Mechanism of Prolongation of the R-R Interval with Electrical Stimulation of the Carotid Sinus Nerves in Man

By Dwain L. Eckberg, Gerald F. Fletcher, and Eugene Braunwald

ABSTRACT

To elucidate the mechanism by which stimulation of the carotid sinus nerves prolongs the R-R interval, the effects of activating an implanted carotid sinus nerve stimulator were studied in eight patients at varying levels of background autonomic activity and with varying types of efferent autonomic blockade. Beta-receptor blockade was induced with intravenous propranolol, 0.20 mg/kg, and parasympathetic blockade with intravenous atropine, 0.04 mg/kg. In the supine position, average prolongation of the R-R interval due to stimulation of the carotid sinus nerves was 269 ± 56 msec prior to autonomic blocking drugs, 442 ± 214 msec after propranolol (NS), and 44 ± 13 msec after propranolol and atropine (P < 0.025). Comparable changes were produced in the standing position. With moderate treadmill exercise, stimulation of the carotid sinus nerves prolonged the R-R interval by only 40 ± 30 msec prior to blocking drugs, 62 ± 19 msec after propranolol, and 40 ± 30 msec after propranolol and atropine. It is concluded that the prolongation of the R-R interval produced by stimulation of the carotid sinus nerves is secondary to augmented parasympathetic activity, and the attenuation of this response during erect exercise appears to be due to a centrally mediated reduction in the responsiveness of the parasympathetic nervous system to baroreceptor stimuli.

KEY WORDS

baroreceptor    carotid sinus reflex    parasympathetic blockade
beta-receptor blockade   autonomic nervous system

The baroreceptor reflex is of fundamental importance to circulatory control. Although it is generally agreed that baroreceptor-induced vasodilatation results from central withdrawal of adrenergic tone (1, 2), considerable controversy exists about the mechanism of baroreceptor-induced slowing of heart rate. It has been proposed that, like reflex vasodilatation, reflex reduction of sinoatrial automaticity is mediated primarily by withdrawal of adrenergic tone (3). Most investigators believe that this reduction of automaticity is secondary to reciprocal withdrawal of adrenergic stimulation and augmentation of parasympathetic restraint (4-6). Other studies, however, in experimental animals and man suggest that it results primarily from increased parasympathetic activity (7-12).

The baroreceptor reflex has been studied extensively in anesthetized dogs by measuring the effects of increasing afferent nerve traffic in the carotid sinus nerves (4, 13-15). We have had the unique opportunity to study baroreceptor function in unsedated man, using direct electrical stimulation of the carotid sinus nerves, and have utilized this opportunity to clarify the mechanism of baroreceptor-induced prolongation of the R-R interval. Selective blockade of the adrenergic and parasympathetic systems was accomplished pharmacologically, and observations were carried out at three levels of background autonomic activity.

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Methods

Eight patients averaging 62 years of age (range 43 to 77 years) were studied without sedation in the postabsorptive state. Bilateral carotid sinus nerve stimulator electrodes had been implanted in a manner described previously (16) for treatment of uncontrollable recurrent supraventricular tachycardia in two patients (17), incapacitating angina pectoris in five patients (18, 19), and angina associated with recurrent paroxysmal atrial tachycardia in one patient. Three patients had undergone selective coronary arteriography and were found to have occlusion of the right coronary artery and extensive disease of the major branches of the left coronary artery. All patients were free of signs and symptoms of congestive heart failure at the time of study. One patient had systolic hypertension; all other patients had normal resting systolic and diastolic arterial pressures.

All patients were in sinus rhythm throughout the study. Carotid sinus nerve stimulation (CSNS) did not alter the P-R intervals significantly, and therefore R-R intervals were used to express sinoatrial automaticity. Changes in the R-R interval were studied in preference to changes in heart rate, because the R-R interval is a directly measured function that responds linearly to changes in baroreceptor activity, whereas heart rate is derived mathematically and is a reciprocal function that responds hyperbolically.

