Effects of Resting Vagal Tone on Accessory Atrioventricular Connections

Fred Morady, MD, Alan H. Kadish, MD, Stephen Schmaltz, MPH, Shimon Rosenheck, MD, and Joni Summitt, DO

The purpose of this study was to determine the effects of resting vagal tone on accessory atrioventricular (AV) connections. Atropine (0.04 mg/kg) was administered to 13 patients with the Wolff-Parkinson-White syndrome and was found to have the following effects on the accessory AV connection: the anterograde block cycle length shortened from 305±51 to 279±54 msec (mean±SD; p<0.001); the retrograde block cycle length shortened from 288±57 to 251±50 msec (p<0.001); and the effective refractory period measured at a basic drive cycle length of 400 msec shortened from 295±45 to 265±47 msec in the anterograde direction (p<0.001) and from 283±18 to 261±12 msec in the retrograde direction (p<0.01). During atrial fibrillation, the mean ventricular cycle length decreased from 434±88 to 352±56 msec (p<0.001), and the shortest preexcited RR interval decreased from 302±56 to 256±43 msec (p<0.01). In another seven patients, propranolol (0.2 mg/kg) was administered before atropine, and atropine lengthened the anterograde block cycle length and the effective refractory period of the accessory AV connection; the magnitude of these effects was similar to that in the patients who did not receive propranolol. In conclusion, these data demonstrate that resting vagal tone exerts a direct depressant effect on accessory AV connections that does not require background sympathetic activity to be manifest. (Circulation 1990;81:86–90)

It has been demonstrated that β-adrenergic stimulation shortens the refractory periods of atrial and ventricular muscle and shortens refractoriness and accelerates conduction in accessory atrioventricular (AV) connections. In contrast, vagal tone has been found to prolong refractoriness in ventricular muscle and may either prolong or shorten atrial refractoriness. However, the influence of vagal activity on accessory AV connections has not been described previously.

In the present study, the effects of resting vagal tone on accessory AV connections were determined indirectly by muscarinic blockade with atropine in patients with the Wolff-Parkinson-White syndrome.

Methods

Patients Studied

The subjects of this study were 20 patients with the Wolff-Parkinson-White syndrome and symptomatic tachycardia undergoing an electrophysiologic test. There were 12 men and eight women, and their mean age was 30±13 years (mean±SD). Each patient had manifest ventricular preexcitation, a single accessory AV connection, and inducible orthodromic reciprocating tachycardia in the baseline state. The accessory AV connection was located in the left free wall in 12 patients, in the right free wall in two patients, and in the posterior septum in six patients. None of the patients had structural heart disease.

Electrophysiologic Testing

Electrophysiologic studies were performed in the fasting, unsedated state after informed consent was obtained and at least five half-lives after discontinuation of antiarrhythmic drug therapy. Quadripolar electrode catheters that had been inserted through a femoral, internal jugular, or subclavian vein were positioned against the high lateral right atrium, across the tricuspid valve to record the His bundle depolarization, against the right ventricular apex, and within the coronary sinus. Electrocardiographic leads V, I, and III and the intracardiac electrograms were recorded at a paper speed of 100 mm/sec on a Siemens-Elema (Solna, Sweden) Mingograf 7 recorder. Pacing was performed by a programmable stimulator (Bloom Associates, Narbeth, Pennsylva-
nia) with stimuli at 2-msec duration and twice the late diastolic threshold.

**Study Protocol**

The study protocol was approved by the Human Research Committee at the University of Michigan. The spontaneous sinus cycle length was determined, and the blood pressure was measured with an arm cuff. The longest atrial and ventricular pacing cycle lengths associated with anterograde and retrograde block in the accessory AV connection were determined in 10-msec steps. The anterograde and retrograde effective refractory periods of the accessory AV connection were measured by the extrastimulus technique with eight-beat atrial or ventricular basic drive trains at cycle lengths of 500 and 400 msec, an intertrain pause of 3 seconds, and 10-msec decrements in the extrastimulus coupling interval. Orthodromic reciprocating tachycardia was induced by programmed atrial or ventricular stimulation; the tachycardia cycle length, the atrial-His interval, the His-ventricle interval, and the shortest ventriculo-atrial interval during tachycardia were measured. Atrial fibrillation was induced by rapid atrial pacing, and the shortest preexcited RR interval, the mean RR cycle length, and the percentage of QRS complexes that were preexcited were determined from at least 30 seconds of atrial fibrillation. If atrial fibrillation did not terminate spontaneously within 15 minutes, electrical cardioversion was performed after short-term general anesthesia with medazolam.

