Proarrhythmic Effects of Antiarrhythmic Drugs During Programmed Ventricular Stimulation in Patients Without Ventricular Tachycardia

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The proarrhythmic effects of class IA antiarrhythmic drugs were prospectively evaluated during programmed ventricular stimulation in 24 consecutive patients with frequent ventricular premature beats whose baseline study, performed while no antiarrhythmic drugs were being taken, showed no inducible sustained ventricular arrhythmias. No patient had nonsustained (>5 beats) or sustained ventricular tachycardia by history or baseline 24 hour ambulatory electrocardiographic monitoring. Sequential stimulation studies using up to three extra-stimuli were performed after administration of procainamide, quinidine and disopyramide on different days. Proarrhythmic response was defined as induction of one or more of the following: 1) sustained monomorphic ventricular tachycardia; 2) sustained polymorphic ventricular tachycardia; 3) ventricular fibrillation; 4) reproducibly inducible nonsustained monomorphic ventricular tachycardia.

During 55 antiarrhythmic drug trials (24 of procainamide, 21 of quinidine, 10 of disopyramide) in the 24 patients, 6 patients had a proarrhythmic response: sustained monomorphic ventricular tachycardia in 3, ventricular fibrillation in 2, nonsustained monomorphic ventricular tachycardia in 1. Thus, 11% of drug trials resulted in a proarrhythmic response and 25% of patients had a proarrhythmic response to one of the drugs tested. A proarrhythmic response to one drug did not predict a similar response to another drug of the same class. The 6 patients with a proarrhythmic response did not differ significantly from the other 18 patients with regard to underlying heart disease, electrocardiographic or baseline 24 hour ambulatory electrocardiographic characteristics; however, they did have a higher incidence of digoxin usage ($p < 0.02$), a shorter baseline right ventricular effective refractory period ($p < 0.01$) and a smaller increment in effective refractory period during antiarrhythmic drug testing ($p = 0.06$). Two of these six patients had clinical occurrence of sustained ventricular arrhythmias while taking an antiarrhythmic agent. All others have continued to do well during a mean follow-up period of 9 ± 0.8 months.

It is concluded that antiarrhythmic agents may induce ventricular tachyarrhythmias in patients with ventricular premature beats but no prior ventricular tachycardia, and this should be taken into consideration when treating patients with ventricular arrhythmias of uncertain prognostic significance.

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rhythmic drug-induced arrhythmias during programmed ventricular stimulation; and 2) determine whether a proarhythmic response to one class IA antiarrhythmic drug predicts a similar response to another drug of the same class.

Methods

Study patients. Between September 1984 and April 1985, 37 patients were referred to the electrophysiology/arrhythmia service of the Section of Cardiology for evaluation of frequent symptomatic ventricular premature beats, and they were screened for the study. None of them had a prior history of sustained ventricular tachycardia or cardiac arrest. Ventricular premature beats were not related to any identifiable acute precipitating factor or recent (<4 months) myocardial infarction and they occurred in the absence of antiarrhythmic drug therapy. Thirteen of the 37 patients were excluded because of the following predetermined exclusion criteria: 1) history of syncope (4 patients); 2) presence of spontaneous ventricular tachycardia (>5 beats) during 24 hours of ambulatory electrocardiographic monitoring while taking no antiarrhythmic drugs (3 patients); and 3) induction of sustained ventricular tachycardia or ventricular fibrillation during the baseline electrophysiologic study (6 patients). The remaining 24 consecutive consenting patients formed the study cohort.

There were 15 men and 9 women ranging in age from 24 to 77 years (mean 56 ± 4). Clinical diagnoses included coronary artery disease in 6 of the 24 patients, 5 of whom had previous myocardial infarction, congestive cardiomyopathy (6 patients), hypertensive heart disease (4 patients), valvular heart disease (4 patients) and no demonstrable heart disease (4 patients). Twelve patients had mild to moderate congestive heart failure (New York Heart Association functional classes II and III). Cardioactive medications included diuretics in 13 patients, digoxin in 6 patients, nitrates in 12, and calcium channel blocking agents in 2 patients; these medications were continued throughout the study. Antiarrhythmic drugs (five patients) and beta-adrenergic blocking agents (two patients) were discontinued 48 hours before ambulatory electrocardiographic monitoring. No patient was receiving amiodarone.

