Selective Prolongation of QRS Late Potentials by Sodium Channel Blocking Antiarrhythmic Drugs: Relation to Slowing of Ventricular Tachycardia

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Sodium channel blocking antiarrhythmic drugs have preferential effects on diseased, slowly conducting myocardium, and slowing of tachycardia caused by these drugs may result primarily from further prolongation of conduction time in slowly conducting tissue. In patients with sustained ventricular tachycardia, late potentials detected by signal-averaged electrocardiography (ECG) are thought to arise from slowly conducting ventricular myocardium. This study tested the hypothesis that sodium channel blocking drugs selectively prolong the late potential, or terminal low amplitude signal, portion of the signal-averaged QRS complex and that prolongation of the late potential would correlate with slowing of ventricular tachycardia.

Fifty-six drug trials in 32 patients with spontaneous and inducible ventricular tachyarrhythmias were studied. Prolongation of the late potential (11 ± 15 ms) was significantly greater than prolongation of the initial portion of the QRS complex (4 ± 9 ms) (p = 0.01). Selective prolongation of the late potential by drugs resulted in significantly greater QRS prolongation detectable by signal-averaged ECG than by standard ECG (p < 0.0001). In 40 trials in which ventricular tachycardia remained inducible during drug therapy, the increase in induced tachycardia cycle length correlated strongly with the increase in late potential duration (p = 0.005) but not with change in the initial portion of the QRS complex.

These data suggest that in patients with ventricular tachycardia, sodium channel blocking antiarrhythmic drugs have preferential effects on slowly conducting tissue and that drug effect on slowly conducting tissue contributes to prolongation of ventricular tachycardia cycle length.

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Late potentials are low amplitude, high frequency terminal extensions of the QRS complex and can be detected by signal-averaged electrocardiography (ECG) in the majority of patients with spontaneous and inducible ventricular tachyarrhythmias (1–3). Late potentials are thought to arise from diseased, slowly conducting regions of the ventricular myocardium. It is possible that late potentials arise specifically from myocardium that participates in reentrant tachycardia as the slowly conducting limb; however, there is no direct evidence for this and alternatively it is possible that late potentials reflect more global ventricular disease, only a small part of which, if any, participates in reentrant arrhythmias.

Antiarrhythmic drugs that block sodium channels result in prolongation of conduction time and may have a preferential effect on diseased, slowly conducting myocardium (4–7), possibly as a result of their enhanced effects on partially depolarized cells (8–10). Additionally, there is evidence (6,7) that tachycardia cycle length is prolonged by sodium channel blocking drugs primarily as a result of increased conduction time through diseased, slowly conducting tissue.

We hypothesized that in patients with spontaneous and inducible ventricular tachyarrhythmias, sodium channel blocking antiarrhythmic drugs would have selective effects on the late potential portion of the signal-averaged ECG and that these effects would correlate with changes in the rate of induced ventricular tachycardia.

Methods

Study patients. Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) (11) is a multicenter trial sponsored by the National Institutes of Health to compare the accuracy of electrophysiologic study and
Holter ECG monitoring in predicting antiarrhythmic drug efficacy in patients with spontaneous sustained ventricular tachyarrhythmias. All patients provided written informed consent according to the guidelines of the human subjects committees of the participating hospitals. Patients in this trial (11) are randomized to therapy assessment by electrophysiologic study or Holter monitoring and undergo serial testing with drugs chosen randomly from a specified set of antiarrhythmic drugs.

