Postrepolarization Refractoriness Versus Conduction Slowing Caused by Class I Antiarrhythmic Drugs

Antiarrhythmic and Proarrhythmic Effects

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Background—Conduction block may be both antiarrhythmic and proarrhythmic. Drug-induced postrepolarization refractoriness (PRR) may prevent premature excitation and tachyarrhythmia induction. The effects of propafenone and procainamide on these parameters, and their antiarrhythmic or proarrhythmic consequences, were investigated.

Methods and Results—In 11 isolated Langendorff-perfused rabbit hearts, monophasic action potentials (MAPs) were recorded simultaneously from six to seven different right and left ventricular sites, along with a volume-conducted ECG. All recordings were used to discern ventricular tachycardia (VT) or ventricular fibrillation (VF) induced by repetitive extrastimulation (S2-S5) or 10-second burst stimulation at 25 to 200 Hz at baseline and after addition of procainamide (20 \( \mu \text{mol/L} \)) or propafenone (1 \( \mu \text{mol/L} \)) to the perfusate. MAPs were analyzed for action potential duration at 90% repolarization (APD\(_{90}\)), conduction times (CT) between the pacing site and the other MAPs, and PRR (effective refractory period = APD\(_{90}\) - PRR) and related to the induction of VT or VF. During steady-state pacing, procainamide and propafenone prolonged APD\(_{90}\) by 12% and 14%, respectively. Procainamide slowed mean CT by 40% during S2-S5 pacing, whereas propafenone slowed mean CT by up to 400% (P<0.001 versus baseline and procainamide). Wavelength was not changed significantly by procainamide but was shortened fourfold by propafenone at S5. Both drugs produced PRR, which was associated with a 70% decrease in VF inducibility with procainamide and elimination of VF with propafenone. Despite this protection from VF, monomorphic VT was induced with propafenone in 57% of burst stimulations.

Conclusions—Drug-induced PRR protects against VF induction. Propafenone promotes slow monomorphic VT, probably by use-dependent conduction slowing and wavelength shortening. (Circulation. 1998;97:2567-2574.)

Key Words: fibrillation • conduction • propafenone • procainamide

The mechanisms by which so-called class I antiarrhythmic drugs suppress tachyarrhythmias or exert proarrhythmic effects are still not well understood, nor has a measure for proarrhythmia caused by these drugs been clearly defined. The CAST I and II trials have demonstrated that sodium channel–blocking drugs with slow dissociation kinetics (encainide, flecainide, and moricizine) increase mortality in patients with structural heart disease.\(^1\)\(-\)\(^4\) It has been suggested that the proarrhythmic effect of these drugs is mediated by conduction slowing, which shortens the excitation wavelength or creates unidirectional block, thereby providing conditions for reentry, especially in structurally altered hearts.\(^5\)\(^6\) Propafenone is another agent with slowly dissociating, rate-dependent sodium channel block\(^7\)\(^8\) that has been shown clinically to have proarrhythmic effects in the treatment of ventricular tachyarrhythmias.\(^3\)\(^10\) On the other hand, drugs with sodium channel–blocking activity may delay the time-dependent recovery of excitability, thereby prolonging in a rate-dependent manner refractoriness beyond repolarization of the action potential to its resting state.\(^11\)\(^-\)\(^13\) Although the ionic mechanisms resulting in this drug-induced postrepolarization refractoriness (PRR) are not yet well defined, PRR has been suggested to have an antiarrhythmic effect, based on the rationale and previous observations that PRR shields the myocardium against very premature excitation with its associated conduction slowing and wavelength shortening.\(^12\)\(^-\)\(^14\)

This study was designed to distinguish the antiarrhythmic and proarrhythmic potential of two clinically used drugs with sodium channel–blocking properties: procainamide, which has relatively fast dissociation kinetics and is known to prolong the action potential, and propafenone, which has slow dissociation kinetics\(^14\) and divergent action potential duration effects. Specifically, we tested the hypotheses that drug-induced PRR is antiarrhythmic and that persistent sodium channel block producing conduction slowing even during regular stimulation is proarrhythmic. This was done by comparing the effects of procainamide and propafenone on action potential duration (APD), conduction time (CT), and PRR in the intact, isolated, Langendorff-perfused rabbit heart during regular pacing, repetitive extrastimulation, and high-
frequency burst pacing. These data were correlated with the incidence and type of induced tachyarrhythmias.

