Influence of Brief Vagal and Stellate Nerve Stimulation on Pacemaker Activity and Conduction within the Atrioventricular Conduction System of the Dog

By Joseph F. Spear and E. Neil Moore

ABSTRACT

Experiments were performed on open-chest anesthetized dogs to determine the quantitative effects of autonomic nerve stimulation on pacemaker activity and conduction. The lead II electrocardiogram together with bipolar electrograms were recorded from the atria, the His bundles, and the vestibules. The vagi or the stellate ganglia were stimulated in dogs which exhibited either sinus rhythm, ectopic atrial rhythm, junctional rhythm, or ectopic ventricular rhythm. The time courses of the change in heart rate in response to vagal or stellate stimulation were characteristic for each type of rhythm. The characteristic responses of different cardiac pacemaker sites to autonomic influence were demonstrated to be important factors in the production of wandering pacemakers and in the emergence of ectopic beats. Sinus pacemaker activity was more sensitive to modification by autonomic stimulation than was atrioventricular (AV) conduction. However, subliminal autonomic effects on AV transmission were brought out during conduction of premature atrial beats, thereby demonstrating a coupling interval dependency of autonomic influences on AV conduction. The present experiments also showed how fluctuations in autonomic activity could result in Mobitz type II second-degree heart block, pseudosupernormal conduction, and the concertina effect observed in the preexcitation syndrome.

KEY WORDS

His bundle electrograms autonomic innervation cardiac arrhythmias
junctional arrhythmias atrial arrhythmias
ventricular arrhythmias vagal stimulation
cardiac electrophysiology sympathetic stimulation AV conduction

Cardiac arrhythmias can be classified in two general categories: those due to disturbances in impulse formation and those due to disturbances in impulse conduction. Autonomic nerve activity can modify impulse formation and conduction within the heart, and the importance of the influence of autonomic activity on various cardiac arrhythmias has been well documented (1). Several laboratories have shown that discrete stimulation of the brain and direct stimulation of vagal and sympathetic nerves can result in a wide spectrum of cardiac arrhythmias (2-5). The autonomic nervous system has also been implicated in arrhythmias generated by drug application and coronary artery occlusion (6, 7). However, the specific mechanisms involved in the production of arrhythmias by sympathetic and parasympathetic nerve influences in general remain poorly understood. The recent study of de la Fuente et al. (8) suggested that the sinus node and the atrioventricular (AV) node may exhibit different characteristic responses to vagal stimulation.

The present investigation was undertaken to determine the quantitative effects of controlled vagal and stellate stimulation on the specific responses of and the interactions between sinus, atrial, junctional, and ventricular cardiac pacemaker sites. These experiments provided new comparative data concerning the interrelationships and the influence of autonomic stimulation on impulse formation and conduction in various regions within the heart. The data elucidated specific mechanisms by which the sympathetic and parasympathetic nervous systems are involved in the production of such clinical arrhythmias as Mobitz type II AV block and pseudosupernormal conduction.

Methods

Experiments were performed on 23 adult mongrel dogs of either sex weighing 13-15 kg and anesthetized...
with sodium pentobarbital (30 mg/kg, iv). Sodium pentobarbital was chosen as the anesthetic to depress cardiovascular response to ensure stable control of pacemaker discharge rates (5). The chest was opened using either a right thoracotomy or a midsternotomy, and the dogs were ventilated by a positive-pressure respirator at a minute volume determined from a body weight nomogram. Close bipolar plunge electrodes (10) were used to record simultaneously from the right atrium, the His bundle, and the anterior free wall of the right ventricle, along with the lead II electrocardiogram (ECG). The right atrial recording electrode was positioned at the low atrial septum except when the node was experimentally crushed. In these cases, the electrode was positioned at the high right atrium in an uncrushed region adjacent to the crushed sinus region. Electrodes were also applied to the right atrial appendage for pacing the hearts. In all preparations both vagi were isolated in the neck and decentralized; stimulating electrodes were applied to the peripheral end. The left and right stellate ganglia were exposed, and stimulating electrodes were attached. In all procedures involving the study of vagal stimulation, the experiments were performed with and without the application of propranolol (1.0 mg/kg, iv) to verify that the effects were not complicated by adrenergic influences. Unless specified otherwise, nerve stimulation was accomplished using square pulses 4 msec in duration delivered at 100 Hz for 100 msec. Both the heart pacing stimuli and the nerve stimulations were controlled by a digital stimulator. The intensity of the stimulating current was monitored by recording the voltage drop across a precision 1000 ohm resistor in series with the stimulating electrodes. The intensity of stimulation varied between 2.0 and 20.0 ma. The stimuli were supramaximal for all experiments except those involving the time course of vagal influences on AV conduction. The intensity of stimulation was that necessary to produce maximal conduction delay without causing blocked beats, except in those experiments in which blocked beats were specifically being studied.

