Synchronization of the Cardiac Pacemaker with Repetitive Stimulation of the Carotid Sinus Nerve in the Dog

By Matthew N. Levy and Harrison Zieske

ABSTRACT
In anesthetized open-chest dogs, the right carotid sinus nerve was stimulated with brief bursts of electrical impulses. When a single burst was given with each heart beat, the reflexly induced change in heart rate depended on the time within the cardiac cycle that the stimulus was applied. The maximum response was obtained when the P-St interval (i.e., the time from the beginning of the P wave to the beginning of the stimulus burst) was approximately zero. At this P-St interval the cardiac cycle (P-P interval) was prolonged to a mean value of 583 ± 145 (SD) msec from a prestimulation control value of 408 ± 80 msec. The minimum response, a mean P-P interval 45 ± 20 msec less than the maximum, was obtained at a mean P-St interval of 322 ± 48 msec. As a consequence of this phase dependency, over a definite but small range of stimulation frequencies, the discharge of the cardiac pacemaker became synchronized with the neural activity in the baroreceptor reflex arc. Within this critical range of stimulation frequencies, the cardiac pacemaker responded paradoxically to carotid sinus nerve stimulation: a change in the frequency of stimulation evoked a parallel, rather than the well-known inverse, change in heart rate.

KEY WORDS baroreceptor reflex biological control system heart rate pacemaker response curve vagus nerve paradoxical heart rate response parasympathetic nervous system sinoatrial arrhythmia sinoatrial node

Several studies have shown that the response of the cardiac pacemaker to efferent vagal activity depends on the phase of the cardiac cycle at which the neural impulse arrives at the sinoatrial (SA) node (1-6). As a consequence of this phase dependency, certain peculiar phenomena may be observed in response to repetitive efferent vagal stimulation: (1) a paradoxical effect, such that increasing frequencies of vagal activity may accelerate rather than decelerate the heart, (2) synchronization of SA node discharge with the repetitive activity in the vagus nerves, and (3) SA arrhythmias.

Recording the impulse traffic in efferent cardiac vagal fibers revealed a distinct tendency for the nerve impulses to be clustered during certain phases of the cardiac cycle (7, 8). This natural grouping of efferent vagal activity probably reflects the periodic stimulation of the baroreceptors by the arterial pulse wave. A single stimulus applied to the carotid sinus nerve appears reflexly as a discrete burst of impulses in efferent cardiac vagal fibers (9, 10).

Since this peculiar cardiac behavior which appears during repetitive efferent vagal stimulation might also be evoked reflexly, the experiments to be described were designed to test whether the paradoxical heart rate response, cardiac synchronization, and SA arrhythmias could be elicited by repetitive stimulation of the carotid sinus nerves.

Methods
Mongrel dogs were anesthetized with morphine sulfate, 2 mg/kg im, followed in 30 minutes by...
chloralose, 75 mg/kg iv, dissolved in polyethylene glycol. A tracheal cannula was inserted through a midline cervical incision and loose ligatures were placed around both vagosympathetic trunks. The right carotid sinus nerve was located, and a bipolar platinum electrode was applied for subsequent stimulation. Liquid paraffin was poured into the incision to prevent desiccation of the nerve.

An incision was made at the level of the right fourth intercostal space, and artificial respiration was instituted. A bipolar electrode catheter was introduced into the right atrial cavity through a small incision at the tip of the auricle. The right atrial electrogram and the mean arterial blood pressure were recorded on a Brush Mark 200 eight-channel ink-writing oscillograph and on Honeywell 7600 magnetic tape. The atrial electrogram served as an input to a parallel-logic analog computer (EAI 580). The computer was also used to generate square-wave electrical pulses for stimulation of the right carotid sinus nerve during the early phases of the experiment and of the right vagus nerve later in the experiment. The electrical pulses were 1 msec in duration and of supramaximal voltage (usually 4 v for the carotid sinus nerve, 10 v for the vagus nerve). The pulses were delivered to the nerves in bursts of ten, with a 2-msec interval between pulses.