**Methods**

Hearts from 11 White New Zealand rabbits were isolated, mounted on a modified vertical Langendorff apparatus, and retrogradely perfused with oxygenated Tyrode’s solution as described in detail previously.\(^{15-17}\) The atrioventricular junction was ablated mechanically to create a complete atrioventricular conduction block.

**Recordings**

Six to seven monophasic action potentials (MAPs) were recorded simultaneously with the use of special silver–silver chloride contact pacing electrodes that permit recording and pacing from the same site (EP Technologies Inc) and reproduce the time course of the transmembrane action potential with high accuracy.\(^{15}\) MAPs were recorded simultaneously from four to five epicardial sites and one to two left ventricular endocardial sites. The epicardial recordings were located as follows: one on the right ventricular free wall, one on the right ventricle close to the septum, one or two on the left ventricular free wall, and one on the left ventricle close to the ventricular septum. The epicardial MAP electrodes were mounted on a custom-designed spring mechanism that provided constant contact pressure and was positioned for maximal interelectrode distance in every direction.\(^{16,17}\) The endocardial MAP recordings were obtained from standard 7F MAP-pacing combination catheters (EP Technologies Inc). The two endocardial catheters were positioned at disparate sites on the left ventricular endocardium. ECG recordings were derived from four silver–silver chloride electrodes placed in the immersion bath in an Eihithoven configuration, and a standard ECG amplifier was used for signal amplification.\(^{16,17}\) Repetitive extrastimulation (S2–S5) and burst pacing were performed through one of the endocardial MAP catheters. In three experiments, burst stimuli were also applied through a bipolar hook electrode consisting of two platinum wires inserted into the left ventricular free wall with an interelectrode distance of 2 to 3 mm. The hook electrode was positioned in close proximity (<3 mm) to one of the epicardial MAP electrodes.

All recordings were preamplified and recorded with an eight-channel thermal paper recorder (Gould Inc, model TA 4000). All parts of the experiment important for detailed analysis and all arrhythmias were recorded at a paper speed of 100 mm/s; the rest of the experiment was recorded at a paper speed of 1 mm/s.

**Experimental Protocols**

Hearts were paced at 400-ms basic cycle length and twice diastolic threshold, with the following arrhythmogenic interventions applied during baseline and after adding procainamide or propafenone to the perfusate.

(a) Repetitive extrastimulation (S2–S5) was performed at twice diastolic threshold. S2 was introduced at a 200-ms coupling interval, which was progressively shortened in steps of 5 ms after every 40th S2 until an action potential was no longer elicited, that is, the effective refractory period (ERP) was reached. With S2 remaining at the earliest coupling interval that still elicited a new action potential (ERP + 5 ms), S3 was introduced at 200 ms and decremented gradually, as was S2. This process was repeated for S4 and S5 until the closest coupling interval for all five extrastimuli was reached or until a sustained arrhythmia was induced. If a sustained arrhythmia was induced, the diastolic threshold was again checked and if necessary adjusted, and the process was repeated with the adjusted twice-diastolic threshold to ensure reproducibility. If a sustained arrhythmia was not induced, the process was repeated with an increased stimulus strength of three times diastolic threshold and, if arrhythmia was still not induced, five times diastolic threshold. Stimulation at higher stimulus strengths was performed on the basis of the previously published observation that higher stimulus strengths can elicit action potentials at shorter coupling intervals, thereby creating more premature, and hence possibly more arrhythmogenic, excitations, and a wider range of PRR values.\(^{19}\)

