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Effects of Procainamide on the Signal-Averaged Electrocardiogram in Relation to the Results of Programmed Ventricular Stimulation in Patients With Sustained Monomorphic Ventricular Tachycardia

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Objectives. The aim of this study was to assess the ability of the signal-averaged electrocardiogram (ECG) to predict the efficacy of procainamide.

Background. The main role of the signal-averaged ECG has been the identification of postinfarction patients at risk of sudden death. Prediction of the efficacy of antiarrhythmic drugs represents another potential clinical application of this technique.

Methods. The study examined the effects of procainamide on the time domain and spectral temporal analysis of the signal-averaged ECG in relation to the results of programmed ventricular stimulation studies in 31 patients with inducible sustained monomorphic ventricular tachycardia.

Results. Procainamide significantly prolonged the total and the initial QRS complex and low amplitude signal durations (mean ± SD 135 ± 30 vs. 161 ± 46 ms, $p < 0.0001$; 87 ± 16 vs. 98 ± 20 ms, $p < 0.0001$, and 48 ± 23 vs. 63 ± 36 ms, $p < 0.001$, respectively) whereas the root-mean-square voltage of the total QRS complex and of the last 40 ms of the QRS complex was significantly reduced (mean ± SD 112 ± 36 vs. 87 ± 36 μV, $p < 0.0001$; 21 ± 19 vs. 13 ± 12 μV, $p < 0.002$, respectively). The results of spectral temporal mapping of the signal-averaged ECG were similar before and after procainamide administration. Procainamide prevented the inducibility of sustained ventricular tachycardia or prolonged the cycle length of ventricular tachycardia by ≥100 ms in 16 patients (52%) (responders). The fractional prolongation of the total QRS duration was significantly greater in responders (26 ± 15%) than in nonresponders (10 ± 10%) ($p < 0.002$) and, when this prolongation was ≥15%, identified responders with a sensitivity of 94%, a specificity of 87% and an overall predictive accuracy of 90%.

Conclusions. The effects of procainamide on inducibility of ventricular tachycardia during programmed ventricular stimulation can be predicted by the degree of drug-induced prolongation of the signal-averaged QRS complex.

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Late potentials, which are low amplitude signals occurring at the end of the QRS complex, are believed to emanate from areas of slow conduction in myocardium from which reentrant arrhythmias can arise (1). They can be detected noninvasively from the body surface by the signal-averaged electrocardiogram (ECG) (2). To date, the main clinical role of late potentials is the identification of patients at risk of sustained ventricular tachycardia and sudden death (3–7).

Prediction of the efficacy of antiarrhythmic drugs represents another potential clinical application of the signal-averaged ECG. There is growing evidence that class IA, class IC and class 3 antiarrhythmic drugs significantly alter the signal-averaged ECG (8–12), but few reports have examined the relation between drug-induced signal-averaged ECG changes and antiarrhythmic efficacy (10,11).

To address this issue, we examined the effects of procainamide, a potent and widely used antiarrhythmic drug, on signal-averaged ECG variables in relation to the results of programmed ventricular stimulation in a group of patients with sustained ventricular tachycardia.

Methods

Patients

The study group was prospectively selected from 110 consecutive patients admitted to our department after October 1990 for serial drug testing because of a history of sustained ventricular tachycardia. In 58 patients a sustained monomorphic ventricular tachycardia was induced. Of this group, 31 consecutive patients (25 men with a mean age of

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61 ± 10 years) who underwent testing of procainamide among other antiarrhythmic drugs met the following entry criteria: 1) at least one spontaneous episode of sustained monomorphic ventricular tachycardia documented on a 12-lead ECG; 2) sustained monomorphic ventricular tachycardia inducible at baseline programmed ventricular stimulation, and identical to the clinical arrhythmia; 3) no other sustained monomorphic ventricular tachycardia inducible at baseline stimulation; 4) no bundle branch block on the baseline ECG. The underlying heart disease was previous myocardial infarction in 24 patients and idiopathic dilated cardiomyopathy in 7. Angiographically assessed ejection fraction was <30% in 8 patients (26%).

All patients gave written consent. The protocol of the study was approved by the local Ethics Committee.

Signal-Averaged Electrocardiography

Acquisition. The signal-averaged ECG was recorded from X, Y and Z orthogonal leads using a recorder from Arrhythmia Research Technology (model 1200 EPX). The end point of recording was a noise level of ≤0.3 μV.

To assess the short-term reproducibility of the signal-averaged ECG, two recordings were performed within 15 min in 24 patients, usually 1 day before the electrophysiologic study. Care was taken to obtain similar noise levels at both recordings. A mean of 234 ± 38 heartbeats (range 160 to 280) were averaged to achieve a mean noise level of 0.25 ± 0.06 μV (range 0.2 to 0.4).

The recordings before and after procainamide infusion were obtained from the same electrode position as the recordings of the reproducibility study. A mean of 240 ± 41 cardiac cycles (range 170 to 360) were averaged and the noise level ranged from 0.2 to 0.5 μV (mean 0.26 ± 0.08). In no patient was the difference in the noise level between the baseline recording and the recording during procainamide treatment >0.2 μV. A noise level ≤0.3 μV was achieved in 50 recordings (81%); in the remaining 12 recordings the noise level was 0.4 to 0.5 μV because of noise produced by the equipment in the electrophysiology laboratory.

There were 11 oral and 20 intravenous drug studies. In oral drug studies the baseline signal-averaged ECG was recorded before and after 4.2 ± 1.3 days (range 3 to 7) of procainamide therapy (median dose 2,364 mg/day [range 1,500 to 4,000]) within 2 h of the electrophysiologic study. In intravenous drug studies, the first signal-averaged ECG was recorded 5 min before the baseline stimulation, and the second signal-averaged ECG was obtained using the same electrodes between 5 and 10 min after termination of the procainamide infusion (750 to 1,000 mg over 10 min), and it was immediately (1 to 3 min) followed by programmed ventricular stimulation.