Protocol. Informed consent was obtained from each patient. All patients underwent baseline 24 hour ambulatory electrocardiographic monitoring and programmed ventricular stimulation while taking no antiarrhythmic drugs. Subsequently, serial electrophysiologic studies were performed with procainamide (24 trials), quinidine (21 trials) or disopyramide (10 trials) on three different days separated by a 24 hour washout period. In 23 patients, procainamide was administered intravenously, immediately after completion of baseline programmed ventricular stimulation, at a dose of 15 mg/kg body weight (infusion rate, 50 mg/min) followed by a constant infusion at 3 mg/min; repeat study was performed 10 minutes after starting the constant infusion. In one patient, procainamide (500 mg) was administered orally every 4 hours for seven doses. In all trials with quinidine and disopyramide, these drugs were administered orally every 6 hours for at least five doses (quinidine sulfate, 300 mg; disopyramide, 150 mg). At the end of each electrophysiologic drug trial, a serum level of the given antiarrhythmic drug was obtained. At any time during the serial antiarrhythmic drug testing, patients could voluntarily withdraw and be managed in the usual clinical fashion.

All three drugs were tested in 9 patients, two drugs in 13 patients (procainamide and quinidine in 12, procainamide and disopyramide in 1) and procainamide alone was tested in 2 patients. Disopyramide was not tested in all 12 patients with a history of congestive heart failure. The duration of drug testing averaged 7 days and a total of 79 electrophysiologic studies were performed in the 24 patients (average 3.3 studies/patient). During that time serum potassium level was normal in all patients (range 3.8 to 4.7 mEq/liter), and in patients taking digoxin the serum digoxin level ranged from 0.3 to 0.9 ng/ml. On completion of the study, patients were followed up in the outpatient clinic at intervals of 1 to 3 months.

Programmed ventricular stimulation. The study was performed with the patient in the postabsorptive and nonsedated state. For the baseline study, a 6F quadripolar electrode catheter was introduced percutaneously into the subclavian vein under local anesthesia with 1% lidocaine. In no patient did the amount of lidocaine administered exceed 5 ml. The catheter was advanced to the right ventricular apex and then the outflow tract. After completion of baseline programmed ventricular stimulation, this electrode catheter was left in place for subsequent serial studies. The external portion of the catheter was protected by a sterile sleeve to allow further manipulation.

The stimulation protocol consisted of the following: 1) 8 to 10 beat burst pacing at the right ventricular apex beginning at a cycle length of 500 ms and decrementing to a cycle length of 280 ms; 2) one, two and three extrastimuli delivered to the right ventricular apex during ventricular overdrive pacing at two different cycle lengths. The right ventricle was driven with a pacing train of five beats at a cycle length of 500 ms and again at a cycle length of 400 ms with an intertrain interval of 4 seconds; and 3) the protocol outlined in steps 1 and 2 was repeated at the right ventricular outflow tract. The end point for the stimulation protocol was induction of sustained ventricular tachycardia, ventricular fibrillation or completion of the protocol. Bipolar electrograms were filtered (30 to 500 Hz), displayed on a memory oscilloscope together with surface electrocardiographic leads V1, I and aVF and recorded on a strip chart recorder (VR-12, E for M/Honeywell) at a paper speed of 25 to 50 mm/s. Data were also recorded on a 12 channel frequency modulated tape recorder (Honeywell 5600E) for later replay and analysis. Baseline RR interval, QRS duration and QT interval were recorded at a paper speed of
Table 1. Frequency of Proarrhythmic Responses in 24 Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Trials</th>
<th>Proarrhythmic Responses (%)</th>
<th>Drug Level*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(µg/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(range)</td>
</tr>
<tr>
<td>Procaignamide</td>
<td>24</td>
<td>2(8%)</td>
<td>8.7 ± 0.6</td>
</tr>
<tr>
<td>Quinidine</td>
<td>21</td>
<td>3(14%)</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>10</td>
<td>1(10%)</td>
<td>4.0 ± 0.5</td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>6(11%)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SEM.