In our studies, we observed no consistent differences between right and left nerve stimulations regarding the intensity of current necessary to produce an effect. We felt that inherent uncertainty about variability in the electrochemical coupling prevented us from quantitatively studying this aspect.

To test the effect of autonomic nerve stimulation on pacemaker activity, our experiments were performed on dogs in sinus rhythm, ectopic atrial rhythm, junctional rhythm, or ectopic ventricular rhythm. All of the dogs were initially in sinus rhythm. This fact was verified by the normal F wave and P-R interval in the ECG. Also, the earliest atrial activity was recorded from the region of the sinus node. To produce either ectopic atrial or junctional rhythms, the sinus node was crushed. In 5 of 11 dogs, the preparations exhibited ectopic atrial rhythms when the node was crushed. The ectopic atrial rhythm was defined as a nonsinus rhythm which produced supraventricular QRS configurations and in which the low atrial activity always preceded His bundle activity in the His bundle electrograms. In these cases, the F waves were usually inverted and the P-R intervals were shortened. The precise location of the ectopic atrial pacemaker was not determined; however, it was probably within the atrium itself or in the upper regions of the AV node.

In dogs with junctional rhythms, the QRS complex was of supraventricular configuration and the His bundle spike in the His bundle electrogram preceded the atrial atrial spike and was the earliest activity recorded with our electrodes. Also, retrogade conduction to the atrium always occurred. The pacemaker in these cases was either within the His bundle in the lower regions of the AV node.

To produce ectopic ventricular rhythms, complete AV block was induced either by localized sectioning of the His bundle with a 25-gauge needle introduced through the right atrial free wall or by a local 40-watt second electrical discharge through the His bundle recording electrode. Following complete AV block a stable multifocal ectopic ventricular pacemaker usually took over ventricular control, resulting in the stable rate and the constant configuration of the QRS complex.

The spontaneous basic cycle lengths for the preparations exhibiting the various rhythms were 0.371 ± 0.042 (SD) seconds for sinus rhythm, 0.511 ± 0.110 seconds for ectopic atrial rhythm, 0.639 ± 0.184 seconds for junctional rhythm, and 1.223 ± 0.372 seconds for ectopic ventricular rhythm. That the locus of the pacemakers was not greatly shifting during the autonomic response determinations was confirmed by the constancy of the configurations of the local electrograms and the time relationships between them. We could not rule out localized shifts in pacemakers with our technique.

All analog data during the experiments were displayed on a Tektronix 365 eight-channel oscillograph and recorded on 35-mm film. The analog data were then projected on a film reader (Microfiche Inc.), and the time intervals were measured. These measurements were reproducible with an accuracy of within 2 msec.

### Results

#### Autonomic Influence on Pacemaker Activity

Figure 1 presents representative time courses of changes in basic cycle length following a 100-msec train of stimuli delivered to the vagi of dogs exhibiting either sinus, ectopic atrial, junctional, or ectopic ventricular rhythms. The results for each individual experiment are summarized in Table 1. The time course data for Figure 1 were derived by measuring the successive intervals between beats following a vagal stimulus train. These values were then plotted on the ordinates as the respective pacemaker intervals. The abscissa values were derived by plotting the times from the beginning of the vagal trains to the beat closing the respective cycle lengths plotted on the ordinates. To obtain a sufficient number of points for the graphs of each experiment, the vagal stimuli were repeated several
AUTONOMIC EFFECTS ON THE HEART

Representative time courses of the changes in basic cycle length following brief vagal stimulation during sinus rhythm, ectopic atrial rhythm, junctional rhythm, and ectopic ventricular (ventr.) rhythm are shown. Each graph represents a single experiment. The data from all experiments in this series are summarized in Table 1. A 100-msec burst of stimuli was delivered to the left or the right vagus at time zero in all cases. In the examples presented, all effects were produced by right vagal stimulation except in the case of the ectopic ventricular rhythm which was left vagal. The examples for sinus rhythm and junctional rhythm were determined in the presence of propranolol (1.0 mg/kg, i.v.). Notice the change in the scaling factor for the abscissa of the ectopic ventricular rhythm as compared with the other rhythms.

Times following the return of the pacemaker intervals to control values. Table 1 was compiled by measuring the latency, the time to peak, the duration, and the percent change from control for each experimental time course determination, and it exhibits the range of variability of these parameters for the experiments.