The subjects of this report are 32 patients qualifying for randomization in the ESVEM study who underwent signal-averaged ECG at baseline (that is, in the absence of antiarrhythmic drug) and on at least one study drug. These patients were consecutively enrolled from the three ESVEM participating sites with the ability to obtain signal-averaged ECGs at the time of the study (University of Utah, 25 patients; Columbia University, 5 patients; University of Oklahoma, 2 patients). The qualifying criteria for the ESVEM Study have been described previously (11) in detail and include: 1) at least one episode of spontaneous sustained (duration ≥ 15 s) ventricular tachycardia or fibrillation, aborted sudden death or unmonitored syncope, and 2) reproducibly (at least twice) inducible sustained (duration ≥ 15 s) ventricular tachycardia or fibrillation at baseline electrophysiologic study. Patients with bundle branch block, although not excluded from ESVEM, were excluded from the present study. Table 1 summarizes baseline demographic, cardiac and electrophysiologic data for these 32 patients. Ejection fraction was determined by contrast or radionuclide ventriculography.

Electrophysiologic study. Baseline electrophysiologic study was performed after discontinuing antiarrhythmic drugs for at least five half-lives of drug and any active metabolites. Electrophysiologic study was performed according to a rigid stimulation sequence (11). Stimulus duration was 2 ms and current was twice diastolic threshold. The protocol for ventricular arrhythmia induction began with pacing at the right ventricular apex that used in sequence a single extrastimulus during sinus rhythm, two extrastimuli during sinus rhythm, one extrastimulus after ventricular drive and two extrastimuli after ventricular drive. The protocol then continued at the right ventricular outflow tract with one, two and three extrastimuli after ventricular drive. The final step in the sequence was three extrastimuli after ventricular drive at the right ventricular apex. Drive cycle lengths were 600, 500 and 400 ms. Coupling intervals of extrastimuli were started at 400 ms and were decremented by 10 ms until refractoriness was reached. The coupling interval was kept at 10 ms above the refractory period when a subsequent extrastimulus was introduced. Each combination of extrastimuli was delivered twice before any change in coupling interval was made. This stimulation protocol was followed until sustained (duration ≥ 15 s) ventricular tachycardia (rate ≥ 100 beats/min) or ventricular fibrillation was induced twice.

Follow-up electrophysiologic study was performed in 43 of the 56 drug trials, but was not performed in the remaining 13 trials because these were evaluated solely by Holter monitoring according to the ESVEM protocol randomization of the patients included in this report. The stimulation protocol used for the follow-up study was identical to that used for the baseline study. If ventricular arrhythmias had been induced with one or two extrastimuli during the baseline study, three extrastimuli were not used during the follow-up study. The end point of stimulation for the follow-up study was the induction of ≥ 15 beats of ventricular tachycardia (rate ≥ 100 beats/min) or completion of the protocol.

Tachycardia cycle length was measured using hand-held calipers from the recorded ventricular electrograms (100 mm/s). Discrete ventricular electrograms were recorded during all episodes of induced ventricular tachyarrhythmia. Cycle lengths from 10 consecutive cycles were averaged in cases of irregular tachycardias. When more than a single episode of tachycardia was induced, the cycle length used for data analysis was the average of the measured cycle lengths.

Signal-averaged ECG. A baseline signal-averaged ECG was recorded at least five half-lives after the last dose of an antiarrhythmic drug and within 48 h of baseline electrophysiologic study. A follow-up signal-averaged ECG was recorded after steady state had been reached on the final dosage of the drug and within 24 h of the follow-up electrophysiologic study, if one was performed. A Corazonix Predictor or an Arrhythmia Research Technology model 1200EPX was used for the recordings and analysis. Three bipolar signals were simultaneously recorded and digitized at 2 kHz. The X lead was recorded between the left midaxillary line at the fifth intercostal space (positive) and the right midaxillary line at the fifth intercostal space (negative). The Y lead was recorded between the left anterior superior iliac spine (positive) and the suprasternal notch (negative). The Z lead was recorded between standard precordial lead V2.
position (positive) and a position directly posterior to V2 (negative). Two hundred to 600 beats were averaged. Final noise levels (zero mean standard deviation (SD) of all three leads within a 5 ms window in the TP segment) were 0.2 to 0.5 µV.

Averaged X, Y and Z recordings were filtered with use of a bidirectional four pole Butterworth high pass digital filter with 40 Hz corner frequency (1). Filtered X, Y and Z recordings were combined into a single filtered QRS complex according to the formula \((X^2 + Y^2 + Z^2)^{1/2}\).