(b) High-frequency burst pacing was used because it probes myocardial excitability in a more continuous fashion than intermittent extrastimulation and uncovers the rate-dependent relation between repolarization and refractoriness with greater resolution and sensitivity.\(^{20}\) Burst pacing at twice diastolic threshold was applied for 10 seconds by one of the left ventricular MAP catheters (n = 11) or through a hook electrode mounted in the apex (n = 3) at burst cycle lengths of 10, 20, 30, and 40 ms in random order. The pacing threshold was verified immediately after each burst episode. The heart was allowed to recover for 4 minutes between the burst episodes. If sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) were induced, defibrillation was performed after a waiting period of ≥20 seconds, and the recovery period to the next burst episode was extended to 6 minutes. The stimulus strength was increased to three times diastolic threshold, and the protocol was repeated for all burst stimuli cycle lengths that did not induce arrhythmias at a stimulus strength of twice diastolic threshold. If a sustained arrhythmia was not induced at all burst frequencies, the process was repeated at 5 and, if necessary, at 10 times diastolic pacing threshold.\(^{20}\) Selected burst pacing intervals (n = 5) were repeated after completion of the protocol to test reproducibility.

The order of parts a and b of the protocol was varied randomly. Like selected burst stimuli, multiple extrastimulation was repeated at least once to ensure reproducibility.

(c) Antiarrhythmic drug interventions: After addition of either propafenone at a concentration of 1 μmol/L or procainamide at a concentration of 20 μmol/L to the perfusate, a drug loading time of at least 45 minutes was observed. During drug loading time, the drug effect was monitored by analyzing the MAP duration. Drug concentrations were titrated according to their effect on MAPs in preliminary experiments.\(^{11,12}\) Once MAP prolongation by the drug had reached a new steady state, parts a and b of the protocol were repeated in the same heart in the order selected for baseline. For multiple extrastimulation, the initial coupling interval of the extra-stimuli was prolonged according to the prolonged MAP duration. All burst stimuli applied at baseline were repeated to ensure a direct comparability of the arrhythmia induction between baseline and drug data.

The entire experimental protocol lasted an average of 5.2 ± 1 hours. This was feasible because the isolated heart preparation and MAP recording technique used in this study have been fine-tuned in our laboratory to provide electrophysiological stability and stable recordings from the same sites for up to 7 hours.\(^{16,23,24}\)

**Data Analysis**

APD at 90% repolarization (APD\(_{90}\)) was measured as the interval between the fastest MAP upstroke to the subsequent 90% repolarization level in each of the MAP recordings.\(^{7,16}\) CT was measured as the time between the fastest upstroke of the MAP at the pacing site and each of the other MAP recordings. CT and APD\(_{90}\) were measured during steady-state pacing and for each extrastimulus (S2–S5) at the shortest possible capturing coupling interval (= ERP + 5 ms). During repetitive extrastimulation, PRR was defined as the difference between the shortest coupling interval eliciting a new action potential (ERP + 5 ms) and the preceding APD\(_{90}\) at the pacing site (Figure 1).
During burst stimulation, PRR was measured as the interval between the end point of APD_{90} and the stimulus artifact preceding the following action potential (Figure 1). In the case of encroachment of excitation (negative PRR), APD_{90} was measured in the last steady-state beat before burst stimulation. During repetitive extrastimulation, APD_{90} of the preceding action potential was measured at a time when the following extrastimulus was not yet introduced. Data were excluded from analysis if APD_{90} shortened by more than 10 ms in more than two MAP recordings or if other signs of ischemia were visible.^{10,21} All analyses were performed manually with an accuracy of 5 ms (0.5 mm) at a paper speed of 100 mm/s. Relative excitation wavelength was calculated by dividing APD_{90} by maximal conduction time, the inverse linear correlate of conduction velocity.

