the atrial a wave and the effect thereof on left ventricular diastolic pressure and segment length changes. This response was also observed in the dog without heart block and in which the heart rate was either maintained constant or allowed to decrease during vagal stimulation (fig. 11, lower). Vagal stimulation not only produced bradycardia in the unpaced heart; the atrial quieting during mild vagal stimulation also diminished the end-diastolic augmentation of both the ventricular pressure and myocardial segment length.

Discussion

The central nervous system has available direct efferent pathways to the heart over which it can, at any given heart rate, systematically regulate the ventricle's contraction by either of 2 means. First, it can control the atrial contraction over a wide range, augmenting the atrial contraction by sympathetic stimulation (fig. 6) and diminishing it with vagal stimulation (fig. 11). The ventricle is thereby presented with more or less blood at the end of diastole, its end-diastolic pressure and fiber length are modified, and a consequent alteration is made in the vigor of its contraction. This can transpire in the absence of any change in the contractile characteristics of the ventricle, i.e., with no change in V.F.C.L.V (fig. 10, left).

Secondly, the central nervous system, by way of cardiac sympathetic efferents, can directly cause the ventricle to contract more or less forcefully from whatever end-diastolic pressure and fiber length has been obtained. The magnitude of the observed changes is noteworthy.

During sympathetic stimulation, the aug-
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§ 20

Figure 8
Curves showing relation between mean left atrial pressure and left ventricular stroke work while stimulating the distal cut end of the vagus nerve (5.2 volts 5 msec.) at frequencies of 0, 2.0, 3.5 and 6.0/sec.

A more precise appreciation of the net effect of sympathetic impulses on the heart beating at any given rate is best appreciated by an analysis of the tracings shown in figure 6 (lower), the values in table 1 taken in conjunction with the experiments shown in figures 1, 2, 3, 4, and 5 and the data on ventricular pressure-length curves shown elsewhere. The more forceful ventricular contraction resulting from sympathetic stimulation produces more complete systolic emptying and, consequently, a lower diastolic impedance to ventricular inflow, i.e., the more complete systolic emptying places the ventricle on a more sensitive portion of its ventricular pressure-length and pressure-volume curve. Finally, it is in this circumstance, in which a smaller increase in pressure produces a larger fiber length increase, that the more vigorous atrial systole propels blood and elevates ventricular end-diastolic pressure.

It remains to consider the altered timing of events which accompanies these phenomena. Reference is made to table 1, in which it can be seen that sympathetic stimulation substantially reduced the total period of the heart's active state (from the beginning of atrial systole to the "relaxation" point, i.e., lowest pressure in diastole). The shortening of the duration of each of the components of the heart's activity during sympathetic stimulation resulted in a 25 per cent longer ventricular diastole. The cardiac sympathetic nerves may thus be construed, in an important sense, as the guardian of diastole, a view implicit in the experiments of Wiggers in 1927.

The shorter the diastolic interval, the more important it is for blood to enter the ven-
tricle at an increased rate. Thus, not only does the contribution of atrial systole become most important at high heart rates, but it may, in addition, be expected that the extent to which the atrial systole becomes shorter and more forceful will determine the extent of ventricular filling under these circumstances. There can be little doubt that efferent sympathetic cardiac nerve stimulation produces an increase in the myocardial levels of catechol amines. Pertinent to this view are the observations of Outschoorn and Vogt, who found marked elevations of norepinephrine in coronary sinus blood during stellate ganglion stimulation, as well as similar observations in this laboratory. Our experiments (figs. 1B, 4 and 6), in which each of the consequences of stellate ganglion stimulation could be mimicked with norepinephrine given intravenously, are in accord with this position.

