Effect of Continuous Enhanced Vagal Tone on Atrioventricular Nodal and Sinoatrial Nodal Function in Humans

Richard L. Page, Anthony S. L. Tang, and Eric N. Prystowsky

A constant intravenous infusion of phenylephrine (0.74±0.41 μg/kg/min) was given to 10 patients to cause a continuous augmentation in reflex vagal tone. After the infusion, the diastolic blood pressure increased from 76±7 to 89±11 mm Hg (p<0.01). The sinus cycle length and atrial-His (AH) interval were measured, and incremental atrial pacing was performed before and during phenylephrine infusion until atrioventricular (AV) nodal block was achieved. For each patient, the AV nodal function curve (i.e., the AH interval plotted as a function of the atrial pacing cycle length) was compared during both the control state and phenylephrine infusion; the AH intervals during each condition at chosen short (AH₃) and long (AH₄) cycle lengths were compared. The sinus cycle length increased during phenylephrine infusion from 941±294 to 1,115±347 msec (p=0.013). The AH interval during sinus rhythm was not significantly prolonged (77 versus 82 msec, p=NS). The shortest atrial pacing cycle length yielding 1:1 AV nodal conduction increased during phenylephrine infusion from 412±120 to 575±211 msec (p<0.01). Of note, the degree of sinus cycle length prolongation did not correlate with the degree of prolongation in the shortest atrial pacing cycle length yielding 1:1 AV nodal conduction. The AV nodal function curve was shifted markedly to the right and only slightly upward. Thus, even though there was a significant increase in both AH₃ (from 84±24 to 102±48 msec, p=0.05) and AH₄ (from 127±40 to 186±66 msec, p<0.01), the mean increase in AH₄ was substantially greater (59 versus 18 msec, p<0.01). We conclude that during baroreflex-induced enhanced vagal tone there is a significant depression of AV nodal conduction, primarily related to the stressed portion of the AV nodal function curve. Although baroreflex-induced changes in sinus automaticity and AV nodal conduction generally move in the same direction, the degree of negative dromotropic effects on AV nodal conduction cannot be predicted by the magnitude of change in sinus rate. (Circulation Research 1991;68:1614–1620)

Parasympathetic and sympathetic influences on atrioventricular (AV) nodal conduction at rest have been shown to be balanced in both human and canine experiments. However, increased reflex vagal tone induced by several methods, including carotid sinus massage or phenylephrine bolus infusion, may have markedly variable effects on AV nodal conduction. For example, during supraventricular tachycardia when AV nodal conduction is stressed, enhanced vagal tone often terminates tachycardia by blocking impulses in the AV node. In contrast, heightened parasympathetic tone usually has minimal effect on AV nodal conduction during normal sinus rhythm. Further, in some patients a discordance is noted during periods of expected increase in vagal tone, such as sleep; for example, minimal PR prolongation may occur with substantial sinus slowing, or slight increases in sinus rate may be accompanied by Mobitz type I second-degree AV block. The purpose of this investigation was to evaluate systematically the effects of reflex-induced parasympathetic tone during steady-state conditions on the AV nodal function curve and to correlate changes in AV nodal conduction with sinus node automaticity.

Materials and Methods

Study Population

The study included 10 patients (80% men), 22–65 (mean, 47) years of age. In nine patients, electrophysiological study was performed because of syncope or presyncope; one patient (patient 1) was admitted for atypical chest pain and was studied because of a
15-second pause observed during sleep (see Table 1). No patient showed evidence of coronary artery disease. All patients had normal intervals on the surface electrocardiogram except for one (patient 3), who had first-degree AV block. No patient was receiving a cardioactive drug at the time of the study.

Electrophysiological Study

This protocol was approved by the Institutional Review Board, and informed written consent was obtained in each case. Patients were studied in the postabsorptive state, typically with mild diazepam sedation (5.25±5.7 mg i.v.). Activity within the laboratory was minimized during the study. Three multipolar catheters were introduced percutaneously from the femoral vein and advanced under fluoroscopic guidance to the right atrial appendage, the tricuspid anulus (His bundle electrogram), and to the right ventricular apex. The catheter positions were stable throughout the study. Intracardiac bipolar electrograms (filtered at 50–500 Hz) and standard electrocardiographic leads I, II, III, V1, and V6 were displayed simultaneously on a multichannel oscilloscope and recorded at paper speeds of 100 mm/sec. Electrical stimulation was performed using a programmable stimulator delivering 2.0-msec constant-current pulses at twice late-diastolic threshold. The atrial pacing protocol involved pacing at a cycle length just less than that of sinus rhythm and incremental shortening of the pacing cycle length until AV nodal block was observed. No arrhythmia was induced.

