Depression of Ventricular Contractility by Stimulation of the Vagus Nerves

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Numerous workers have investigated the effects of stimulating the vagus nerves upon ventricular contractility in the mammalian heart. Many of these investigators concluded that vagal stimulation has little or no influence on the contractility of the ventricles, while others deduced that it elicits a negative inotropic effect. Currently, the former opinion appears to be almost universally accepted. However, certain experimental observations encouraged us to reinvestigate this problem. It was found that electrical stimulation of the distal ends of the cervical vagi provokes a more marked increase of coronary flow during systole than during diastole in the paced, canine heart which is perfused at constant pressure. In other experiments, it was observed that the negative inotropic effect upon the canine ventricles which is elicited by stimulation of the carotid body chemoreceptors is abolished by bilateral cervical vagotomy. These observations suggest that the vagus nerves may play a definite role in the nervous regulation of the contractility of the ventricular myocardium in the mammalian heart. The experiments described in this paper confirm this hypothesis. A preliminary report of some of these experiments upon isovolumetric preparations has recently been published. These studies have been extended in the present report. Furthermore, because most of the previous, negative findings of other investigators have been derived from experiments upon hearts pumping blood, additional experiments upon two separate pumping heart preparations were conducted and are also included in the present report.

Methods

Thirty-three experiments were performed upon mongrel dogs which weighed 9.0 ± 1.4 kg (mean ± sd). They were anesthetized with morphine sulfate, 2 mg/kg, administered intramuscularly, followed 30 minutes later by a warmed, intravenous solution of methane, 600 mg/kg, and chloralose, 60 mg/kg. Three experimental preparations were used in this study.

PREPARATION 1: ISOVOLUMETRIC LEFT VENTRICLE

In 22 dogs, both cervical vagi were transected, and intermittent positive pressure breathing was instituted through a tracheal cannula. A bilateral thoracotomy and transverse sternotomy were performed at the level of the fourth intercostal space. Heparin, 3.4 mg/kg, was administered intravenously to prevent blood coagulation, and additional doses were given every 30 minutes. A large-bore cannula was inserted into the descending aorta (Ao, fig. 1), just distal to the origin of the left subclavian artery. By means of a roller pump, the cephalic portion of the animal was perfused via this cannula with blood from an oxygenator (OXY) through which was passed a gas mixture consisting of 95% O₂ and 5% CO₂. Perfusion pressure was kept constant at 99.0 ± 7.0 (sd) mm Hg by means of an overflow system (RES). Cephalic venous blood was returned to the oxygenator by means of a cannula inserted into the superior vena cava (SVC). Coronary venous blood was returned by means of a cannula inserted through the right atrial appendage into the right atrium and ventricle. The inferior vena cava and the hili of the lungs were ligated. Through an incision in the

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FIGURE 1


Apex of the left ventricle, a latex balloon, attached to the tip of a rigid cannula, was introduced into the left ventricular cavity; it was fixed to the apical myocardium by means of a purse-string suture. In all experiments, a cannula with multiple side-holes at the tip was inserted into the left ventricle in order to prevent accumulation of blood (Thesbian drainage) in the ventricular cavity. In some experiments, for the same reason, a similar cannula was passed into the left atrium through a pulmonary lobar vein. Depending upon the size of the experimental animal, the latex balloon was filled with 2 to 15 cc of saline, which was always less than the volume of the unstretched balloon. The perfusion pressure of the heart and head was always kept higher than the left ventricular systolic pressure. When desired, the heart rate was kept constant at a mean level of 211 ± 19 (SD) beats/min, by simultaneously pacing the right atrial appendage and ventricle by means of a square-wave electronic stimulator (Grass, model S4). In three experiments, the atrium alone was paced. The peripheral end of either sectioned cervical vagus was stimulated, in the paced and un-paced heart, by means of a second Grass stimulator. The intensity of the pulses was varied from 1 to 20 v; the frequency, from 1 to 50 cycles/sec; and the duration of each pulse was always 5 msec.

Pressures were recorded from the latex balloon and from the cephalic perfusion system on a Sanborn oscillographic recorder by means of Statham strain gauges. Heart rate was recorded from the left ventricular pressure tracing by means of a tachometer. In three experiments, during electrical pacing of the heart, bipolar epicardial electrocardiograms were recorded at high paper speed (100 mm/sec) before, during, and after vagal stimulation. Left ventricular pressure, heart rate, and electrocardiograms were simultaneously stored on an instrumentation tape recorder (Honeywell, model LAR 7400).