The alteration of the mechanical events of the cardiac cycle consequent to sympathetic stimulation correlates well with observed electrical phenomena, such as the increased conduction velocity observed in the atrium, at the atioventricular node and in the ventricle. There is also a shortening of the total refractory period and, with administered catecholamines, an increased excitability. With this in view, it is desirable to evaluate what contribution the altered electrical phenomena might be making to the hemodynamic phenomena observed. It is obvious that if the sequence of ventricular contraction is so prolonged that each fiber or group of fibers is contracting while the others are relaxed, little or no external work will be produced. Conversely, if each of these fibers contract with the same vigor but simultaneously, the external work and power produced will be at its maximum. On this basis, the extent to which the contraction is a synchronous one will determine the external work and power produced when each of the myocardial fibers is contracting from any given initial length and with the same vigor.

The suggestion that such changes in synchronicity are of sufficient importance to be operative was postulated and later apparently abandoned by Wiggers. Recently, data have been obtained in which the synchronicity of the ventricle’s contraction was varied by changing the site of pacing and without changing the norepinephrine background. When the ventricular contraction was made to be less synchronous, as evidenced by the lower rate of development of pressure, less external stroke work and power were produced from any given ventricular end-diastolic pressure. This mechanism has also been invoked to explain the changes under hypothermia. It would thus appear unwise to attribute the increased ventricular work and power produced under sympathetic stimulation solely to a direct effect of the catechol amines on the myocardial fibers without making allowance for the obvious increase in the synchronicity with which they contract. This aspect of ventricular performance is construed to be a matter of importance.

The net effect of efferent vagal impulses, at least with the intensities of vagal stimulation used in these experiments, was to diminish the vigor of atrial contraction; they did
not directly modify ventricular contractility. These observations are in accord with the apparent lack of vagal fiber distribution to the ventricular myocardium. Schreiner, Berglund, Borst and Monroe did not find evidence that efferent vagal stimulation altered the relationship between mean atrial pressure and stroke work and concluded that such stimulation does not modify the contractility of the ventricle, a conclusion reaffirmed by our present experiments. It is not entirely clear, however, why these authors did not obtain a higher mean left atrial pressure for any given level of left ventricular stroke work, as shown in figures 8 and 10. A partial explanation appears to be that since some of their experiments were performed in dogs with complete heart block and with an atrial rate much higher than the ventricular rate, the depression of atrial contractility during vagal stimulation was perhaps less likely to diminish ventricular filling. This is especially true when, as in some dogs with heart block, the mitral valve apparently does not close after each of the several a waves that occur during diastole. Other experiments in their study were done with ventricular pacing which, by itself, can eliminate or diminish the contribution of atrial systole to ventricular filling prior to vagal stimulation.

The above experiments on vagal stimulation are not consonant with the experiments of Wang, Blumenthal and Wang, or with the suggestion of Peterson that vagal fibers produce a negative inotropic effect on the ventricle. They do support the recent observations of Carlsten, Folkow and Hamberger in man suggesting that vagal stimulation does not influence the ventricular myocardium, and are in essential agreement with the elegant experiments of Gesell in 1916, who attributed the changes in arterial pressure during vagal stimulation to the diminished contribution of the atrium to ventricular filling.

Nervous Control of the Frank-Starling Mechanism: Principles of the Innervated Heart

As a formal means of broadening the basic Frank-Starling relationship and of integrating it with the activity of the central nervous