Each pacemaker site responded in a characteristic way following vagal stimulation (Fig. 1, Table 1). Latency (the period from the beginning of the vagal stimulation train to the initial increase in the cycle length) increased in the following order: sinus rhythm, junctional rhythm, ectopic atrial rhythm, and ectopic ventricular rhythm. Both sinus rhythm and junctional rhythm graphs consistently demonstrated double peaks. The troughs between the peaks occurred between 0.80 and 1.20 seconds after vagal stimulation, and the troughs in some dogs undershot the baseline. The double peak in the sinus rhythm response to vagal stimulation was first reported by Brown and Eccles (11) and has been observed subsequently by other investigators (18). The junctional rhythm response was characteristically different from the sinus rhythm response in that the junctional response exhibited a larger second peak compared with the second peak of the sinus rhythm response. In two dogs the second peak exceeded the amplitude of the first peak during junctional rhythm. The presence of propranolol (1.0 mg/kg) did not change the timing or the appearance of the pacemaker responses to vagal stimulation. Brown and Eccles (11) and Levy et al. (12) concluded that the double peaks were not caused by shifts in pacemaker sites but rather by the intrinsic response of the pacemaker receptor to the neural transmitter. A similar mechanism may be operable during the heart's positive rebound overshoot following the negative inotropic response to vagal stimulation (13) or the injection of acetylcholine into the coronary artery (14).

The response of ectopic atrial pacemakers to vagal stimulation was most variable. The time course usually exhibited a smooth single-peaked curve, but in one preparation there was a double peak. The latency was 0.400-0.445 seconds in four of the six preparations, but two experiments produced latencies of 0.230 and 0.300 seconds. In complete A-V dissociation had been induced (Table 1), vagal stimulation produced slowing of the ectopic ventricular rhythm. The time course always had a single peak and showed extremely long latencies of 0.800-1.300 seconds compared with the other pacemaker sites. The total duration of the effect was also relatively long, lasting from 14.00-18.00 seconds.

In our experiments, we detected no difference in the time courses of the various pacemaker sites in response to left vs. right vagal stimulation. This reaction also was observed by Brown and Eccles (11) for left and right vagal effects on sinus
TABLE I

<table>
<thead>
<tr>
<th>Pacemaker</th>
<th>Midpoint latency (ms)</th>
<th>Peak effect (ms)</th>
<th>Duration (ms)</th>
<th>% Change from control</th>
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<td>Sinus node</td>
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<td>0.20, 1.45</td>
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</tr>
<tr>
<td></td>
<td>LV</td>
<td>0.200</td>
<td>0.20, 1.70</td>
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</tr>
<tr>
<td>Ectopic atrial</td>
<td>RV</td>
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<td>LV</td>
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<td>0.20, 1.70</td>
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</tr>
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<tr>
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<td>LV</td>
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<td>0.20, 1.70</td>
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<td>LV</td>
<td>0.200</td>
<td>0.20, 1.70</td>
<td>5.00</td>
</tr>
</tbody>
</table>

RV = right vagus, LV = left vagus. * = value not obtained.

1.0 mg/kg propranolol added.

rhythm. However, many investigators have reported left and right differences in the intensity of inotropic and chronotropic responses of the heart to both vagal and stellate stimulation (15-18).

Figure 2 presents representative results of similar studies in which the stellate ganglia were stimulated. The graphs were generated in the same way as those in Figure 1. The data for the individual stellate ganglia stimulation experiments are summarized in Table 2. The time courses of the responses to stellate stimulation were much more uniform among the various pacemaker sites than were the responses to vagal stimulation (Fig. 1). The latency from the beginning of the stellate stimulus to the first shortening of the cycle lengths was consistently between 0.800 and 1.120 seconds for sinus, ectopic atrial, and junctional rhythms. Ectopic ventricular rhythms had somewhat longer latent times of 0.950-3.000 seconds; they also exhibited the longest times to peak effect and the longest durations. In all four types of rhythm, the phases of the individual pacemaker response to stellate stimulation were of much longer duration than the comparable phases in response to vagal stimulation (Figs. 1 and 2, Tables 1 and 2). Only the time course of the changes in ectopic ventricular rhythm following vagal stimulation was similar to the time courses of the stellate responses. In 9 of the 21 experiments, there was a slight overshoot of the base line after the pacemaker returned to control rhythm following stellate stimulation. The average overshoot was 2.35, and examples are shown in Figure 2 for the sinus rhythm and the ectopic ventricular rhythm. The overshoot was abolished by atropine (0.5 mg/kg) and, therefore, probably represented a rebound decrease in sympathetic tone following the stellate stimulation.