PREPARATION II: PUMPING LEFT HEART; CONSTANT VENOUS RETURN

After preliminary surgery similar to that described above, in six experimental animals the cephalic and coronary venous blood was drained to an oxygenator (OXY, fig. 2) which was equilibrated with 95% O₂ and 5% CO₂. A roller pump transferred blood at a constant rate from the oxygenator to the left heart through a cannula inserted in the left atrial appendage (LA). Cardiac output could be varied by changing the speed of this pump. A combination bubble trap and de-pulsating chamber (DC) was included in this circuit. The descending aorta was ligated just distal to the origin of the left subclavian artery. The hilus of both lungs and the inferior vena cava were also ligated. Both carotid sinuses were denervated in five of the six experiments.

Heart rate was kept constant at a mean level of 201 ± 28 (SD) beats/min by sequentially pacing the right atrial appendage and the right ventricle.

FIGURE 2

Schema of preparation II, pumping left heart, with constant venous return. DC: de-pulsating chamber; FM: extracorporeal probe of square-wave electromagnetic flowmeter; LA: left atrial appendage; other abbreviations as in figure 1.

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with an A-V delay of 50 msec (in one experiment, 100 msec) by means of two coupled electronic stimulators (Grass, model S4). In one experiment, only the right atrial appendage was paced.

The peripheral end of either sectioned cervical vagus nerve was stimulated, usually for periods of 1 min, by means of a third electronic stimulator (Harvard Apparatus Company). The intensity of the pulses was varied from 5 to 20 v, at a constant frequency of 20 cycles/sec.

Catheters were inserted through a pulmonary vein into the left atrium and through the left subclavian artery into the aorta for the registration of pressure. Phasic left ventricular pressure was recorded through a short, rigid cannula which was introduced through a small apical incision into the left ventricular cavity, and which was fixed to the apical myocardium by means of a purse-string suture. A three to fivefold amplification of the diastolic portion of the same pressure tracing was registered on another channel of the same recorder. In three experiments, left atrial inflow was recorded from an extracorporeal probe of a square-wave electromagnetic flowmeter (Carolina Medical Electronics). In the three other experiments, flow was determined from the calibrated settings of the pump-speed adjustment. Left ventricular stroke work was estimated as the product of the left ventricular stroke volume and the difference between mean aortic pressure and left ventricular end diastolic pressure.

PREPARATION III: PUMPING LEFT VENTRICLE; LEFT ATRIUM AND MITRAL VALVE EXCLUDED

In five experiments, the head and heart were perfused as described for preparation I. The pulmonary hilii and the inferior vena cava were ligated. Through an incision in the apex of the left ventricle, a latex balloon, attached to the tip of a rigid cannula, was introduced into the left ventricular cavity. The cannula was fixed to the apical myocardium by means of a purse-string suture. Drainage of the Thebesian blood flow was achieved as described for preparation I. At the end of each experiment, the left atrial and ventricular cavity were opened to verify the position of the latex balloon. The balloon was connected to an artificial circuit filled with saline at room temperature (fig. 3). During ventricular diastole, saline entered the balloon from a reservoir (RES 2) through valve 1 (V1). The left ventricle pumped saline during systole through valve 2 (V2) and through an adjustable resistance (TPR) back to the "atrial" reservoir (RES 2).

Cephalic perfusion pressure and pressure in the "arterial" limb of the artificial circuit were recorded by means of Statham strain gauges (SG) on a Sanborn oscillographic recorder. Flow in the "arterial" limb of the circuit was recorded by means of an extracorporeal probe of an electromagnetic flowmeter (FM). Pacing of the
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heart and vagal stimulation were achieved as for preparation I. The duration of the vagal stimulation was 60 seconds.

