Effects of vagal stimulation on S-A and A-V nodes

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This paper describes stimulus-strength-response curves equating the degrees of either chronotrope or dromotrope to strength of stimulus applied to either right or left vagosympathetic trunk during sinus rhythm before and after beta adrenergic blockade.

MATERIALS AND METHODS

Healthy mature dogs (31 male and 31 female), weighing between 12 and 26 kg, were anesthetized, intravenously, with fentanyl (0.04 mg/kg) and droperidol (2 mg/kg) (Innovar-Vet, McNeil Laboratories, Fort Washington, Pa.), followed by an intravenous injection of sodium pentobarbital (6 mg/kg). A tripolar cardiac electrode catheter was placed via the right jugular vein so that one electrode lay at the posterior vena caval-right atrial junction, one in the mid-right atrium, and a third at the anterior vena caval-right atrial junction. Position of the electrodes within the right atrium was monitored almost continuously under fluoroscopy. Radiographs of the cardiac silhouette were taken during various stages of vagal stimulation and assured constant position of electrodes within the atrium.

Both vagosympathetic trunks were exteriorized in the neck. Three endoatrial electrograms and lead aVF were recorded, simultaneously, at up to 200 mm/sec paper speed on a direct-writing oscillograph and on an FM tape recorder.

During continuous recording in seven dogs, left vagosympathetic trunk and then right vagosympathetic trunk were cut. In seven dogs, trunks were sectioned in opposite order. A bipolar stimulating electrode was attached to the peripheral end of each trunk. First the left and then the right vagus was stimulated by square pulses of 3 msec duration at 60 cycles/sec for 15 sec duration. Strength varied from 0 to 9 v in 0.5- or 1.0-v increments. In a search for hysteresis in three dogs, left and right vagal stimulation was repeated; but with voltages decreasing from 9 to 0 in 1-v decrements. One minute elapsed between each 15 sec of stimulation.

Next, beta adrenergic efferent activity was blocked with 0.3 mg/kg of propranolol, intravenously, and the
program of stimulation was repeated. Previous studies established the effectiveness of this blockade (7).

Endo-right atrial electrograms were analyzed for configuration and for the instant of the rapid, negative-going deflection. Duration between nadirs of successive P waves permitted estimation of heart rate and reflected chronotropic influences of vagal stimulation. P-Q intervals were measured as the time between onset of P wave in the endoatrial electrogram in which it occurred earliest, and onset of QRS in the lead in which it occurred earliest; thus, this interval was established on occasion from analysis of two electrograms.

Relative effects of left or right vagal stimulation were expressed as plots of P-P and P-Q intervals against amplitude of stimulus. Voltage at which second-degree A-V block appeared was recorded.

RESULTS

All dogs maintained, during anesthesia, a normal sinus arrhythmia (Fig. 1) with an average ventricular rate of 68 beats/min—a value established as normal for the healthy, spontaneously sleeping dog (6).

Satisfactory endoatrial electrograms were recorded in real time and with amplified time axis from the tape (Fig. 2) for precise analysis of P-Q and R-R intervals.

Following section of left vagus in seven dogs with beta adrenergic blockade, heart rate accelerated an average of 3 (SD = 2) % (P = 0.1), while P-Q interval decreased insignificantly (P > 0.3). Following section of right vagus in seven dogs with beta adrenergic blockade, heart rate accelerated an average of 17 (SD = 5) % (P < 0.01) and P-Q interval abbreviated 12 (SD = 4) % (P < 0.05). Following section of both vagi in these dogs, heart rate accelerated 78 (SD = 22) % (P < 0.001) and P-Q interval abbreviated 15 (SD = 8) % (P < 0.01) over the control values. In three dogs, section of both vagi altered neither heart rate nor P-Q interval.

As measured by the time required for the impulse to travel between the unipolar intra-right atrial electrodes located 25 mm apart, conduction velocity through right atrium is 875 (±90 mm/sec) (Fig. 3). Presence of the impulse in the vicinity of the electrode was determined by a rapid negative-going deflection.

Vagal stimulation altered the time course of atrial excitation so that conduction velocities could not be estimated reliably by this method using only three intra-atrial electrograms (Fig. 4). Notice that during vagal stimulation the pacemaker is "pushed" posteriorly into the right atrium so that electrograms recorded from the intra-atrial electrodes in mid-right atrium and at the posterior vena caval-right atrial junction both contained rapid negative-going deflections occurring simultaneously (15). From analysis of such electrograms, one would estimate, incorrectly, the conduction velocity to be infinite. When an obvious progression of time skewing between successive electrodes was not obtained, velocities were not estimated.