**Onset and offset of the filtered QRS complex** were determined automatically as the points where the signal exceeded three times the SD of noise levels at the beginning and end of the signal, respectively. The **signal-averaged QRS duration** was the difference between QRS onset and offset. The **terminal low amplitude signal duration** was defined as the duration of the terminal filtered QRS complex not <40 µV (2). The **initial QRS duration** was defined as the duration of the QRS complex preceding the low amplitude signal.

**Standard ECG.** The ESVEM protocol does not require submission of standard 12 lead ECGs, but they were available for review for all 32 patients at baseline study and for 46 (82%) of the 56 drug trials. Standard ECGs were recorded at standard gain (10 mm/mV) and standard paper speed (25 mm/s). The QRS duration was determined visually and with hand-held calipers in multiples of 10 ms as the longest duration of the QRS complex of the six limb lead recordings.

**Drug selection and dosage.** Five sodium channel blocking antiarrhythmic drugs were in use in ESVEM at the time of study: quinidine, procainamide, mexiletine, imipramine and propafenone. For all drugs except mexiletine, serum drug levels were determined at steady state on the day of the study. Drug therapy was administered consistently for 1 week as indicated by the patient's baseline ECG. Serum levels were determined at steady state, usually after 2 days of treatment, for all drugs except propafenone (5). Drug levels were determined at steady state after 24 h (all patients had a serum creatinine level <2.2 mg/dl and no patient had significant hepatic dysfunction). Trough (within 60 min before a dose) serum drug levels were determined at steady state on the same dosage the patient was receiving at the time of follow-up signal-averaged ECG and electrophysiologic study (Table 2).

**Statistics.** Values are expressed as mean values ± SD. Samples of continuous variables are compared using paired or unpaired Student's t statistic. All p values assume a two-tailed hypothesis. Correlations between continuous variables were tested with use of the Pearson correlation coefficient (r). A statistic was considered significant if associated with a p value <0.05; however, larger p values are indicated to indicate trends.

### Table 2. Drug Doses and Serum Levels in 56 Drug Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Trials</th>
<th>Dose (mg/day)</th>
<th>Trough Serum Level (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propafenone</td>
<td>12</td>
<td>1.002 ± 254</td>
<td>1.2 ± 0.9</td>
</tr>
<tr>
<td>Quinidine</td>
<td>7</td>
<td>2.367 ± 928</td>
<td>3.1 ± 0.8</td>
</tr>
<tr>
<td>Procainamide</td>
<td>13</td>
<td>4.846 ± 1,573</td>
<td>8.0 ± 1.6</td>
</tr>
<tr>
<td>Imipramine</td>
<td>13</td>
<td>261 ± 124</td>
<td>0.21 ± 0.07*</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>11</td>
<td>914 ± 217</td>
<td>1.4 ± 0.4</td>
</tr>
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</table>

*Sum of imipramine and desmethylimipramine levels.

### Results

Comparison of changes in total QRS, initial QRS and late low amplitude signal at baseline and during drug therapy (Table 3, Fig. 1). The absolute increment in low amplitude signal duration (30 ± 1% and 30 ± 10%) and the fractional increase in total QRS duration (30 ± 48%) exceeded the fractional increase in total QRS duration (30 ± 1%) and the fractional increase in initial QRS duration (6 ± 12%) (p = 0.01 and p = 0.004, respectively). Prolongation of the low amplitude signal exceeded that of the initial QRS duration for all drugs studied except mexiletine (Table 3), for which the prolongation of total QRS duration was much less than for the other drugs. Differences in the extent of low ampli-