Results

PREPARATION I: ISOVOLUMETRIC LEFT VENTRICLE

In the representative experiment displayed in figure 4, the peripheral end of the sectioned right cervical vagus nerve was electrically stimulated, first in the unpaced (upper row of tracings) and then in the paced heart (lower row) with a stimulus strength of 10 v and at frequencies varying from 1 to 20 cycles/sec, as indicated along the bottom of the figure. Frequencies were varied in a random sequence, although the responses are arranged in an ascending sequence in the figure. In the spontaneously beating heart, depending upon the frequency of stimulation, ventricular rate diminished by 7.8 to 73.6% (upper panel). When the heart was paced at a constant rate of 210 beats/min, left ventricular systolic pressure decreased by 7.0 to 34.2%, depending also upon the frequency of stimulation (lower panel). To show the contours of the left ventricular pressure curves, the data stored on tape were played back to the heated-stylus recorder at a paper speed of 10 cm/sec. Left ventricular pressure curves before, during, and after stimulation at 20 cycles/sec (from the lower right segment of fig. 4) are displayed in figure 5.

In 14 experiments, both cervical vagi were stimulated individually when the heart was paced and when it was beating spontaneously. In each experiment, the priority for stimulation of the right or left vagus was determined by chance. The duration of stimulation was 15 seconds in the unpaced heart and 30 seconds in the paced heart. A statistically significant correlation ($P < 0.001$) was found between the percentage decrease in heart rate and in left ventricular systolic pressure for right ($r = 0.80$) and for left ($r = 0.88$) vagal stimulation.

In the paced heart, supramaximal vagal stimulation elicited a highly significant ($P < 0.001$) decrease in left ventricular pressure of $23.1 \pm 1.8 \text{ (SE)}$ and $23.3 \pm 2.1 \text{ (SE)}$ per cent for the right and left vagus, respectively. A comparison of the effects of supramaximal stimulation of the right and left vagus nerves upon left ventricular systolic pressure in the paced heart is displayed in figure 6 for 18 experiments. The ordinates represent the percentage changes in left ventricular systolic pressure evoked by supramaximal stimulation of the left vagus nerve, and the abscissae represent those produced by identical stimuli applied to the right vagus nerve. Points lying above the diagonal line indicate a greater effect induced by the left than by the right vagus nerve, while the reverse condition is signified by points lying below the diagonal line.

![Figure 5](http://circres.ahajournals.org/)

**FIGURE 5**

Left ventricular pressure curves before, during, and after efferent stimulation of the right vagus nerve at 10 v, 5 msec, 20 cycles/sec. These tracings are segments of the bottom, right segment of figure 4, as played back from the tape recorder to the heated stylus recorder at a paper speed of 100 mm/sec.

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below the diagonal line. Although more points lie above than below the line, most points do lie close to the line, and the difference between the effects of right and left vagal stimulation is not statistically significant ($P = 0.5$).

The relationships between the frequency of stimuli of identical strength and the percentage changes in rate in the unpaced heart and in left ventricular systolic pressure in the paced heart are displayed in figure 7 for six experiments. At all frequencies, the relative changes in heart rate (represented by the upper set of symbols) are greater than the changes in left ventricular systolic pressure (double arrows); the differences are greater at the higher frequencies of stimulation. This relationship tends to be parabolic for the effects of stimulation of either vagus nerve on left ventricular systolic pressure and also for the effects of right vagal stimulation upon heart rate. The relationship appears to be more irregular, however, for the changes of heart rate produced by left vagal stimulation. This is ascribable to the more frequent occurrence of atrioventricular block during left vagal stimulation.

In three experiments (six observations), in which the right atrial appendage alone was paced, the vagi were stimulated weakly in order to prevent the occurrence of atrioventricular block. A significant ($P < 0.001$) decrease in left ventricular systolic pressure of $5.9 \pm 0.1$ (se) per cent occurred during vagal stimulation.

When the right or left vagus nerve was stimulated in the paced heart for periods of 1.5 to 5 min, no difference was found between the percentage reduction of left ventricular systolic pressure at the end of the first minute and at the end of the total period of stimulation in four observations in four experiments. In two other observations in two of these experiments, the effects diminished progressively during stimulation.

Electrocardiograms were recorded directly from the ventricular surface at paper speeds of 100 mm/sec in three experiments (13 observations). In the paced heart, the QRS complex duration was not significantly altered.
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during supramaximal stimulation of either cervical vagus nerve. In five experiments (17 observations), the duration of mechanical systole was prolonged by $0.06 \pm 0.03$ (sec) sec ($P = 0.02$).