Prior to nerve stimulation, propranolol, 1 mg/kg iv, was given to block the beta receptors. Completeness of blockade was verified by absence of a change in heart rate during intense stimulation of the right stellate ganglion. The carotid sinus nerve and vagus nerve were subjected to two types of stimulation, as described previously (6). In the first type, the analog computer was programmed so that one burst of stimuli was delivered each cardiac cycle, and the timing was such that each stimulus burst was given slightly later in successive cardiac cycles. Hence, the stimulus burst was made to sweep the entire cardiac cycle in a ramp of P-St intervals (the interval from the beginning of the P wave to the beginning of the stimulus burst). In the second type of stimulation, the stimulus bursts were not coordinated with cardiac pacemaker activity. The bursts were delivered as a ramp of constantly increasing frequency, from 0 to 2.5 bursts/sec, at a rate of change of about 0.4 bursts/sec min⁻¹. Also, small step changes of burst frequency were employed over a selected frequency range, the range being chosen on the basis of the response to the ramp of stimulus frequencies.

Results

RAMP OF P-ST INTERVALS

Figure 1 illustrates the experiment in which the greatest variation in the cardiac cycle (P-P interval) was observed as a function of phase. One burst of 10 stimuli was delivered to the right carotid sinus nerve each cardiac cycle, but the P-St interval was changed by a constant increment each beat.

An ascending and a descending sequence of P-St intervals was employed twice in succession. As recorded at the left of the figure, the

Changes in the P-P interval with changes in the P-St interval. One burst of 10 stimuli was delivered to the right carotid sinus nerve each cardiac cycle. On the left, each stimulus burst was given just after the beginning of the P wave (P-St \(=0\)). Then the P-St interval was changed in a duplicate set of ascending and descending sequences. The downward deflections of the time marker at the top denote 10-sec intervals.
stimuli were given just after the beginning of the P wave (P-St ≈ 0), and the P-P interval was approximately 0.56 seconds. The small periodic variations in the P-P interval represent a respiratory sinus arrhythmia, i.e., the frequency equaled that of the artificial respirator.

As the P-St interval was progressively increased, the P-P interval decreased; a minimum P-P interval of 0.49 seconds was reached at a P-St interval of 0.27 seconds. Continued increase in the P-St interval beyond this value resulted in a rise in the P-P interval, and it reached a maximum at the maximum P-St interval, i.e., when the stimulus was delivered at the end of the cardiac cycle, just prior to the next P wave. Subsequent reduction in the P-St interval at the same (but negative) rate of change produced reverse changes in the P-P interval. When the P-P intervals were plotted as a function of the P-St interval by an x-y plotter, the curve for the ascending sequence of P-St intervals was not appreciably different from that for the descending sequence. Also, a second series of stimuli in an ascending and a descending ramp of P-St intervals (right of Fig. 1) evoked a response very similar to that obtained with the first series of stimuli (left of Fig. 1).

Several brief disturbances in cardiac rhythm are evident in the top tracing of Figure 1. These arrhythmias became manifest only when the P-P interval was decreasing during the ascending ramp of P-St intervals and when the P-P interval was increasing during the descending ramp of P-St intervals. Hence, when the P-P interval is plotted as a function of the P-St interval, arrhythmias occur only when the stimulus is delivered at P-St intervals where the slope (d[P-P]/d[P-St]) of the function is negative.

The characteristic features of the reflex response of the cardiac pacemaker to stimulation of the right carotid sinus nerve were compared with those to subsequent stimulation of the transected right vagus nerve in seven animals (Table 1). Right carotid sinus nerve and vagus nerve stimuli consisted of 1 burst/cardiac cycle, with 10 stimuli/burst. When the bursts were delivered to the right carotid sinus nerve at the beginning of each cardiac cycle (P-St = 0), the P-P interval increased to 583 ± 145 msec from a prestimulation control value of 408 ± 80 msec. The maximum P-P interval was produced when such repetitive stimuli were applied near the beginning of the P wave, i.e., at the beginning (or end) of the cardiac cycle (Fig. 1). The minimum P-P interval was elicited when stimuli were given at a mean P-St interval of 322 ± 48 msec. The mean amplitude of the reflex pacemaker response curve, i.e., the difference between maximum and minimum P-P intervals, was 45 ± 20 msec. For comparison, the data obtained during right vagal stimulation after bilateral vagotomy are presented in the second column of Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic of the Mean Responses of the Cardiac Pacemaker to Stimulation of the Right Carotid Sinus Nerve and the Right Vagus Nerve</th>
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<tbody>
<tr>
<td>P-P (msec)</td>
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<tr>
<td>Carotid sinus nerve</td>
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<td>Before stimulation</td>
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<td>At P-St ≈ 0</td>
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<td>Amplitude</td>
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<td>P-St (msec)</td>
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<td>At max P-P</td>
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<td>At min P-P</td>
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Values are means ± 0.0, N = 7. P-P = duration of the cardiac cycle (interval between two successive P waves; P-St = interval between P wave and stimulus.