The alternating periods of “noble” and “puny” P waves described by Levine (14) in peripheral electrocardiograms during sinus arrhythmia were seen (Fig. 5); but they did not correlate well with the nobility or puniness of intra-atrial electrograms. During inspiration when the P wave in lead aVf is most peaked, the amplitude of the P wave in the intra-atrial electrogram is lowest.
Fig. 2. Same records as previous figure, only recorded from FM tape played back at 1/16th the speed of recording. Fine vertical times lines appear every 3.125 msec.

Ta wave amplitude did not contain the longest P-Q interval. Ta amplitude decayed (Fig. 7) with an average half-time of 5 beats following cessation of vagal restraint.

Plots of P-P and P-Q intervals against volts applied to either vagus (Fig 8) show that within physiological magnitude of stimulation to either vagus, nearly identical responses were exerted on S-A and A-V nodes. At equivalent voltages, P-P intervals prolong equally with right or left vagal stimulation. A similar parallel increase in duration occurred to P-Q intervals with stimulation to either vagus. At voltages just below those required to elicit this negative chronotrope and dromotrope (4-6 v) either positive chronotrope and dromotrope or oscillations in P-P and P-Q intervals occurred in 40% of the dogs.

Hysteresis was not found. That is, equal degrees of P-P and P-Q prolongation were observed at a given voltage when stimulation magnitude ascended to that voltage from 0 to 9 v as when it descended to the voltage from 9 to 0 v. In the three dogs in which left and right vagi were stimulated alternately, no difference in negative chronotrope or dromotrope was observed over when the same magnitude of stimulation was reached by stimulating first one nerve at all voltages and then the other nerve.

Following beta adrenergic blockade with propranolol, P-P and P-Q intervals were prolonged in the absence of vagal stimulation. These intervals prolonged further when vagi were stimulated. The prolongation paralleled closely the prolongation which occurred during vagal stimulation with intact sympathetics. The positive chronotrope and dromotrope or oscillations in P-P and P-Q intervals which occurred during relatively low-
voltage stimulation to either vagus was either abolished or minimized by beta blockade. A quantitative summary of effects of left and right vagal stimulation on all dogs is shown (Table 1).

Second-degree A-V block occurred more prevalently following left vagal stimulation than following right vagal stimulation. It occurred, however, not necessarily during or surrounded by the longest P-Q interval. This observation is true in dogs (Fig. 9), horses, and man.

DISCUSSION

In our experiments, we varied vagal efferent activity by varying strength of stimulus and holding frequency and duration of pulse constant. Russell and Warner (23) and Rosenbleuth and Simeone (19) obtained similar degrees of negative chronotrope by varying frequency and holding strength at a supramaximal 20 v.

Responses are termed “physiologic” because the degree of bradycardia (produced by vagal stimulation) paralleled, closely, that seen in healthy dogs during expiration (6, 7).

That section of right vagus accelerated heart rate 17% (P < 0.01) while section of left vagus accelerated heart rate insignificantly (P = 0.1) in absence of sympathetic efferent activity, suggests that normally right vagal efferent activity exerts greater restraint on the S-A node than does left vagal efferent activity.

That A-V conduction as measured by P-Q interval is abbreviated only 15% by bilateral cervical vagotomy yet abbreviates 85% during exercise (6) suggests that acceleration of this conduction during physiologic stress must arise from either humoral catecholamines or increasing sympathetic efferent activity.

Unilateral vagotomy of the right and left nerve increased the heart rate 17 and 3%, respectively, a statistically significant difference in degree of acceleration (P < 0.01). Bilateral vagotomy resulted in a 78% increase in rate. The limited increase following unilateral vagotomy indicates possibly a reflex inhibitory response (mediated over the remaining intact vagal nerve) to an increase in arterial pressure produced by cardioacceleration. This mechanism is supported by observation of a slight but statistically significant (P < 0.05) increase in mean systemic arterial pressure following right vagotomy. An alternate explanation may be one of “saturation” or “limitation,” in which stimulation of both vagi together would not produce as great a negative chronotropic response as the sum of both nerves stimulated separately. Such an explanation would require convergence of preganglionic parasympathetic fibers with “overlap” of some left and right vagal preganglionic fibers at a common synapse. This is a restriction incompatible with the 1:1 relationship described between preganglionic and postganglionic parasympathetic fibers. Stimulation of both vagi in these experiments demonstrated an equal distribution of the nerves to pacemaker tissue and on heart rate. Different rate effects following unilateral section of the vagus nerves may be due possibly to a central mechanism governing their discharge rates. It seems clear that the true role of the vagi on heart rate is not revealed by unilateral or bilateral vagotomy nor by stimulation of the separate nerves.