### Table 3. Effects of Drugs on Signal-Averaged Electrocardiogram Measurements (ms)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>Drug</th>
<th>Increment</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propafenone</td>
<td>136 ± 20</td>
<td>165 ± 24</td>
<td>29 ± 17</td>
<td>0.0001</td>
</tr>
<tr>
<td>Quinidine</td>
<td>76 ± 14</td>
<td>82 ± 14</td>
<td>5 ± 15</td>
<td>0.2</td>
</tr>
<tr>
<td>Procainamide</td>
<td>60 ± 25</td>
<td>84 ± 27</td>
<td>24 ± 19</td>
<td>0.001</td>
</tr>
<tr>
<td>Imipramine</td>
<td>133 ± 22</td>
<td>147 ± 27</td>
<td>14 ± 6</td>
<td>0.0007</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>3 ± 9</td>
<td>3 ± 9</td>
<td>4 ± 10</td>
<td>0.2</td>
</tr>
</tbody>
</table>

LASS = late low amplitude signal.
Figure 1. Duration of initial QRS complex and low amplitude signal (LAS) at baseline (top) and during drug therapy (bottom) in all 56 drug trials. All values are in ms. Most of the increase in total signal-averaged QRS duration results from prolongation of the late low amplitude signal.

Prolongation of the initial QRS complex ranged only from 3 to 5 ms among the drugs studied, whereas prolongation of low amplitude signal ranged from 1 to 24 ms, with propafenone resulting in the greatest low amplitude signal prolongation among the drugs accounted for almost all of the differences in overall QRS prolongation. Prolongation of the initial QRS complex ranged only from 3 to 5 ms among the drugs studied, whereas prolongation of low amplitude signal ranged from 1 to 24 ms, with propafenone resulting in the greatest low amplitude signal prolongation among the drugs accounted for almost all of the differences in overall QRS prolongation.

Changes in QRS duration on signal-averaged ECG compared with changes in QRS duration on standard ECG (Table 4). The average increase in QRS duration detected by the signal-averaged ECG during drug therapy was more than twice that detected by the standard ECG (Fig. 2, Table 4). The increase in signal-averaged QRS duration exceeded the increase in standard QRS duration by ≥10 ms in 20 (43%) of the 46 drug trials (Fig. 3). In these 20 trials, prolongation of the low amplitude signal (19 ± 15 ms) was significantly greater than in the other 26 drug trials (6 ± 14 ms) (p = 0.005) (Fig. 4). Thus, selective prolongation of the low amplitude signal, which is not detectable by standard ECG, contributes to the greater prolongation of total QRS duration detected by signal-averaged compared with standard ECG.

Most of the standard ECGs were performed with use of an electrocardiograph (Marquette Electronics) that automatically measures QRS duration. Comparisons of standard QRS durations measured automatically at baseline study and during drug therapy were available for 37 trials. In these 37 trials, the increment in standard QRS duration measured automatically (7.4 ± 11.9 ms) was less than the increment detected by signal-averaged ECG (13.4 ± 14.1 ms) (p = 0.02) and not significantly different from that detected manually on the standard ECG (5.1 ± 9.0 ms).

Change in QRS duration detected by signal-averaged electrocardiogram (ECG) resulting from antiarrhythmic drugs compared with change in QRS duration detected by standard ECG. Most of the points lie above the line of identity (arrow), indicating that the signal-averaged ECG detects more QRS prolongation than does the standard ECG (p < 0.0001 by paired t test). All values are in ms.

Relation to effects of drugs on induced and spontaneous arrhythmias. Electrophysiologic study was performed in all 32 patients at baseline, and the cycle length of the induced ventricular tachyarrhythmia was 268 ± 66 ms. No significant correlation was found between baseline induced tachycardia cycle length and baseline signal-averaged QRS duration or low amplitude signal duration. Follow-up electrophysiologic study was performed for 43 of the 56 drug trials. Of these, ventricular tachycardia of ≥15 beats' duration was reinduced during 40 trials (20 patients); ventricular tachycardia was noninducible in just 3 drug trials included in this report. In the 40 drug trials in which ventricular tachycardia was reinduced, the cycle length of the induced arrhythmia was 332 ± 57 ms, significantly greater than the tachycardia cycle length at baseline study (261 ± 49 ms) (p < 0.0001). There was a significant positive correlation between the increment in tachycardia cycle length associated with antiarrhythmic drug therapy and the increment in duration of the low amplitude signal portion of the signal-averaged ECG (p = 0.005) (Fig. 5). The slope of the regression line relating the change in cycle length to the change in low amplitude signal was greater than unity, which indicates that on average the absolute prolongation of cycle length exceeded the absolute prolongation of the low amplitude signal. In contrast, there was no correlation between change in cycle length and prolongation of the initial portion of the signal-averaged QRS duration.