The intensity of the electrical stimulus and the frequency of stimulation were adjusted individually to provide optimum therapeutic effects and were held constant during each series of experiments on each patient. Impulses of 0.3-msec duration were delivered at an average frequency of 81 cps (range 40 to 125) at 4.1 ± 1 (se) v with an external radiofrequency stimulator (Angistat, Medtronic, Inc.).

Brachial arterial pressure, obtained through an indwelling Courand needle connected to a Statham P23AA strain gauge, and a modified V-1 electrocardiographic lead were recorded on a multichannel recorder. The effects of CSNS were studied when the patients were supine and when they were standing and during horizontal treadmill exercise at 1.7 mph. CSNS was begun after 90 seconds of treadmill exercise. Stimulation was continued for 2 minutes in most instances but was terminated earlier if symptoms due to bradycardia or hypotension appeared. Measurements of R-R intervals and systolic, diastolic, and mean arterial pressures were made immediately prior to the onset of stimulation and, commencing 15 seconds after the onset of stimulation, at 15-second intervals for 2 minutes or until the cessation of CSNS. Thus, measurements of hemodynamic changes were not made until at least 15 seconds of CSNS had elapsed. The maximum changes produced by CSNS are reported. Statistical analyses were performed with Student's paired t-test to compare the average responses to CSNS under different conditions. Differences were considered to be statistically significant when P < 0.05.

The role of the adrenergic system in inducing reflex changes in the R-R interval was elucidated in six patients by comparing the response of the R-R interval to CSNS before and within 15 minutes after the intravenous administration of propranolol, 0.20 mg/kg. Jose and Taylor (20) have shown that following this dose of propranolol given to supine subjects additional propranolol produces no further slowing of the heart rate, and studies from our own laboratory (21) have shown that propranolol, 0.15 mg/kg, reduces the effectiveness of infused isoproterenol by at least 90%.

The role of the parasympathetic system was determined by examining the effects of the intravenous administration of atropine sulfate, 0.04 mg/kg, on the response to CSNS in four of the patients who had received propranolol. In addition, the effects of isolated parasympathetic blockade on the response to CSNS were determined in the other four patients. Jose and Taylor (20) and Chamberlain and co-workers (22) have shown that atropine doses in excess of 0.04 mg/kg produce no further acceleration of the heart rate, suggesting that the parasympathetic blockade produced by this dose is complete. Atropine was given within 20 minutes after the administration of propranolol, and all studies were completed within 20 minutes after the administration of atropine.

Results

HEMODYNAMIC RESPONSES TO CSNS

A typical hemodynamic response to CSNS in the control condition is depicted in Figure 1. The R-R interval rose abruptly with the onset of stimulation and then gradually returned toward control levels as electrical stimulation was continued. Systolic and diastolic arterial pressures also fell rapidly with the onset of stimulation, gradually drifted lower as stimulation was continued, and returned rapidly toward normal with the cessation of stimulation. Maximum prolongation of the R-R interval occurred within the first 30 seconds in most instances (73%), whereas maximum fall in mean arterial pressure occurred during the first 30 seconds in a minority of studies.
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Typical R-R interval and arterial pressure responses to bilateral carotid sinus nerve stimulation (CSNS). The arrows indicate the onset and duration of CSNS. AP = arterial pressure; R-R = R-R interval.

Neither beta-receptor nor parasympathetic blockade altered the time sequence of the heart rate and arterial pressure responses to carotid sinus nerve stimulation.

MEAN ARTERIAL PRESSURE CHANGES IN RESPONSE TO CSNS

The mean arterial pressure declined by 36 ± 5 mm Hg during CSNS in the supine position. This decline was not altered significantly by the erect position, exercise, or adrenergic or parasympathetic blockade (Table 1). Changes in systolic and diastolic pressure paralleled those observed in mean arterial pressure.

TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>R-R interval (msec)</th>
<th>Mean arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>782 ± 22</td>
<td>1051 ± 53</td>
</tr>
<tr>
<td>Standing</td>
<td>727 ± 38</td>
<td>965 ± 56</td>
</tr>
<tr>
<td>Walking</td>
<td>598 ± 32</td>
<td>682 ± 40</td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
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<tr>
<td>Supine</td>
<td>975 ± 21</td>
<td>1417 ± 108</td>
</tr>
<tr>
<td>Standing</td>
<td>971 ± 29</td>
<td>1217 ± 66</td>
</tr>
<tr>
<td>Walking</td>
<td>791 ± 15</td>
<td>853 ± 28</td>
</tr>
<tr>
<td>Propranolol and atropine</td>
<td></td>
<td></td>
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<tr>
<td>Supine</td>
<td>888 ± 45</td>
<td>931 ± 42</td>
</tr>
<tr>
<td>Standing</td>
<td>854 ± 32</td>
<td>927 ± 38</td>
</tr>
<tr>
<td>Walking</td>
<td>807 ± 23</td>
<td>846 ± 23</td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
<td></td>
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<tr>
<td>Supine</td>
<td>667 ± 52</td>
<td>749 ± 85</td>
</tr>
<tr>
<td>Standing</td>
<td>619 ± 31</td>
<td>697 ± 42</td>
</tr>
<tr>
<td>Walking</td>
<td>593 ± 42</td>
<td>642 ± 49</td>
</tr>
</tbody>
</table>

C = control, prior to stimulation; S = observations during stimulation; values are means ± se.
The average prolongation of the R-R interval was 269 ± 56 msec in the control state. Beta-receptor blockade did not diminish this response; in fact, after propranolol, the average prolongation of the R-R interval was increased to 442 ± 214 msec. However, this was not a significant change. One patient experienced an inordinate amount of prolongation of the R-R interval with CSNS after propranolol (1412 msec) and was primarily responsible for the increased average for the entire group. The average change for the other five patients was 230 msec prior to propranolol and was almost identical, 228 msec, after propranolol. Thus, in the supine position, there was no evidence that withdrawal of adrenergic stimulation of the sinoatrial node contributed to the prolongation of the R-R interval during CSNS.

In contrast, CSNS resulted in significantly less prolongation of the R-R interval in all patients after administration of atropine with or without prior treatment with propranolol, the R-R interval increased by an average of only 44 ± 13 msec in the four patients who received atropine after propranolol and by 82 ± 36 msec in the other four patients who received atropine without prior treatment with propranolol.

The effects of CSNS on patients in the standing position were similar to those observed in the supine position (Fig. 3). Prolongation of the R-R interval in the control state averaged 238 ± 60 msec and was almost identical after propranolol, averaging 246 ± 55 msec. Similarly, atropine reduced the prolongation of the R-R interval produced by CSNS; when atropine was given following propranolol, CSNS produced a prolongation of the R-R interval which averaged only 73 ± 40 msec, and when atropine was given without prior treatment with propranolol, it averaged 78 ± 25 msec.

During treadmill exercise, the responses to CSNS were significantly reduced, regardless of the presence or absence of autonomic blocking drugs (Fig. 4). Lengthening of the R-R interval averaged only 85 ± 13 msec prior to drug administration, 62 ± 19 msec after propranolol, 40 ± 15 msec after atropine and propranolol, and 49 msec after atropine alone. Changes in the R-R interval with CSNS during physiological and pharmacological interventions are summarized in Figure 5.

Discussion
In this investigation, the mechanism of the baroreceptor-induced lengthening of the R-R interval was studied using direct electrical stimulation of the carotid sinus nerves in unsedated patients. Since the mechanism of prolongation of the R-R interval might be a function of background autonomic activity, the latter was varied physiologically by...
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Control Propranolol

Atropine and Propranolol

Effects of CSNS on the R-R interval during light treadmill exercise. See Figure 2 for explanation.