50 mm/s. The corrected QT interval (QTc) was calculated according to Bazett’s method.

The heart was paced by means of a programmable stimulator (Bloom Associates Ltd.) that delivered square wave stimuli of 1.5 ms duration at twice diastolic threshold (always ≤1.5 mA).

Definitions. Ventricular tachycardia was defined as a tachycardia of ventricular origin with a cycle length ranging between 200 and 500 ms. Sustained ventricular tachycardia was defined as a ventricular tachycardia that lasted longer than 30 seconds or required an intervention (overdrive pacing or cardioversion) for hemodynamic compromise. Nonsustained ventricular tachycardia was defined as a tachycardia that lasted from six beats to 30 seconds and terminated spontaneously. Ventricular fibrillation was defined as organized or disorganized ventricular activity with a cycle length of less than 200 ms requiring immediate defibrillation.

Criteria defining a proarrhythmic response during programmed ventricular stimulation. An antiarrhythmic drug was considered to have caused a proarrhythmic response if one or more of the following arrhythmias were induced: 1) sustained monomorphic ventricular tachycardia; 2) sustained polymorphic ventricular tachycardia; 3) ventricular fibrillation; and 4) reproducibly inducible nonsustained monomorphic ventricular tachycardia that was not initiated during the baseline study.

Statistical methods. Continuous variables were reported as the mean ± SEM. Comparisons between normally distributed continuous variables were made using two-tailed t tests with appropriately chosen variances. Nonnormally distributed continuous variables were analyzed by the Wilcoxon nonpaired rank sum test. Comparisons between discrete variables were done by the Fisher exact test. The statistical test used to derive each probability value is identified in the given table.

Results

Baseline study. Baseline programmed ventricular stimulation in the 24 study patients induced a maximal response of 0 to 3 beats in 14 patients, 4 to 5 beats in 5 patients and

nonsustained polymorphic ventricular tachycardia of 6 to 16 beats in 5 patients. The induction of nonsustained polymorphic ventricular tachycardia required two ventricular extrastimuli in one patient and three ventricular extrastimuli in four patients.

Frequency of proarrhythmic responses during drug testing. During the 55 prospective drug trials performed in the 24 patients, six proarrhythmic responses occurred in six

Figure 1. Induction of ventricular tachycardia during procainamide therapy. During the control study (top panel), a maximum of two repetitive ventricular responses were induced with triple extrastimuli (S3,S4,S5). After testing with procainamide (lower panel), sustained monomorphic ventricular tachycardia was induced. In each panel, from top to bottom are leads V1, I, aVF (F) and an intracardiac electrogram recorded from the right ventricle (RV). CL = cycle length. Heavy time lines represent 1 second.
Figure 3. Induction of ventricular fibrillation during quinidine therapy. During the control study (top panel), a maximum of two repetitive ventricular beats were induced. After testing with quinidine (lower panel), burst pacing at a cycle length of 350 ms induced sustained polymorphic ventricular tachycardia that degenerated into ventricular fibrillation. Note that the onset of this arrhythmia is preceded by a pause of 1.5 seconds interrupted by a sinus beat (Fig. 3). One hour after completion of electropharmacologic testing, the patient had a spontaneous episode of sustained torsade de pointes requiring resuscitation and defibrillation. The remaining patient (Patient 4) with inducible nonsustained monomorphic ventricular tachycardia had moderate left ventricular hypertrophy secondary to systemic hypertension.