Analysis. The signal-averaged ECG recordings were stored and subsequently analyzed (FFT-Plus, version 3.10 software, Arrhythmia Research Technology); all measurements and computations were made automatically without manual intervention.

Time domain analysis. The time domain analysis of the signal-averaged ECG was performed at high pass filter settings of 25 and 40 Hz using a bidirectional four-pole Butterworth filter. After amplification, averaging and filtering, the signals were combined into a vector magnitude $\sqrt{(x^2 + y^2 + z^2)}$, and three conventional time domain indexes were calculated: the duration of the total QRS complex, the duration of the low amplitude (<40 μV) signals at the terminal portion of the QRS complex and the root-mean-square voltage of the last 40 ms of the QRS complex. The result of the time domain signal-averaged ECG was abnormal when at least two of three conventional variables were beyond the normal range: total QRS duration >120 ms; duration of low amplitude (<40 μV) signals >40 ms, and root-mean-square voltage of the last 40 ms of the QRS complex <25 μV at a 25-Hz filter setting (7) and >114 ms, >38 ms and <20 μV, respectively, at a 40-Hz filter setting (13). In addition, two other signal-averaged ECG variables were calculated: the root-mean-square voltage of the total QRS complex and, as described by Freedman and Steinberg (10), the initial QRS duration, which was defined as the duration of the QRS complex preceding the low amplitude signal (i.e., the duration of the QRS complex measured from the beginning of the complex to the point when vector-summed QRS forces last decreased to <40 μV). The analysis was performed at both filter settings because a significant difference may exist between the results obtained at 25 and 40 Hz. The use of a 40-Hz filter attenuates the voltage to a greater extent than does use of a 25-Hz filter (14) and in some postinfarction patients, especially during antiarrhythmic therapy, more than half of the total QRS duration can be <40 μV, meeting the criteria for late potentials. The noise level is also affected by the filtering and is lower at 40 Hz (14), an effect that may cause discrepancies in the detection of the end of filtered QRS duration by the noise-dependent algorithm when different filter settings are used.

Spectral temporal mapping. Spectral temporal mapping of the signal-averaged ECG was performed with fast Fourier transform analysis by analyzing 25 overlapping 80-ms segments in 2-ms steps. The first segment began 20 ms before the end of the standard QRS complex. The mean adjustment was set at zero to eliminate any ST segment elevation or depression. The data were multiplied by a Blackman-Harris window. Results of the spectral temporal mapping were expressed as a factor of normality. This factor was calculated on the basis of a reference spectrum, which was the average of the most distal 5 segments (i.e., spectra 21 to 25). Two mathematic computations were made for the frequencies between 40 and 140 Hz. The first value to be derived was the correlation coefficient of the frequency content of each of the 25 spectra as compared with the reference spectrum. The second derivative was based on the area under the curve for each spectrum as compared with the

reference spectrum. The abnormal result of the spectral temporal mapping was defined as the value of the normality factor <30% in any lead, according to Haberl et al. (15).

Standard electrocardiogram. The standard ECG was recorded using the ART 1200 EPX recorder immediately after the signal-averaged ECG was acquired. The standard QRS and QT interval durations were measured automatically by the computer algorithm. The corrected QT interval was calculated using Bazett's formula (16): corrected QT interval = QT interval/$\sqrt{\text{RR interval}}$.

Programmed ventricular stimulation. Baseline stimulation was performed after discontinuation of antiarrhythmic drugs for at least 5 half-lives before the study. Three quadripolar electrode catheters were introduced percutaneously to the femoral and subclavian veins and positioned under fluoroscopic guidance in the high right atrium, His bundle position and right ventricular apex. Intracardiac recordings were filtered at 30 to 500 Hz and displayed simultaneously with three surface ECG leads (I, aVF and V_1) on an eight-channel Siemens-Elema Mingograf chart recorder. Programmed ventricular stimulation was performed using a Medtronic model 5326 programmable stimulator with rectangular pulses of 2.0-ms duration, delivered at twice diastolic threshold. A strict 12-step stimulation protocol consisted of introducing single- and double-extrastimuli at the right ventricular apex during sinus rhythm and after eight-beat extrastimulus (S_1) drive trains at paced cycle lengths of 600, 500 and 400 ms. If a sustained arrhythmia was not inducible, the procedure was repeated using triple extrastimuli. According to the patient selection criteria, the end point of the baseline stimulation was the induction of clinical sustained ventricular tachycardia. The end point of the study performed during procainamide therapy was the induction of sustained ventricular tachycardia or ventricular fibrillation or completion of the protocol.

Definitions. Sustained ventricular tachycardia was defined as a tachycardia of ventricular origin, with a uniform QRS configuration, lasting ≥30 s or causing hemodynamic collapse. Nonsustained ventricular tachycardia was defined as six or more beats of repetitive ventricular activity that was well tolerated and lasted <30 s. A sustained ventricular tachycardia was defined as clinical when, in comparison with spontaneous ventricular tachycardia, the induced arrhythmia had an identical or nearly identical QRS axis and configuration and a similar rate (a difference in a cycle length ≤20 ms). The mode of termination of sustained ventricular tachycardia was classified as 1) spontaneous; 2) by introduction of one premature ventricular beat; 3) by introduction of two ventricular premature beats; 4) by overdrive pacing; 5) by cardioversion or defibrillation. The longest interval (defined to the nearest 5 ms) at which a second extrastimulus, S_2, introduced during sinus rhythm (5 patients) or pacing at a cycle length of 600 ms (26 patients), failed to evoke a depolarization was termed the effective refractory period of the ventricle. The cycle length of ventricular tachycardia and of the ventricular effective refractory period were measured by hand calipers at a paper speed of 100 mm/s.