In two experiments (nine observations), after the administration of atropine (1 to 4 mg), supramaximal stimulation of the vagi elicited a small increase in heart rate (1.3 to 16.1%) in the unpaced heart, and in left ventricular systolic pressure (2.1 to 11.2%) in the paced heart. In a third experiment, in which vagal stimulation had elicited an 18% decrease in left ventricular systolic pressure, the administration of atropine reduced the response to vagal stimulation to a 3.5% decrease in ventricular pressure.

In two experiments, most of the left atrium was excised in order to rule out the possibility that the atrium was in any manner involved in the ventricular response to vagal stimulation. This procedure did not alter detectably the results of vagal stimulation.

PREPARATION II: PUMPING LEFT HEART; CONSTANT VENOUS RETURN

Figure 8 displays a representative example of the effects of vagal stimulation upon left ventricular and atrial pressure in the paced, pumping heart with constant venous return.

During the time interval indicated by the black bar (left panel), the distal end of the sectioned, left, cervical vagus nerve was stimulated with pulses of 15 v, 20 cycles/sec. Left atrial inflow was constant at 404 cc/min during the control and recovery periods and during vagal stimulation. Left ventricular end diastolic pressure started to rise immediately after the onset of left vagal stimulation, and showed a maximum increase of 2.4 mm Hg. Left ventricular systolic pressure decreased during the first 20 sec of vagal stimulation by 12 mm Hg, rose thereafter to 3 mm Hg below the control level, and then exceeded its control value by 14 mm Hg during the initial stages of recovery. From the tracings at high paper speed, it can be seen that the upward slope of the ventricular pressure tracing decreased during vagal stimulation. The a wave of the left atrial pressure tracing became less conspicuous and mean atrial pressure increased. Mean aortic pressure (not included in fig. 8) showed at first a decrease of 12 mm Hg, rose thereafter to 6 mm Hg below its control value of 102 mm Hg, and then exceeded the control value by 12 mm Hg during the initial stages of recovery.

Ventricular function curves were obtained by varying the rate of atrial inflow, and by stimulating the vagus nerves at each level of flow. Examples from two experiments are depicted in figure 9. The open squares represent the control data; the solid triangles, the values obtained during vagal stimulation. In both experiments, the ventricular function curve was shifted to the right by vagal stimulation. Thus, for any given left ventricular end diastolic pressure, the ventricle performs less external work during vagal stimulation.

Figure 10 displays the effects of left and right vagal stimulation on left ventricular end diastolic pressure in six experiments; observations at more than one level of atrial inflow are included from each experiment. Each line connects the values of end diastolic pressure observed during the control period and during vagal stimulation, for a given, constant, left atrial inflow. A highly significant
Effects in two representative experiments of left vagal stimulation on the relationship between external stroke work and ventricular end diastolic pressure in the pumping left heart (preparation 11). Open squares: control observations; closed triangles: during left vagal stimulation. Left panel: right atrium alone paced at 205 beats/min; vagal stimulation: 5 v, 5 msec, 20 cycles/sec for 1 min; left atrial inflow constant at each point, but varied from 196 to 713 cc/min to obtain entire curve. Right panel: right atrium and ventricle paced sequentially, with an interval of 50 msec, at 160 beats/min; vagal stimulation: 15 v, 5 msec, 20 cycles/sec for 1 min; left atrial inflow varied from 222 to 494 cc/min.

A (P = 0.005) increase in left ventricular end diastolic pressure of 3.7 ± 0.6 (SE) cm H$_2$O was observed during left vagal stimulation, and of 4.6 ± 1.3 cm H$_2$O during right vagal stimulation. During left vagal stimulation, the amount of external work performed at a given left atrial inflow was 0.14 ± 0.05 (SE) gram-meter less than during the control observations (P = 0.01); the analogous decrease was 0.25 ± 0.06 gram-meter (P < 0.001) during right vagal stimulation. For a given left atrial inflow, mean aortic pressure was less by 0.68 ± 1.18 (SE) mm Hg (P = 0.6) and 3.84 ± 1.17 (SE) mm Hg (P = 0.003) during stimulation of the left and right cervical vagus nerves respectively, than during control observations.