Figure 2. Provocation of sustained monomorphic ventricular tachycardia during quinidine therapy. During the control study (top panel), nonsustained polymorphic ventricular tachycardia with a maximal duration of eight beats was induced. Retesting with quinidine induced sustained monomorphic ventricular tachycardia. Recording format and abbreviations as in Figure 1.

Different patients (Group I). Thus, 25% of the patients (6 of 24) had a proarrhythmic response to one class IA antiarrhythmic drug, and 11% of drug trials (6 of 55) led to a proarrhythmic response (Table 1). These responses included induction of sustained monomorphic ventricular tachycardia in three patients (Fig. 1 and 2), ventricular fibrillation in two patients (Fig. 3) and reproducibly inducible nonsustained monomorphic ventricular tachycardia in one patient. Induction of the proarrhythmic responses required three ventricular extrastimuli in five patients and burst pacing in one. Proarrhythmic responses were caused by quinidine in three patients (sustained ventricular tachycardia in two, ventricular fibrillation in one), procainamide in two patients (sustained ventricular tachycardia in one, ventricular fibrillation in one) and disopyramide in one patient (nonsustained monomorphic ventricular tachycardia). Five of the six Group I patients underwent testing with one (three patients) or two (two patients) other class IA antiarrhythmic drugs but did not show additional proarrhythmic responses (Table 2).

Five of the six Group I patients had underlying heart disease. All three patients (Patients 1 to 3) with inducible sustained monomorphic ventricular tachycardia had a transmural myocardial infarction 6, 14 and 21 months, respectively, before entry into the study. One patient with congestive cardiomyopathy (Patient 6) had induction of ventricular fibrillation during testing with quinidine; this occurred in association with prolongation of the QTc interval to 575 ms from a baseline of 470 ms. This arrhythmia was reproducibly induced by burst pacing on two different occasions during the same study, and on both occasions its onset was preceded by a long pause interrupted by a sinus beat (Fig. 3). One hour after completion of electropharmacologic testing, the patient had a spontaneous episode of sustained torsade de pointes requiring resuscitation and defibrillation. The remaining patient (Patient 4) with inducible nonsustained monomorphic ventricular tachycardia had moderate left ventricular hypertrophy secondary to systemic hypertension.
Table 2. Characteristics of Proarrhythmic Responses in the Six Group I Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Dx</th>
<th>Baseline Response</th>
<th>Proarrhythmic Type</th>
<th>Cl (ms)</th>
<th>Proarrhythm Blood Level (µg/ml)</th>
<th>%Change</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAD</td>
<td>2 RVR</td>
<td>SMVT</td>
<td>350</td>
<td>Proc</td>
<td>4.5</td>
<td>11.6</td>
</tr>
<tr>
<td>2</td>
<td>CAD</td>
<td>NSPVT (8 RVR)</td>
<td>SMVT</td>
<td>300</td>
<td>Proc</td>
<td>9.1</td>
<td>3.5</td>
</tr>
<tr>
<td>3</td>
<td>CAD</td>
<td>NSPVT (6 RVR)</td>
<td>SMVT</td>
<td>290</td>
<td>Proc</td>
<td>4.3</td>
<td>4.9</td>
</tr>
<tr>
<td>4</td>
<td>HHD</td>
<td>2 RVR</td>
<td>NSMVT (12 RVR)</td>
<td>300</td>
<td>Diso</td>
<td>8.7</td>
<td>6.0</td>
</tr>
<tr>
<td>5</td>
<td>&quot;Normal&quot; heart</td>
<td>NSPVT (16 RVR)</td>
<td>VF</td>
<td>170</td>
<td>Proc</td>
<td>0</td>
<td>4.5</td>
</tr>
<tr>
<td>6</td>
<td>CCM</td>
<td>2 RVR</td>
<td>VF</td>
<td>230</td>
<td>Quin</td>
<td>22</td>
<td>2.1</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CCM = congestive cardiomyopathy; CI = cycle length; diso = disopyramide; Dx = diagnosis; HHD = hypertensive heart disease; LAD = left axis deviation; LBBB = left bundle branch block; Morph = morphology; NSPVT = nonsustained polymorphic ventricular tachycardia; Proarrh = proarrhythmic; Proc = procainamide; Quin = quinidine; RAD = right axis deviation; RY ERP = right ventricular effective refractory period during 500 ms ventricular cycle drive; RVR = repetitive ventricular response; SMVT = sustained monomorphic ventricular tachycardia; VF = ventricular fibrillation; %Change = percent increase in effective refractory period.