### Statistical Evaluations

APD_{90}, CT, ERP, PRR, and excitation wavelength were compared between baseline and drug data with the use of ANOVA or paired Student’s t tests with Bonferroni correction where appropriate. The inducibility of arrhythmia was compared between drug and baseline induction time, the inverse linear correlate of conduction velocity. Student’s t tests were replaced by unpaired tests with paired inducibility of arrhythmia was compared between drug and baseline when the following extrastimulus was not yet introduced. Data were excluded from analysis if APD_{90} shortened by more than 10 ms in more than two MAP recordings or if other signs of ischemia were visible.^{10,21} All analyses were performed manually with an accuracy of 5 ms (0.5 mm) at a paper speed of 100 mm/s. Relative excitation wavelength was calculated by dividing APD_{90} by maximal conduction time, the inverse linear correlate of conduction velocity.

**TABLE 1. Effective Refractory Periods During Premature Extrastimulation (S2-S5)**

<table>
<thead>
<tr>
<th>Stimulus No.</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>168±20</td>
<td>156±19</td>
<td>138±21</td>
<td>133±20</td>
</tr>
<tr>
<td>Procainamide</td>
<td>142±18</td>
<td>138±18</td>
<td>133±18</td>
<td>125±14</td>
</tr>
<tr>
<td>Propafenone</td>
<td>209±28</td>
<td>206±21</td>
<td>199±15</td>
<td>187±8</td>
</tr>
</tbody>
</table>

Effective refractory periods during premature extrastimulation (S2-S5) at baseline, with procainamide, and with propafenone. Procainamide did not modify effective refractory periods significantly. Propafenone prolonged effective refractory periods more during premature extrastimulation than during pacing at 400 ms, concordant with use-dependent lengthening of effective refractory periods. All values are given in milliseconds, as mean±SD.

### Results

#### Steady-state Pacing

At baseline, the average APD_{90} was 171±11 ms at 400-ms basic pacing cycle length. Procainamide and propafenone prolonged APD_{90} significantly by 12% and 14%, respectively. CT between the MAP upstroke at the pacing site and that of the six other MAP recordings ranged from 5 to 55 ms, with an average of 13±8 ms. Procainamide prolonged average CT by an average of 11±11 ms (85±85%), and propafenone prolonged average CT by an average of 21±11 ms (161±85%) (P<.05 for procainamide versus propafenone).

#### Repetitive Extrastimulation

**Effects on ERP**

Figure 2 shows an example of six simultaneously recorded MAPs and the tissue bath ECG during multiple extrastimulation at baseline. During baseline, repetitive premature extrastimulation caused a progressive decrease in ERPs from 168±21 ms (S2) to 133±21 ms (S5, Table 1). Procainamide did not significantly change ERPs during repetitive extrastimulation, whereas propafenone lengthened ERPs from 209±28 ms at S2 to 187±8 ms at S5 (Table 1). The progressive decrease in ERP observed during multiple extrastimulation at baseline and with procainamide was less pronounced with propafenone.

**Conduction Time**

Baseline CT between the pacing site and the other MAP recording sites increased progressively for S2 and S3 and remained at an elevated plateau value for S4 and S5. The increase in average CT was 4±4 ms (31±31%) for S2 and 6±5 ms (46±38%) for S3 (Table 2). With procainamide, average and maximal CT increased slightly at steady-state pacing.