PREPARATION III: PUMPING LEFT VENTRICLE; LEFT ATRIUM AND MITRAL VALVE EXCLUDED

Figure 11 displays the effects of electrical stimulation of the distal end of the left vagus nerve on phasic and mean pressure and flow in the "arterial" limb of the artificial circuit for varying degrees of peripheral resistance. The level of the inflow reservoir was constant. When peripheral resistance was low (left panel), left vagal stimulation elicited a definite reduction in peak and mean "aortic" flow and in pulse pressure, but mean pressure stayed virtually constant. On the other hand, when peripheral resistance was high (right panel), a decrease in systolic, diastolic, and mean pressure and in peak flow occurred, but mean flow exhibited only minor changes. Mean flow and pressure and peak flow and pressure all decreased when peripheral resistance was at an intermediate level (center panel).

Similar observations were made in four other experiments. In three of these experiments, with moderate peripheral resistance, mean flow was diminished by 22, 22, and 45% during supramaximal vagal stimulation. In the fourth experiment, in which phasic flow only was recorded, vagal stimulation reduced peak flow by 27%, and minimum flow was virtually unchanged. In one of these experiments, opening the left atrium to the atmosphere by excision of the auricular appendage did not change the results detectably.

Discussion

EVALUATION OF METHODS AND RESULTS

In the isovolumetric left ventricle prepara-
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L. VAGAL STIMULATION

CONTROL

R. VAGAL STIMULATION

FIGURE 10

Effects of supramaximal left and right vagal stimulation for 1 min upon left ventricular end diastolic pressure in the sequentially-paced, pumping left heart (preparation II), in six experiments. Lines connect values of left ventricular end diastolic pressure at given levels of left atrial inflow, during control observations and during vagal stimulation.

A negative inotropic effect was also provoked by vagal stimulation in preparation II, the pumping left heart provided with a constant venous return (e.g., fig. 8). The left ventricular end diastolic pressure was appreciably elevated while the external stroke work changed only slightly. Concomitantly, mean left atrial pressure increased, and slight, transient reductions in mean aortic and left ventricular systolic pressure were also observed.

It could be argued that the increase of left ventricular end diastolic pressure during vagal stimulation in preparation II does not necessarily reflect a depression of ventricular contractility. Instead, the elevation of end diastolic pressure might be attributable to (a) changes in mean aortic pressure, (b) the development of mitral insufficiency, (c) changes in the sequence of activation of the left ventricular myocardium, or (d) alterations of ventricular distensibility.

The reduction of mean aortic pressure was never marked; toward the end of vagal stimulation, its mean value was less than 4 mm Hg below control values. Consequently, changes in aortic pressure probably did not affect ventricular performance appreciably by modifying afterload, by changing coronary perfusion pressure, or by evoking homeometric autoregulation. Since bilateral carotid sinus denervation was performed in five of these six experiments, and since both left and right vagal stimulating nerves were connected to the vagal nerve stimulator, the negative inotropic effect observed in preparation II probably was not due to vagal stimulation per se.

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vagus nerves were sectioned in all experiments, baroreceptor reflexes upon the heart, which might have been elicited by changes in arterial pressure, were of little or no consequence in the present study. The observed slight fall in mean aortic pressure must have resulted either from a reduction in left ventricular output or from a decrease in total peripheral resistance. Since left atrial inflow was kept constant, it is a safe assumption that by the end of a one-minute period of vagal stimulation, left ventricular output must have been equal to left atrial inflow. By exclusion, therefore, the total peripheral resistance must have been reduced. Most likely, the decrease in resistance to flow occurred in the coronary vascular bed, either as a consequence of the direct vasodilating effect of vagal stimulation upon the coronary vessels or due to mechanical or metabolic changes in the myocardium. The initial, greater drop in mean aortic pressure was probably also due to a temporary drop in left ventricular output by increased distension of the left atrium and ventricle and by accumulation of additional blood in the depulsating chamber. The increase in mean atrial and left ventricular end diastolic pressure is presumptive evidence of such an increase in left atrial and ventricular volume.