None of the 24 study patients demonstrated clinical or electrocardiographic evidence of antiarrhythmic drug toxicity, and serum antiarrhythmic drug levels were within the accepted therapeutic range (Tables 1 and 2).

Comparison of patients with versus those without proarrhythmic responses. The six Group I patients were compared with the other 18 patients (Group II) with respect to their clinical characteristics (Table 3). Four of the six Group I patients were taking digoxin compared with only 2 of the 18 Group II patients (p < 0.02). Group I patients tended to have a higher prevalence of previous myocardial infarction compared with Group II patients (50% versus 11%, p < 0.08). The two groups did not differ significantly with regard to age, sex, functional class, presence of hypertension or type of heart disease. There was no significant difference in the mean hourly frequency of ventricular premature beats or presence of repetitive ventricular premature beats on 24 hour ambulatory electrocardiographic monitoring.

The baseline ventricular effective refractory period measured at the right ventricular apex was significantly shorter in Group I patients than in Group II patients (223 ± 3 versus 242 ± 4 ms, p < 0.01) (Fig. 4). During testing of their proarrhythmic drugs, Group I patients showed an increment of 8 ± 4% in the effective refractory period compared with an increment of 15 ± 1% in Group II patients (p = 0.06) (Fig. 4). However, the QRS duration and QTc interval of the two groups were not statistically different at

Table 3. Clinical Profile of Patients With (Group I) or Without (Group II) Proarrhythmic Responses

<table>
<thead>
<tr>
<th></th>
<th>Group I (6 patients)</th>
<th>Group II (18 patients)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55 ± 7</td>
<td>57 ± 3</td>
<td>NS*</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>1(17%)</td>
<td>11(61%)</td>
<td>NS†</td>
</tr>
<tr>
<td>Class II to III</td>
<td>5(83%)</td>
<td>7(39%)</td>
<td>NS†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4(67%)</td>
<td>8(44%)</td>
<td>NS†</td>
</tr>
<tr>
<td>Prior MI</td>
<td>3(50%)</td>
<td>2(11%)</td>
<td>&lt;0.08†</td>
</tr>
<tr>
<td>Digoxin</td>
<td>4(67%)</td>
<td>2(11%)</td>
<td>&lt;0.02†</td>
</tr>
<tr>
<td>VPBs/h (range)</td>
<td>307 ± 84</td>
<td>366 ± 87</td>
<td>NS‡</td>
</tr>
<tr>
<td>(15 to 581)</td>
<td></td>
<td>(30 to 1196)</td>
<td></td>
</tr>
<tr>
<td>Repetitive VPBs</td>
<td>4(67%)</td>
<td>13(72%)</td>
<td>NS‡</td>
</tr>
</tbody>
</table>

*Two-tailed test equal variances; †Fisher’s exact test; ‡Wilcoxon nonpaired rank sum test. MI = myocardial infarction; NS = not significant; NYHA = New York Heart Association functional class; repetitive VPBs = two to five consecutive ventricular beats during ambulatory electrocardiographic monitoring.
baseline or during drug testing. During the control study, the sinus cycle length was shorter in Group I than in Group II patients (690 ± 55 versus 847 ± 32 ms, p < 0.02). In Group I patients, sinus cycle length was 650 ± 27 ms after procainamide (p = NS), 656 ± 29 ms after quinidine (p = NS) and 730 and 780 ms, respectively, after disopyramide. The sinus cycle length in Group II patients was 753 ± 23 ms after procainamide (p < 0.05), 778 ± 20 ms after quinidine (p = 0.09) and 805 ± 29 ms (p = NS) after disopyramide.