**TABLE 2. Conduction Times and Postrepolarization Refractoriness During Premature Extrastimulation (S2-S5) at Baseline**

<table>
<thead>
<tr>
<th>Stimulus No.</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CT</td>
<td>13.1±8</td>
<td>16.3±10</td>
<td>19.6±10</td>
<td>18.6±10</td>
<td>18.3±9</td>
</tr>
<tr>
<td>Maximal CT</td>
<td>22.1±13</td>
<td>28.2±17</td>
<td>33.8±18</td>
<td>32.2±17</td>
<td>32.6±16</td>
</tr>
<tr>
<td>PRR</td>
<td>2±11</td>
<td>-8±11</td>
<td>-7±8</td>
<td>-7±7</td>
<td></td>
</tr>
</tbody>
</table>

Prolongation of average and maximal conduction time (CT) and development of postrepolarization refractoriness (PRR) during premature extrastimulation (S2-S5) at baseline. CT increased progressively, whereas PRR decreased. All values are given in milliseconds, as mean±SD.
pacings without additional conduction delaying effects during multiple extrastimulation (Figure 3). Propafenone prolonged average CT at steady-state pacing by an average of 21 ms. In addition to this effect during steady-state (S1-S1) pacing, propafenone progressively prolonged CT during multiple extra stimulation in a use-dependent fashion: Average CT increased up to 400% at S5, and similar effects were observed on maximal CT (Figure 3). Neither the site of maximal CT nor the order of activation between the seven MAP recordings was modified by procainamide or propafenone.

**Postrepolarization Refractoriness**

At baseline, ERPs for S2-stimuli were nearly equal to the basic APD(90). During repetitive extrastimulation, ERPs not only shortened in absolute terms but also relative to the concomitant APD(90). This allowed the subsequent extrastimulus to elicit a new propagated response earlier in the repolarization phase (Figure 2). The last of the series of repetitive extrastimuli (S5) was able to elicit a new response 10 ms before the 90% repolarization level (P<.05, Table 2). Both procainamide and propafenone prolonged the ERP during repetitive extrastimulation relative to their concomitant APD(90) to an extent that the earliest capture by an extrastimulus occurred after 90% repolarization and often at even later diastolic intervals (PRR). While procainamide-induced PRR remained constant from S2 to S4, propafenone progressively prolonged PRR in a use-dependent fashion, increasing from S2 to S4 (Figure 4).

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**BURST STIMULATION**

A total of 178 burst stimulation episodes of different stimulus strengths and cycle lengths were available for analysis. At baseline, 65% of all burst stimuli induced VF. The probability of VF induction increased with increasing stimulus strength and was highest for intermediate burst cycle lengths (20 to 30 ms, Table 3). Pacing thresholds were verified directly after each burst stimulus to exclude artificial PRR caused by changes in pacing threshold. Pacing thresholds remained stable throughout the protocol, ranging from 0.02 to 0.2 mA for the MAP-pacing electrode and from 0.2 to 1.2 mA for the hook electrode.

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**TABLE 3. Probability of Arrhythmia Induction During Burst Stimulation**

<table>
<thead>
<tr>
<th>Stimulus Strength</th>
<th>Burst Interval, ms</th>
</tr>
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<tbody>
<tr>
<td>Twice Threshold</td>
<td>10 20 30 40</td>
</tr>
<tr>
<td>3 Times Threshold</td>
<td>10 20 30 40</td>
</tr>
<tr>
<td>5 to 10 Times Threshold</td>
<td>10 20 30 40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>37.5</td>
<td>37.5</td>
<td>0</td>
<td>50</td>
<td>87.5</td>
<td>86</td>
<td>40</td>
<td>66</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Procainamide</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Propafenone</td>
<td>20</td>
<td>50</td>
<td>33.3</td>
<td>24</td>
<td>50</td>
<td>80</td>
<td>75</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Probability of arrhythmia induction in percent during burst stimulation with different stimulus strengths from 2 to 10 times diastolic threshold (column groups) and different burst cycle lengths (burst interval, given in milliseconds; columns) at baseline, with procainamide, and with propafenone (rows). The probability of arrhythmia induction increased with increasing stimulus strength and was highest for intermediate burst cycle lengths (20 to 30 ms, Table 3). Pacing thresholds were verified directly after each burst stimulus to exclude artificial PRR caused by changes in pacing threshold. Pacing thresholds remained stable throughout the protocol, ranging from 0.02 to 0.2 mA for the MAP-pacing electrode and from 0.2 to 1.2 mA for the hook electrode.

