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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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 ventricles. 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 vagal stimulation
junctional arrhythmias atrial arrhythmias sympathetic stimulation
cardiac electrophysiology ventricular arrhythmias 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. 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. The autonomic nervous system has also been implicated in arrhythmias generated by drug application and coronary artery occlusion. 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 the parasympathetic nervous system may be involved in the generation 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
reflex cardiovascular responses to ensure stable control
of pacemaker discharge rates (5). The chest was opened
either by a right thoracotomy or a mid-
 sternotomy, and the dogs were ventilated by a positive-
pressure respirator at a minute volume determined from
the body weight nomogram. Close bipolar pace
electrodes (10) were used to record simultaneously
from the right atrium, His bundle, and the anterior
free wall of the right ventricle, along with the lead II
electrocardiogram (ECG). The right atrial recording
electrode was located near the sinus node except when
the node was experimentally crushed. In these cases,
the electrode was positioned as high in the right atrium
as an uncrushed region adjacent to the crushed sinus
region. Electrodes were also applied to the right atrial
appendage for pacing the heart. In all preparations
both vagi were isolated in the neck and decentralized;
stimulating electrodes were applied to the peripheral
ends of 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 stimula-
tion was accomplished using square pulses 4 msec in
duration delivered at 100 Hz for 100 msec. Both the
cardiac pacing stimuli and the nerve stimuli were
controlled by a digital stimulator. The intensity of the
stimulating current was monitored by recording the
time 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 atrial fibrillation, the QRS complex
was of supraventricular configuration and the His
bundle spike in the His bundle electrogram preceded
the QRS complex. In these cases was either within the His
bundle or 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 unifocal 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 ±
0.154 seconds for junctional rhythm, and 1.220 ± 0.272
seconds for ectopic ventricular rhythm. That the locus
of the pacemakers was not grossly 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 oscillo-
scope and recorded on 35-mm film. The analog data
were then projected on a film reader (Microsurance
Inc.), and the time intervals were measured. The
measurements were reproducible within ±5%.

Results

AUTONOMIC INFLUENCE ON PACEMAKER ACTIVITY

Figure 1 presents representative time courses of
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 I.
The time course data for Figure 1 were derived by
measuring the successive intervals between beats
following 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 during 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
times.
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 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 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, in). 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 lengths) 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 trough in some dogs undershot the base line. 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 (12). The junctional rhythm response was characterized differently 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 0.600-0.645 seconds in four of the six preparations, but two experiments produced latencies of 0.230 and 0.300 seconds. In the four preparations in which complete AV 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 pacemakers.
rhythm. However, many investigations 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 train to the first shortening of the cycle length was consistently between 0.800 and 1.120 seconds for sinus, ectopic atrial, and junctional rhythms. Ectopic ventricular rhythms had somewhat longer latencies 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 not 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...
Figure 2

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. As of the examples shown resulted from right stellate stimulation. The scaling factor for the abscissa is the same in all cases.

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. In beat 3, the P wave was obscured 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 atrial electrogram. Following vagal stimulation the third beat was delayed somewhat. Notice also that the retrograde conduction time from the His 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](http://circres.ahajournals.org/)

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 3. The V indicates the timing of a 105-msec train of stimuli delivered to the left vagus. The timing signal (T) denotes 100-msec intervals.

delayed to such an extent that an ectopic ventricular pacemaker escaped. In contrast to Figure 3, there was no functional ectopic atrial pacemaker to take over; therefore, the rhythm suddenly shifted from junctional 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 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