Effective treatment was defined as noninducibility of ventricular tachycardia or prolongation of the cycle length of ventricular tachycardia, which was hemodynamically stable, by ≥100 ms during treatment with procainamide. Patients with effective treatment were termed responders. Patients with ineffective treatment were termed nonresponders.

Statistical methods. Continuous variables are presented as the mean value ± 1 SD. The paired *t* test was used to compare the signal-averaged ECG indexes before and during procainamide therapy. An unpaired *t* test was used to compare the numeric values of signal-averaged ECG variables between effectively and ineffectively treated patients, and between patients with no inducible tachycardia and patients whose cycle length of ventricular tachycardia was prolonged by ≥100 ms. A chi-square test or Fisher exact test was used when appropriate to compare the results of the signal-averaged ECG before and during procainamide therapy. The effects of procainamide on the inducibility (stage of pacing protocol) and the mode of termination of ventricular tachycardia were examined using the Wilcoxon signed-rank test.

The absolute change in the time domain variables caused by procainamide was calculated as the difference between two signal-averaged ECG observations. The fractional (percent) change was calculated as the absolute difference between two measurements divided by the value of the first measurement. The baseline reproducibility of the signal-averaged ECG, and the correlations between the signal-averaged ECG variables and the cycle length of ventricular tachycardia and the ventricular effective refractory period, were tested with the use of Pearson's correlation coefficient.

In all statistical tests, a two-tailed p value < 0.05 was required for statistical significance. Sensitivity was defined as the number of true positive results divided by the number of true positive plus false negative results. Specificity was defined as the number of true negative results divided by the number of true negative plus false positive results. The overall predictive accuracy was defined as the number of true positive plus true negative results divided by the total study group. The sensitivity and specificity of identification of effectively treated patients were computed for the fractional changes of each signal-averaged ECG variable and for all possible dichotomizing values.

When testing for statistical associations of the signal-averaged ECG results with drug inhibition of ventricular tachycardia, the Bonferroni correction (multiply the probe by the number of tests) was applied to the 10 analyzed p values (see Table 3).

Results

Baseline reproducibility of the signal-averaged ECG. The reproducibility of the time domain signal-averaged ECG variables at a 25-Hz filter setting was high: the Pearson's

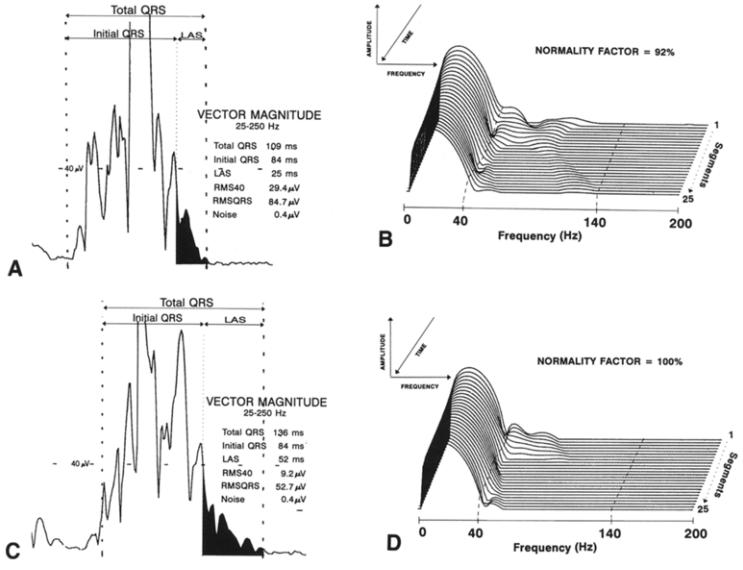
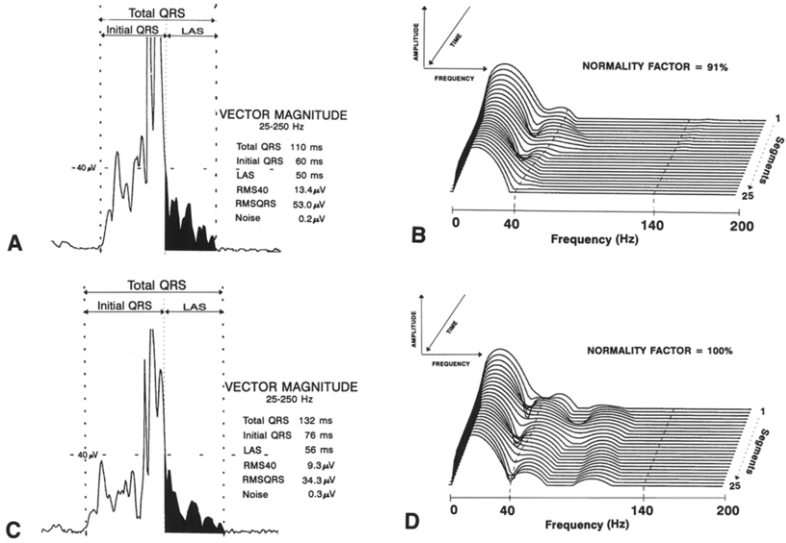


Figure 1. Patient 1. Signal-averaged electrocardiographic (ECG) recordings from a patient with an anterolateral infarction. The baseline time domain signal-averaged ECG was normal (**A**) and the results of the spectral temporal mapping were within normal limits (for example, the normality factor in lead Z was 92%) (**B**). Procainamide prevented inducibility of sustained ventricular tachycardia. After drug administration, all conventional time domain signal-averaged ECG indexes became abnormal (**C**). The prolongation of the total QRS duration (the fractional increase was 25%) was caused by prolongation of the low amplitude signal duration whereas the duration of the initial QRS complex remained unchanged. The results of the spectral temporal mapping were similar to those of the baseline recording (the normality factor in lead Z was 100%) (**D**). LAS = low amplitude signal duration; RMS40 = the root-mean-square voltage of the last 40 ms of the QRS complex; RMSQRS = the root-mean-square voltage of the total QRS complex.

correlation coefficient was 0.99 for the total QRS duration, 0.98 for the low amplitude signal duration, 0.99 for the initial QRS duration, 0.94 for the root-mean-square voltage of the last 40 ms of the QRS complex and 0.99 for the root-mean-square voltage of the total QRS complex. The qualitative results of the time domain signal-averaged ECG (normal or abnormal) were consistent. The use of the 40-Hz filter setting did not change the results.

