OBJECTIVES

The purpose of this study was to determine whether verapamil has rate-dependent effects on the atrial effective refractory period (AERP).

BACKGROUND

Block of calcium current (ICa) and rapid component of the delayed rectifier potassium current (IKr) by verapamil is frequency-dependent. This may result in variable effects of verapamil on the AERP, depending on the rate.

METHODS

The subjects of this study were 30 adults with a mean age of 45 ± 13 years who did not have structural heart disease. In 20 subjects, the AERP was measured at basic drive cycle lengths (BDCLs) of 650 to 250 ms, in 50 ms decrements, before and after infusion of 0.1 mg/kg verapamil. The effective refractory periods (ERPs) were measured in the setting of autonomic blockade in 10 subjects and without autonomic blockade in 10 subjects. Ten subjects served as a control group and received a saline infusion instead of verapamil.

RESULTS

Verapamil significantly prolonged the AERP at BDCLs of 650 to 500 ms (p < 0.01 or p < 0.05) and significantly shortened the ERP at BDCLs of 300 and 250 ms (p < 0.01). In the control group, there were no significant differences between the baseline and post-saline measurements of ERP.

CONCLUSIONS

Verapamil prolongs AERP at slow rates and shortens AERP at rapid rates. These findings are consistent with a predominant effect on ICa at rapid rates and a predominant effect on IKr at slow rates. (J Am Coll Cardiol 2003;41:446–51) © 2003 by the American College of Cardiology Foundation

Verapamil blocks both the slow inward calcium current and the delayed rectifying current (1). Block of calcium current (ICa) and rapid component of the delayed rectifier potassium current (IKr) by verapamil is frequency-dependent (1), suggesting that verapamil may have variable effects on atrial refractoriness depending on the rate. However, no prior studies have directly assessed the rate-dependent effects of verapamil on the atrial effective refractory period (AERP). Therefore, this study was designed to determine the effect of verapamil on the AERP over a range of pacing rates.

METHODS

Characteristics of subjects. The subjects of this study consisted of 30 patients referred to the University of Michigan Medical Center for radiofrequency catheter ablation of supraventricular tachycardia. The inclusion criteria consisted of sinus rhythm as the baseline rhythm and a structurally normal heart. The exclusion criteria were as follows: treatment with any medication within 72 h of the procedure; a contraindication to propranolol, atropine, or verapamil; or failure to achieve a stable catheter position within the right atrial appendage, with a pacing threshold consistently <1.0 mA. No patient had been treated with amiodarone. Among 39 patients recruited for the study, 9 patients were withdrawn because they developed atrial fibrillation (AF) in the course of the study protocol. Therefore, the study protocol was successfully completed in 30 subjects.

There were 7 men and 23 women, and their mean age was 45 ± 13 years. In accord with the selection criteria for the study, all patients had a normal echocardiogram. The mean left ventricular ejection fraction was 0.60 ± 0.03. The mechanism of tachycardia was atrioventricular (AV) nodal re-entrant tachycardia in 22 patients, orthodromic AV re-entrant tachycardia in 4 patients, paroxysmal atrial flutter in 2 patients, and idiopathic right ventricular tachycardia in 2 patients. The effects of verapamil were tested in 20 patients, and 10 patients served as a control group. There were no significant differences in the demographic or clinical characteristics of the subjects in the two groups.

Electrophysiology procedure. The electrophysiologic procedures were performed in the fasting state. After informed consent was obtained, three quadripolar electrode catheters with an interelectrode spacing of 2-5-2 mm were positioned in the high right atrium, His-bundle position, and right ventricular apex. Patients were sedated with midazolam and fentanyl and received 3,000 U of heparin. Several electro-
cardiographic leads and the intracardiac electrograms were displayed on a screen and recorded digitally (EP Med Systems, Inc., Mount Arlington, New Jersey). Pacing was performed with a programmable stimulator (EP Med Systems, Inc.) with stimuli that had a pulse width of 2 ms and an amplitude three times the pacing threshold. 