Table 4. Comparison of QRS Durations Measured by Standard Versus Signal-Averaged Electrocardiography (ECG)

<table>
<thead>
<tr>
<th></th>
<th>Standard ECG</th>
<th>Signal-Averaged ECG</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>QRS duration at baseline (ms)</td>
<td>97 ± 15</td>
<td>130 ± 18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QRS duration on drug (ms)</td>
<td>104 ± 18</td>
<td>146 ± 24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Increment (ms)</td>
<td>7 ± 10</td>
<td>16 ± 14</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Figure 3. An example of signal-averaged electrocardiogram (ECG), standard ECG and induced ventricular tachycardia in a patient at baseline (top) and during therapy with propafenone (bottom). The total QRS duration of each signal-averaged ECG is divided into an initial QRS portion and a low amplitude signal (LAS) portion; these two portions are demarcated by the point where the amplitude of the terminal QRS complex reaches 40 μV (dashed line). Total signal-averaged QRS duration increased from 151 ms at baseline study to 177 ms during drug therapy. The 26 ms increase in total QRS duration comprised a 20 ms prolongation of low amplitude signal and only a 6 ms prolongation of initial QRS duration. The standard ECG detected only a 10 ms increase in QRS duration (from 100 to 110 ms). Sustained ventricular tachycardia was induced with two ventricular extrastimuli after ventricular drive (arrows) in baseline state and on drug, and there was a large increase (115 ms) in tachycardia cycle length (CL) resulting from drug therapy. The large increase in tachycardia cycle length in this case was associated with a large prolongation of low amplitude signal, but only a small prolongation of the initial QRS duration and a small prolongation of QRS duration detected by standard ECG.
complex nor was there a correlation between the change in cycle length and prolongation of the QRS complex on standard ECG (Fig. 5).

Ventricular tachycardia cycle length was prolonged >100 ms in 10 (25%) of the 40 drug trials in which tachycardia was reinduced. The increase in low amplitude signal in these 10 trials (18 ± 12 ms) was significantly greater than in the other 30 trials (6 ± 11 ms) (p = 0.007). The low amplitude signal was prolonged by ≥5 ms in all 10 trials in which tachycardia cycle length increased by >100 ms, whereas the low amplitude signal failed to prolong ≥5 ms in 15 (50%) of 30 drug trials in which the increase in tachycardia cycle length was <100 ms. Thus, an increase in the low amplitude signal of ≥5 ms identified patients whose tachycardia cycle length increased >100 ms with a sensitivity of 100% (10 of 10 trials), a specificity of 40% (10 of 25 trials) and an overall predictive accuracy of 63% (25 of 40) trials.

Antiarrhythmic drugs prevented induction of ventricular tachycardia by strict ESVEM criteria in only three trials included in this report, so no meaningful analysis could be performed comparing trials with and without persistent arrhythmia inducibility.

**Discussion**

The principal findings of this study are that sodium channel blocking antiarrhythmic drugs selectively prolong the low amplitude, late potential portion of the signal-averaged QRS complex and that the magnitude of late potential prolongation correlates with the increase in the cycle length of induced ventricular tachycardia. Furthermore, selective prolongation of the late potential accounts for part of the greater sensitivity of the signal-averaged ECG in detecting QRS prolongation compared with the standard ECG.