The reproducibility of the spectral temporal mapping was worse than that of the time domain analysis. The Pearson's correlation coefficients for the normality factors computed for the X, Y, Z leads, and the composite leads were 0.79, 0.51, 0.72 and 0.48, respectively. In four patients the results of spectral temporal mapping were inconsistent.

Effects of procainamide on the signal-averaged ECG. The examples of the effects of procainamide on the signal-averaged ECG are presented in Figures 1 and 2. At the baseline study (before procainamide infusion), an abnormal signal-averaged ECG at a 25-Hz filter setting was diagnosed in 16 trials (52%), and at 40 Hz in 23 recordings (74%). During procainamide therapy, 24 recordings (77%) at 25 Hz and 27 recordings (87%) at 40 Hz were classified as abnormal. Procainamide significantly changed all time domain variables. The overall results are presented in Figure 3, and the fractional changes in the signal-averaged ECG indexes with corresponding absolute changes in the cycle length of ventricular tachycardia in individual patients are shown in Table 1. The total and initial QRS complex and low amplitude signal durations were prolonged (135 ± 30 vs. 161 ± 46 ms, $p = 0.0001$; 87 ± 16 ms vs. 98 ± 20 ms, $p = 0.0001$, and 48 ± 23 ms vs. 63 ± 36 ms, $p = 0.001$, respectively) whereas the root-mean-square voltage of the total QRS complex and of the last 40 ms of the QRS complex was reduced 112 ± 36 μV vs. 87 ± 36 μV, $p = 0.0001$) and (21 ± 19 μV vs. 13 ± 12 μV, $p = 0.002$. The most consistent



changes occurred in the total QRS duration, which was prolonged in all but one recording, and in the root-mean-square voltage of the total QRS complex, which was reduced in 28 trials (90%). The low amplitude signal duration was prolonged in 23 trials (74%), the initial QRS duration was prolonged in 26 (84%), whereas the root-mean-square voltage of the last 40 ms of the QRS complex was reduced in 26 recordings (84%) (all results at 25 Hz). The absolute prolongation of the initial QRS complex and the low amplitude signal durations were similar (11 ± 10 ms vs. 15 ± 22 ms at 25 Hz, p = NS and 9 ± 10 ms vs. 10 ± 18 ms at 40 Hz, p = NS). The absolute increment in the low amplitude signal duration constituted 57% (25 Hz) or 52% (40 Hz) of the absolute increment in the total QRS duration. The fractional increase in the low amplitude duration exceeded the fractional increase in the initial QRS duration (32 ± 45% vs.

Figure 3. Effects of procainamide on the mean total QRS, low amplitude signal and initial QRS durations and on the root-mean-square voltage of the last 40 ms and of the total QRS complex. **Black bars** = measurements before procainamide; **white bars** = measurements during procainamide therapy. IQRS = initial QRS duration; TQRS = total QRS duration; other abbreviations as in Figure 1.

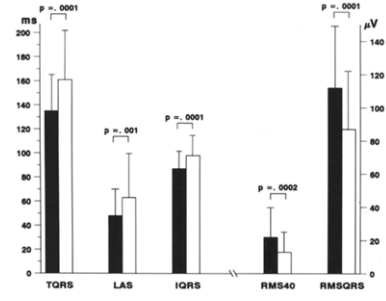


Figure 2. Patient 3. The signal-averaged electrocardiographic (ECG) recordings from a patient with an anterior infarction. The baseline time domain signal-averaged ECG was abnormal **(A)**, whereas results of the spectral temporal mapping were within normal limits (for example, the normality factor in lead X was 91%) **(B)**. Procainamide prevented inducibility of sustained ventricular tachycardia. On the time domain signal-averaged ECG **(C)**, the total QRS duration was prolonged by the drug by 22 ms (the fractional increase of 20%). The initial QRS prolongation was greater than the low amplitude signal prolongation (17 vs. 6 ms, or 27% vs. 12%). The results of spectral temporal mapping were similar to those of the baseline recording (the normality factor in lead Z was 100%) **(D)**. Abbreviations as in Figure 1.

13 ± 11% at 25 Hz, p = 0.037 and 20 ± 28% vs. 12 ± 11% at 40 Hz, p = NS).

No significant difference was noted between the fractional changes in the time domain signal-averaged ECG variables in patients with late potentials and those in patients with a normal signal-averaged ECG. Among 24 postinfarction patients, the initial QRS duration was more prolonged in those with an anterior versus an inferior site of infarction (14 ± 12 vs. 6 ± 6 ms, p = 0.05 or 18 ± 13% vs. 8 ± 7%, p = 0.016).

The effects of the drug on the results of spectral temporal mapping of the signal-averaged ECG were not significant: the values of the normality factor were similar before and during procainamide therapy in all leads (57 ± 32% vs. 56 ± 32% in lead X, 43 ± 30% vs. 43 ± 32% in lead Y, 52 ± 33% vs. 51 ± 30% in lead Z and 44 ± 31% vs. 45 ± 29% in the composite lead, p = NS for all differences). The abnormal spectral temporal mapping was diagnosed in 20 patients (65%) before procainamide therapy and in 19 (61%) after procainamide therapy (p = NS).