Study protocol. The study protocol was approved by the Human Research Committee and written consent was obtained before the electrophysiology procedure. The study protocol was performed after completion of the radiofrequency catheter ablation procedure. A quadripolar electrode catheter was positioned in the right atrial appendage such that there was a stable pacing threshold <1 mA. The mean pacing threshold was 0.8 ± 0.1 mA. This catheter was used to measure the AERP. A second electrode catheter was positioned against the low lateral right atrial wall to record an atrial electrogram. Pharmacologic autonomic blockade was achieved in 10 subjects in the verapamil group and in the 10 subjects in the control group by infusion of 0.04 mg/kg of atropine and 0.2 mg/kg of propranolol over 5 min (2). The mean body weight of the 20 subjects was 64 ± 15 kg, with no significant difference between the verapamil and control groups.

Whenever possible, the AERP was measured at basic drive cycle lengths (BDCLs) of 650 to 250 ms, at decrements of 50 ms. At each BDCL, there was a conditioning train of 100 S1s. During continuous pacing, an atrial extrastimulus then was introduced after every eighth S1, with an initial coupling of 150 ms and with no pauses in the drive train. The coupling interval of the extrastimulus then was increased in steps of 5 ms until there was atrial capture. The AERP was defined as the longest S1S2 coupling interval that failed to result in atrial capture.

In 10 patients in the verapamil group, the effective refractory periods (ERPs) first were measured after autonomic blockade, then again after infusion of verapamil. In the other 10 patients in the verapamil group, autonomic blockade was not used. The dose of verapamil was 0.1 mg/kg over 3 min, followed 5 min later by infusion of 0.005 mg/kg/min until the study protocol was completed (3,4). The mean total verapamil dosage was 7.7 ± 2.3 mg. The sinus cycle length sometimes was <650 ms after autonomic blockade; therefore, among the patients who received autonomic blockade, the AERP could be measured in only four patients at a BDCL of 650 ms and in five patients at a BDCL of 600 ms. The AERP was measured in all 10 patients at BDCLs of 550 to 250 ms.

In the control group, the AERP was measured in exactly the same fashion as in the verapamil group. The ERPs were measured after autonomic blockade, then after infusion of 0.1 ml/kg of saline, followed 5 min later by infusion of saline at a rate of 0.005 ml/kg/min until the study protocol was completed. Because the sinus cycle length after autonomic blockade was <650 ms in some patients, the AERP could be measured in only two patients at a BDCL of 650 ms and in six patients at a BDCL of 600 ms. The AERP was measured in all 10 patients at BDCLs of 550 to 250 ms.

The blood pressure was measured periodically during the study protocol with an automated brachial artery cuff. 

Statistical analysis. Continuous variables are expressed as mean ± 1 SD. Student’s t test and the Fisher exact test were used to compare clinical and demographic variables between the verapamil group and the control group. Analysis of variance with repeated measures was used to compare the ERPs before and after verapamil or saline at different BDCLs. The Newman-Keuls test was used for post-hoc analysis, and the p values presented in Tables 1 to 3 refer to the results of the Newman-Keuls multiple comparisons test. In the autonomic blockade/verapamil group, ERPs at BDCLs of 650 and 600 ms were feasible in only four and five patients, respectively, and a paired t test was used for comparing the ERP before and after verapamil at these

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### Table 1. AERPs Before and After Infusion of Verapamil During Autonomic Blockade