**RAMP AND STEP CHANGES OF STIMULUS FREQUENCY**

In nine animals, bursts of 10 stimuli were delivered at a progressively greater frequency over a range of 0 to 2.5 bursts/sec, at a rate of increase of approximately 0.4 bursts/sec min⁻¹. An example of the response of the cardiac pacemaker is shown in Figure 2. At low-frequency stimulation (on the left) the response to each stimulus burst was evident. As the burst frequency was increased, there was, in general, a progressive increase in the P-P interval. However, in each experiment, over a small range of frequencies, a paradoxical response (between the right pair of arrows.
Effects of a progressive increase in the burst frequency of stimulation (bottom) of the right carotid sinus nerve on the P-P and the P-St intervals in the same animal from which data for Figure 1 were obtained. Each burst consisted of 10 pulses, and the burst frequency was increased at a constant rate over a range of 0 to 2.5 bursts/sec, most of which is included in the figure. On the left where the burst frequency is low, responses (changes in the P-P interval) to individual bursts of stimuli are evident. Between the pairs of arrows, the cardiac pacemaker is synchronized with the neural activity in the baroreceptor reflex arc in ratios of stimulus bursts to cardiac cycles of 1:2 and 1:1, respectively. Note that during synchronization, the P-P interval decreases as stimulus frequency increases (paradoxical response). Time scale is the same as that in Figure 1.

In Fig. 2) was observed; it was similar to that previously described in response to vagal stimulation (3, 6). As the stimulation frequency was increased from 1.70 to 2.07 bursts/sec, there was a progressive decrease in the P-P interval from 0.59 to 0.48 seconds, i.e., there was a significant decrease in the P-P interval (and a corresponding increase in heart rate) as the frequency of carotid sinus nerve stimulation was increased within the limits of the above frequency range. Over this range of frequencies, examination of tracings at fast paper speed revealed that one burst of stimuli occurred during each cardiac cycle. This represented a 1:1 synchronization of the cardiac pacemaker with the reflex neural activity, as will be shown below.

During 1:1 synchronization, the bursts of stimuli were not delivered during the same portion of each cardiac cycle, but there was a progressive shift in the P-St interval (middle tracing, Fig. 2). At the lowest frequency at which 1:1 synchronization occurred (first arrow of the right pair), the bursts were delivered shortly after the beginning of the P waves. With increasing burst frequency, the P-St interval progressively diminished until the stimuli fell just before the P wave, i.e., at the end of the preceding cycle. This event is signaled by the sharp vertical deflection in the P-St tracing just to the right of the first arrow, which denotes the beginning of 1:1 synchronization. Further increase in stimulation frequency evoked a progressive reduction in the P-St intervals. The periodic oscillations of the P-P and P-St intervals within the range of 1:1 synchronization occurred at the frequency of respiration and represented a respiratory sinus arrhythmia. The record between the left pair of arrows in Figure 2 illustrates 1:2 synchronization, with one stimulus burst occurring every second cardiac cycle.
In each experiment the paradoxical response and 1:1 synchronization were verified by changing the stimulus burst frequency in small steps approximately every 30 seconds, instead of in a ramp of constantly increasing frequency. Figure 3 is a record from the same animal as that from which the tracing for Figure 2 was made. A frequency of 1.79 bursts/sec (on the left in Fig. 3) just failed to produce synchronization, as manifested by the continuous change in the P-St intervals in the middle tracing. Earlier in the same experiment (Fig. 2), this frequency was within the range that evoked 1:1 synchronization; this response represents a slight variation in the condition of the animal with time. A small step increase in stimulation frequency to 1.82 bursts/sec (second level, bottom tracing, Fig. 3) did elicit 1:1 synchronization, with the point of stimulation fluctuating from just before to just after the beginning of the P wave, as indicated by the abrupt, repetitive shifts in the P-St tracing. With subsequent step increases in stimulation frequency, there was a concomitant reduction in the mean P-P interval so that it equaled the St-St interval at each step, i.e., 1:1 synchronization persisted. Each change in the P-P interval was also accompanied by a change in the P-St interval. At the greatest stimulation frequency, 2.05 bursts/sec (on the right in Fig. 3), the cardiac pacemaker was no longer synchronized with the reflex neural activity; this situation was manifested by the continuous change in the P-St interval. With this last step change in stimulation frequency, there was an abrupt rise in the mean P-P interval. In the nine animals in which ramp and step changes in stimulation frequency were produced, 1:1 synchronization was observed in all experiments, although the frequency range over which synchronization was observed was not so extensive as in the experiments depicted in Figures 2 and 3.
Discussion