In the presence of high heart rates (200 beats/min), a delay of 50 to 100 msec between atrial and ventricular pacing stimuli is within normal limits, and should not interfere with the normal mechanism of mitral valve closure. It is unlikely, therefore, that during the control and recovery periods, any mitral regurgitation was present in this preparation. Vagal stimulation does not affect the latent period of the atrial and ventricular myocardium in the mammalian heart. For these reasons the temporal relationship between left atrial and ventricular contraction was not changed during vagal stimulation, and was not a cause of improper mitral valve closure. This was confirmed by inspection of the individual tracings at high paper speeds in each experiment (e.g., fig. 8).

In the left atrial pressure tracing, the height of the a wave, which is known to reflect the magnitude of an important factor in atrioventricular valve closure, decreased during vagal stimulation; this could have been a cause for improper mitral valve closure, perhaps resulting in some mitral regurgitation. However, the changes in left ventricular end diastolic pressure during vagal stimulation were usually larger than those which were observed when left atrial inflow was doubled. In order to explain the increase in end diastolic pressure during vagal stimulation by mitral insufficiency alone, it would be necessary to postulate a marked degree of regurgitation. Since the capacity of the left atrium in the intact animal is small, one would expect a large, progressive rise in the left atrial pressure tracings during ventricular systole under such conditions, but this was not the case.

Vagal stimulation does not affect the velocity of conduction in the mammalian heart. No changes in the duration of the QRS complex were observed during vagal stimulation in the present study. Therefore, the increase in end diastolic pressure could not have been caused by a less synchronous contraction of the ventricular myocardium, consequent to a slowing of the impulse transmission.

It has been reported that vagal stimulation does not affect the static distensibility of the ventricular myocardium under pumping or isovolumetric conditions. This implies that changes in ventricular distensibility were not responsible for the observed changes in end diastolic pressure in the experiments upon the pumping left heart (preparation II). It must be recognized, however, that under the conditions of these other studies, changes in systolic pressure were not observed during vagal stimulation in the isovolumetric preparation or in external stroke work in the pumping preparation from a given end diastolic pressure. Since this is at variance with our results, it becomes doubtful if these conclusions concerning ventricular distensibility are necessarily applicable under the conditions of our experiments. Since we did not measure left ventricular volume in the pump-
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When left heart preparation, it is not possible to exclude a decrease of left ventricular distensibility concomitant with the depression of myocardial contractility.

The data from our experiments upon the pumping left ventricle (preparation III) afford further evidence that vagal stimulation depresses contractility. During vagal stimulation, decrease of ventricular output, of mean arterial pressure, or of both were found, depending upon the level of total peripheral resistance. Left ventricular volume and end diastolic pressure were not measured. In this preparation, heart rate, coronary perfusion pressure, total peripheral resistance, and the level of the left ventricular inflow reservoir were kept constant and could not be influenced by vagal stimulation. Changes in ventricular output and arterial pressure during vagal stimulation, therefore, indicate alterations in ventricular performance, and reflect a reduction of ventricular contractility, and possibly also of distensibility.

SIGNIFICANCE OF THE RESULTS

It is generally accepted that the vagi exert a tonic, inhibitory effect upon the heart rate. In our experiments, electrical stimuli which reduced heart rate to the level existing before bilateral vagotomy, exerted a definite, negative inotropic effect upon left ventricular contractility. Our results, therefore, suggest that in the intact animal, the vagi exert a tonic, negative inotropic effect upon the ventricular myocardium, and that they play a role in the nervous control of ventricular performance. This idea is supported by the fact that bilateral cervical vagotomy abolishes the negative inotropic effect upon the ventricles elicited by hypoxia of the carotid bodies.24, 25

The quantitative effects of left and right vagal stimulation on the sino-atrial and atrioventricular node differ,41 and this is confirmed by the heart rate data in figure 7. No differences were observed, however, between the maximal effects of the left and right vagus nerves upon left ventricular contractility in the isovolumetric preparation (fig. 6). This suggests that the left and right vagal fibers are equally distributed over the left ventricle. Gonzáles-Serrato and Alanís,42 however, from their study of the effect of vagal stimulation upon idioventricular rhythm, reported that the left vagus was more potent than the right.

For stimuli of equivalent intensity and duration, we found in the isovolumetric ventricle preparation a parabolic relationship between the frequency of vagal stimulation and the effects upon left ventricular pressure and heart rate. A similar type of relationship has been described previously by Rosenblueth43 and by Carlsten et al.8 for the effects of vagal stimulation upon the sino-atrial node, and by Gonzáles-Serrato and Alanís42 for the effects upon idioventricular rhythm.