We anticipated that stimulating left and right vagi alternately or stimulating one nerve either incrementally from 0 to 9 v or decrementally from 9 to 0 v would not alter our results, since sufficient time between successive stimulation periods permitted apparent complete “recovery” of efferent pathways. This is corroborated by obtaining statistically identical (P < 0.4) degrees of negative chronotrope when a nerve was stimulated for 15 sec at 1 v every 90 sec.

Lack of correlation between amplitudes of P waves recorded from peripheral electrocardiograms and amplitudes of P waves recorded from endocardial electrograms suggests that the height of an intra-atrial electrogram may be dependent, primarily, on contact between electrode and endocardium, and little on the time course of activation.

Whether or not the unipolar electrode is in contact with the endocardium of the atrium is, however, consequential to conduction velocities estimated by registering the time difference between the onset of the rapid, negative-going deflections in leads from unipolar electrodes a known distance apart. Assuming that right atrial activation occurs from sinoatrial node toward both interatrial septum and tricuspid annulus, and
FIG. 4. Intra-atrial electrograms and lead aVF during stimulation at various voltages to right vagus. Notice time skewing of rapid negative-going deflections of P waves registered in the 1.5-v record. Top electrogram deflects before middle, which deflects before bottom. Notice that during 6-v stimulation, rapid negative-going deflections in the bottom and next to the bottom electrograms are synchronous. This represents an alteration in the time course of atrial activation, so that the front of depolarization does not proceed from anterior vena cava toward posterior vena cava, but must proceed at right angles to a line connecting the posterior two electrodes. Notice also the slight abbreviation of P-Q interval during 5-v stimulation (positive dromotrope), and prolongation of P-Q interval during 6-v stimulation (negative dromotrope).

FIG. 5. Three intra-atrial electrograms and lead aVF during sinus arrhythmia. Expiration begins during the middle of the three cardiac cycles at the left. The P wave during inspiration is peaked (noble), and becomes flattened (puny) during expiration. Notice that the P waves (recorded intra-atrially) when the external P wave is peaked are of lower amplitude; whereas the opposite is true when the external P wave is flat.
FIG. 6. Intra-atrial electrogram during increasing amplitude of stimulation to left vagus. Notice Ta wave elevates from 6 to 8 v stimulation while P-Q interval prolongs; however, as voltage increased to 9 v, Ta wave did not elevate further. Second degree A-V block occurred at 8 v.

FIG. 7. Cardiac arrest caused by 8-v stimulation to right vagus. Notice that during recovery of beating, Ta elevation decreased with an approximate half-time of 5 beats. Notice that Ta wave elevated equally with right vagal stimulation as with left vagal stimulation seen in Fig. 9.
FIG. 8. Plots of P-P (left ordinate) and P-Q (right ordinate) in milliseconds against volts of stimulation to right vagus (solid line) and left vagus (broken line). Intervals are shown immediately following anesthesia (intact), and as labeled following left vagal and right vagal sections. Labels followed by P-P indicate postpropranolol.

TABLE 1. Results of left and right vagal stimulation: percent of dogs having particular effects

<table>
<thead>
<tr>
<th></th>
<th>Equal Gains</th>
<th>Right Vagus Dominant</th>
<th>Left Vagus Dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-A node (-chronotrope)</td>
<td>75</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>A-V node (-Dromotrope)</td>
<td>85</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>(2nd-degree block)</td>
<td>10</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>S-A node (+chronotrope)</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A-V node (+dromotrope)</td>
<td>40</td>
<td>0</td>
<td>0</td>
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spreads nearly tangential to both endocardial and epicardial planes; then unipolar electrodes placed either in the middle of the chamber of the right atrium or in contact with endocardium midway between S-A node and either tricuspid orifice or interatrial septum would record first positive activity (as the front approaches the electrodes) then negative activity (as the front passes and travels away from the electrodes). The only differences between deflections recorded would be the increased magnitude recorded from the electrode in contact with the endocardium.

To magnitudes of stimulation great enough to cause either sinus arrest or complete A-V block, we concur with the impressions of others that stimulation of the right vagus has a greater tendency to cause sinus arrest, while stimulation of the left vagus has a greater tendency to cause A-V block.