On the standard ECG, procainamide significantly prolonged the duration of both the QRS complex (98 ± 13 vs. 109 ± 18 ms, p = 0.0001) and the corrected QT interval (448 ± 36 vs. 472 ± 34 ms, p = 0.002).

The effects of oral versus intravenous procainamide on the time domain signal-averaged ECG variables were similar: the fractional changes in the signal-averaged ECG indexes in both groups are presented in Table 1.

Effects of procainamide on the results of programmed ventricular stimulation. Procainamide prevented inducibility of sustained ventricular tachycardia in six drug trials (19%): in five patients no arrhythmia was inducible and in one patient only short runs (up to eight QRS complexes) of tachycardia could be induced. In the remaining 25 trials sustained ventricular tachycardia remained inducible but its cycle length was significantly prolonged (308 ± 62 vs. 384 ± 91 ms, p < 0.001). Individual results are presented in Table 1. In five patients the axis of the QRS complex during ventricular tachycardia was different from that in the baseline study but the configuration of the QRS complex during tachycardia was unchanged (the same bundle branch block-like pattern). No patient had spontaneous occurrence of arrhythmia or acceleration of a rate of induced ventricular tachycardia after procainamide administration. In summary, an effective treatment was achieved in 16 drug trials (52%): in 6 trials (5 intravenous and 1 oral) sustained ventricular tachycardia became noninducible, and in 10 trials (5 intravenous and 5 oral) the cycle length of sustained ventricular tachycardia was prolonged by ≥100 ms.

Procainamide significantly increased the ventricular effective refractory period (267 ± 34 vs. 292 ± 37 ms, p = 0.0001).

Of 25 studies in which ventricular tachycardia was still inducible during procainamide therapy, arrhythmia was induced in 11 (44%) at a lower stage of the protocol, at the same stage in 8 (32%) and at a higher stage in 6 (24%). Overall, procainamide did not effect an induction of ventricular tachycardia: the mean difference in the stage of the pacing protocol at which tachycardia was inducible was 0.4 (5.6 stage at baseline versus 5.2 stage on procainamide, p = NS). The mode of termination of ventricular tachycardia during procainamide therapy was less aggressive than the termination of the baseline arrhythmia in 9 studies (36%), unchanged in 12 (48%) and more aggressive in 4 studies (16%). Overall, procainamide facilitated termination of ventricular tachycardia: the mean difference in the stage at which tachycardia was terminated was 0.9 (4.4 stage at baseline vs. 3.5 stage during therapy, p < 0.03).

Correlation between signal-averaged ECG and electrophysiologic study findings. At baseline stimulation, a significant correlation was found between the cycle length of ventricular tachycardia and the total QRS complex at 25 Hz (Table 2). After procainamide administration, a correlation between the signal-averaged ECG variables and the cycle length of tachycardia was stronger. Only the voltage of the total QRS complex did not correlate with the cycle length of tachycardia. The magnitude of the total QRS duration correlated better than did other variables with the cycle length of ventricular tachycardia.

No correlation was found between the ventricular effective refractory period and the signal-averaged ECG in either the baseline or the procainamide studies.

Relation between procainamide-induced signal-averaged ECG changes and results of programmed ventricular stimulation. The percent changes of the signal-averaged ECG variables caused by procainamide in effectively treated patients (responders) versus those in patients whose treatment was unsuccessful (nonresponders) are compared in Table 3. The variable that showed the most consistent significant difference between groups was the fractional increase in the total QRS duration, which was greater in responders than in nonresponders (26 ± 15% vs. 10 ± 10% at 25 Hz, p = 0.002 and 20 ± 9% vs. 8 ± 10% at 40 Hz, p = 0.001). The individual values of the fractional changes in the total QRS duration at both filter settings are presented in Figure 4. The total QRS duration was prolonged by ≥15% at 25 Hz (vertical line in Fig. 4) in 15 responders (94%) (6 whose arrhythmia became noninducible and 9 whose ventricular tachycardia cycle length was prolonged by ≥100 ms), but this degree of prolongation occurred in only 2 nonresponders (13%) (p = 0.001), resulting in a sensitivity of 94%, a specificity of 87% and an overall predictive accuracy of 90% for this variable. The same level of sensitivity but lower levels of specificity (67%) and overall predictive accuracy (81%) were achieved for fractional prolongation of the total QRS complex by ≥13% at 40 Hz (horizontal line in Fig. 4). The sensitivity and specificity curves also showed that for various dichotomy points the fractional prolongation of the total QRS duration at 25 Hz provided higher sensitivity without a corresponding significant decrease in specificity than did the fractional change in

Table 1. Procainamide-Induced Fractional Changes in the Signal-Averaged Electrocardiographic Indexes and in the Cycle Length of Ventricular Tachycardia in the 31 Study Patients

Pt No.	Diag	ΔTQRS (%)	ΔLAS (%)	ΔIQRS (%)	ΔRMS40 (%)	ΔRMSQRS (%)	ΔVTCL (ms)
				Intravenous Procainamide (n = 20)			
1	MI	25	108	0	−69	−38	NI
2	CM	23	42	8	−61	−33	100
3	MI	24	33	16	3	−37	102
4	MI	3	−4	5	−8	4	30
5	MI	17	14	19	−31	−50	NI
6	MI	14	−4	28	−23	−32	60
7	MI	25	−6	38	17	−22	NI
8	MI	10	0	12	−14	−8	0
9	CM	14	78	−7	−35	−41	0
10	MI	21	19	22	−81	−54	290
11	MI	9	2	16	−10	−35	100
12	MI	5	−5	13	−47	−26	50
13	MI	20	12	27	−31	−35	NI
14	MI	21	36	14	−37	−29	NI
15	MI	5	5	5	−15	−14	80
16	MI	36	97	14	−91	−9	40
17	MI	7	7	6	7	3	60
18	MI	25	39	14	−15	−18	20
29	CM	9	−12	19	−10	−35	70
20	MI	30	57	16	−57	−9	105
Mean		17	26	14	−30	−26	74
SD		±9	±35	±10	±29	±16	±70
				Oral Procainamide (n = 11)			
21	MI	15	13	16	3	−27	110
22	MI	45	50	39	−18	−4	110
23	MI	71	198	0	−48	−43	113
24	CM	40	85	13	−88	−36	NI
25	CM	−3	2	−7	−8	−15	0
26	MI	7	0	10	24	80	0
27	MI	2	−10	10	−14	−18	40
28	CM	13	73	−4	−65	−37	40
29	CM	15	32	11	−70	0	110
30	MI	8	5	10	−15	−13	30
31	MI	18	39	11	−81	−31	230
Mean		21	44	10	−35	−13	78
SD		±22	±60	±12	±37	±34	±71
				Total Group (n = 31)			
Mean		18	32	13	−32	−21	76
SD		±15	±45	±11	±32	±24	±68