FIGURE 4

changing posture and by treadmill exercise. To study the relative importance of the two components of the autonomic nervous system, comparisons of the effects of CSNS before and after selective blockade of the adrenergic and parasympathetic systems were carried out. The effects of sympathetic withdrawal on sinoatrial automaticity are known to appear later than the effects of parasympathetic augmentation (23). For this reason, no hemodynamic measurements were made until at least 15 seconds of CSNS had elapsed; changes observed at this time and later during CSNS should have included both sympathetic and parasympathetic components.

When base-line sympathetic activity was lowest, as in the supine resting subjects, prolongation of the R-R interval induced by CSNS was not reduced by beta-receptor blockade, even though propranolol itself significantly prolonged the average R-R interval (782 to 975 msec). If the slowing of heart rate during CSNS was due to a significant extent to withdrawal of adrenergic stimulation, then propranolol would have reduced the degree of prolongation of the R-R interval. Thus, under the conditions of this study, withdrawal of adrenergic stimulation of the sinoatrial node does not appear to play a significant role in the observed prolongation of the R-R interval by CSNS. In the unblocked state, a moderate reduction in R-R interval was produced by standing; this reduction was prevented by propranolol, which increased the standing R-R interval from 727 to 971 msec, and therefore this postural reduction in R-R interval may be presumed to have resulted from augmented adrenergic nervous activity, as had been suggested by our previous studies (24). Despite this higher level of adrenergic drive, propranolol did not alter the prolongation of the R-R interval produced by CSNS. It appears, therefore, that even in the presence of the heightened adrenergic activity produced by the erect position, prolongation of the R-R interval induced by CSNS does not result to any large extent from adrenergic withdrawal. During light treadmill exercise, a further reduction in R-R interval was observed, and the increase in R-R interval after propranolol (from 598 to 791 msec) suggested that most of the shortening of the R-R interval during exercise was secondary in

FIGURE 5

Average lengthening of the R-R interval for all subjects. Means ± 1 se are shown. The numbers of patients studied are indicated in black circles.

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part to increased adrenergic nervous activity. During exercise, even prior to autonomic blockade, CSNS produced relatively little prolongation of the R-R interval, and propranolol did not modify this response.

These experiments indicate that although the adrenergic nervous system plays a definite role in altering heart rate to levels appropriate to position and activity, it does not appear to be of great importance in changes in R-R interval produced reflexly by activation of the carotid sinus nerves. This conclusion is strengthened by other observations in this (8) and other laboratories (12) in normal subjects whose carotid sinus and aortic arch receptors were activated by increasing the systemic arterial pressure. Instead, the prolongation of the R-R interval resulting from CSNS appears to be due almost entirely to increased parasympathetic restraint. Thus, in contrast to the effects of propranolol, atropine markedly reduced the average lengthening of the R-R interval resulting from CSNS, both in the supine and standing positions. This effect was observed regardless of whether the subject was pretreated with propranolol. Although atropine significantly reduced the average R-R interval in the supine and standing positions, it did not appreciably alter it during treadmill exercise. Thus, it appeared that exercise resulted in physiological withdrawal of parasympathetic tone or reduction in responsiveness of sinoatrial pacemaker cells. In this context, the failure of CSNS to significantly prolong the R-R interval during treadmill exercise prior to the administration of any autonomic blocking agents suggests that the withdrawal of parasympathetic tone is associated with a centrally mediated elevation of threshold or reduction in gain of the carotid sinus reflex or both.

During CSNS, the withdrawal of adrenergically induced vasoconstriction results in hypotension which is perceived by aortic arch baroreceptors which reflexly counteract the hemodynamic effects of CSNS. In this context, the return of the R-R interval toward control levels while arterial pressure remained depressed during continued CSNS suggests that the baroreceptors in the aortic arch are more important in controlling sinoatrial automaticity than those in the carotid sinuses, and the failure of arterial pressure to rise during continued stimulation (Fig. 1) suggests the primacy of the carotid baroreceptors in the physiological regulation of peripheral resistance; this inference is consistent with observations made in conscious dogs (9).