Electrophysiological Measurements

The atrial-His (AH) interval was measured to the nearest 5 msec on the His bundle electrogram from the first rapid atrial deflection crossing the baseline to the onset of the His bundle depolarization. The AH interval was measured for each pacing cycle length after steady state was achieved by allowing several beats to elapse at that cycle length. Intervals during sinus rhythm were measured and were typically averaged over six or more beats.

Phenylephrine Infusion

A constant infusion of phenylephrine was used.® Phenylephrine (100 μg/ml) was administered via a side-arm sheath located in the femoral vein starting with a dose of 0.2 μg/kg/min for 10 minutes; the dose was then doubled every 5–10 minutes until a diastolic blood pressure increase of 10–15 mm Hg was observed or until a maximum dose of 1.6 μg/kg/min was administered. After the initial 10–15 mm Hg blood pressure increase was achieved, incremental atrial pacing was performed. The primary purpose of this study was to evaluate the effects of phenylephrine on AV nodal conduction; thus, if no change in 1:1 AV nodal conduction was observed, the next higher dose of phenylephrine was given. The dose was increased in stages until 1) the highest level was achieved, 2) some negative dromotropic effect on AV nodal conduction occurred, or 3) a 30 mm Hg rise in diastolic blood pressure was achieved. When AV block was observed to occur during very long pacing cycle lengths or spontaneously during sinus rhythm, the infusion rate was reduced to allow the measurement of the AH interval at several pacing cycle lengths. Doses of phenylephrine were not altered on the basis of change in the sinus cycle length. Blood pressure was measured every minute during the infusion by an automatic blood pressure recording device (Infrasonde model D4000, Puritan-Bennett Corp., Wilmington, Mass.).

AH Intervals at Short and Long Cycle Lengths

AHo refers to the AH interval at the shortest A1-A1 pacing cycle length where consistent AV nodal conduction was seen during both control and phenylephrine infusion. The A1-A1 pacing interval at which AHo was measured was the same for both conditions in each patient, but the A1-A1 pacing interval used for each case depended on the individual AV nodal function curve.

AH3 refers to the AH interval at the longest A1-A1 pacing cycle length where there were data available for both control and phenylephrine infusion. Again, data were obtained at the same cycle length in each patient, but a unique pacing cycle length was used in each patient, depending on the sinus cycle length.

Statistical Analysis

Statistical evaluation was performed using the Wilcoxon signed rank test for paired data; significance was determined at p<0.05. Spearman’s rank correlation coefficient was calculated where appropriate. All data are expressed as mean±SD.

Results

Phenylephrine Infusion

The infusion rate used in these patients was 0.74±0.40 μg/kg/min, yielding an increase in diastolic blood pressure of 13.0±6.2 mm Hg. There were no side effects of the infusion.

Effects of the Baroreflex During Sinus Rhythm

The baseline (control) sinus cycle length was 941±294 msec; during steady-state phenylephrine
infusion, the sinus cycle length was significantly prolonged to 1,115±347 msec \((p=0.013)\). There was no correlation between the initial sinus cycle length and the degree of sinus slowing with phenylephrine. As seen in Table 2 and Figure 1, the degree of prolongation varied considerably.

The AH interval during normal sinus rhythm was insignificantly prolonged (from 77±19 to 82±21 msec) in response to phenylephrine. The His-ventricular interval did not change, measuring 47±9 msec during control and 47±8 msec during phenylephrine infusion.