There were no significant differences in values between patients who received procainamide intravenously and patients treated with oral procainamide (unpaired *t* test). Abbreviations: CM = cardiomyopathy; ΔIQRS(%) = fractional change in the initial QRS duration; ΔLAS(%) = fractional change in the low amplitude signal duration; ΔRMS40(%) = fractional change in the root-mean-square voltage of the last 40 ms of the QRS complex; ΔRMSQRS(%) = fractional change in the root-mean-square voltage of the total QRS complex; ΔTQRS(%) = fractional change in the total QRS duration; ΔVTCL = absolute change in the cycle length of ventricular tachycardia; Diag = diagnosis; MI = myocardial infarction; NI = ventricular tachycardia was noninducible during procainamide therapy; Pt = patient.

the total QRS duration analyzed at a 40-Hz high pass filter setting (Fig. 5).

On the standard ECG, the fractional prolongation of the QRS complex was significantly greater in responders than in nonresponders (15 ± 11% vs. 7 ± 9%, p = 0.029) whereas corrected QT prolongation was similar in these groups (4 ± 10% vs. 7 ± 7%, p = NS).

In the responders, procainamide-induced signal-averaged ECG alterations were similar in 6 patients whose ventricular tachycardia became noninducible and in 10 patients whose cycle length of ventricular tachycardia was prolonged by ≥100 ms (Table 4).

The absolute and fractional prolongation of the ventricular effective refractory period was significantly greater in

Table 2. Correlation Between the Time Domain Signal-Averaged Variables and the Cycle Length of Ventricular Tachycardia at the Baseline Study and During Procainamide Therapy

Variable	Pearson's Correlation Coefficient (baseline study) (n = 31)	p Value	Pearson's Correlation Coefficient On Procainamide (n = 25)	p Value
Total QRS duration				
25 Hz	0.364	0.045	0.655	0.0001
40 Hz	0.338	NS	0.517	0.008
LAS				
25 Hz	0.335	NS	0.531	0.006
40 Hz	0.361	NS	0.466	0.044
Initial QRS duration				
25 Hz	0.192	NS	0.558	0.004
40 Hz	0.124	NS	0.5136	0.009
RMS40 voltage				
25 Hz	−0.299	NS	−0.541	0.005
40 Hz	−0.324	NS	−0.459	0.021
RMSQRS voltage				
25 Hz	0.095	NS	−0.138	NS
40 Hz	0.266	NS	0.047	NS

p = significance of the correlation coefficient. LAS = low amplitude signal duration; RMS40 = root-mean-square voltage of the last 40 ms of the QRS complex; RMSQRS = root-mean-square voltage of the total QRS complex.

responders than in nonresponders (37 ± 15 vs. 13 ± 18 ms, $p < 0.001$ and 14 ± 7% vs. 5 ± 7%, $p < 0.002$, respectively). The changes in refractoriness in patients whose tachycardia became noninducible and in patients in whom ventricular tachycardia was still inducible but with the cycle length prolonged by ≥100 ms were similar (37 ± 12 vs. 37 ± 18 ms and 14 ± 7% vs. 14 ± 7%, respectively).

Table 3. Comparison of the Procainamide-Induced Fractional Changes in the Signal-Averaged ECG Variables in Responders Versus Nonresponders

Variable	Responders (n = 16)	Nonresponders (n = 15)	p Value
ΔTQRS (%)			
25 Hz	26 ± 15	10 ± 10	0.002
40 Hz	20 ± 9	8 ± 10	0.001
ΔLAS (%)			
25 Hz	46 ± 50	18 ± 36	NS
40 Hz	32 ± 23	7 ± 29	0.013
ΔIQRS (%)			
25 Hz	17 ± 11	9 ± 10	0.037
40 Hz	14 ± 14	10 ± 10	NS
ΔRMS40 (%)			
25 Hz	−41 ± 33	−22 ± 28	NS
40 Hz	−39 ± 28	−22 ± 165	NS
ΔRMSQRS (%)			
25 Hz	−30 ± 15	−12 ± 29	0.043
40 Hz	−25 ± 16	−15 ± 20	NS

p = unadjusted statistical significance of the difference between responders and nonresponders to procainamide therapy (unpaired *t* test). After applying the Bonferroni correction, only Δ% TQRS (at both filter settings) was statistically significant. Responders = patients with noninducible ventricular tachycardia or with inducible slow ventricular tachycardia (prolongation of the cycle length by ≥100 ms) during procainamide therapy. Abbreviations as in Table 1.

Discussion

Findings of the study. Our major findings are that 1) procainamide significantly alters the time domain signal-averaged ECG variables, and 2) some of the drug-induced changes in these variables predict procainamide efficacy, defined as noninducibility of sustained arrhythmia or prolongation of the cycle length of ventricular tachycardia by ≥100 ms.