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Procainamide decreased the inducibility of VF to 14% of the burst stimuli applied in this study \((P<0.05\) versus baseline). Propafenone did not reduce the incidence of arrhythmia inducibility per se, with 63% of all bursts inducing significant arrhythmias \((P=NS\) versus baseline), but changed the type of the induced arrhythmia from VF (Figure 5A) to a slow monomorphic VT (Figure 5B). Burst stimulation induced a slow monomorphic VT with propafenone in 57% and VF in only 6% of the bursts applied. Activation sequence of the multiple MAP recordings and QRS morphology in the tissue bath ECG were constant during tachycardias induced with propafenone (Figure 5B).

**PRR and Arrhythmia Inducibility**

Take-off potentials of earliest reexcitation during burst stimulation changed with different burst frequencies and stimulus strengths. At baseline, the average take-off point was 3±5 ms after repolarization to 90%, that is, PRR of 3 ms. PRR during burst stimulation was only observed with low stimulus strengths and burst frequencies. Reexcitation occurred earlier (at less repolarized “take-off” potentials) during burst stimulation inducing VF than during bursts not inducing arrhythmias (Figure 6).

PRR occurred with increasing magnitudes after either procainamide or propafenone had been administered, with propafenone producing greater PRR than procainamide (procainamide, 8±9 ms; propafenone, 34±17 ms). Similar to baseline data, bursts inducing VF showed significantly less PRR than other bursts not inducing arrhythmias with procainamide (Figure 6). In contrast to baseline and procainamide, bursts inducing arrhythmias with propafenone (mostly monomorphic VT) were not associated with less PRR than bursts with different frequencies and/or stimulus strengths not inducing arrhythmias (Figure 6). PRR was associated with protection against induction of VF with procainamide but not protection against monomorphic VT with propafenone during repetitive extrastimulation and burst stimulation.

The effects of procainamide and propafenone on CT, PRR, and arrhythmia inducibility are summarized in Table 4. Procainamide produced PRR without significant shortening of excitation wavelength and suppressed the induction of ventricular arrhythmias. Propafenone equally produced PRR and equally prevented induction of VF but shortened excitation wavelength threefold to fourfold \((P<.05\) versus baseline), associated with induction of monomorphic VT.

**Discussion**

This study investigated the differential effects of conduction slowing and PRR in the intact rabbit heart by comparing the influence of procainamide and propafenone on these parameters and on arrhythmia inducibility. The following main results were obtained: Both procainamide and propafenone caused PRR in a rate-dependent (use-dependent) fashion. With either drug, PRR was associated with protection against VF, but propafenone produced greater PRR and greater protection against induction of VF. Use-dependent conduction slowing (caused primarily by propafenone) increased the inducibility of slow monomorphic VT, even in the presence of marked PRR.

**Action Potential Duration**

Both procainamide and propafenone prolonged APD\(_{90}\) during steady-state pacing at a cycle length of 400 ms. Action potential–prolonging effects of procainamide have been reported previously in vitro and in vivo. Propafenone has
increasing numbers or frequencies of S1-stimuli,27 use-dependent stimulation in a use-dependent fashion. While this effect prolonged action potential at short cycle lengths.7,28 In this study, potential shortening at long cycle lengths and action potential of this study conform to previous studies showing action repolarization levels with repetitive extrastimulation has been variable effects on APD, depending on the pacing cycle length and on the type of heart cell analyzed.7,26–28 The results of this study conform to previous studies showing action potential shortening at long cycle lengths and action potential prolongation at short cycle lengths.7,28 In this study, propafenone prolonged APD90 and ERP during repetitive extrastimulation in a use-dependent fashion. While this effect is comparable to cumulative effects of propafenone with increasing numbers or frequencies of S1-stimuli,27 use-dependent action potential prolongation with propafenone during multiple premature extrastimulation has not been demonstrated directly.

