Effects of Continuous Enhanced Vagal Tone on Dual Atrioventricular Node and Accessory Pathways

Chuen-Wang Chiu, MD; Shih-Ann Chen, MD; Ming-Ho Kung, MD; Mau-Song Chang, MD; Eric N. Prystowsky, MD

Background—The aim of this study was to test the electrophysiological effects of continuous enhanced vagal tone on dual atrioventricular (AV) nodal and accessory pathways.

Methods and Results—This study included 10 patients with typical, slow-fast AV nodal reentrant tachycardia (AVNRT) and 10 patients with AV reciprocating tachycardia. Electrophysiological data were measured before and during continuous vagal enhancement by using phenylephrine infusion (0.6 to 1.5 μg/kg per min). For patients with AVNRT, during phenylephrine infusion, 1:1 conduction times over the anterograde fast and slow and retrograde fast pathways were prolonged (453±64 to 662±120 ms, P<0.001; 379±53 to 443±95 ms, P<0.05; 405±112 to 442±118 ms, P<0.05). The effective refractory period and functional refractory period of the anterograde fast pathway were prolonged with phenylephrine (394±73 to 544±128 ms, P<0.001; 454±60 to 596±118 ms, P<0.001). In contrast, the effective refractory period and functional refractory period of the anterograde slow and retrograde fast fast were not significantly changed. No significant change was observed in the conduction or refractoriness of the accessory pathways in patients with AV reciprocating tachycardia nor in atrial or ventricular refractoriness.

Conclusions—Enhanced vagal tone produces disparate effects on the refractoriness of the slow and fast AV nodal conduction pathways, with the anterograde fast pathway being the most sensitive. These changes are conducive to induction of AVNRT with a premature atrial complex and may explain in part the relatively common occurrence of AVNRT during sleep or other periods of presumed increased parasympathetic tone. (Circulation. 2003;107:2583-2588.)

Key Words: vagus nerve • tachycardia • electrophysiology • Wolff-Parkinson-White syndrome • atrioventricular node

The autonomic nervous system is known to play an important role in the triggering and termination of paroxysmal supraventricular tachycardia (PSVT) confined to the atrioventricular (AV) node or incorporating an accessory pathway.1–12 Sympathetic stimulation is commonly used to facilitate induction of these tachycardias,1–6 whereas enhanced vagal tone by use of pharmacological or physical maneuvers is commonly used to terminate tachycardias.7–12 However, in some patients, the onset of AV nodal reentrant tachycardia (AVNRT) occurs at times of presumed increased vagal tone, for example, during sleep or after sudden bending forward or squatting. The mechanism responsible for the tachycardia initiation is not known. It is well known that enhanced vagal tone produces slowing of sinus node automaticity, prolongation of AV node conduction time, effective refractory period (ERP) shortening in the atria, and ERP prolongation in the ventricles.13–22 Nevertheless, little is known about the effects of vagal tone on dual AV nodal and accessory pathways. Thus, the purpose of this study was to investigate the effects of reflex-induced parasympathetic tone during steady-state conditions on conduction and refractoriness in dual AV nodal and accessory pathways.

Methods

Patients

The study population comprised 20 patients with recurrent, symptomatic supraventricular tachycardia who were referred for electrophysiological study and radiofrequency catheter ablation. Ten patients (mean age, 46±18 years) had typical AVNRT, and 10 patients (mean age, 40±9 years) had orthodromic AV reciprocating tachycardia (AVRT). Six of the 10 patients with AVRT had anterograde and retrograde accessory pathway conduction, and 4 had retrograde accessory pathway conduction only. Patients were excluded if they had structural heart disease, a systemic disorder involving autonomic function (for example, diabetes mellitus), or hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg). Also excluded were patients with typical AVNRT whose dual AV nodal pathways could not be demonstrated clearly by atrial decremental pacing and single premature atrial stimulation.