Direct electrical CSNS simulates the physiological response to mechanical distention of the carotid sinuses resulting from rising arterial pressure; the present study, therefore, does not shed light on the effects of lowering arterial pressure, and it is entirely possible that the adrenergic system plays a more important role in the shortening of the R-R interval resulting from hypotension. This suggestion is supported by earlier findings in our laboratory; cardioacceleration in dogs resulting from nitroglycerin-induced hypotension can be attenuated by propranolol (7), as can that produced in humans by upright tilting (18).

The findings in the present investigation are consistent with the findings of Scher and Young (10) and Vatner and co-workers (9) who studied the response to electrical CSNS in experimental animals. However, our conclusions are at variance with those of Devleeschhouwer and Heymans (4) who measured the slowing of heart rate which occurs after release of bilateral common carotid artery occlusive cuffs in dogs and found that this response was significantly reduced by drugs that block beta-receptors but not by atropine. Similarly, Berkowitz and co-workers demonstrated in dogs that slowing of heart rate produced by CSNS can be blocked largely by propranolol but not by atropine (3). Both of these latter studies were carried out under general anesthesia after extensive surgical procedures, and the disparity between these results and those of the present study may have resulted from changes in autonomic cardiovascular regulation produced by anesthetic agents (25-28). In addition to interfering with the normal parasympathetic responses to baroreceptor stimulation,
general anesthesia may also alter the pattern of adrenergic responses to CSNS. Thus, Vatner and co-workers found that CSNS produced more cardiac slowing after atropine in anesthetized animals than it did in conscious animals (26).

In addition to providing increased understanding of the physiological control of heart rate and arterial pressure, this study carries implications regarding the therapeutic uses of electrical CSNS. The failure of propranolol to modify the hemodynamic effects of CSNS suggests that treatment with this drug does not contraindicate the use of therapeutic electrical CSNS in the treatment of angina pectoris. Indeed, the two modalities could be considered complementary in reducing myocardial oxygen requirements, CSNS by reducing arterial pressure and propranolol by slowing heart rate. On the other hand, our data suggest that anticholinergic therapy may compromise the effectiveness of therapeutic CSNS.

The present findings also shed light on the mechanism of interruption of paroxysms of supraventricular tachycardia by means of electrical CSNS. This mode of therapy abolished almost all episodes in the three patients in this investigation who suffered from this disorder. The increase in vagal activity demonstrated in this study to result from CSNS would not be expected to terminate the tachycardia if the latter were due to rapid impulse formation in an ectopic focus (29). However, it has been proposed that paroxysmal atrial tachycardia is related to reentrant activity resulting from reciprocation of an impulse between the atrium and the AV node (30), and the efficacy of CSNS in terminating episodes may be related to the parasympathetically mediated extinction of a stimulus in the atrioventricular node.

In conclusion, the results of this study on the effects of direct electrical stimulation of the carotid sinus nerves indicate that: (1) Although augmented beta-receptor stimulation of the sinoatrial node reduces the R-R interval, withdrawal of this stimulation does not appear to play a significant role in the prolongation of the R-R interval produced by CSNS. (2) Prolongation of the R-R interval with CSNS is nearly abolished by atropine, and it is therefore believed to result from increased parasympathetic nervous activity. (3) Light treadmill exercise, which is associated with augmented sympathetic drive and withdrawal of parasympathetic restraint, produces a centrally mediated reduction in the responsiveness of the parasympathetic nervous system to CSNS. (4) CSNS-induced reductions in arterial pressure do not appear to be influenced in a major way by posture, activity, or by beta-receptor or parasympathetic blockade.

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**References**


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