AUTONOMIC INFLUENCES ON PACEMAKER INTERACTIONS

Following sinus node destruction our preparations established either junctional rhythms or ectopic atrial rhythms. Because of the differing characteristics between junctional and ectopic atrial pacemakers in response to autonomic nerve stimulation (Figs. 1 and 2), the pacemaker site in some preparations could be transiently shifted from one locus to another. These interactions among pacemakers are demonstrated in the subsequent experiments.

Figure 3 is an example of a heart that was in a stable junctional rhythm after crushing of the sinus node. The first two beats in the figure demonstrate the characteristics of the junctional rhythm. The initial activity in the His bundle electrogram was the His spike. There was retrograde capture of the atrium indicated by the P wave which followed the QRS complex in the electrocardiogram. The low atrial septal component of the His bundle electrogram was obscured by the ventricular septal.
AUTONOMIC EFFECTS ON THE HEART

31

So.

ECTOPIC ATRIAL RHYTHM

ECTOPIC JUNCTIONAL RHYTHM

ECTOPIC VENTRICULAR RHYTHM

5.00

TIME AFTER STIM.

FIGURE 1

Representative time courses of the changes in basic cycle length following brief stellate stimulation during sinus rhythm, ectopic atrial rhythm, junctional rhythm, and ectopic ventricular (ventr.) rhythm are presented. Each graph represents a single experiment. The data from all experiments in this series are summarized in Table 2. A 100-msec burst of stimuli was delivered to the left or the right stellate ganglia at time zero in all cases. The examples shown resulted from right stellate stimulation. The scaling factor for the abscissa is the same in all cases.

component. Following left vagal stimulation the interval between His spikes began to increase. In the third beat, the junctional pacemaker had been delayed sufficiently so that it no longer captured the atrium, and an independent ectopic atrial pacemaker was manifest at this time. To beat 5, the P wave was observed by the QRS complex, and the atrial septal component could now be distinguished in the His bundle electrogram between the His spike and the ventricular septal component. The vagal stimulation influenced the junctional pacemaker more than it influenced the ectopic pacemaker so that the junctional pacemaker was delayed more than the ectopic pacemaker. When the junctional pacemaker had been delayed sufficiently relative to the ectopic atrial pacemaker, the atrial site was able to capture the junctional site, and the system shifted to an ectopic atrial rhythm in beat 4. The capture of the junctional pacemaker is indicated by the sudden shortening of the interval between His bundle spikes between beats 4 and 5. Notice the inverted P wave preceding the QRS complex. As the effects of the vagal stimulation began to wear off (not shown in the figure), the ventricular rate followed the dominant ectopic atrial pacemaker until the recovering junctional pacemaker escaped at a rapid enough rate to suppress the ectopic atrial site. The system then returned to the previous state, i.e., a stable junctional rhythm.

Figure 4 demonstrates the different characteristics of another preparation in a stable junctional rhythm. The first and the second beats showed an initial His spike in the His bundle electrogram, and there was retrograde capture of the atrium indicated by the right atrium electrogram. Following vagal stimulation the third beat was delayed somewhat. Notice also that the retrograde conduction time from the His spike to the right atrium increased, suggesting the low nodal or His bundle character of the junctional beats. Following the slightly delayed third beat, the fourth beat was

FIGURE 2

Vagal stimulation caused a shift from a junctional rhythm to an ectopic atrial rhythm. Bipolar electrodes were used to record the His bundle electrogram (BH) simultaneously with a lead II electrocardiogram (II). In the His bundle electrogram, a indicates the atrial septal activity, h the His bundle spike, and s the ventricular septal activity. Consecutive beats are labeled 1-5. P indicates a retrograde P wave in beats 1 and 2. The V indicates the timing of a 100-msec train of stimuli delivered to the left vagus. The timing signal (T) denotes 100-msec intervals.

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Stellate Influence on Pacemaker Activity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Inhibition (%)</th>
<th>Time to peak (sec)</th>
<th>Reaction (sec)</th>
<th>% Change from control</th>
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<tr>
<td>Ventricular</td>
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<td>7.80</td>
<td>14.00</td>
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<tr>
<td></td>
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<td></td>
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<tr>
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<td>1.45</td>
<td>6.30</td>
<td>14.50</td>
<td>6.4</td>
</tr>
</tbody>
</table>

RS = right stellate ganglion, LS = left stellate ganglion.

delayed to such an extent that an ectopic ventricular pacemaker escaped. In contrast to Figure 5, there was no functional ectopic atrial pacemaker to take over, therefore, the rhythm suddenly shifted from functional to ventricular.