Electrophysiological Study and Pacing Protocol

As described previously,23–25 each patient underwent baseline electrophysiological study in the fasting, nonmedicated state. All cardio-
active drugs were discontinued for at least 5 half-lives before the study. Written informed consent for the study and for radiofrequency catheter ablation was obtained from each patient. Electrode catheters were positioned in the high right atrium, right ventricular apex, His bundle position, coronary sinus, and left ventricle as needed for pacing, mapping, and ablation. The pacing protocol was a modification of our standard protocol for determining ERPs of dual AV nodal and accessory pathways and atrial and ventricular myocardium. The basic drive consisted of 8 right atrial stimuli (S1) at a constant interval. The longest possible cycle length was chosen that allowed atrial capture and the ERPs of dual AV nodal pathways to be evaluated in patients with typical AVNRT or that allowed atrial capture and the AV node and accessory pathway to be evaluated in patients with AVRT. Longer cycle lengths were used to avoid Wenckebach block during the atrial drive train in the presence of vagal enhancement. The ERPs were determined by using the extrastimulus technique with the same paced cycle length at control and during vagal enhancement. Standard criteria used for determining the mechanisms of AVNRT or orthodromic AVRT and the dual AV node physiology were used.24–25 The sinus cycle length, atrial-His (AH) interval, 1:1 conduction in dual AV nodal and accessory pathways, ERPs and functional refractory periods (FRPs) in atrial and ventricular myocardium and in dual AV nodal and accessory pathway were determined in the baseline setting and during phenylephrine infusion. Patients underwent radiofrequency catheter ablation after all measurements were done.

Phenylephrine Infusion to Enhance Vagal Tone

A constant intravenous phenylephrine infusion (30 μg/mL) was administered through the femoral vein starting with a dose of 0.6 μg/kg per min for 10 minutes. The dose of phenylephrine was titrated with an increase of 0.3 μg/kg per min every 5 to 10 minutes until a systolic blood pressure increase of 30 to 50 mm Hg was observed or until a maximum dose of 1.5 μg/kg per min was administered. Electrophysiological study was begun when the blood pressure was stable for 3 minutes at a given dose.

### TABLE 1. Changes in Electrophysiological Data of Anterograde Conduction During Phenylephrine Infusion in Patients With AVNRT (N=10)

<table>
<thead>
<tr>
<th>Patient</th>
<th>S1–S1, ms</th>
<th>Slow</th>
<th>Fast</th>
<th>Atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ERP</td>
<td>FRP</td>
<td>ERP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1:1</td>
<td></td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Echo Zone</td>
<td>ERP</td>
<td>FRP</td>
</tr>
<tr>
<td>1</td>
<td>700</td>
<td>220</td>
<td>426</td>
<td>310</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>320</td>
<td>567</td>
<td>370</td>
</tr>
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<td>3</td>
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<td>7</td>
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<td>8</td>
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<td>330</td>
<td>596</td>
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</tr>
<tr>
<td>10</td>
<td>650</td>
<td>280</td>
<td>533</td>
<td>350</td>
</tr>
</tbody>
</table>

Mean±SD 283±40 525±50 379±53 394±73 454±60 453±64 231±21 249±24 78±10 858±8

P value* 0.01 NS NS

Slow indicates slow pathway; Fast, fast pathway; 1:1, atrioventricular 1:1 conduction; A, atrial; SCL, sinus cycle length; and NS, not significant.

*Versus baseline.

### TABLE 2. Changes in Electrophysiological Data of Retrograde Fast Pathway During Phenylephrine Infusion in Patients With AVNRT

<table>
<thead>
<tr>
<th>Patient</th>
<th>S1–S1, ms</th>
<th>Baseline</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>VA 1:1</td>
<td>F-ERP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V-ERP</td>
<td>VA 1:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V-FRP</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>550</td>
<td>330</td>
<td>350</td>
</tr>
<tr>
<td>2</td>
<td>550</td>
<td>240</td>
<td>353</td>
</tr>
<tr>
<td>3</td>
<td>550</td>
<td>230</td>
<td>353</td>
</tr>
<tr>
<td>4</td>
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<td>470</td>
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</tr>
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<td>345</td>
</tr>
<tr>
<td>10</td>
<td>550</td>
<td>340</td>
<td>387</td>
</tr>
</tbody>
</table>

Mean±SD 585±67 316±88 393±76 405±112 231±14 244±13 341±88 404±71 442±118 228±11 241±13

P* NS NS <0.01 NS NS

F indicates retrograde fast pathway; VA 1:1, ventriculoatrial 1:1 conduction; V, ventricular; and NS, not significant.