**Relation to selective drug effect on slowly conducting portions of the myocardium.** It is thought that the late potential portion of the signal-averaged QRS complex arises from areas of the ventricular myocardium in which depolarization is delayed and conduction is slow. The selective prolongation of the late potential by antiarrhythmic drugs observed in this study suggests that these drugs delay conduction more in myocardium where baseline conduction is slow than in myocardium where baseline conduction velocity is normal. Such conduction delay could result from a delay in the onset of local activation or a further prolongation of conduction time, or both.

Previous studies in canine infarct models have shown selective effects of sodium channel blocking antiarrhythmic drugs on abnormal myocardium. Patterson et al. (4) showed that lidocaine prolonged electrogram duration in infarcted tissue more than in noninfarcted tissue. DeLangen et al. (5) showed that procainamide resulted in more delay and prolongation among electrograms occurring late with respect to the QRS complex than among those electrograms occurring earlier. However, in a study in humans, Schmitt et al. (12) failed to detect a differential effect of antiarrhythmic drugs on normal versus abnormal electrograms.

The mechanism whereby sodium channel blocking antiarrhythmic drugs may selectively influence diseased myocardium is not known. Some studies (13–15) have shown reduced membrane potentials at rest in chronically infarcted myocardium, and selective effects of antiarrhythmic drugs in such tissue can be explained by the well known enhanced effects of antiarrhythmic drugs on partially depolarized cells.
(8–10). However, a more recent study (16) found normal action potentials in chronically infarcted myocardium displaying fractionated electrograms and slow conduction, and the electrophysiologic abnormalities of this tissue were postulated to result from abnormal cell to cell coupling. It is less clear why antiarrhythmic drugs might selectively affect myocardium with normal action potentials but impaired cell to cell coupling.

Late potential duration and tachycardia cycle length. We found no correlation between baseline late potential duration and baseline ventricular tachycardia cycle length. There are several possible explanations for this finding. First, it is possible that late potentials arise predominantly from tissue not directly involved in reentrant circuits utilized during tachycardia. Second, it is possible that the tachycardia cycle length primarily is determined not by slowly conducting tissue, but rather by conduction around an anatomic obstacle (17). Third, the degree of conduction slowing in tissue generating late potentials may be greatly different during tachycardia than during sinus rhythm. Finally, the late potential detectable by signal-averaged ECG probably represents only a portion of the slowly conducting area of myocardium; potentials from slowly conducting areas of the myocardium that are engaged early with respect to the QRS complex during sinus rhythm may be buried within the initial portion of the QRS complex and not contribute to the late potential, yet these areas may participate in reentrant tachycardias.

However, there was a significant correlation between the increase in late potential duration caused by antiarrhythmic drugs and the prolongation of ventricular tachycardia cycle length. This observation may indicate that portions of the presumed reentrant circuit respond to antiarrhythmic drugs in a quantitatively similar way to tissue generating late potentials, and it suggests that tissue generating late potentials actually may constitute a portion of the reentrant circuit. Conversely, there was comparatively little effect of antiarrhythmic drugs on the initial portion of the signal-averaged QRS complex. This finding suggests that slowing of tachycardia by drugs is not a result of drug effect on the presumably normally conducting tissue generating the initial portion of the signal-averaged QRS complex.

Figure 5. Correlations between changes in cycle length of induced ventricular tachycardia and low amplitude signal (LAS) (left), initial QRS duration (middle) and QRS duration on the standard electrocardiogram (ECG) (right). The increase in cycle length correlated significantly with increases in low amplitude signal. There was no relation between the change in cycle length and the change in initial QRS duration or change in QRS duration on the standard ECG.