In Figure 5 the preparation was initially in an ectopic atrial rhythm. The atrial or upper nodal character of this rhythm is indicated by the atrial septal spike preceding the His bundle spike in the His bundle electrogram and by the fact that the electrogram from the high right atrium followed the atrial septal spike. Following stellate stimulation, the acceleration of the ectopic atrial rhythm gradually developed, in contrast to the more rapidly developing vagal effects (Figs. 1-3 and 5). Notice that in beat 6, the His bundle spike had moved in front of the right atrial spike, indicating that a functional pacemaker had escaped. The junctional pacemaker accelerated faster than the ectopic atrial pacemaker, and by beat 9 the junctional pacemaker

![Figure 4](http://circres.ahajournals.org/)

**Figure 4**

Vagal stimulation caused a shift from a junctional rhythm to an ectopic ventricular escape. Bipolar electrograms were recorded from the right atrium (RA), the bundle of His (BH), and the right ventricle (RV) simultaneously with a lead II electrocardiogram (EKG). In the His bundle electrogram is indicated the His bundle spike. V indicates the timing of a 135-msec train of stimuli delivered to the right vagus. The timing signal (T) indicates 100-msec intervals.
Autonomic effects on the heart

Stellate stimulation caused a shift from an ectopic atrial rhythm to a junctional rhythm. Bipolar electrodes were used to record from the right atrium (RA), the bundle of His (BH), and the right ventricle (RV) simultaneously with a lead II electrocardiogram (ECG). In the His bundle electrogram, a and h indicate the atrial septal and the His bundle activation, respectively. Consecutive beats are labeled 1-9. The ST indicates the timing of a 275-msec train of stimuli delivered to the right stellate ganglion. The timing signal (T) denotes 100-msec intervals.

Captured the ectopic atrial pacemaker, the system then shifted to a junctional rhythm with retrograde capture of the atrium. The interval between the His bundle spike and the right atrium spike remained constant as long as the junctional pacemaker remained dominant. During recovery from the stellate effects (not shown in the figure), the system again shifted back to its original ectopic atrial rhythm. This shift was reproducible with successive stellate stimulations for this 2-hour phase of the experiment.

Autonomic influences on atrioventricular conduction

Figure 6 compares examples of the effect of 100-msec vagal or stellate stimulation on AV conduction. Table 3 summarizes these data from all of the experiments. Preparations were paced at a constant basic cycle length from electrodes located on the right atrial appendage. A train of right or left vagal or stellate stimuli were then applied, and the time interval between the electrograms from the low atrial septum and the His bundle was determined and plotted on the ordinates. The times from the beginning of the burst of stimuli to the successive His bundle electrograms were plotted on the abscissa. The graphs, therefore, give an index of the time course of changes in the duration of impulse conduction through the AV node following either vagal or stellate stimulation. In Table 3 following vagal stimulation, the latency to the beginning of conduction delay was 0.165-0.230 seconds, and, following stellate stimulation, the latency for acceleration of conduction was 1.000-1.500 seconds. The vagal response rose rapidly to its peak values and returned to control values within 0.80-1.15 seconds. The stellate response moved slowly to its peak and returned in 13.0-21.0 seconds. Thus, the vagal effect ran its full course in the time equal to the latency during stellate stimulation. For both the vagal stimulation and the stellate stimulation, the latencies for the effect on AV nodal conduction were comparable to their respective latencies for the effect on a junctional pacemaker (Figs. 1 and 2).
TABLE 1

Vagal and Sural Influence on Atrioventricular Conduction

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Latency (sec)</th>
<th>Duration to peak (sec)</th>
<th>Duration (sec)</th>
<th>% Change from control</th>
</tr>
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<tbody>
<tr>
<td>RV</td>
<td>0.220</td>
<td>0.350, 0.745, 1.045</td>
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<tr>
<td>RV</td>
<td>0.212</td>
<td>0.410, 0.730</td>
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<td>RV</td>
<td>0.195</td>
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<tr>
<td>RV</td>
<td>0.192</td>
<td>0.350</td>
<td>0.80</td>
<td>20.0</td>
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<tr>
<td>LV</td>
<td>0.160</td>
<td>0.370, 0.879</td>
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<td>45.0</td>
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<tr>
<td>LV</td>
<td>0.180</td>
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<tr>
<td>RS</td>
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<td>5.000</td>
<td>21.00</td>
<td>16.5</td>
</tr>
<tr>
<td>LS</td>
<td>1.300</td>
<td>4.600</td>
<td>12.00</td>
<td>10.0</td>
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</table>

RV = right vagus, LV = left vagus, RS = right stellate, and LS = left stellate.