Follow-up. Of the six Group I patients, two were discharged receiving procainamide and flecainide, respectively, for control of symptomatic ventricular premature beats; both patients had shown a proarrhythmic response during programmed ventricular stimulation with quinidine. The remaining four Group I patients received no antarrhythmic therapy. During a mean follow-up period of 8.2 ± 0.8 months (range 6 to 18), all have stayed free of spontaneous sustained ventricular tachycardia or sudden cardiac arrest, with the exception of Patient 3, who developed sudden nonfatal cardiac arrest after being started on tocainide therapy (1,200 mg/day) by her private physician. This patient had shown a proarrhythmic response to quinidine in the laboratory (sustained monomorphic ventricular tachycardia), and subsequent treatment with flecainide and amidarone also resulted in incessant ventricular tachycardia requiring multiple defibrillations. She received an automatic implantable defibrillator 6 months after the initial electrophysiologic testing and, while taking no antiarrhythmic drugs, had no shock delivered in an 8 month follow-up period.

None of the 18 Group II patients were discharged on antiarrhythmic therapy. One patient was lost to follow-up at 1 month. Subsequently, two patients had to be treated with flecainide and one with procainamide for intolerable symptoms of palpitation. During a follow-up period of 9.5 ± 0.8 months (range 7 to 14), none has developed spontaneous sustained ventricular tachycardia or sudden death, although the majority have continued to experience occasional episodes of palpitation.

**Discussion**

Proarrhythmic effects of antiarrhythmic drugs. Our results show that in patients with frequent ventricular premature beats but no sustained ventricular arrhythmias, class IA antiarrhythmic drugs caused a proarrhythmic response during programmed ventricular stimulation in 6 (11%) of the 55 prospective drug trials and in 6 (25%) of the 24 patients. A proarrhythmic response to one drug did not predict a similar response to a different drug of the same class.

These findings are comparable with those of several previous studies (9–12) of patients with sustained ventricular arrhythmias in which drug-induced proarrhythmic responses occurred in about 15% of the patients during ambulatory electrocardiographic monitoring or programmed ventricular stimulation. However, the criteria we used to define a proarrhythmic response and our patient group differed from those of the previous studies. Velebit et al. (12) retrospectively studied 155 patients, more than 75% of whom presented with sudden cardiac arrest or sustained ventricular tachycardia, and reported aggravation of ventricular arrhythmias in 11% of the 722 drug trials evaluated by ambulatory electrocardiographic monitoring. However, in patients with clinical ventricular tachycardia undergoing ambulatory electrocardiographic monitoring, there is significant short-term spontaneous variability in the frequency and complexity of ventricular premature beats and in the frequency of sustained or nonsustained ventricular tachycardia (13–15). Thus, it is difficult to determine whether the augmented arrhythmias were due to proarrhythmic effects or merely represented spontaneous variability of the arrhythmias. Other recent studies (10,11) in patients with recurrent sustained ventricular arrhythmias suggested that antiarrhythmic drugs
caused aggravation of arrhythmias during electropharmacologic testing in 13 to 16% of drug trials. In both studies, a less aggressive mode of induction of ventricular tachycardia during antiarrhythmic drug testing was considered to represent a proarrhythmic effect of the drug and accounted for nearly one-half of all proarrhythmic responses reported. However, there is no general agreement on this criterion because several studies (16–19) have shown that in patients with inducible sustained ventricular tachycardia, the mode of ventricular tachycardia induction (number of ventricular extrastimuli, paced cycle length, stimulation location) varies spontaneously from day to day. In our study, we did not consider a change in the induction mode to represent a proarrhythmic effect. None of our patients had ventricular tachycardia during antiarrhythmic drug testing was considered to represent a proarrhythmic effect of the drug and accounted for nearly one-half of all proarrhythmic responses reported. However, there is no general agreement on this criterion because several studies (16–19) have shown that in patients with inducible sustained ventricular tachycardia, the mode of ventricular tachycardia induction (number of ventricular extrastimuli, paced cycle length, stimulation location) varies spontaneously from day to day. In our study, we did not consider a change in the induction mode to represent a proarrhythmic effect. None of our patients had ventricular tachycardia during their history or 24 hour ambulatory electrocardiographic monitor or during baseline programmed ventricular stimulation using up to three ventricular extrastimuli. Nonetheless, even in this group of patients, we demonstrated proarrhythmic effects of antiarrhythmic drugs in 11% of drug trials and 25% of the patients.