TABLE 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean stimulation latency (ms)</th>
<th>Time to peak (ms)</th>
<th>Reaction (ms)</th>
<th>% Change from control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus node</td>
<td>R5</td>
<td>0.80</td>
<td>2.50</td>
<td>7.00</td>
</tr>
<tr>
<td></td>
<td>R8</td>
<td>0.50</td>
<td>4.00</td>
<td>12.50</td>
</tr>
<tr>
<td></td>
<td>L5</td>
<td>1.00</td>
<td>2.00</td>
<td>12.00</td>
</tr>
<tr>
<td></td>
<td>L8</td>
<td>1.50</td>
<td>3.50</td>
<td>11.00</td>
</tr>
<tr>
<td>Ectopic atrial</td>
<td>R5</td>
<td>1.00</td>
<td>4.00</td>
<td>9.00</td>
</tr>
<tr>
<td></td>
<td>R8</td>
<td>0.50</td>
<td>5.00</td>
<td>13.00</td>
</tr>
<tr>
<td></td>
<td>L5</td>
<td>1.00</td>
<td>3.00</td>
<td>11.00</td>
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<td></td>
<td>L8</td>
<td>1.50</td>
<td>4.50</td>
<td>11.00</td>
</tr>
<tr>
<td>AV junctional</td>
<td>R5</td>
<td>0.80</td>
<td>3.00</td>
<td>11.50</td>
</tr>
<tr>
<td></td>
<td>R8</td>
<td>1.00</td>
<td>3.00</td>
<td>7.00</td>
</tr>
<tr>
<td></td>
<td>L5</td>
<td>0.50</td>
<td>2.00</td>
<td>7.00</td>
</tr>
<tr>
<td></td>
<td>L8</td>
<td>0.35</td>
<td>2.00</td>
<td>7.00</td>
</tr>
<tr>
<td></td>
<td>L8</td>
<td>1.00</td>
<td>3.00</td>
<td>14.00</td>
</tr>
<tr>
<td></td>
<td>R8</td>
<td>1.00</td>
<td>3.00</td>
<td>13.50</td>
</tr>
<tr>
<td>Ventricular</td>
<td>R5</td>
<td>2.50</td>
<td>7.00</td>
<td>11.00</td>
</tr>
<tr>
<td></td>
<td>R8</td>
<td>5.00</td>
<td>7.00</td>
<td>14.50</td>
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<tr>
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<td>L5</td>
<td>0.35</td>
<td>5.00</td>
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</tr>
<tr>
<td></td>
<td>L8</td>
<td>1.00</td>
<td>6.00</td>
<td>14.25</td>
</tr>
</tbody>
</table>

R5 = right stellate ganglion, L5 = left stellate ganglion.

FIGURE 4

Vagal stimulation caused a shift from a junctional rhythm to an ectopic ventricular escape. Regular extrastimuli were delivered from the right atrium (RA), the bundle of His (BH), and the right ventricle (RV) simultaneously with a lead II electrocardiogram (II). The timing signal (T) indicates the timing of a 135-msec train of stimuli delivered to the right vagus. The timing signal (T) indicates 100-msec intervals.
Figure 5

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 (II). In the His bundle electrogram, a and b 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.

Figure 6 compares examples of the effect of 100-msec vagal or stellate stimulation on AV conduction. Each graph is a representative experiment. The interval from the atrial septal activation to the His bundle spike was used as the index of AV nodal conduction time. In the example shown in this figure 100-msec trains of stimuli were delivered to the left aortic (top) and the right stellate ganglion (bottom). Notice the twofold difference in the scaling factor of the abscissa between the vagal and the stellate effects.

The effects of vagal and stellate stimulation on AV nodal conduction are compared. Each graph represents a typical experiment. The interval between the atrial septal activation to the His bundle spike was used as the index of AV nodal conduction time. In the example shown in this figure 100-msec trains of stimuli were delivered to the left aortic (top) and the right stellate ganglion (bottom). Notice the twofold difference in the scaling factor of the abscissa between the vagal and the stellate effects.