<table>
<thead>
<tr>
<th>BDCL (ms)</th>
<th>No. of Patients</th>
<th>Baseline AERP (ms)</th>
<th>Post-Verapamil AERP (ms)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>650</td>
<td>4</td>
<td>230 ± 9</td>
<td>250 ± 12</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>600</td>
<td>5</td>
<td>228 ± 8</td>
<td>244 ± 13</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>550</td>
<td>10</td>
<td>218 ± 14</td>
<td>229 ± 14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>500</td>
<td>10</td>
<td>216 ± 14</td>
<td>224 ± 11</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>450</td>
<td>10</td>
<td>214 ± 13</td>
<td>217 ± 13</td>
<td>0.6</td>
</tr>
<tr>
<td>400</td>
<td>10</td>
<td>210 ± 9</td>
<td>207 ± 13</td>
<td>0.4</td>
</tr>
<tr>
<td>350</td>
<td>10</td>
<td>207 ± 10</td>
<td>202 ± 12</td>
<td>0.2</td>
</tr>
<tr>
<td>300</td>
<td>10</td>
<td>196 ± 7</td>
<td>187 ± 8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>250</td>
<td>10</td>
<td>186 ± 6</td>
<td>173 ± 9</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Effective refractory periods expressed as mean ± SD.

AERP = atrial effective refractory period, BDCL = basic drive cycle length.

### Table 2. AERPs Before and After Infusion of Verapamil, in the Absence of Autonomic Blockade

<table>
<thead>
<tr>
<th>BDCL (ms)</th>
<th>No. of Patients</th>
<th>Baseline AERP (ms)</th>
<th>Post-Verapamil AERP (ms)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>650</td>
<td>10</td>
<td>221 ± 14</td>
<td>232 ± 16</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>600</td>
<td>10</td>
<td>218 ± 16</td>
<td>229 ± 15</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>550</td>
<td>10</td>
<td>215 ± 17</td>
<td>222 ± 17</td>
<td>0.1</td>
</tr>
<tr>
<td>500</td>
<td>10</td>
<td>211 ± 18</td>
<td>215 ± 15</td>
<td>0.6</td>
</tr>
<tr>
<td>450</td>
<td>10</td>
<td>208 ± 17</td>
<td>212 ± 16</td>
<td>0.6</td>
</tr>
<tr>
<td>400</td>
<td>10</td>
<td>204 ± 13</td>
<td>202 ± 16</td>
<td>0.7</td>
</tr>
<tr>
<td>350</td>
<td>10</td>
<td>198 ± 13</td>
<td>196 ± 16</td>
<td>0.7</td>
</tr>
<tr>
<td>300</td>
<td>10</td>
<td>190 ± 11</td>
<td>183 ± 13</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>250</td>
<td>10</td>
<td>180 ± 12</td>
<td>164 ± 12</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Effective refractory periods expressed as mean ± SD.

Abbreviations as in Table 1.
drive cycle lengths. Because the sample size in the control group at a drive cycle length of 650 ms was only two, this data point was excluded from the analysis. A p value of <0.05 was considered statistically significant.

RESULTS

Sinus cycle length and blood pressure. In the verapamil group, among the patients who received autonomic blockade, the pre-verapamil sinus cycle length of 650 ± 94 ms lengthened to 688 ± 94 ms after infusion of verapamil (p < 0.05). In the patients in the verapamil group who did not receive autonomic blockade, the pre-verapamil sinus cycle length of 771 ± 35 ms shortened to 745 ± 54 ms after infusion of verapamil (p < 0.05). In the control group, the baseline sinus cycle length (after autonomic blockade) was 651 ± 63 ms, and 649 ± 67 ms after infusion of saline (p = 1.0).

In the verapamil group, among the patients who received autonomic blockade, the pre-verapamil mean blood pressure was 75 ± 7 mm Hg, compared with 70 ± 7 mm Hg after infusion of verapamil (p = 0.3). In the patients in the verapamil group who did not receive autonomic blockade, the pre-verapamil mean blood pressure was 88 ± 11 mm Hg, compared with 84 ± 11 mm Hg after infusion of verapamil (p = 0.3). In the control group, the baseline mean blood pressure (after autonomic blockade) was 78 ± 8 mm Hg, and 81 ± 3 mm Hg after infusion of saline (p = 0.8).