Although initial reports (17) suggested a lack of influence of antiarrhythmic drugs on the signal-averaged ECG, more recent reports have shown that class IA drugs (procainamide, quinidine, imipramine) (8,10), class IC drugs (pro-

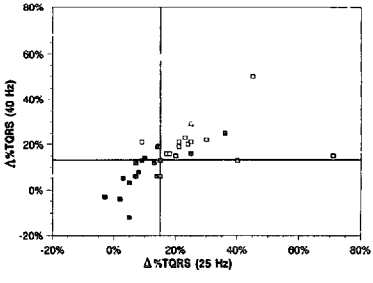


Figure 4. Scatter plot showing procainamide-induced fractional changes (Δ%) in the total QRS duration (TQRS) at 25-Hz and 40-Hz filter settings in responders (**open squares**) and nonresponders (**closed squares**) to procainamide therapy. The lines correspond to the dichotomy points (15% for 25 Hz, **vertical line**, and 13% for 40 Hz, **horizontal line**) discussed in the text.

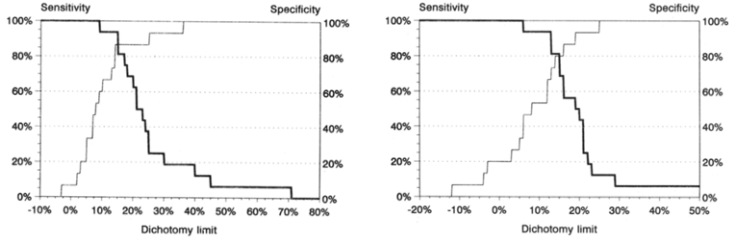


Figure 5. Plots of sensitivity and specificity curves of fractional changes (Δ%) of the total QRS durations that were analyzed using 25 Hz (**left**) and 40 Hz (**right**) high pass filters to identify patients in whom procainamide prevented inducibility of ventricular tachycardia or prolonged its cycle length by ≥100 ms. **Horizontal axes** correspond to dichotomy points, and **vertical axes** show values for sensitivity and specificity. Values for sensitivity (**thick line**) and specificity (**thin line**) are shown for each possible dichotomy point.

pafenone, flecainide) (10–12), and amiodarone (9) significantly change the signal-averaged ECG. Freedman and Steinberg (10) have also suggested that class I drugs selectively prolong late potentials whereas other variables are less affected. However, Lombardi et al. (11) have postulated that class IC drug-induced signal-averaged ECG changes reflect an inhomogeneous slowing of intramyocardial impulse propagation.

In the present study we also observed significant procainamide-induced alterations in all time domain variables. The root-mean-square voltage of the total and of the final 40 ms of the QRS complex were reduced, whereas the total QRS duration was prolonged. Both components of the total QRS complex, the initial QRS and the low amplitude signal durations, were also significantly prolonged, and the absolute increase of these variables was similar. The fractional increase in the low amplitude signal duration tended to be greater than an increase in the initial QRS duration but it reached borderline significance only at a 25-Hz filter setting. This observation may suggest some preferential effects of procainamide on late potentials as reported by Freedman and Steinberg (10). However, in our study the total and the initial QRS durations were prolonged more consistently than was the low amplitude signal duration, and the absolute increment in the low amplitude signal duration constituted 52% to 57% of the absolute increment in the total QRS duration compared with the increment of 73% reported by Freedman and Steinberg (10). The discrepancies between their findings and our results may be explained by differences in study groups (they also studied patients with ventricular fibrillation and syncope), the use of other than procainamide class I antiarrhythmic drugs in their study and possible differences in the baseline frequency of late potentials in the two studies.

Table 4. Fractional Changes in Time Domain Signal-Averaged Electrocardiographic Indexes (at 25 Hz) in Patients in Whom Procainamide Prevented Inducibility of Ventricular Tachycardia or Prolonged Its Cycle Length by ≥100 ms

Variable	VT Noninducible (n = 6)	CL of VT Prolonged ≥100 ms (n = 10)
ΔTQRS (%)	25 ± 8	27 ± 18
ΔLAS (%)	42 ± 45	48 ± 56
ΔIQRS (%)	19 ± 13	16 ± 10
ΔRMS40 voltage (%)	−40 ± 36	−42 ± 33
ΔRMSQRS voltage (%)	−35 ± 9	−27 ± 18

There were no statistically significant differences between groups (by unpaired *t* test). Results at the 40-Hz filter setting were similar to those at the 25-Hz setting. CL = cycle length; VT = ventricular tachycardia; other abbreviations as in Table 1.

Procainamide significantly prolonged the duration of the QRS complex on the standard ECG but the fractional increase in the QRS duration detected by the signal-averaged ECG was greater than that detected by the standard ECG.

Procainamide did not significantly alter the results of the spectral temporal mapping of the signal-averaged ECG. The values of normality factor as well as visual inspection of spectral temporal maps did not reveal any significant or specific changes produced by the drug. These findings, although of limited value because of the poor reproducibility of the spectral temporal mapping in the present study and a previous study from this laboratory (18), further suggest that procainamide-induced changes in the time domain signal-averaged ECG may be nonspecific rather than selective prolongation of late potentials. This concept is in accord with the findings of another study from this laboratory (12), in which flecainide-induced alterations in time domain variables were identical in patients with ventricular tachycardia and late potentials and in patients with supraventricular tachycardia, no structural heart disease and a normal signal-averaged ECG.