The experiments reported here revealed that the reflex effects of carotid sinus nerve stimulation on heart rate depend on the time in the cardiac cycle at which the stimuli are delivered to the nerve. The response depends not only on the total number of impulses applied to the nerve per unit time but also on the pattern of delivery. Douglas et al. (11) observed that, in rabbits with bilateral vagotomy, the depressor response to stimulation of the central end of the sectioned aortic nerve was not appreciably different with various patterns of stimulation as long as the total number of impulses applied to the nerve was constant. Since the vagi were sectioned, vagally mediated changes in heart rate were precluded. The results might have been different had such changes in heart rate been permitted to contribute to the overall arterial blood pressure response.

However, in the present study, where the heart rate response of dogs did depend on the pattern of stimulation of the right carotid sinus nerve, the blood pressure response did not differ appreciably with changes in the pattern of stimulation. Carotid sinus nerve stimulation, consisting of one burst of 10 stimuli/heart beat, resulted in a mean decrease in arterial blood pressure of 20 mm Hg from a mean control level of 131 mm Hg. In no experiment did the mean arterial blood pressure differ more than 5 mm Hg when the stimulus burst was applied at different points in the cardiac cycle. There are probably two reasons: (1) The left carotid sinus and the aortic arch baroreceptor reflexes were still intact and could moderate any small change in blood pressure ascribable to different patterns of stimulation. (2) The magnitude of the changes in heart rate might have been too small to appreciably alter blood pressure. Although the present data do not contradict the conclusions of Douglas et al. (11) concerning the reflex control of peripheral resistance, they do indicate that the pattern of stimulation influences the response of the cardiac pacemaker.

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It has been amply demonstrated that the heart rate response to vagal stimulation is intimately dependent on the timing of the stimulus relative to the cardiac cycle (1-6). Therefore, the analogous phase dependency of carotid sinus nerve stimulation is perhaps mainly ascribable to the facts that such a stimulus traverses the brain stem and appears in efferent vagal fibers as a discrete group of impulses (9) and that the efficacy of this cluster of impulses depends on the time of its arrival at the SA node.