Criteria of proarrhythmic response during programmed ventricular stimulation. When using programmed ventricular stimulation to evaluate drug-induced arrhythmias, it is difficult to be certain if the induced arrhythmias represent random variability of the induced response or if they are indeed caused by the antiarrhythmic agent. The reproducibility of induced response with the stimulation protocol similar to that used in our study has varied between 87% and 100% (18–20). Bigger et al. (20) performed two baseline studies 4 days apart in 52 patients with a history of sustained ventricular tachycardia; their stimulation protocol consisted of triple extrastimuli and burst pacing delivered at two right ventricular sites and two paced cycle lengths. Of 47 patients with inducible sustained ventricular tachycardia at the first study, 41 (87%) had the same arrhythmia induced during the second study. The remaining six patients had induction of nonsustained ventricular tachycardia (three patients) or no ventricular tachycardia (three patients). The reproducibility of induced response has been lower (43% to 56%) when a single right ventricular site was stimulated at one paced cycle length (21,22). Duff et al. (21) reported a low reproducibility (43%) of the induced response when the electrode catheter was left in place for the repeat stimulation study. However, when the electrode catheter was repositioned for the second study, the reproducibility of induced response was 100%. In all 24 patients in our study, we stimulated two right ventricular sites at two paced cycle lengths for each programmed stimulation test both before and after administration of antiarrhythmic agents, and therefore, the development of proarrhythmic responses in 25% of our patients is unlikely to be merely a manifestation of lack of reproducibility of the induced response to programmed stimulation. Moreover, five of the six patients showing a proarrhythmic response underwent seven additional drug trials without induction of ventricular tachycardia or fibrillation.

We did not consider nonsustained polymorphic ventricular tachycardia as a positive response because stimulation with triple extrastimuli has been shown to induce this arrhythmia in up to 50% of patients with no previous history of ventricular tachycardia (23–27). On the other hand, nonsustained or sustained monomorphic ventricular tachycardia is almost never induced in patients with no prior history of ventricular tachycardia, and induction of ventricular fibrillation in such patients is also an infrequent finding, occurring in 0 to 10% of the studied patients (23,26,27). We did not include patients with recent (<4 months) myocardial infarction because programmed ventricular stimulation in the survivors of acute myocardial infarction has been demonstrated to induce sustained ventricular tachycardia or ventricular fibrillation in 17% to 46% of the studied patients, and only a small minority of patients with inducible tachyarrhythmia had subsequent occurrence of spontaneous sustained ventricular tachycardia or sudden death (28–30). None of our 24 patients had induction of monomorphic ventricular tachycardia or ventricular fibrillation during the baseline study; therefore, the induction of these arrhythmias during repeat study while taking an antiarrhythmic agent most likely represented the proarrhythmic effects of the drug. Previous data from trials of encainide (31) suggested that there may be a correlation between aggravation of electrically induced arrhythmia and recurrence of spontaneous arrhythmia during treatment with antiarrhythmic agents. Our follow-up data support this contention in that two of the six Group I patients (Patients 3 and 6) had clinical occurrence of sustained ventricular tachyarrhythmias while taking an antiarrhythmic drug; these arrhythmias were similar in configuration to those induced during programmed ventricular stimulation. Both patients have continued to do well without any antiarrhythmic therapy during a follow-up period of 8 and 14 months, respectively.