Tables 1 and 2). At high intensities of vagal stimulation, conduction could be completely blocked within the AV node. The AV node appeared less sensitive to stellate stimulation, because, to demonstrate the acceleration of AV nodal conduction, the preparations had to be paced relatively rapidly to place an initial delay on AV conduction time. In addition, the magnitude of the change in AV conduction in response to stellate stimulation was also smaller than the changes induced by vagal stimulation (Table 3). In our experiments using brief vagal and stellate stimuli we were not able to demonstrate an influence on atrial, His-Purkinje, or ventricular conduction. Wallace and Sarnoff (19) found prominent shortening of AV nodal conduction during stellate stimulation with minimal effects on His-Purkinje and ventricular muscle conduction.

In three of six experiments, the time course of the delay in AV conduction following vagal stimulation exhibited two or three peaks. One such experiment is presented in Figure 7. The basic cycle length of the preparation determined the time of occurrence of the second and third peaks. In Figure 7, the basic cycle length was 0.330 seconds, and the second and third peaks occurred approximately 0.330 and 0.660 seconds after the first. The experiment illustrated by Figure 8 demonstrates the mechanism of the secondary peaking of AV conduction following vagal stimulation. Figure 8A is an example of the
The influence of vagally delayed AV conduction on the conduction time of subsequent beats. Bipolar electrograms were recorded from the right atrium (RA), the bundle of His (BH), and the right ventricle (RV) simultaneously with a lead II electrocardiogram (II). In the right atrium electrogram, A indicates the beats initiated before vagal stimulation, and A', A'' and A''' indicate successive beats following vagal stimulation. In the His bundle electrogram, a and h indicate atrial septal and His bundle activation, respectively. The a-h intervals are indicated in milliseconds for the A, A', A'', and A''' beats. V indicates the timing of a 100-msec train of stimuli delivered to the left vagus. The timing signal (T) denotes 100-msec intervals.

Type of data that was used to generate the graphs presented in Figures 6 and 7. The heart was paced from the right atrium at a basic cycle length of 0.330 seconds. The AV nodal conduction time is indicated by the interval between atrial septal activation and His bundle activation in the His bundle electrogram. Before vagal stimulation the AV nodal conduction time was 50 msec, and the AV nodal conduction times for the three following beats were 112, 88, and 69 msec, respectively. The multiple peaking effect of brief vagal stimulation was produced in the following way. After the vagal stimulus in Figure 6A the AV nodal conduction time of the beat labeled A' was prolonged. The following beat labeled A'' was influenced by two different factors. First, the vagal stimulus train caused the usual slowing of AV nodal conduction. The second factor was a change in the preceding conduction coupling interval; the delayed nodal conduction of the previous beat (A') caused beat A'' to be conducted through the node at a shorter His spike interval. Beats are conducted more slowly at shorter coupling intervals. Therefore, when the atria are driven at a constant basic cycle length, the greater the vagally induced conduction delay of the first beat is, the greater the effective reduction in coupling interval for the subsequent beats will be. Consequently, the coupling interval influence on subsequent conduction should be most pronounced following those initial beats which are most delayed.
The sinus node was allowed to escape. The figure shows the increased (interval between the atrial septal and the His spikes) of the beat labeled A and the sinus escape interval. By sequentially changing the timing between the vagal burst and the paced and escape beats, we were able to simultaneously generate the two graphs of Figure 9B, providing coincident information about the influence of vagal stimulation on AV conduction and pacemaker activity.

In Figure 9B, the top ordinate is the sinus escape interval, the bottom ordinate is the interval between atrial septal and His spikes. The abscissa in both graphs is the time after vagal stimulation. In these experiments it was possible to deliver vagal stimulus trains at sufficiently low intensity so that no discernible delay in AV nodal conduction occurred, but the same intensity of vagal stimulation was sufficient to influence the sinus pacemaker. Figure 9B illustrates an increase in the sinus escape interval in the top graph without any change in the interval between the atrial septal and His spikes. At a higher intensity of stimulation there was both an increase in the sinus escape interval and an increase in the interval between the atrial septal and the His spikes. We observed identical results in five dogs, using both left and right vagal stimulation.