The slope of the regression line relating prolongation of the tachycardia cycle length to prolongation of the late potential (Fig. 5) indicates that the absolute prolongation of tachycardia cycle length resulting from drugs tends to exceed the absolute prolongation of late potential duration. There are several possible explanations for this. First, prolongation of conduction time resulting from drugs is greater at faster heart rates, as suggested by the modulated receptor hypothesis of antiarrhythmic drug action (18). Second, prolongation of ventricular refractoriness resulting from antiarrhythmic drugs may contribute to slowing of tachycardia (19), and these changes in refractoriness may not be reflected by any change in late potential duration. Third, regions of slowly conducting myocardium that are depolarized simultaneously during sinus rhythm may form sequential components of the presumed reentrant circuit.
There are other reports suggesting that changes in tachycardia cycle length resulting from antiarrhythmic drugs result primarily from drug effect on slowly conducting tissue. Kay et al. (6) used entrainment techniques in five patients with ventricular tachycardia to demonstrate that procainamide prolonged conduction times principally in the slowly conducting portion of the reentrant circuit and that the degree of this prolongation correlated with prolongation of tachycardia cycle length. By contrast, there was little effect of procainamide in normally conducting myocardium and there was no correlation between changes in normally conducting myocardium and changes in tachycardia cycle length. Schoels et al. (7), using a canine model of atrial flutter, found that increases in flutter cycle length resulting from procainamide were primarily from the effect of procainamide on a zone of slow conduction and that procainamide had comparatively little effect on the other portions of the reentrant circuit.

It has been suggested (20) that in patients with sustained tachyarrhythmias, therapy with drugs that prolong the cycle length of induced ventricular tachycardia by $\geq 100$ ms is associated with a favorable prognosis. In the current study, prolongation of the late potential by $\geq 5$ ms predicted such a prolongation in cycle length with a sensitivity of 100% and a specificity of 40%. It is possible that analysis of change in late potential duration could be used as a screening test to identify drug therapy resulting in large prolongations of tachycardia cycle length.

Previous reports of effect of antiarrhythmic drugs on signal-averaged ECG. Prolongations of total QRS duration and late potential duration have been reported by most (5,21,22) but not all (23) authors studying the effects of antiarrhythmic drugs on time domain features of the signal-averaged ECG. In a canine infarct model, de Langen et al. (5) demonstrated a greater prolongation by procainamide of the late potential portion of the QRS complex than of the initial portion of the QRS complex in a pattern similar to that demonstrated in the present study. DeLangen et al. (5) also performed epicardial recordings in their dogs before and after procainamide and found that selective prolongation of the late potential portion of the QRS complex coincided with selective delay of electrograms occurring later with respect to the QRS complex. Such a mechanism may have been operative in the patients in the present study.

Several authors (21–24) have reported persistence of late potentials during drug therapy in patients with ventricular tachycardia regardless of whether the drugs prevented induction of tachycardia. Thus, block of conduction into diseased tissue generating late potentials during sinus rhythm does not appear to be a prerequisite for prevention of tachycardia induction. These reports (21–24) did not examine quantitative relations between changes in the signal-averaged QRS complex and changes in tachycardia cycle length.

Limitations. We interpreted the results of the study using the assumption that the initial portion of the signal-averaged QRS complex arises from normally conducting myocardium and the late potential, or low amplitude signal portion, arises from slowly conducting tissue. This assumption undoubtedly is an oversimplification. For example, slowly conducting tissue that is activated early during sinus rhythm may contribute primarily to the initial portion of the QRS complex. Conversely, it is possible that late potentials arise in part from tissue that is activated late but has normal conduction properties.

Implications. Application of the signal-averaged ECG for assessment of antiarrhythmic drug therapy has been limited and currently there is no clinical role for signal-averaged ECG for guidance of drug therapy. This study suggests that the signal-averaged ECG may provide information on the electrophysiologic effect of sodium channel blocking drugs on slowly conducting areas of the ventricular myocardium in patients with sustained ventricular tachyarrhythmias. Among patients with sustained ventricular tachyarrhythmias, changes in late potential duration may be helpful in predicting changes in tachycardia cycle length resulting from drug therapy. In the future, the signal-averaged ECG may prove useful in noninvasively assessing other electrophysiologic effects—both antiarrhythmic and proarrhythmic—of antiarrhythmic drugs.

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References