Potential mechanisms of proarrhythmic effects. The mechanism by which a class IA antiarrhythmic drug causes ventricular arrhythmias is unknown. Termination of a reentrant arrhythmia by an antiarrhythmic drug is achieved when the effective refractory period in tissues proximal to the site of reentry is prolonged sufficiently so that a returning wave front, despite slowed conduction, still finds those tissues refractory (32,33). Conceivably, if an antiarrhythmic drug were to minimally affect refractoriness but still prolong impulse conduction time, then areas of the reentrant pathway might recover sufficiently to allow the returning wave front to continue and perpetuate the reentrant arrhythmia. That this mechanism might have been operative in our patients was supported by the observation that the patients with proarrhythmic responses (Group I) had a significantly shorter
baseline effective refractory period and a smaller increment in effective refractory period while taking a proarrhythmic drug despite achieving a serum drug concentration in the high therapeutic range. This was more evident in the four patients with drug-induced monomorphic ventricular tachycardia whose mean effective refractory period was increased by only 6.6% (Table 2). Drug-induced increments in QRS duration (reflecting impulse conduction time) did not differ between the two groups. However, these electrophysiologic measurements are, at best, an indirect and gross estimate of the changes in cellular electrophysiologic properties of the reentrant circuit, and a true understanding of drug-induced arrhythmias must await precise definition of the basis for therapeutic action of antiarrhythmic drugs.

Limitations. This study has certain limitations. Because the six Group I patients were not rechallenged on the drug that was proarrhythmic during performed ventricular stimulation, it is not known whether they would have experienced similar arrhythmias while taking these drugs clinically. A definitive answer to this question will require treating these patients with the antiarrhythmic drug shown to be proarrhythmic during programmed ventricular stimulation and monitoring them closely for development of proarrhythmic effects. Clinically, there was no justification for continuing a patient without a history of ventricular tachycardia on treatment with a drug suspected of being arrhythmogenic. Because none of our patients underwent ambulatory electrocardiographic monitoring or exercise testing during antiarrhythmic drug therapy, we do not know whether ambulatory monitoring would have been equally efficacious in detecting proarrhythmic effects of the antiarrhythmic agents, or whether there was any concordance between the two methods (programmed ventricular stimulation versus ambulatory monitoring) in detecting proarrhythmic effects. Also, in all six Group I patients with proarrhythmic responses, stimulation with triple extrastimuli or burst pacing mode was required to induce the proarrhythmic event. It is possible that aggressiveness of the stimulation protocol contributed to induction of these arrhythmias, which might not have otherwise manifested during long-term antiarrhythmic therapy. However, two of these six patients (Patients 3 and 6) had the clinical occurrence of similar arrhythmias during the follow-up period while taking antiarrhythmic agents.

Finally, it would have been desirable to perform two baseline tests in each patient to address the issue of reproducibility of the induced response in our patients was also addressed earlier in the Discussion section.

Clinical implications. The present study is the first to prospectively examine the proarrhythmic effects of antiarrhythmic drugs during programmed ventricular stimulation in patients with frequent ventricular premature beats but no sustained ventricular arrhythmias, and it emphasizes the potential risk of antiarrhythmic drug therapy in such patients. Twenty-five percent of the patients had a proarrhythmic response. The incidence of induced proarrhythmic responses (11% of drug trials, 25% of patients) reported by us is similar to that reported by others who were studying different patient populations (10–12). These findings stress the need for a careful assessment of potential risks and benefits of antiarrhythmic agents when treating patients with ventricular arrhythmias of uncertain prognostic significance.

We acknowledge the expert technical assistance of Judith Clarke, RN and Sharon Blue, RN.

References