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 Stellate 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>
</thead>
<tbody>
<tr>
<td>RV</td>
<td>0.230</td>
<td>0.255, 0.715, 1.045</td>
<td>1.15</td>
<td>150.0</td>
</tr>
<tr>
<td>RV</td>
<td>0.212</td>
<td>0.415, 0.730</td>
<td>0.80</td>
<td>120.0</td>
</tr>
<tr>
<td>RV</td>
<td>0.105</td>
<td>0.230</td>
<td>1.00</td>
<td>23.4</td>
</tr>
<tr>
<td>RV</td>
<td>0.192</td>
<td>0.320</td>
<td>0.80</td>
<td>20.0</td>
</tr>
<tr>
<td>LV</td>
<td>0.180</td>
<td>0.270, 0.870</td>
<td>0.80</td>
<td>45.0</td>
</tr>
<tr>
<td>LV</td>
<td>0.180</td>
<td>0.320</td>
<td>0.86</td>
<td>290.0</td>
</tr>
<tr>
<td>RS</td>
<td>1.500</td>
<td>0.200</td>
<td>1.50</td>
<td>14.5</td>
</tr>
<tr>
<td>RS</td>
<td>1.000</td>
<td>0.300</td>
<td>1.00</td>
<td>20.0</td>
</tr>
<tr>
<td>RS</td>
<td>1.000</td>
<td>0.300</td>
<td>2.00</td>
<td>20.0</td>
</tr>
<tr>
<td>LS</td>
<td>1.300</td>
<td>0.400</td>
<td>13.00</td>
<td>10.0</td>
</tr>
</tbody>
</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

**FIGURE 7**

The effect of vagal stimulation in producing several prominent peaks in the time course of changes in AV nodal conduction. In this example the data were derived in the same manner as those of Figure 6. The response was caused by a 100-msec train of stimuli delivered to the right vagus. The x-axis interval is the interval from the atrial ventricular activation to the His bundle activation.
The influence of vagal 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.

The 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 80 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 8A 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.
by the vagus. Therefore, as shown in Figure 7, the points where the influence of coupling interval is most pronounced necessarily must fall at intervals following the first peak, which are equal to the basic cycle length of the atrial pacing beats.

The influence of vagally delayed AV conduction on subsequent beats is exemplified by Figure 8B. In this instance, the atrial pacing rate and the duration of the vagal train were exactly the same as that described in Figure 8A except that the vagal train was moved 10 msec earlier relative to the control atrial beat (A). This brought the A' beat under maximal vagal influence, resulting in this beat being completely blocked within the AV node. The A'' beat was no longer experiencing any AV nodal conduction delay due to a shorter effective coupling interval between His spikes resulting from the delayed conduction of the A' beat. In fact, because the A' beat was blocked in this case, the A'' beat was conducted at a longer effective coupling interval than in the control situation before vagal stimulation. The result of the longer coupling interval was that the A'' beat was conducted with an AV nodal delay of only 59 msec in Figure 8B compared with a delay of 88 msec in Figure 8A. The continued presence of the vagal influence at the time of conduction of the A'' beat in Figure 8B is verified because the conduction of the next beat (A'') was still slightly delayed (6 msec).

AV nodal conduction was less sensitive to the influence of stellate stimulation than it was to vagal stimulation. In addition, the experiments presented in Figure 9 demonstrate that the threshold for a vagal effect on the sinus node pacemaker is lower than that for an effect on AV nodal conduction, i.e., AV nodal conduction is less sensitive to vagal influences than is sinus pacemaker activity. Figure 9A demonstrates the technique that was used for simultaneously determining the influence of a vagal burst on AV nodal conduction and on the intact sinus pacemaker. The preparation was paced from the atrial appendage for 12 beats, and then the sinus node was allowed to escape. The figure shows the last three paced beats and the escape beat. Notice the difference in configuration between the last paced beat and the escape beat, indicating the shift in pacemaker site. The sinus escape interval is, therefore, the interval between the last paced beat and the escape beat. The vagal stimulus train therefore, had a simultaneous influence on the AV conduction (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 this same intensity of vagal stimulation was sufficient to influence the sinus pacemaker. Figure 9B illustrates a 42% increase in the sinus escape interval in the top graph without any change in the interval between the atrial septal and the 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. 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.