In 13 patients, 0.04 mg/kg atropine was infused at a rate of 2 mg/min after baseline parameters had been measured. This dose of atropine was previously demonstrated to result in block of cholinergic effects on the sinus rate. Two minutes after infusion of atropine, the parameters described above were remeasured. If atrial fibrillation did not terminate spontaneously within 15 minutes, it was converted by an infusion of 300–1,000 mg procainamide at a rate of 50 mg/min.

The effects of atropine in the setting of β-adrenergic blockade were determined in seven additional patients. In these patients, 0.2 mg/kg propranolol was infused at a rate of 1 mg/min after baseline parameters had been measured. This dose of propranolol was previously demonstrated to block the effects of β-adrenergic stimulation on the sinus rate and on ventricular refractory periods. The loading dose was followed by a continuous infusion of 0.1 mg/min, previously demonstrated to maintain a constant plasma propranolol concentration. Five minutes after infusion of the loading dose of propranolol, the parameters that had been measured in the baseline state were remeasured. However, to avoid the need for more than one electrical cardioversion, atrial fibrillation was not induced if a countershock had been required to terminate atrial fibrillation in the baseline state. Atropine was then infused as described above, and the blood pressure, sinus cycle length, and electrophysiologic parameters were remeasured.

**Analysis of Data**

The effects of atropine in the absence of propranolol were analyzed by a paired *t* test. The effects of propranolol and propranolol plus atropine were analyzed by a repeated-measures analysis of variance. Fisher’s least significant difference method was used for multiple comparisons. A mixed model analysis of variance was used to analyze the data for the variables that had missing data. The reasons for missing data included the following: 1) The effective refractory period of the accessory AV connection was shorter than the atrial functional refractory period. 2) The sinus cycle length was less than the basic drive cycle length used to measure refactoriness. 3) The retrograde effective refractory period of the accessory AV connection was shorter than the right ventricular functional refractory period. 4) Atrial fibrillation at least 30 seconds in duration was not inducible. 5) Orthodromic tachycardia was not inducible after the administration of propranolol. The effects of atropine in the presence and absence of propranolol were also compared with a mixed model analysis of variance. Comparisons of the percentage of QRS complexes during atrial fibrillation that were preexcited were performed by weighted least-squares analysis with linear models. A value of *p* < 0.05 was considered significant. Values are expressed as mean ± 1 SD.

**Results**

**Effects of Atropine**

The mean dose of atropine in the 13 patients who received only atropine was 2.9 ± 0.5 mg. The mean blood pressure was 91 ± 8 mm Hg in the baseline state and 93 ± 9 mm Hg after atropine (*p* = 0.4). The mean sinus cycle length shortened significantly from 840 ± 120 to 502 ± 44 msec after atropine (*p* < 0.001). The anterograde and retrograde block cycle lengths of the accessory AV connection and each of the measured accessory AV connection refractory periods were shortened significantly by atropine (Table 1). The mean cycle length of orthodromic tachycardia decreased from 366 ± 60 to 308 ± 48 msec after atropine (*p* < 0.001). The atrial-His and ventriculoatrial intervals during orthodromic tachycardia were significantly shorter after atropine, whereas the His-ventricle interval was unchanged (Table 1). The mean ventricular cycle length and the shortest preexcited RR interval during atrial fibrillation were both significantly shortened by atropine (Table 1). The percentage of QRS complexes that were preexcited was 79 ± 23% baseline and decreased significantly to 64 ± 32% after atropine (*p* < 0.001).

**Effects of Propranolol**

The mean loading dose of propranolol in the seven patients who received both propranolol and atropine was 13.6 ± 2 mg. The mean blood pressure was 94 ± 11 mm Hg in the baseline state and did not change.
Table 1. Effects of Atropine on Accessory Atrioventricular Connections

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement (msec)</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Atropine</td>
<td>p</td>
<td></td>
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<tr>
<td>Sinus CL</td>
<td>840±120</td>
<td>502±44</td>
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<tr>
<td>AV block CL</td>
<td>305±51</td>
<td>279±54</td>
<td>&lt;0.001</td>
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<tr>
<td>ERP at BDCL 400 msec</td>
<td>309±45</td>
<td>265±47</td>
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<td>ERP at BDCL 500 msec</td>
<td>301±75</td>
<td>251±50</td>
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<tr>
<td>VA block CL</td>
<td>283±18</td>
<td>261±12</td>
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<tr>
<td>Orthodromic tachycardia</td>
<td>309±66</td>
<td>270±14</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>CL</td>
<td>366±60</td>
<td>309±46</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>AH</td>
<td>188±56</td>
<td>138±44</td>
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<tr>
<td>HV</td>
<td>48±5</td>
<td>49±9</td>
<td>NS</td>
<td></td>
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<tr>
<td>VA</td>
<td>111±33</td>
<td>106±33</td>
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<td>Atrial fibrillation</td>
<td>434±88</td>
<td>352±56</td>
<td>&lt;0.001</td>
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<tr>
<td>Shortest PRR</td>
<td>310±53</td>
<td>256±43</td>
<td>&lt;0.01</td>
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</tr>
</tbody>
</table>

Values are mean±SD.
Number of patients indicates those in whom measurements were available at baseline and after atropine administration.