The transit time from the stimulation of the carotid sinus nerve till the appearance of the resulting burst of impulses in the cervical vagi probably accounts for part of the phase differences between the reflex pacemaker response curves obtained in the present study and the curves obtained in this (Table 1) and previous (3, 6) studies with direct stimulation of efferent vagal fibers. With reflex stimulation of the carotid sinus nerve, the maximum P-P intervals were obtained when the stimuli were given at the beginning or end of the cardiac cycle (i.e., almost coincident with the beginning of the P wave; Fig. 1 and Table 1). The minimum P-P intervals were obtained when the carotid sinus nerve was stimulated, on the average, 322 ± 48 msec after the beginning of the P wave (Table 1). These times of occurrence differ considerably from those obtained with analogous stimulation of the efferent vagus nerve (247 ± 108 and 491 ± 117 msec, respectively; Table 1). The transit time of the impulse from the carotid sinus nerve to the cardiac vagal efferent fibers has been estimated to be 50-100 msec in the dog (9, 10). This fact accounts for part, but not all, of the phase differences between the responses to reflex and efferent neural activity (Table 1). The remaining contributory factors are related to the differences in intensity of the responses engendered by the afferent and efferent neural stimuli. Analogous supramaximal stimulation produces a much greater effect when it is applied directly to the efferent vagus nerve than when it is applied reflexly to the carotid sinus nerve. This effect is reflected by the much greater response to
the former than to the latter mode of stimulation when the stimuli were applied at $P-St = 0$ (Table 1) and also by the much greater amplitude of the direct than of the reflex pacemaker response curve (Table 1). Thus the effect of carotid sinus nerve stimulation is attenuated in traversing the brain, and in a sense it corresponds to stimulation of efferent vagal fibers with fewer stimuli per burst and with a delay of 50–100 msec. Changes in the number of stimuli per burst produce changes in the timing of the maximum and minimum of the pacemaker response curve (6) in the same direction denoted by the values incorporated in Table 1, i.e., with greater numbers of stimuli per burst the values of the $P-St$ interval at the maximum and minimum values of the $P-P$ interval are progressively increased.

If the heart rate responses to carotid sinus nerve stimulation may be considered to be analogous to those produced by efferent vagal stimulation, with account being taken of the reflex transit time and attenuation, then the occurrence of synchronization, the paradoxical response, and arrhythmias can readily be understood. It has been shown (3, 6) that 1:1 synchronization of the SA node with efferent vagal activity will occur when the vagus nerve is stimulated at a frequency such that the $St-St$ interval lies between the minimum and maximum $P-P$ intervals of the pacemaker response curve. This curve is a plot of the $P-P$ intervals as a function of the $P-St$ intervals, and the data are obtained by delivering one stimulus burst per cardiac cycle to the vagus nerve over the entire range of $P-St$ intervals (in the manner of stimulation of the carotid sinus nerve in Fig. 1). Synchronization will occur when the $P-St$ interval is such that the resulting $P-P$ interval is equal to the $St-St$ interval, and when the stimulus burst is delivered in that portion of the cardiac cycle during which the slope $(d[P-P]/d[P-St])$ of the pacemaker response curve is positive. During this portion of the cardiac cycle, negative feedback prevails (3) and is essential for stable synchronization.

The slope of the reflex pacemaker response curve was positive from the $P-St$ interval producing the minimum $P-P$ interval (mean value, $322 \pm 48$ msec; Table 1) to the end of the cardiac cycle. Since the mean $P-P$ interval was $583 \pm 145$ msec at $P-St = 0$ (Table 1), the positive-slope region of the reflex pacemaker response curve occupied approximately the latter half of the cardiac cycle. At the lowest two frequencies that produced synchronization, the $P-St$ interval was approximately zero (Fig. 3). At greater frequencies at which synchronization occurred, the stimuli were delivered during the latter half of the cardiac cycle.

Similar phenomena are also evident in Figure 2. At the lowest frequency at which 1:1 synchronization occurred (near the first arrow of the right pair), the $P-St$ interval was slightly greater than zero. As the stimulation frequency was progressively increased, the stimulus was delivered just before the beginning of the P wave, i.e., the $P-St$ interval became maximal. Further increases in stimulation frequency were attended by concomitant reductions in the $P-St$ interval. However, as the time of stimulation approached the middle of the cardiac cycle (near the second arrow of the right pair), synchronization was lost. At $P-St$ intervals below this critical value, the slope of the reflex pacemaker response curve is negative, and over this range, positive feedback prevails (3). This condition is incompatible with synchronization, and if the gain of the positive feedback is sufficiently great, arrhythmias will develop (3, 6). Such arrhythmias are evident in Figure 1, and they appear only when $d[P-P]/d[P-St]$ is negative. That their occurrence is not merely coincidental is indicated by their appearance during both ascending and descending ramps of $P-St$ intervals in each of the two sets of stimulation sequences.

**References**


*Circulation Research, Vol. XXX, June 1972*
HEART RATE CONTROL


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Circ Res. 1972;30:634-641
doi: 10.1161/01.RES.30.6.634

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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