In preparations in which AV conduction was not affected by low intensity vagal or stellate stimulation, autonomic influences could be emphasized by causing conduction during the nodal relative refractory period, using premature atrial beats. Results of such an experiment are shown in Figure 10. The intensity of vagal stimulation was constant and below the threshold necessary to cause an effect on the AV conduction of the normally driven beats. This value varied from dog to dog but was usually less than 1.0 ma. Nevertheless, it was sufficient to cause some delay in the sinus escape interval following the premature atrial beat. This difference was previously demonstrated in Figure 9B. The constancy of the degree of delay of a sinus escape beat was used as an index of the stability of the vagal stimulation during the determinations. Notice in the top graph that there was no deviation in AV conduction time from control values during vagal stimulation for premature beats at long A1-A2 cycle lengths. However, premature beats at A1-A2 cycle lengths below 300 msec were delayed within the AV node to a greater degree during vagal stimulation than during the control situation. During vagal stimulation the functional refractory period (the shortest A1-A2 interval between two conducted beats from the atrium) was increased from 235 msec to 255 msec. The effective refractory

**Circulation Research. Vol. XXII, January 1975**
AUTONOMIC EFFECTS ON THE HEART

A

RA

BH

RV

Differences between AV nodal conduction and pacemaker activity in their sensitivities to vagal stimulation are presented. A: An example of the analog data. Bipolar electrograms were recorded from the right atrium (RA), the bundle of His (BH), and the right ventricle (RV) simultaneously with the lead II electrocardiogram (II). In the right atrium electrogram, A indicates the last of a series of 12 driven beats; A1 is the spontaneous atrial escape beat following the cessation of atrial pacing. The atrial pacing signals can be noted in the record labeled S. In the His bundle electrogram, a and h indicate the atrial septal and His bundle activation, respectively. V above the right ventricle trace indicates the timing and the duration of a train of stimuli delivered to the right vagus nerve. The interval V-h indicates the vagal stimulation to His bundle time, and the interval V-A1 indicates the vagal stimulation to sinus node escape time. The timing signal (T) indicates 100-msec intervals. B: Plots of the data derived from measurements such as those demonstrated in A are presented. The abscissa is time after vagal stimulation plotted as the V-A1 intervals (top) and the V-h intervals (bottom). Crosses indicate the measurements made at a stimulation intensity of 2.0 ma, and circles indicate measurements made at a greater stimulation intensity of 10.0 ma.
A comparison of the effects of vagal and stellate stimulation on AV nodal conduction during premature atrial beats is shown. The $A_t - A_t$ intervals (the intervals between the last of a series of 12 basic atrial beats and a premature atrial beat introduced at progressively more premature times) are on the abscissa. The ordinates are the $h_t - h_t$ intervals (the intervals between the His bundle activation of the last of a series of basic atrial beats and the His bundle activation of a premature atrial beat). The crosses connected by the solid lines are the control points determined without background nerve stimulation, and the circles connected by the broken lines are the experimental points determined during nerve stimulation. The experimental points of the top graph were determined during continuous 100-Hz stimulation of the right vagus. The experimental points of the bottom graph were determined during continuous 100-Hz stimulation of the right stellate ganglion. In this preparation the sinus node was crushed, and the heart was paced from the right atrial appendage.

The effect of vagal stimulation on ectopic ven- tricular pacemakers was unexpected; however, other reports indicate that the vagus can directly influence ventricular contractility and rate (21-23). The prolonged latency and the long time course of the vagal effect on the ventricular ectopic rhythm contrasts with the rapid vagal effect on the other pacemaker sites and may be a reflection of a comparatively sparse vagal innervation of the ventricle (24).

In Figures 1-5, autonomic nerve stimulation caused shifts in the site of the dominant pacemaker; the shifts followed predictable patterns that were dependent on the characteristic responses of the individual pacemaker sites involved. The latency for a vagal effect on a junctional pacemaker was shorter than that for an ectopic atrial pacemaker. Also, the time to peak effect was usually shorter and the magnitude of the effect (percent change from control) was usually greater for the junctional pacemaker than it was for the ectopic atrial pacemaker. Consequently, in Figure 3, the junctional pacemaker was more effectively depressed than was the ectopic atrial pacemaker following the vagal burst, and the ectopic atrial pacemaker could, therefore, escape and transiently control the heart. In the situation where an ectopic atrial pacemaker site was not available to assume control during the depression of the junctional site, an ectopic ventricular pacemaker escaped (Fig. 4).
AUTONOMIC EFFECTS ON THE HEART

An example of a reduction in the severity of second-degree heart block following stellate ganglion stimulation is presented. Bipolar electrograms were recorded from the right atrium (RA) and the right ventricle (RV) simultaneously with a lead II electrocardiogram (II). ST indicates the timing of a 1.66-second train of stimuli delivered to the right stellate ganglion. The time signal (T) denotes 100-msec intervals. The arrow indicates the beat that was conducted due to the stellate stimulation.