Table 2. Effects of Propranolol and Atropine on Accessory Atrioventricular Connections

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement (msec)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
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<tr>
<td></td>
<td>Baseline</td>
<td>Propranol</td>
<td>Atropine</td>
<td>P vs. B</td>
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<tr>
<td>Sinus CL</td>
<td>747±118</td>
<td>826±170</td>
<td>548±54</td>
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<td>AV block CL</td>
<td>288±72</td>
<td>297±65</td>
<td>268±60</td>
<td>NS</td>
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<tr>
<td>ERP at BDCL 400 msec</td>
<td>265±19</td>
<td>280±14</td>
<td>248±13</td>
<td>&lt;0.01</td>
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<tr>
<td>ERP at BDCL 500 msec</td>
<td>292±54</td>
<td>292±50</td>
<td>265±50</td>
<td>NS</td>
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<tr>
<td>VA block CL</td>
<td>260±32</td>
<td>314±130</td>
<td>254±40</td>
<td>NS</td>
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<td>Retro ERP at BDCL 400 msec</td>
<td>262±10</td>
<td>272±15</td>
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<td>Retro ERP at BDCL 500 msec</td>
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<td>274±17</td>
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<td>NS</td>
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<tr>
<td>Orthodromic tachycardia</td>
<td>350±57</td>
<td>347±25</td>
<td>351±73</td>
<td>NS</td>
</tr>
<tr>
<td>CL</td>
<td>177±53</td>
<td>163±23</td>
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<td>NS</td>
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<td>VA</td>
<td>92±10</td>
<td>100±10</td>
<td>90±10</td>
<td>NS</td>
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<tr>
<td>Atrial fibrillation</td>
<td>344±38</td>
<td>398±27</td>
<td>338±46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shortest PRR</td>
<td>268±126</td>
<td>297±133</td>
<td>252±88</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean±SD.
Number of patients indicates those in whom a complete set of measurements was available.

Effects of Atropine After Pretreatment With Propranolol

The mean dose of atropine in the seven patients who received both propranolol and atropine was 2.7±0.4 mg. The mean blood pressure after atropine was 96±11 mm Hg, which was not significantly different from the baseline or postpropranolol values.

Significantly after propranolol. The mean sinus cycle length increased from 747±118 to 826±170 msec after propranolol (p<0.05). Among the electrophysiologic parameters that were measured, the anterograde and retrograde effective refractory periods of the accessory AV connection and the mean ventricular cycle length and shortest preexcited RR interval during atrial fibrillation were lengthened significantly by propranolol, whereas the other parameters remained unchanged (Table 2). In three patients, orthodromic tachycardia was no longer inducible after propranolol.
Atropine decreased the sinus cycle length to 548±54 msec ($p<0.001$). Compared with postpropranolol values, atropine significantly shortened the anterograde block cycle length and each of the measured effective refractory periods of the accessory AV connection (Table 2). Compared with baseline values, atropine significantly shortened the anterograde block cycle length and each of the measured refractory periods (Table 2).

The magnitude of atropine’s effects on the block cycle lengths and the effective refractory periods of the accessory AV connection were similar in the patients who did and did not receive propranolol ($p=0.5$).

In the four patients in whom orthodromic tachycardia was inducible after propranolol, atropine did not significantly change the tachycardia cycle length or the atrial-His, His-ventricle, or ventriculoatrial intervals (Table 2).

Compared with the postpropranolol values, atropine significantly shortened the mean ventricular cycle length and the shortest preexcited RR interval during atrial fibrillation (Table 2). The percentage of QRS complexes that were preexcited increased from a baseline of 74±27% to 98±2% after propranolol administration ($p<0.001$) and then remained unchanged after atropine administration (95±5%).

**Discussion**

**Effects of Vagal Tone**

The results of this study demonstrate that atropine significantly accelerates conduction and shortens refractoriness in accessory AV connections. This response to muscarinic blockade with atropine implies that resting vagal tone exerts a significant depressant effect on accessory AV connections. Whereas prior studies have demonstrated that vagal tone may lengthen refractoriness in atrial and ventricular muscle, the results of this study provide the first demonstration of an inhibitory effect of vagal tone on accessory AV connections.