CORROBORATING DATA

Elicitation of a negative inotropic effect upon the ventricle by vagal stimulation presupposes the presence of postganglionic parasympathetic fibers in the ventricular myocardium. Anatomical evidence for a parasympathetic innervation of the mammalian ventricles is contradictory. Nonidez44 observed few parasympathetic fibers in the mammalian ventricular myocardium. According to Tcheng,45 using the same method, such fibers are not at all rare, however. Davis et al.46 denied the presence of nerve cells in the ventricles of most mammals. Mitchell et al.47 however, reported the existence of subepicardial cells in the ventricles of the monkey and the rabbit, and Tcheng48 described intramural ganglia in the substance of the right ventricle of young dogs.

Recent pharmacological studies suggest that the ventricular myocardium of mammals receives parasympathetic innervation. Bielecki and Lewartowski99 observed in the cat that, after administration of hemicholinium no. 3, repeated vagal stimulation elicited a marked drop in the acetylcholine content of the atria and right ventricle.

Eckey50 observed an inhibitory effect of vagal stimulation upon the automaticity of human ventricles. From a review of the previous literature, he concluded that most earlier workers had observed similar effects. More recent reports42, 51 have confirmed this conclusion (for other mammalian species). The
work of González-Serrato and Alanís42 clearly shows that in the adrenalectomized dog, after extirpation of the stellate and the upper vertebral ganglia and section of the bundle of His, efferent vagal stimulation may reduce ventricular rate by more than 50%. These observations suggest strongly that vagal fibers reach the ventricular myocardium. Additional support for this assertion is afforded by the experiments cited above, in which it was found that efferent vagal stimulation exerted a direct vasodilating effect upon the coronary vessels.23, 26, 30 The magnitude of the change in flow was too great in most instances to be accounted for by dilatation of the atrial blood vessels only. The presence of a vagal innervation of the coronary arterioles in the ventricular myocardium favors the existence of a vagal innervation of the ventricular myocardial cells themselves.

EVALUATION OF PREVIOUS WORK

In most earlier studies13, 15, 17-21 in which it was reported that vagal stimulation evoked a negative inotropic effect upon the mammalian ventricle, heart rate was not held constant, so that interpretation is uncertain. Howell and Duke14 reported that weak vagal stimulation (of an intensity which did not affect heart rate) caused a decrease in the force of the ventricular beat in the cat heart perfused in situ. Gesell10 concluded, from experiments upon a canine heart-lung preparation in which the ventricles were paced, that vagal stimulation lowered aortic pressure more than could be expected from complete inhibition of the atrial transport function. He conceded the possibility of a negative inotropic effect upon the ventricular myocardium. Wang et al.8 recently observed that vagal stimulation diminished the external work performed by the paced left ventricle. In their preparation, left ventricular end diastolic pressure was not recorded. Even though the ventricles (but not the atria) were artificially paced, the effects of vagal stimulation could have been due, at least partially, to the well-known influence upon the atrial transport function. The authors directed attention to the effects of the continuously varying synchronization of atrial and ventricular contraction during the control observations, and of the changes elicited by vagal stimulation. In only one experiment, in which the atria were fibrillating, could the decrease in cardiac output and stroke work be attributed exclusively to a negative inotropic effect upon the ventricular myocardium.

Several investigators who concluded that vagal stimulation has no effect upon ventricular contractility failed to keep heart rate constant.1-3, 8 In some older studies, in which heart rate was maintained constant, no changes were detectable in left ventricular pressure8 or in myocardiograph1 tracings. Although such data are suggestive, definite conclusions cannot be drawn from them, since no other aspects of ventricular function were measured.

From experiments upon paced, canine, isovolumetric, left and right ventricle preparations, Ullrich et al.9 concluded that vagal stimulation does not have any effect upon ventricular contractility. Their preparations were produced by occluding temporarily the venae cavae, pulmonary artery, and aorta. However, conclusions from experiments in which the coronary perfusion pressure was continually decreasing and in which baroreceptor stimulation was progressively diminishing are hazardous.