The duration of the signal-averaged QRS complex correlated with the cycle length of ventricular tachycardia but not

with the ventricular effective refractory period at the baseline study. Similar findings have been reported by Borbola et al. (19). During procainamide therapy, more signal-averaged ECG variables correlated with the cycle length of ventricular tachycardia, and the correlation was stronger than at the baseline study. This finding may be explained in part by the observations of De Langen et al. (20), who have shown that procainamide caused greater prolongation of electrograms ending late in the QRS complex than of those that end earlier, resulting in a greater prolongation of the terminal portion of the QRS complex on the surface signal-averaged ECG. However, Schmitt et al. (21) were unable to detect a differential effect of antiarrhythmic drugs on normal and abnormal electrograms in humans. In the present study the QRS duration correlated better with the cycle length of ventricular tachycardia than did the low amplitude signal duration, a finding that agrees with the observation (22) that local electrogram duration does not necessarily correlate with the cycle length of tachycardia.

Comparison with previous work. The relation between drug-induced signal-averaged ECG changes and antiarrhythmic efficacy has been examined in only two previous studies. In the first of these, Freedman and Steinberg (10) showed that prolongation of the low amplitude signal duration by class I antiarrhythmic drugs correlated with the increase in the cycle length of ventricular tachycardia. The number of patients in whom antiarrhythmic drugs prevented inducibility of ventricular tachycardia was too small to make any conclusions. In the second study Lombardi et al. (11) showed that propafenone- and flecainide-induced changes in the signal-averaged ECG were not related to antiarrhythmic efficacy assessed by Holter monitoring.

Procainamide is effective and widely used as first-line therapy in many patients with ventricular tachycardia. There is evidence (23) that noninducibility or prolongation of the cycle length of ventricular tachycardia by ≥100 ms during procainamide therapy is associated with a favorable prognosis. In the present study the best signal-averaged ECG variable for identification of such patients was the increase in the total QRS duration, which represents procainamide-induced prolongation of conduction (24). Some investigators have also documented that these effects are related to drug efficacy. Marchlinski et al. (25) showed that the degree of increase in the QRS duration, measured at a paced cycle length similar to that of ventricular tachycardia, correlated with the degree of slowing of the cycle length of tachycardia. In other studies (24–27), the degree of prolongation of ventricular refractoriness identified responders more accurately than did the degree of prolongation of conduction. In the present study responders had greater prolongation of the ventricular effective refractory period than did nonresponders, a finding that is in agreement with these studies. However, it is unclear why the prolongation of conduction and refractoriness was similar in two subgroups of responders (in patients whose tachycardia was rendered noninducible and in patients with inducible but slow and stable ventricular tachycardia). Presumably, complete suppression of inducible ventricular tachycardia requires development of bidirectional block, which may depend not only on the magnitude of the drug-induced changes but also on the electrophysiologic properties of the substrate in individual patients.

Technical considerations. Detailed analysis of the effects of antiarrhythmic drugs on late potentials detected by the signal-averaged ECG may be difficult. There is growing evidence (28) that in many patients, especially those with an anterior site of myocardial infarction, late potentials are hidden within the QRS complex and cannot be detected on the time domain signal-averaged ECG. Our finding that the initial QRS duration was prolonged by procainamide to a greater extent in patients with anterior than in those with inferior infarction agrees with this concept. Currently, only spectral turbulence analysis of the signal-averaged ECG attempts to detect late potentials located inside the QRS complex (29).

The assumption that the low amplitude signal portion arises in each case from slowly conducting tissue is undoubtedly an oversimplification. Even if it holds true in a significant proportion of postinfarction patients, it is still difficult to prove that the low amplitude signals at the end of the QRS complex indeed represent the slowly conducting area from where the clinical or inducible ventricular tachycardia originates.

The cutoff voltage of 40 μV used for definition for late potentials was established in patients while they were receiving no antiarrhythmic treatment. Because these drugs significantly reduce the voltage of the total QRS complex (in our study by 20%), a large portion of the QRS complex may meet this criterion not because of true prolongation of late potentials but because of a nonspecific reduction in the total QRS voltage. Therefore, total QRS duration and other signal-averaged ECG variables that do not depend on QRS voltage may be more accurate than other variables for assessing the effects of antiarrhythmic drugs on the signal-averaged ECG.

Some studies have shown that the total QRS duration is more reproducible than the terminal QRS measurements, which are highly sensitive to the signal to noise ratio (18,30,31). Steinberg et al. (32) recently reported that the total QRS duration, but not the low amplitude signals or terminal QRS voltage, contributed independently to the prognostic value of the signal-averaged ECG in postinfarction patients. Because relatively small changes in the QRS offset are likely to reduce the accuracy of terminal QRS measurements, the total QRS duration may be a less arbitrary measurement that includes the late potentials and the standard QRS complex. These findings may also partly explain the results of the present study.

Limitations of the study. Patients who were treated with intravenous procainamide underwent electrical stimulation

15 min after termination of the drug infusion rather than the prolonged infusion during stimulation that some investigators (33) have advocated. Procainamide was administered orally in 11 trials and intravenously in the remaining 20 trials. However, the effects of oral and intravenous procainamide on the signal-averaged ECG indexes were similar. Although we did not routinely measure procainamide and N-acetylprocainamide plasma levels, the doses used in the present study are comparable to procainamide doses tested in other studies (23–25). Furthermore, even if pharmacokinetic differences influenced the results of programmed stimulation in individual cases, they are unlikely to have altered the relation between the drug-induced signal-averaged ECG changes and antiarrhythmic efficacy.

In the present study no patient manifested proarrhythmic effects of procainamide, defined as acceleration of clinical arrhythmia, or induction of new sustained arrhythmia. Thus, we cannot exclude the possibility that some signal-averaged ECG changes, such as an increase in total QRS or low amplitude signal durations greater than those reported in the present study, may identify proarrhythmic effects of procainamide. We also cannot exclude the possibility of acceleration of a rate of ventricular tachycardia with corresponding shortening of total QRS and low amplitude signal duration.

Future directions. This study concentrated on the relation between procainamide-induced signal-averaged ECG changes and results of ventricular stimulation studies. Further prospective studies are required to establish the role of signal-averaged ECG in predicting the long-term outcome in patients treated with procainamide.

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