**AERPs in the verapamil group.** The AERPs measured at BDCLs of 650 to 250 ms before and after infusion of verapamil in the setting of autonomic blockade are shown in Table 1 and Figure 1. Compared with baseline, verapamil resulted in a significant lengthening of the AERP at BDCLs of 650, 600, 550, and 500 ms, and in a significant shortening of the AERP at BDCLs of 300 and 250 ms.

The AERPs measured at BDCLs of 650 to 250 ms before and after infusion of verapamil in the absence of autonomic blockade are shown in Table 2 and Figure 2. Compared with baseline, verapamil resulted in a significant lengthening of the AERP at BDCLs of 650 and 600 ms, and in a significant shortening of the AERP at BDCLs of 300 and 250 ms.

**AERPs in the control group.** Both before and after infusion of saline, the AERP progressively shortened as the BDCL decreased from 600 to 250 ms. In the control group, there were no significant changes in the AERPs measured at BDCLs of 600 to 250 ms before and after infusion of saline (Table 2, Fig. 3).

DISCUSSION

**Rate-dependent effects of verapamil.** The results of this study demonstrate that verapamil has opposite effects on the
AERP that are rate-dependent. At relatively slow heart rates, verapamil prolongs the atrial ERP, whereas at relatively rapid heart rates, the AERP is shortened by verapamil. These rate-dependent effects of verapamil on atrial refractoriness are consistent with a variable predominance of \( I_{Ca} \) and \( I_{Kr} \) blockade by verapamil at slow and rapid rates, respectively.

**Underlying mechanisms.** The mechanisms underlying the variable effect of verapamil on AERP may be explained by rate-dependent block of calcium and potassium channels by verapamil. Block of \( I_{Ca} \) by verapamil decreases the plateau calcium current, thereby shortening the action potential duration and the ERP (5), and blockade of \( I_{Ca} \) by verapamil is enhanced at rapid rates (1). However, verapamil also blocks \( I_{Kr} \) (6), resulting in lengthening of the action potential duration and ERP that may be manifest at relatively slow rates. Therefore, use-dependent block of \( I_{Ca} \) and reverse use-dependent prolongation of action potential duration may underlie the variable effects of verapamil on the AERP observed in this study.

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**Figure 2.** Atrial effective refractory periods (AERP) before and after infusion of verapamil, measured at basic drive cycle lengths (BDCL) of 650 to 250 ms, in the absence of autonomic blockade. *Error bars* = 1 standard deviation. *p < 0.01, †p < 0.05.

**Figure 3.** Atrial effective refractory periods (AERP) in the control group, before and after infusion of saline, at basic drive cycle lengths (BDCL) of 600 to 250 ms. *Error bars* = 1 standard deviation. There were no significant differences between the effective refractory periods measured before and after saline infusion.
Effect of verapamil on atrial refractoriness. In some prior studies, verapamil was found to shorten the AERP, whereas in others, it was found to lengthen the ERP. The rate-dependent effects of verapamil demonstrated in the present study may explain the variable effects of verapamil on atrial refractoriness in prior studies. For example, in a prior experimental study, verapamil was found to shorten the AERP (7). In that study, the BDCL at which the ERP was measured was 300 ms. In contrast, in a prior clinical study, verapamil was found to lengthen the AERP, and in that study, the BDCL was 500 ms (8). Based on the results of the present study, the opposite effects of verapamil on atrial refractoriness reported in prior studies are attributable, at least in part, to different BDCLs used to measure the refractory period.

Effects of verapamil in the setting of AF. Verapamil has been demonstrated to shorten the AF cycle length (7,9–11). The AF cycle length is directly related to the AERP (12,13). Therefore, because the atrial cycle length during AF typically is <250 ms, the effect of verapamil on AF cycle length is consistent with the results of the present study, in which verapamil shortened the AERP at BDCLs ≤300 ms. Shortening of the AERP when the atrial rate is rapid is likely to explain why verapamil may prolong an episode of AF and lower the probability of spontaneous cardioversion (7,9,11,14,15).