Rushmer9 observed a definite, depressant effect upon ventricular performance during vagal stimulation in only one out of thirteen experiments. In the remainder only small reductions in left ventricular systolic pressure were found. From his figure 1B, it is evident that when the atrium was paced, vagal stimulation at 5 cycles/sec decreased left ventricular pressure and stroke work only slightly, with no detectable change in left ventricular diastolic pressure. At higher frequencies of stimulation, atrioventricular block occurred. It is likely, however, that if the ventricles rather than, or in addition to, the atria had been paced, stronger stimuli could have been applied to the vagi; greater reduction in ventricular stroke work might then have been evoked.
Schreiner et al. assessed ventricular contractility during vagal stimulation on the basis of ventricular function curves in which the stroke work of paced hearts was plotted as a function of left atrial mean pressure. They detected no significant differences between such curves obtained before, during, and after vagal stimulation. It was concluded, therefore, that efferent vagal stimulation exerts no appreciable influence upon ventricular contractility.

The conclusions derived by Sarnoff and his collaborators from their experiments were identical to those of Schreiner et al., although there was an important contradiction in their experimental results. In the curves of Sarnoff et al., in which stroke work was plotted as a function of left atrial mean pressure, the data obtained during vagal stimulation were distinctly unlike those secured under control conditions, in contrast to the findings of Schreiner et al. When the data of Sarnoff et al. were plotted as functions of left ventricular end diastolic pressure rather than of left atrial mean pressure, then no differences could be detected between the control curves and those derived from data obtained during vagal stimulation. Hence, it was concluded that the vagi do not directly influence ventricular contractility. In the experiments of Sarnoff et al., however, appreciable changes in aortic flow and pressure occurred during vagal stimulation. The accompanying alterations in ventricular afterload and coronary perfusion pressure in themselves can exert potent influences upon ventricular performance; this undoubtedly complicates the interpretation.

In a recent study by Salem et al. it was concluded that the vagus nerves mediated the depressant effect upon the ventricular myocardium which was elicited when the carotid sinus region was stimulated by venous blood or by certain pharmacological agents. It was concluded further that such stimuli actually excited the baroreceptors as well as the chemoreceptors, and that the ventricular myocardial depression was attributable to the baroreceptor activation. While other evidence indicates the probable validity of their assertions that the depression of myocardial contractile force is ascribable to increased parasympathetic activity, the authors were not justified in making such a deduction from their data. Three studies which showed a reflex relationship between baroreceptors and ventricular contractility were done in dogs with bilateral vagotomy, indicating that the reflex must occur in part via the sympathetic system. Therefore, Salem and his collaborators could not have determined from their data the extent to which the ventricular depression might have been ascribable to a reduction in sympathetic tone, rather than to an augmentation of vagal activity.

**Summary**

In three different types of canine heart preparations, it was demonstrated that efferent vagal stimulation exerts a potent, negative inotropic influence upon the ventricular myocardium. In the paced, isovolumetric, left ventricle preparation, vagal stimulation evoked a reduction of left ventricular systolic pressure which, within limits, varied directly with the magnitude of the stimulus. Supramaximal stimulation elicited a mean reduction of 23% in the peak pressure generated by the left ventricle. No differences could be detected between the effects of the right and left vagi upon ventricular contractility. The percentage changes induced by vagal stimulation upon ventricular contractility in the paced heart were less than the percentage changes in heart rate induced in the spontaneously beating heart.

In a pumping heart preparation in which a constant rate of venous return was delivered to the left atrium, vagal stimulation consistently elicited an appreciable elevation of left ventricular end diastolic pressure. Another pumping heart preparation was employed in which changes in atrial transport function and mitral valve closure were excluded by the expedient of introducing a balloon into the left ventricle through an apical incision. This balloon was connected to an artificial external circuit with fixed venous reservoir height and peripheral resistance. Vagal stimulation consistently diminished stroke volume,
“arterial” pressure, and stroke work in such a circuit.

References


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VAGUS NERVES AND VENTRICULAR CONTRACTILITY


Addendum

Three additional studies which provide corroborating evidence for vagal innervation of the ventricles have appeared since this paper was submitted for publication.


Depression of Ventricular Contractility by Stimulation of the Vagus Nerves
HILAIRE DEGEEST, MATTHEW N. LEVY, HARRISON ZIESKE and RALPH I. LIPMAN

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