**Figure 11**

Upper: Surgically induced heart block and bilateral cervical vagotomy. LA = left atrial and LVD = left ventricular diastolic pressure in cm.Hg; AP = aortic pressure in mm.Hg. Stimulation of distal cut end of left vagus nerve during signal at bottom. Chart speed = 10 mm/sec. Middle: Surgically induced heart block and bilateral cervical vagotomy. Atrium paced at 164/min. LA = left atrial, Ao = aortic and L.V.-D. = left ventricular diastolic pressure. M.S.L. = myocardial segment length, + = elongation, - = shortening; full scale deflection = segment length change of 5 mm. Chart speed = 50 mm/sec. Control tracing at left. Tracing at right taken 1.6 minutes later during stimulation of distal cut end of left vagus nerve with 7 volts, 15/sec; atrium still being paced at 164/min. Lower: Symbols as in middle panel. Sino-atrial node crushed. Chart speed = 100 mm/sec. Bilateral cervical vagotomy. Control tracing at left; arrows in third beat indicate atrial a wave and the consequent increase in left ventricular end-diastolic pressure and myocardial segment length. Tracing at right taken during stimulation of distal cut end of left vagus nerve with 3 volts 20/sec. and 5 msec., which reduced heart rate to 37/min.
system in relation to acutely induced changes, 2 concise statements now appear to be appropriate for the heart operating at any given rate and in the absence of abnormal conditions such as hypoxia and acidosis: 1. If the effective catechol amine stimulus remains constant, the contraction of the ventricle varies directionally with its end-diastolic pressure and fiber length; if the end-diastolic pressure and fiber length remain constant, the contraction of the ventricle varies directionally with the effective catechol amine stimulus. 2. The central nervous system has direct neural connections to the heart by means of which it can vary the left ventricular end-diastolic pressure and fiber length while keeping the effective catechol amine stimulus constant (atrial systole), means by which it can vary the effective catechol amine stimulus, or both.

These general principles are best regarded as describing mechanisms which initiate, and are important for sustaining, changes in the performance of the heart. Their operation can better be predicted, however, if they are appropriately interrelated with other known mechanisms of intrinsic myocardial regulation. For example, in the experiments described above, when the stellate ganglion was stimulated, there ensued an elevation of aortic pressure (figs. 1 and 2) which, of itself, is known to produce an increase in ventricular contractility by homeometric autoregulation. It cannot be reasoned that the rise in aortic pressure was the primary cause of this increased contractility, since it did not precede but followed the onset of stellate stimulation. Further, experiments are available in which it was demonstrated that, with aortic pressure, heart rate and stroke volume held constant, left ventricular end-diastolic pressure fell substantially during stellate stimulation. It should be recognized, however, that, since norepinephrine improves the ventricle's capacity for utilizing its intrinsic mechanisms, some relationship of re-enforcement between the 2 mechanisms undoubtedly exists, i.e., when sympathetic stimulation increases the force of contraction as the result of the local elaboration of norepinephrine, the increase in activity thereby produced contributes to the increased myocardial contractility observed in the new equilibrium state and, further, the increased norepinephrine facilitates this process. Similar considerations apply to changes in rate.

In an address which seems to be less widely known than his other work, Starling said: "No understanding of the circulatory reactions of the body is possible unless we start first with the fundamental properties of the heart muscle itself, and then find out how these are modified, protected and controlled under the influence of the mechanisms—nervous, chemical and mechanical—which under normal conditions play upon the heart." These general guidelines still seem to have merit as the basis for continuing investigation.

Summary
At constant heart rates, efferent stimulation of the vagus nerve and of the left stellate ganglion revealed the following: 1. Vagal stimulation exerts a profound depressant effect on the strength of the atrial contraction and can thereby influence ventricular filling and ventricular stroke work; it elevates mean atrial pressure at any given level of ventricular stroke work. This occurs under experimental conditions wherein the vagal stimulation used does not produce an alteration in the performance characteristics of the ventricle. The effects of vagal stimulation are blocked by atropine. 2. Stellate ganglion stimulation or norepinephrine infusion augments the strength of atrial contraction and thus the atrial contribution to ventricular filling. The augmented atrial contraction takes place in a shorter period of time. 3. Stellate ganglion stimulation or norepinephrine infusion augments the strength of atrial contraction and thus the atrial contribution to ventricular filling. The augmented atrial contraction takes place in a shorter period of time. 4. There is a family of curves representing the relation between end-diastolic fiber length and stroke work, as well as a family of curves representing the relation between mean atrial pressure and end-diastolic pressure and stroke work.
5. When taken together with the well-known sympathetic and parasympathetic effects on heart rate, the above data are believed to comprise a reasonably comprehensive description of the means available to the central nervous system for directly inducing acute changes in the activity of the heart.

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Regulation of Ventricular Contraction: Influence of Cardiac Sympathetic and Vagal Nerve Stimulation on Atrial and Ventricular Dynamics
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