*Versus baseline.
### Statistical Analysis

Data were expressed as mean±SD. Statistical analysis of the measurements before and during phenylephrine infusion was done by paired t test. P<0.05 was considered statistically significant.

### Results

#### Effects of Continuous Enhanced Vagal Tone on AV Node Conduction During Sinus Rhythm and on the Atrial and Ventricular ERPs

There was no significant prolongation of the AH interval during sinus rhythm in patients with AVNRT or AVRT after continuous phenylephrine infusion, despite a significant slowing of the sinus rate (see Tables 1 and 3). Atrial and ventricular ERPs were similar before and during phenylephrine infusion (Tables 1 through 3).

#### TABLE 3 Changes in Electrophysiological Data During Phenylenphrine Infusion in Patients With AVRT (N=10)

<table>
<thead>
<tr>
<th>Phenylephrine</th>
<th>Baseline</th>
<th>Phenylephrine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCL, ms</td>
<td>651±146</td>
<td>804±158</td>
<td>&lt;0.001</td>
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<tr>
<td>AH, ms</td>
<td>73±9</td>
<td>75±10</td>
<td>NS</td>
</tr>
<tr>
<td>Anterograde conduction, ms</td>
<td>262±19</td>
<td>267±20</td>
<td>NS</td>
</tr>
<tr>
<td>AP-ERP</td>
<td>272±19</td>
<td>277±20</td>
<td>NS</td>
</tr>
<tr>
<td>AP-FRP</td>
<td>283±35</td>
<td>293±37</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AP 1:1</td>
<td>218±12</td>
<td>217±10</td>
<td>NS</td>
</tr>
<tr>
<td>A-ERP</td>
<td>240±21</td>
<td>241±21</td>
<td>NS</td>
</tr>
<tr>
<td>Retrograde conduction, ms</td>
<td>247±30</td>
<td>248±31</td>
<td>NS</td>
</tr>
<tr>
<td>AP-ERP</td>
<td>258±30</td>
<td>259±30</td>
<td>NS</td>
</tr>
<tr>
<td>AP-FRP</td>
<td>280±57</td>
<td>282±58</td>
<td>NS</td>
</tr>
<tr>
<td>AP 1:1</td>
<td>221±23</td>
<td>221±21</td>
<td>NS</td>
</tr>
<tr>
<td>V-ERP</td>
<td>236±17</td>
<td>236±17</td>
<td>NS</td>
</tr>
</tbody>
</table>

SCL indicates sinus cycle length; AP, accessory pathway; A, atrial; AP 1:1, shortest paced cycle length maintaining 1:1 conduction over the accessory pathway; V, ventricle; and NS, not significant.

#### Effects of Continuous Enhanced Vagal Tone on Dual AV Nodal Pathways

For patients with AVNRT, in the baseline state, tachycardia could be induced by single atrial extrastimulation in 4 patients and only by rapid atrial pacing in 2 patients. The tachycardia was inducible by single or double extrastimulation after isoproterenol infusion in the remaining 4 patients. The mean duration of stimulation protocol during phenylephrine infusion was 25±6 minutes. The sinus cycle length was similar at the beginning and the end of the stimulation protocol during phenylephrine infusion (1069±134 versus 1061±135 ms). Echo zone for induction of sustained AVNRT could be demonstrated in 4 patients before phenylephrine infusion. After phenylephrine infusion, the echo zone widened in 3 patients and disappeared in 1 (Table 1 and Figure 1). The critical AH intervals for initiation of echoes were not significantly changed during phenylephrine infusion (304±53 versus 307±57 ms) in these 3 patients. The mean anterograde slow pathway ERP and FRP were not significantly prolonged. However, in some patients, there was a marked increase in slow pathway refractoriness. Anterograde 1:1 slow pathway conduction prolonged moderately from 379±53 to 443±95 ms (P<0.05) during phenylephrine infusion. In contrast, there was a marked effect of enhanced vagal tone on anterograde fast pathway ERP (394±73 to 544±128 ms, P<0.001), FRP (454±60 to 596±118 ms, P<0.001), and 1:1 AV conduction (453±64 to 662±120 ms, P<0.001). In 9 of 10 patients, the discontinuous AV nodal conduction curves shifted upward and to the right after phenylephrine infusion (Figure 2). Only patient 6 had no effect on the discontinuous AV nodal conduction curve during phenylephrine infusion. The retrograde fast pathway ERP and FRP were not significantly prolonged, but 1:1 retrograde fast pathway conduction prolonged from 405±112 to 442±118 ms (P<0.01) during phenylephrine infusion (Table 2).
Effects of Continuous Enhanced Vagal Tone on Accessory Pathways