**Direct Cholinergic Effects**

Cholinergic effects on the heart either may result from antagonism of sympathetic activity or may be direct. In the case of ventricular muscle, an experimental study in dogs demonstrated that the prolongation in refractoriness that occurs with vagal stimulation is an indirect effect that is abolished or markedly attenuated by sympathectomy or propranolol. In contrast, clinical studies have indicated that vagal tone lengthens ventricular refractoriness even in the setting of $\beta$-adrenergic blockade and suggest the presence of a direct cholinergic effect on ventricular muscle. In the present study, atropine’s effects on accessory AV connections were manifest in the presence of $\beta$-adrenergic blockade and were similar in magnitude to its effects in the absence of $\beta$-adrenergic blockade. These data suggest that resting cholinergic tone exerts a direct depressant effect on accessory AV connections that does not require background sympathetic activity to be manifest.

**Effects of Resting Sympathetic Tone**

Propranolol increased the anterograde and retrograde effective refractory periods of the accessory AV connection determined at a basic drive cycle length of 400 msec; however, it did not significantly affect any of the other measures of refractoriness or conduction through the accessory AV connection. These results suggest that resting sympathetic activity usually exerted little or no tonic effect on the accessory AV connection in the patients in this study. This is consistent with the results of a prior study in which propranolol was found to have no significant effects on refractoriness or conduction in accessory AV connections.

Atropine significantly shortened the anterograde block cycle length and the effective refractory periods of the accessory AV connection compared with baseline values in the patients who were pretreated with propranolol. This observation indicates that the effects of resting vagal tone on accessory AV connections predominate over the effects of resting sympathetic tone. A similar predominance of tonic cholinergic effects over tonic sympathetic effects has been reported previously in regard to the sinus cycle length and the right ventricular effective refractory period.

**Effects of Propranolol and Atropine on Atrial Fibrillation**

A previous study demonstrated that propranolol often lengthens the mean ventricular cycle length during atrial fibrillation in patients with the Wolff-Parkinson-White syndrome, and this finding was confirmed in the present study. Atropine shortened the mean ventricular cycle length during atrial fibrillation both in the absence and presence of propranolol, in part by accelerating conduction through the AV node. However, the shortest preexcited RR interval during atrial fibrillation was also shortened by atropine; this finding is consistent with a direct effect of cholinergic tone on accessory AV connections. The fact that atropine decreased the percentage of QRS complexes that were preexcited indicates that vagal tone influences the AV node to a greater degree than accessory AV connections.

**Effects on Orthodromic Tachycardia**

In the absence of propranolol, atropine accelerated the rate of orthodromic tachycardia, predominantly by shortening the AV nodal conduction time during tachycardia. After the administration of propranolol, atropine’s effects on orthodromic tachycardia were not statistically significant. However, because propranolol suppressed the induction of tachycardia in three patients, data from only four patients were available for analysis of atropine’s effects; therefore, the statistical power to detect a difference was reduced.
Limitations

A limitation of this study is that the atrial or ventricular functional refractory periods limited the measurement of accessory AV connection refractoriness in some patients; therefore, data from all subjects were not available for analysis. Some of the effects of propranolol or atropine that were not significant may have attained significance with a larger sample size.

A second possible limitation of this study is that, in some patients, to avoid the need for cardioversion, atrial fibrillation was characterized on the basis of a nonsustained episode lasting less than 1 minute. Because autonomic changes during a sustained tachycardia conceivably could affect the tachycardia, measurements obtained during the first minute of atrial fibrillation may not have been representative of the measurements that would have been obtained after several minutes.

Conclusions

In the conductive properties and refractoriness of accessory AV connections are subject to fluctuations not only in sympathetic tone but also in cholinergic tone. This study has demonstrated that resting vagal tone exerts a depressant effect on accessory AV connections and that this is a direct effect that is not mediated by changes in sympathetic activity. As vagal tone diminishes, conduction accelerates, and refractoriness is shortened in accessory AV connections. Therefore, the stimulatory effects of exercise on accessory AV connections may result not only from sympathetic activation but also from the vagal activity that is associated with exercise. Furthermore, the findings of this study suggest that the anticholinergic effects of antiarrhythmic agents such as quinidine and disopyramide may partially offset the therapeutic effects of these drugs on accessory AV connections.

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References


KEY WORDS: Wolff-Parkinson-White syndrome • autonomic nervous system • atropine
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