To our physiologic efferent activity induced along either vagus, equal negative chronotropic and negative dromotropic effects were elicited. Rushmer (22) concluded also that the left vagus had only a slightly less negative chronotropic effect than did the right vagus.

One may not predict the degree of either P-P or P-Q prolongation produced by stimulation to either vagus; for although in most dogs both nerves innervate equally A-V and S-A nodes, in 5% of dogs the left vagus, and in 20% of dogs the right vagus, dominates the S-A node.

Cohn and Lewis (2) in 1912 proposed that the right vagus innervates predominantly the S-A node, while the left vagus innervates predominantly the A-V node. They propose absence of fibers from the left vagus to the S-A node, and very few fibers from the right vagus to the A-V node. Our data, contrary to theirs, suggests that vagal restraint within limits obtained during normal sinus arrhythmia is equal to both S-A and A-V nodes.

We propose (Fig. 10) one addition to the scheme presented by Cohn and Lewis. That is two physiologic areas of the A-V node: one area regulates the total conduction time through the node; whereas the other area determines whether or not the impulse reaches the ventricles. We support the presence of the two physiologic sites by the observation that in at least three species, second-degree A-V block may occur following left vagal stimulation in the absence of prolongation of the P-Q interval. If second-degree A-V block were to occur as an exaggeration of first-degree A-V block (merely prolongation of the P-Q interval until block) then we would expect second-degree block to occur always in or surrounded by the longest P-Q interval.

Since left vagal efferent activity is more influential in producing second degree A-V block, we propose that this vagus “innervates” the first area of the A-V node. Since both vagi exert equal effects in prolonging A-V conduction, if it occurs at all, we postulate that both vagi innervate the second area of the A-V node equally. Watanabe and Dreifus (25) have described that Mobitz-type II (17) (second-degree A-V block without progressive prolongation of the P-Q interval) occurs following stimulation of the left vagus due to blocking of conduction through an area in the A-V node located at the A-V nodal-His junction. From our studies, we were unable to locate, anatomically, the two areas within the A-V node; but only to identify their presence physiologically.

Transatrial conduction velocities established by the methods described here correlate closely with those
FIG. 9. Constant P-Q interval in the presence of second-degree A-V block induced by vagal stimulation. Intra-atrial electrogram taken before stimulation and during 6.5 v to the left vagus. Notice that P-Q interval during conducted beats is not prolonged over the interval before stimulation.

FIG. 10. Schematic representation of distribution of vagal fibers based on our observations. Notice that right and left vagi send equal numbers of fibers to both S-A and A-V nodes, while left vagus sends fibers dominating a region of the A-V node which causes second-degree A-V block. Although in this drawing the second region marked A-V 2 is placed above the region responsible for rate of conduction through this node, Watanabe has demonstrated by microelectrode studies that this zone is in fact near the nodal-His junction.
proposed by Hoffman (10). Our method has the disadvantage that if the pacemaker happens to be located near the middle electrode, estimation of conduction velocities will be incorrect (6, 15). On the other hand, it has the advantage that conduction velocities may be estimated following proper placement of the electrodes in an intact unanesthetized dog.

That stimulation of either vagus with low voltages produces an increase in heart rate and a shortening of P-Q interval is an interesting observation which had been made previously (8, 11, 12, 13, 16). Two mechanisms to explain this positive chronotropic and positive dromotropic responses have been proposed. The first suggests that sympathetic fibers in the vagosympathetic trunk may be stimulated either directly by the stimulator or by irradiation from parasympathetic fibers lying close to sympathetic fibers. If the threshold for these fibers is lower than for parasympathetic, then the sympathetic activity should dominate during stimulation of low voltage. The second explanation may be that acetylcholine produced during stimulation of the vagi causes the release of norepinephrine resulting in the positive chronotropic and dromotropic responses. We are unable to lend support to the correctness of either mechanism, since the reduction in this positive chronotropic and dromotropic following beta adrenergic blockade is compatible with both explanations. That Donald et al. (3) failed to observe this positive activity in isolated hearts perfused with blood from donor dogs undergoing positive activity resulting from vagal stimulation with low voltages suggests the mechanism is a sequel to sympathetic efferent activity and not to the production of a humor.

This research was supported, in part, by grants-in-aid from the National Institutes of Health. HE-11542-01, and Program Project: "Biology of the Heart," HE-09884-03.

This paper was presented before the Fall 1967 American Physiological Society Meeting, Washington, D.C.

Received for publication 15 January 1968.

REFERENCES