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 beats. 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 shorter of A1-b1 interval between two conducted beats from the atrium) was increased from 235 msec to 255 msec. The effective refractory...
AUTONOMIC EFFECTS ON THE HEART

A

RA

BH

RV

V-A

V-A

V-A

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-A indicates the vagal stimulation to His bundle time, and the interval period (the shortest A1-A2 interval at which conduction still occurred) was increased from 170 msec to 200 msec.

Figure 10 (bottom) presents the effect of a constant background of 100-Hz stellate stimulation on AV conduction of premature atrial beats. Because of the lesser sensitivity of the AV node to stellate stimulation, this preparation was paced at a faster basic cycle length than the vagal preparation (250 msec vs. 380 msec) during both the control and the stellate nerve determinations. The constant stellate stimulation was below the threshold necessary to produce accelerated conduction of the normally driven beats. Notice that there was no difference between the control and the stellate stimulation for premature beats at the longer A1-A2 intervals, but that at A1-A2 intervals shorter than 200 msec, stellate stimulation caused accelerated conduction through the AV node when compared with the control situation. During stellate stimulation the functional refractory period was decreased from 210 to 202 msec and the effective refractory period was decreased from 150 msec to 140 msec. These results for vagal and stellate stimulation were recorded in four other dogs, using both right and left nerve stimulation.

Figure 10 demonstrates that stellate stimulation can accelerate AV conduction that has been delayed by premature atrial beats. Figure 11 presents the effect of stellate stimulation on experimentally induced second-degree heart block. In two preparations in which complete heart block had been attempted by either scratching or electrocauterizing the His bundle, stable partial heart block was produced. In Figure 11A, a stable 4:3 second-degree heart block occurred at a relatively slow basic cycle length (450 msec). The severity of heart block was reduced by stellate stimulation (Fig. 11B). The ventricular beat at the arrow was conducted only following stellate stimulation. The delay between the time of stellate stimulation and the conducted beats was character-

V-A indicates the vagal stimulation to sinus node escape time. The timing signal (T) indicates 100-msec intervals. A: 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_A intervals (top) and the V-A 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 paced from the right atrial appendage. The degree to which points deviate from the 45° diagonal line indicates the degree to which the premature beats were delayed within the AV node.

**Discussion**

Figures 1 and 2 and Tables 1 and 2 demonstrate that each of the different pacemaker sites exhibited characteristic patterns of response following vagal or stellate stimulation. The most complex responses were seen during sinus and junctional rhythms following vagal stimulation. The mechanism of the double-peaked time course is not known. However, Brown and Eccles (11) found that, during sinus rhythm, the response could not be explained by shifts in the site of pacemaker activity. In addition, in our experiments propranolol did not change the characteristics of the double-peaked time courses, indicating that they were not due to beta-receptor activity accompanying the vagal stimulation. Our finding that vagal stimulation during ectopic atrial rhythms caused a variable response in different experiments may be related to both inhomogeneity of vagal innervation of the atrium (20) and to different atrial pacemaker sites in the experiments. The effect of vagal stimulation on ectopic ventricular 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 ventricles (24).

In Figures 3-5, 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).
In Figure 5, a brief stellate burst shifted the dominant rhythm from ectopic atrial to junctional. The effects of stellate stimulation on both the junctional 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 conductance. 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 sympathetic and vagal stimulation, 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 during increased autonomic activity becomes apparent. Such considerations are beyond the scope of this 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 heart block (25). The vagal burst caused the suddenly blocked beat without increasing 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 concordina effect observed in some cases of the Wolff-Parkinson-White syndrome, as we have recently reported (27).

Although sympathetic influences on AV conduction were longer lasting and spread over a large number of heart beats, phasic variations in sympathetic activity produced sudden discrete modifications in conduction under some conditions. In the case of Figure II, single beats that were usually blocked were conducted to the ventricle 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 influences. 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 fluctuations in autonomic tone may result in pseudosupernormal conduction, Mobitz type II block, and the concordina effects observed in the preexcitation syndrome.

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References


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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