The mean anterograde and retrograde ERP and FRP of the accessory pathway and 1:1 retrograde accessory pathway conduction were not significantly changed during phenylephrine infusion (Table 3). The 1:1 anterograde accessory pathway conduction minimally prolonged from 283±35 to 293±37 ms (P<0.05) during phenylephrine infusion. In patients who had retrograde accessory pathway conduction only (N=4), the mean ERP (263±16 versus 263±16 ms, P>0.05) and FRP (350±37 versus 380±59 ms, P>0.05) of the anterograde AV nodal conduction were not significantly changed, but the AV 1:1 conduction prolonged significantly (298±34 versus 328±48 ms, P<0.05) during phenylephrine infusion.

Discussion

New Observations

The new observation from this study was that continuous enhanced vagal tone by use of phenylephrine infusion resulted in disparate electrophysiological effects on the slow and fast AV nodal pathways in patients with AV node reentry. There was a marked prolongation of the anterograde ERP and FRP of the fast but not slow pathway, with minimal effect on retrograde ERP of the fast pathway. Enhanced vagal tone modestly reduced conduction over the anterograde slow and retrograde fast pathways but substantially impaired 1:1 anterograde conduction over the fast pathway. For patients with AVRT, increased vagal tone had no significant effects on anterograde and retrograde refractoriness and retrograde conduction in accessory pathways; however, it produced a

Before Phenylephrine Infusion

![Recording A](image1)

![Recording B](image2)

![Recording C](image3)

During Phenylephrine Infusion

![Recording E](image4)

![Recording F](image5)

![Recording G](image6)

![Recording H](image7)

Figure 1. Recordings from a patient (No. 3) with typical slow-fast AVNRT demonstrating change in echo zone for induction of sustained reentrant tachycardia during enhanced vagal tone. Tracings in each panel were surface electrocardiographic lead V1 and intracardiac electrogroms of His-bundle region (HIS) and coronary sinus ostium region (CSO). S1 and S2 were pacing and premature stimuli. A and H were atrial and His bundle electrogram. The high right atrium was driven at a cycle length (S1-S1) of 700 ms. A through D, Echo zone (330 to 250 ms) before phenylephrine infusion. E through H, Echo zone (430 to 250 ms) during phenylephrine infusion. The echo zone for induction of AVNRT markedly increased during phenylephrine infusion.
minimal slowing of anterograde conduction over accessory pathways.

**Effects of Enhanced Vagal Tone on Dual AV Nodal Pathways**

Increased reflex vagal tone by use of physical maneuvers or phenylephrine bolus infusion has been used for many years to terminate PSVT. For patients with AVNRT, vagal enhancement can terminate the tachycardia either in anterograde slow or retrograde fast pathway. Previous studies have shown that increased vagal tone can prolong fast pathway ERP. Olsovsky et al reported that enhancement of vagal tone prolonged the ERP and slowed the conduction in anterograde fast pathway. Furthermore, Page et al demonstrated the effects of continuous vagal tone on the slow and fast pathways.

**Possible Mechanism of Enhanced Vagal Tone in Facilitating Induction of AVNRT**

At electrophysiological study, premature atrial but not ventricular complexes commonly initiate AVNRT. In theory, facilitation of AVNRT induction would occur at a time of selective prolongation of anterograde fast pathway ERP with minimal change in anterograde slow or retrograde fast pathway conduction and refractoriness. Reflex-induced vagal tone using phenylephrine infusion produces these effects. It is not surprising that the echo zone widened in 3 of 4 patients during phenylephrine infusion. In an isolated rabbit AV node preparation, Mazgalev et al showed that critically timed bursts of postganglionic vagal stimulation could allow induction of AVNRT. However, heightened vagal tone can uncommonly have a marked effect on both the slow and fast AV node pathways, even preventing AVNRT induction (patient 1). We have observed clinically that tachycardia often occurs by some physical positions, such as bending forward or squatting, that may increase vagal tone in some patients with typical AVNRT. A sudden change from standing to bending forward or squatting increases venous return and systemic resistance simultaneously. Stroke volume and arterial pressure rise, and the latter may induce transient increased reflex vagal tone. This transient enhanced vagal tone may facilitate the induction of AVNRT, as noted above. It is not clear whether this could occur in sinus rhythm only, with a sudden anterograde block over the fast pathway, or whether a simultaneous premature atrial complex is needed. The latter seems more likely, especially because bending is common but initiation of AVNRT with it is not.