**Postrepolarization Refractoriness**

As expected from previous studies,13,14,29 PRR was not observed in the absence of sodium channel–blocking drugs. On the contrary, during baseline, repetitive extrastimulation caused the ERP to shorten by a greater extent than the concomitant APD90. This shift to capture during earlier repolarization phases with repetitive extrastimulation has been observed previously in the human heart and has been named “facilitated excitability” or “progressive encroachment” of capturing extrastimuli.14 In this isolated heart study, as in the previous human heart study,14 encroachment of repetitive extrastimuli, or burst stimuli, onto the repolarization phase of the preceding action potential was associated with tachyarrhythmia induction (Figure 6). This may be explained by the fact that these most premature responses originated during the phase of relative refractoriness and therefore had slower conduction velocities (Table 2), resulting in shortened excitation wavelengths and subsequently functional reentry arrhythmias. In contrast, drug-induced suppression of excitability during the final repolarization phase (relative refractoriness) eliminated these very premature and arrhythmogenic responses (Figures 4 and 6). Protracting voltage-dependent and time-dependent recovery of sodium channels until a state of more complete sodium channel availability has been reached could be an antiarrhythmic mechanism of sodium channel–blocking drugs.

Complete repolarization at the time of reactivation will also prevent excitation during the vulnerable period in the late repolarization phase, caused by partial excitability due to dispersion of refractoriness, and thereby preclude microreentry.16,23,30,31 By preventing microreentry, PRR would suppress the induction of polymorphic ventricular arrhythmias by burst stimulation or premature extrastimulation, as was observed in this study. This explanation is supported by the association between drug-induced PRR and protection against induction of VF, whereas absence of PRR and presence of facilitated excitability was associated with induction of tachyarrhythmias (Figure 6).

PRR in this study was more pronounced during high-frequency burst stimulation than during the more intermittent extrastimulation, especially with propafenone. These data are consistent with the use-dependent action of sodium channel–blocking drugs26,32,33: The higher stimulus frequency of burst pacing as opposed to repetitive extrastimulation is prone to more effectively maintain drug binding during the open-channel state and thus to create greater use-dependent PRR.

**Conduction Times**

Both procainamide and propafenone block sodium channels.22,25,28,34 This drug effect explains the conduction slowing observed during 400-ms pacing with both drugs. Procainamide has fast dissociation kinetics22 and therefore does not exhibit cumulative, use-dependent conduction slowing with multiple premature extrastimulation. Propafenone, in contrast, has slow dissociation kinetics28,32,34 and is therefore prone to cumulative sodium channel block with higher probabilities of open sodium channels. This effect can explain both the slower conduction

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**Table 4. Summary of Electrophysiologic Effects of Procainamide and Propafenone**

<table>
<thead>
<tr>
<th></th>
<th>Procainamide</th>
<th>Propafenone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action potential duration</td>
<td>+12%</td>
<td>+14%</td>
</tr>
<tr>
<td>Postrepolarization refactoriness</td>
<td>+8 to 15 ms</td>
<td>+10 to 30 ms</td>
</tr>
<tr>
<td>Mean conduction time at S5</td>
<td>+94%</td>
<td>+400%</td>
</tr>
<tr>
<td>Inducibility of arrhythmias</td>
<td>70% less VF</td>
<td>Monomorphic ventricular tachycardia instead of VF</td>
</tr>
<tr>
<td>Mean change in wavelength</td>
<td>−20% (NS)</td>
<td>−80%</td>
</tr>
</tbody>
</table>

Summary of the differential effects of procainamide and propafenone on action potential duration at 90% repolarization, on postrepolarization refactoriness, on conduction time during premature stimulation, and on inducibility of VF (ventricular fibrillation).
times during 400-ms pacing and the additional conduction slowing effect of propafenone but not of procainamide during multiple premature extrastimulation.