**Effects of the Baroreflex on the AV Nodal Function Curve**

The AV nodal curve generated in a typical experiment (patient 2) is shown in Figure 2. Under baseline conditions (unfilled circles in Figure 2), the AH interval is prolonged incrementally as the atrial pacing cycle length shortens until AV nodal Wenckebach block is observed, at a pacing cycle length 360 msec. Note that during incremental atrial pacing in the control state, at relatively long paced cycle lengths, the AH interval is minimally prolonged; the major increase in the AH interval occurs as the Wenckebach cycle length is approached. Compared with the control state at similar long pacing cycle lengths, the AH interval during phenylephrine infusion (filled circles in Figure 2) is only slightly prolonged. However, as the paced cycle length is shortened progressively, the magnitude of AH interval prolongation for the matched pacing cycle lengths markedly increases until Wenckebach block occurs, at a pacing cycle length 470 msec. The shortest pacing cycle length that yielded consistent AV nodal conduction in this patient (1:1) was 370 msec at baseline and 480 msec during phenylephrine infusion.

**TABLE 2. Summary of Experimental Data in 10 Patients**

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<tr>
<th>Patient</th>
<th>BP (mm Hg)</th>
<th>CL(S) (msec)</th>
<th>AH(S) (msec)</th>
<th>AHl (msec)</th>
<th>AH6 (msec)</th>
<th>1:1 (msec)</th>
<th>Dose ((\mu \text{g/kg/min}))</th>
<th>BP (mm Hg)</th>
<th>CL(S) (msec)</th>
<th>AH(S) (msec)</th>
<th>AHl (msec)</th>
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<td>86</td>
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<td>210</td>
<td>490</td>
<td>0.60</td>
<td>148/90</td>
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<td>97</td>
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<td>120</td>
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<td>90</td>
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</table>

BP, blood pressure; CL(S), cycle length during sinus rhythm; AH(S), atrial-His interval during sinus rhythm; AHl and AH6, AH intervals during the longest and shortest, respectively, paced cycle lengths for which there were paired data available; 1:1, the shortest atrial paced cycle length at which there was 1:1 atrioventricular nodal conduction.

**FIGURE 1.** Plot showing sinus cycle length (CL) at baseline and during phenylephrine infusion for all 10 patients. There was a significant prolongation in CL (from 941±294 to 1,115±347 msec) during phenylephrine infusion.

**FIGURE 2.** Plot showing the atrial-His (AH) interval as a function of pacing cycle length (A1,A1) at baseline and during phenylephrine infusion for patient 2. Control (baseline) values are represented by unfilled circles, and data obtained during phenylephrine infusion are represented by filled circles. The diamonds represent the point at which atrioventricular nodal Wenckebach block was observed. Note the shift of the curve to the right and slightly upward during phenylephrine infusion.
Phenylephrine shifted the AV nodal function curve in patient 2 to the right and minimally upward. This effect was noted in eight of the 10 patients and is schematically demonstrated in Figure 3. In two (patients 6 and 8), the AV nodal function curve was minimally affected: the 1:1 cycle length was prolonged by only 0–20 msec (see Figure 4 and Table 2).

FIGURE 3. Schematic representation of the atrioventricular nodal function curve during control (C) and during phenylephrine infusion (PE). These curves are drawn by hand, based on patient data. AH\(_a\), the atrial-His (AH) interval measurement at the shortest A\(_1\)-A\(_1\) interval for which there were paired data available; AH\(_L\), the AH interval for the longest A\(_1\)-A\(_1\) interval for which there were paired data available; CL, cycle length. Typical A\(_1\)-A\(_1\) intervals chosen for measurement of AH\(_L\) and AH\(_a\) are indicated by broken lines (see text for further details). This curve is typical for eight patients; in two patients, the atrioventricular nodal function curve was shifted minimally or not at all. In no patient did phenylephrine cause a shift to the left.

As seen in Figures 1 and 4, phenylephrine caused a statistically significant increase in both sinus cycle length and the shortest atrial pacing cycle length with 1:1 AV nodal conduction, although certain patients showed relatively little change in sinus or AV nodal function. We evaluated whether the degree of sinus slowing during phenylephrine infusion could predict similar degrees of prolongation of the AV nodal 1:1 paced cycle length. In Figure 6, we have plotted the value of sinus cycle length and the shortest 1:1 pacing cycle length obtained during phenylephrine infusion, normalized to the control data for each patient. Note the lack of a relation between the variables, with \(r=0.11\).