**Possible Effects of Vagal Enhancement on Accessory Pathways**

It has been demonstrated that sympathetic stimulation shortens refractoriness and accelerates conduction over accessory pathways. Much less is known about the influence of vagal activity on accessory pathways. Morady et al using atropine demonstrated that resting vagal tone exerts a depressive effect on accessory pathways. Our data showed that increased vagal tone did not affect the anterograde or retrograde refractoriness of accessory pathways nor retrograde accessory pathway conduction; however, it minimally prolonged 1:1 anterograde conduction over accessory pathways. The discrepancy between these 2 studies may be attributable in part to the different interventions used to evaluate the parasympathetic nervous system. Morady et al tested the effects of atropine and showed a shortening of refractoriness and acceleration of conduction in accessory pathways, implying that resting vagal tone has a depressive effect on accessory pathways. Atropine could produce these effects directly or indirectly by prejunctional modulation of sympathetic tone. In this study, we measured the effects of reflex-induced vagal tone using continuous infusion of phenylephrine. It is possible that the level of increased vagal tone induced by phenylephrine infusion may be not high enough to affect the refractoriness and conduction in accessory pathways, and the findings do not contradict those noted by Morady et al on resting vagal tone.

**Different Effects of Vagal Enhancement on Sinus and AV Nodes, Atria, and Ventricles**

This study demonstrated that enhanced vagal tone did not significantly prolong AV node conduction time as assessed from the AH interval duration in sinus rhythm despite a significant prolongation of sinus cycle length. This is in agreement with previous reports, suggesting a preserved balance between direct vagal effects on the AV node and indirect effects of heart rate slowing. Interestingly, the refractoriness in the atrium and ventricle were not affected by enhanced vagal tone. Previous studies have demonstrated that the atrium and ventricle are relatively resistant to vagal tone.

![Figure 2](http://circ.ahajournals.org/doi/fig/10.1161/CIRCULATIONAHA.117.032221)
strated that heightened vagal tone shortens refractoriness in atria and prolongs refractoriness in ventricles. Prystowsky et al. used neck collar suction to increase vagal tone by carotid baroreceptor stimulation, which shortened atrial ERP in humans. Phenylephrine affects a variety of baroreceptors, and the magnitude of effect on the atria may not be as great with the amount of phenylephrine used in this study. The intensity of increased vagal tone induced by phenylephrine infusion is likely too low to affect ventricular refractoriness.

**Study Limitation**

A limitation of this study is that atrial or ventricular FRPs limited the exact measurement of refractoriness in anterograde slow and retrograde fast pathway in some patients. However, the atrial and ventricular FRPs were not changed, and all of the ERPs of anterograde slow and retrograde fast pathways were less than the atrial and ventricular FRPs before and during phenylephrine infusion in these patients. Therefore, we think that phenylephrine infusion did not significantly affect the refractoriness of anterograde slow and retrograde fast pathways in these patients, and we used the atrial and ventricular FRPs to represent the ERPs of anterograde slow and retrograde fast pathways for measurements. Furthermore, if we reanalyzed the data without these 3 patients (1, 3, and 6), the results of effects of phenylephrine infusion on refractoriness and conduction of the anterograde slow pathway did not change.

**Conclusion**

Enhanced vagal tone using phenylephrine infusion produced marked prolongation of refractoriness and conduction in the anterograde fast pathway, had no significant effect on refractoriness, and slowed the conduction in anterograde slow and retrograde fast pathways. These electrophysiologic changes with reflex-induced vagal tone may be responsible for tachycardia initiation that occurs in some patients with AVNRT during periods of presumed heightened parasympathetic tone.

**References**

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