Conduction Slowing Promotes Monomorphic VT

Monomorphic tachycardia is inducible by macroreentry, that is, within a functionally or anatomically preformed reentry circuit. In this setting, reentry can occur as the result of shortening of activation wavelength below the physical length of a preformed reentry circuit. Conduction slowing and action potential shortening both shorten activation wavelength. Given little or no change in APD, a fourfold increase in conduction time as observed with propafenone in this study decreases activation wavelength fourfold (Table 4) and possibly below the perimeter of the heart, a setting that allows for macroreentry around the circumference of the whole heart in this model. This mechanism may explain the induction of monomorphic tachycardia with propafenone but not with procainamide in this study. Because microreentry occurs within very short intervals at the stimulation site, suppression of microreentry was probably achieved by PRR intervals of 10 to 30 ms, whereas this short-term stabilization of excitation at the stimulation site could not prevent macroreentry.

Study Limitations

This study was performed in the intact, isolated rabbit heart. The relation between activation wavelength and heart size is different from the human heart, and some electrophysiological membrane characteristics of the rabbit myocardium differ from those of the human heart. Also, in this isolated heart model, no effort was made to model abnormal electrophysiological and pharmacological characteristics seen in idiopathic or ischemic myocardial disease. The arrhythmias induced in this healthy, isolated rabbit heart cannot be directly compared with ventricular arrhythmias observed in patients. Although the present model could demonstrate protective effects of both procainamide and propafenone against the inducibility of VF and proarrhythmic effects of propafenone for monomorphic tachycardia and associate them with effects on PRR and conduction slowing, these class I drug effects need further verification in the clinical setting, perhaps by using the MAP–pacing catheter technique in patients undergoing electrophysiological testing before and after antiarrhythmic drug treatment.

Although the analysis of MAP morphology, activation sequences between the multiple MAP recordings, and tissue bath ECG morphology provided a reliable distinction between VT and VF, exact reentry circuits could not be visualized in this study. Whether prevention of VF by propafenone was caused by PRR or by conduction slowing alone (and how propafenone induced monomorphic VT in this model) could not be directly demonstrated in this study. Studying the exact mechanism of VT induction by propafenone requires much more detailed epicardial and endocardial mapping. However, constant QRS morphology in conduction times during 400-ms pacing and the additional conduction slowing effect of propafenone but not of procainamide during multiple premature extrastimulation.

Clinical Implications

The results of this experimental study suggest that an important mechanism by which antiarrhythmic drugs with sodium channel–blocking properties suppress induction of tachyarrhythmias is by producing use-dependent PRR. The results of this study further suggest that in the case of propafenone, the antiarrhythmic effects of PRR may be offset by the proarrhythmic effects of conduction slowing, which sets the stage for slow monomorphic VT, even in the structurally normal heart. Sodium channel blockers with slow dissociation kinetics indeed have been shown to cause slow and often incessant monomorphic VT in patients. Risk factors prone to enhance drug-induced conduction slowing, for example, dilated cardiomyopathy, chronic ischemia, or previous myocardial infarction, might further increase the probability of proarrhythmic effects during treatment with propafenone, as suggested by previous clinical studies.

The reported data emphasize the role of PRR in preventing the induction of VF by premature excitations. Procainamide and propafenone achieved this protection to different degrees. Although propafenone produced greater use-dependent PRR than procainamide and was more effective in preventing induction of VF, this desirable effect was offset by a more pronounced slowing of conduction even during regular pacing (attributable to the slow dissociation kinetics of propafenone) and appeared to promote the occurrence of slow monomorphic VT. The ideal antiarrhythmic drug still needs to be designed, as has been suggested before. This study suggests that such an “ideal” drug should produce PRR in a use-dependent fashion with little or no effect on normal impulse propagation.

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References

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