In Figure 5, a brief stellate burst shifted the dominant rhythm from ectopic atrial to junctional. The effects of stellate stimulation on both the functional and the ectopic atrial pacemakers were of long latency and rose to peak effect relatively slowly. However, the magnitude of the effect (percent change from control) was usually greater for the junctional pacemaker than it was for the ectopic atrial pacemaker. Consequently, in Figure 5, the shift in the pacemaker site developed slowly. Nevertheless, the accelerating influence of stellate stimulation on the dominant junctional pacemaker site did cause it to escape and transiently control the heart. These data suggest that an important factor involved in the production of wandering pacemakers and the emergence of single or multiple ectopic beats during increased autonomic activity is the differing sensitivities and response characteristics of the various potential pacemaker sites.

Because AV nodal conduction is sensitive to changes in rate and rhythm, autonomic influences on pacemaker sites can indirectly influence the character of AV conduction by the changing coupling intervals. Figures 7 and 8 show that even during constant pacing of the heart, changes in AV conduction time modified the effective coupling interval at which subsequent beats were conducted; these coupling interval effects were additive with the direct neural influences on AV conduction.

Figure 9 demonstrates that the sinus node pacemaker was more sensitive to vagal stimulation than the AV nodal conduction. However, intensities of vagal and stellate stimulation which normally produce no apparent effect on AV conduction of normal beats can cause an effect on beats conducted during the nodal relative refractory period, e.g., the conduction of premature atrial beats. These data emphasize that a change in the rhythm of the heart can change the sensitivity of the AV node to autonomic influences. These data also suggest that modification of the physiological state of the heart can modify its sensitivity to autonomic influences. Disease processes, myocardial ischemia or injury, etc. would be expected to modify the sensitivity and the response pattern of the heart during autonomic influences.
We considered some of the characteristics of individual tissues within the heart in response to stimulation by vagal and sympathetic activity, and we demonstrated the complex direct autonomic effects on pacemaker activity, impulse conduction, and cardiac cycle length as well as reciprocal interactions between these factors. In animals in which cardiovascular reflex pathways are intact, the possibilities for extremely complex interactions between these factors in arrhythmia production are increased autonomic activity becomes apparent. Such considerations are beyond the scope of the discussion; however, the present study does suggest some ways in which autonomic activity participates in specific arrhythmias.

Direct recordings from the vagi have shown that vagal activity is phasic and can be correlated with arterial pulse pressure and respiratory movements (25). These rapidly changing vagal influences can produce discrete phasic arrhythmias. Our data suggest that vagal activity can modify AV conduction to produce patterns resembling first- and second-degree heart block. Based on the electrocardiogram, Figure 5B is an example of Mobitz type II second-degree block (25). The vagal burst caused the suddenly blocked beat without causing lengthening of the preceding R-R interval. In this case, the beat was blocked in the AV node. In most previously reported cases of Mobitz type II block, the block developed below the AV node within the ventricular specialized conduction system. The phasic changes in AV conduction produced by vagal influences can also be a mechanism of the concertina effect observed in some cases of the Wolff-Parkinson-White syndrome, as we have recently reported (27).

Although sympathetic influence on AV conduction was longer lasting and spread over a larger number of heart beats, phasic variations in sympathetic activity produced sudden discrete modifications in conduction under some conditions. In the case of Figure 11, single beats that were usually blocked were conducted to the ventricles only following stellate stimulation. The facilitation in the conduction of these beats could be interpreted as a case of pseudosupernormal conduction. Moe et al. (28) have described other cases of pseudosupernormal conduction due to phasic variation in vagal tone. The rhythm of each pacemaker site responds in a characteristic way to either vagal or stellate stimulation. In general, vagal influences are more rapidly acting and of greater intensity than the sympathetic influence. Under normal circumstances, sinus pacemaker activity is more sensitive to modification by autonomic stimulation than is AV conduction. However, subliminal autonomic effects can be brought out by beats conducted during the nodal relative refractory period. There are reciprocal influences between changes in pacemaker activity and impulse conduction following autonomic nerve stimulation. It is the specific mode of interaction of these various factors which determines the pattern of arrhythmia production during increased autonomic activity. The present studies have demonstrated how fluctuation in autonomic tone may result in pseudosupernormal conduction, Mobitz type II block, and the concertina effects observed in the preexcitation syndrome.

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AUTONOMIC EFFECTS ON THE HEART


Influence of Brief Vagal and Stellate Nerve Stimulation on Pacemaker Activity and Conduction within the Atrioventricular Conduction System of the Dog

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