Although verapamil decreases the AF cycle length, once sinus rhythm is restored, it attenuates the post-AF shortening of AERP caused by AF (8,11,16,17). This observation also is consistent with the results of the present study. Because the atrial rate during sinus rhythm typically is >600 ms, verapamil would no longer be expected to shorten atrial refractoriness post-AF. During sinus rhythm, verapamil’s predominant effect is to lengthen the AERP. This may be one of the reasons that verapamil decreases the susceptibility towards immediate recurrences of pacing-induced or spontaneous AF (8,18,19).

Autonomic blockade. To prevent the confounding effects of fluctuations in autonomic tone that would be expected to occur in response to variable sedation, rapid pacing, and verapamil infusion, the effects of verapamil on atrial refractoriness were determined in the setting of pharmacologic autonomic blockade. However, in the clinical setting, patients who are treated with verapamil typically are not autonomically blocked. Therefore, to mimic the clinical setting, the effects of verapamil also were tested in the absence of autonomic blockade. In the absence of autonomic blockade, the effects of verapamil were attenuated at BDCLs of 550 and 500 ms. This may be attributable to sympathetic activation that occurred in response to verapamil infusion, as reflected by the shortening of sinus cycle length. However, the effects of verapamil on atrial refractoriness at the longest and shortest BDCLs were manifest even in the absence of autonomic blockade, demonstrating that the results of this study are applicable to the clinical setting.

Pharmacologic autonomic blockade was achieved by infusion of a single dose of propranolol and atropine at the outset of the protocol, and additional dosages of these agents were not administered in the course of the study protocol, which had a duration of approximately 30 min. The degree of autonomic blockade, therefore, may have progressively lessened over time. However, in the control group, the AERPs measured before and after the infusion of saline did not differ significantly at any BDCL. Because the duration of the study protocol was the same in the verapamil and control groups, these data demonstrate that temporal changes in the degree of autonomic blockade during the study protocol were not a confounding variable.

Prior studies. Rate-dependent effects of verapamil have been demonstrated previously in experimental and clinical studies, but only with respect to AV nodal conduction (20,21). Block of the calcium current in the AV node is manifest as slowing of conduction. Accordingly, the degree of prolongation in AV nodal conduction caused by verapamil was found to progressively increase as the BDCL shortened from 1,500 to 300 ms in dogs (21), and from approximately 800 to 350 ms in humans (20).

In these prior studies, the AERP was not measured (20,21). The present study demonstrates that rate-dependent depression of the calcium current also is demonstrable in the atrium, where block of ICaL is manifest as a shortening of the ERP.

Study limitations. A limitation of this study is that the AERP was measured only in the right atrial appendage. Therefore, it is not known whether the effects of verapamil demonstrated in this study are site-dependent.

A second limitation is that all of the subjects in this study had structurally normal hearts, and it is possible that the results of the study do not apply to patients who have structural heart disease.

None of the subjects in this study had AF. Whether the effects of verapamil demonstrated in this study also are applicable in the setting of electrical and structural remodeling associated with AF remains to be determined.

Lastly, the BDCLs used in this study were not tested in random order, but always in the same sequence of longest to shortest cycle length. This was done to avoid having to wait several minutes for the effects of a rapid rate on atrial refractoriness to dissipate before measuring the ERP at a slower basic drive rate (22). The possibility that the ERP measurements were affected by the sequence of BDCLs cannot be ruled out.

Conclusions. Although the effects of several antiarrhythmic drugs are either use-dependent or reverse use-dependent, some drugs may display both use- and reverse use-dependence (23). For example, block of sodium channels by quinidine is use-dependent, whereas the prolongation of action potential duration that occurs as a consequence of quinidine-induced ICaL block is reverse use-dependent (23). Verapamil is similar in that its effects on AERP display both use-dependence and reverse use-
dependence. Shortening of atrial refractoriness at rapid rates and lengthening of refractoriness at relatively slow rates may explain how verapamil can exert either a proarrhythmic or antiarrhythmic effect on AF, depending on the atrial rate.

**REFERENCES**