**Discussion**

In this study, we present a new method for evaluating changes in human AV nodal conduction due to reflexly enhanced vagal tone. The method uses AV nodal function curves generated during incremental atrial pacing, which previously have been shown to have a characteristic shape regardless of the paced Wenckebach cycle length. Because of the universality of these curves, it is possible to investigate both the effect of various induced perturbations on AV nodal conduction in patients with disparate AV nodal function at baseline and the relative magnitude of changes at different phases of AV nodal conduction.

In the presence of augmented vagal tone, we observed that the AV nodal function curve was shifted to the right but minimally upward. Thus, the magnitude of response to the same vagal influence varied; only minor prolongations of the AH interval were seen at the longer cycle lengths, whereas substantial negative dromotropic effects were seen only near the steep portion of the curve at relatively shorter pacing cycle lengths. A similar but opposite effect on human AV nodal function has been dem-
onstrated in the setting of constant isoproterenol infusion, where the curve was shifted to the left (E.N. Prystowsky, unpublished data). The more pronounced effect of isoproterenol on the steep portion of the AV nodal function curve may well be secondary to the decrease in time-dependent refractoriness produced by isoproterenol in slow channel tissue.8

As expected, during sinus rhythm, augmentation of vagal tone slowed the sinus rate and caused no significant change in AV nodal conduction, a finding previously reported by Mancia et al13 in humans and Martin9 in dogs. In contrast, Warner and Loeb10 showed significant prolongation in both the canine sinus cycle length and AH interval in sinus rhythm after a bolus injection of phenylephrine. Minimal effects on AV nodal conduction occur in sinus rhythm during augmentation of vagal tone because of the resultant long atrial cycle lengths that are on the flat portion of the AV nodal curve where vagal influence is slight. Even if the sinus rate did not slow, there might be little increase in the AH interval unless, as noted below, there was an exceptionally marked effect on AV nodal conduction that shifted the curve far to the right with the steep part close to the sinus cycle length.

Since the AV nodal action potential duration is not prolonged under vagal influence,11,12 we propose that the observed effects of enhanced vagal tone on AV nodal function are due to changes in time-dependent refractoriness, a property that is characteristic of AV nodal tissue.13 The slow conduction occurring on the steep portion of the AV nodal function curve probably is due, in part, to an excitation wave front that encroaches on the time-dependent refractory period of the AV node. Shortening of the time-dependent refractoriness in slow channel action potentials has been demonstrated with isoproterenol, and the effect of isoproterenol is seen primarily on the steep part of the function curve.14 It is reasonable to postulate that increased vagal tone also will exert its major influence during time-dependent refractoriness, only in an opposite direction. In addition, this may be a more universal response of AV nodal tissue, since other agents such as verapamil and β-adrenergic receptor blockers also primarily affect stressed AV nodal conduction while minimally affecting baseline conduction.15,16

It is interesting to note that two of the three patients with the most enhanced baseline AV nodal conduction demonstrated minimal change with phenylephrine in the cycle length that yielded 1:1 AV nodal conduction. Although the existence of a distinct syndrome of “enhanced AV nodal conduction” has been questioned,7 it has been observed that patients with relatively enhanced AV nodal conduction may demonstrate a lessened response to a variety of agents that have negative dromotropic effects on AV nodal conduction.17-20 The reason for the minimal shift in AV nodal conduction in these patients is unknown but could relate to anatomic variations such as a decrease in the N region, where predominant slowing of conduction occurs, or partial bypass of normal AV nodal tissue. Alternately, there

**Figure 5.** Plot showing atrial-His (AH) intervals at comparable long (AHL) and short (AHL) pacing cycle lengths at baseline and during phenylephrine infusion. Although both AHL and AHs were prolonged, there was a greater effect seen at the shorter paced cycle length (p<0.01). See text and Figure 3 for further details.

**Figure 6.** Plot showing sinus cycle length (CL) versus shortest atrial pacing cycle length with 1:1 atrioventricular nodal conduction during phenylephrine infusion (normalized to baseline measurements). Note the lack of a relation between the degree of prolongation of the sinus cycle length and the change in atrioventricular nodal conduction. The correlation coefficient observed was 0.11.
also may be functional abnormalities (e.g., a decrease in time-dependent refactoriness in an AV node without associated morphological abnormalities).

**Comparison of Sinus Automaticity and AV Nodal Conduction**

We found no relation between sinus and AV nodes in their response to enhanced vagal tone, and the degree of change in sinus rate did not predict the negative dromotropic alteration of AV nodal conduction, as measured by the atrial-paced Wenckebach cycle length. In general, directional changes were similar; that is, increased vagal tone slowed the sinus rate and prolonged the Wenckebach cycle length. However, it was common to observe minimal changes in sinus rate associated with rather pronounced increases in the Wenckebach cycle length. Alternatively, substantial slowing of the sinus rate could be associated with small changes in AV nodal conduction. Clearly, one cannot judge the effect of heightenved vagal tone on overall AV nodal conduction by observed changes in sinus automaticity.

It is possible that the disparity between the response of the sinus and AV nodes to phenylephrine-induced enhanced vagal tone is due to differential efferent nerve traffic to these structures. Randall and Armour21 demonstrated a variable and selective input of autonomic stimuli to the sinus and AV nodes. Discordant effects of autonomic influence on these structures also have been reported by others.1,2,22 and preliminary data in humans have demonstrated selective vagal effects on the sinus and AV nodes with local discrete parasympathetic nerve stimulation.23,24 Alternatively, there may be similar degrees of efferent nerve impulses to both nodes but a greater sensitivity of the AV or sinus node to enhanced parasympathetic tone in a given patient.

**Clinical Correlations**

There are several clinical implications of the findings in this study. Termination of paroxysmal supraventricular tachycardia with carotid sinus massage typically involves anterograde block of the impulse in the AV node; in sinus rhythm, however, block in the AV node is markedly unusual. We have observed that the cycle length during paroxysmal supraventricular tachycardia is most commonly within 30–40 msec of the Wenckebach cycle length, with AV nodal conduction near the steep part of the function curve; this is where one would expect enhanced vagal tone to exert a prominent effect. The cycle length of sinus rhythm is on the flat part of the curve, and changes in vagal tone typically alter AV nodal conduction only minimally. Another clinical correlation is observed during sleep, a period associated with an increase in vagal tone. Sinus slowing without AV nodal block is usual, but when the sinus rate is not significantly changed, transient type I second-degree AV nodal block may occur, presumably due to a significant divergence of the vagal effect on the two nodes. On the other hand, abrupt AV nodal block accompanied by sinus slowing can occur in patients with normal AV nodal function in response to a vagal surge,25 demonstrating that large increases in parasympathetic activity can shift the AV nodal function curve substantially to the right, causing block even at slower sinus rates.

**Limitations**

We assume that the effects noted during phenylephrine infusion are due to reflex vagal tone, although a direct effect of phenylephrine should be considered. In isolated canine Purkinje fibers, phenylephrine can decrease (low concentrations) or increase (high concentrations) automaticity.26 However, direct canine sinus nodal artery infusion of phenylephrine, at concentrations higher than those used in this study, caused acceleration of the sinus rate.27 Sympathectomy and vagotomy abolished the reflex sinus and AV nodal slowing in dogs in spite of a continued pressor effect of phenylephrine.10 Also, the canine bradycardic response to phenylephrine is blunted when the hypertensive effect is mechanically buffered.28 Detailed electrophysiological evaluation of the effects of phenylephrine in vagotomized dogs, in the presence of atropine and nadolol, demonstrated that AV nodal function was unchanged and that the sinus rate was accelerated slightly; this sinus node effect persisted after blood pressure normalization with nitroprusside but was abolished by prazosin, suggesting that it was due to a direct effect of phenylephrine.29 In humans, the reflex bradycardia observed with phenylephrine infusion has been shown to be abolished by atropine22 and is not present in the denervated heart status after cardiac transplantation.30 On the basis of these data, we consider it highly unlikely that phenylephrine in the doses used exerted a significant direct effect on either the sinus or AV nodes.

Increases in blood pressure induced by phenylephrine may diminish sympathetic tone, which could affect sinus and AV nodal function. Warner and Loeb10 observed a markedly reduced slowing of the sinus rate and AV conduction in dogs with phenylephrine after vagotomy. Further, Mancia et al3 noted that the reflex effect of phenylephrine on the human sinus and AV nodes was abolished by atropine. Thus, with the doses of phenylephrine used in this study, the major effect appears to be secondary to enhanced parasympathetic tone, although there may be a minor contribution due to sympathetic withdrawal.

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