Flecainide-related alterations in the signal-averaged electrocardiogram: similarity between patients with or without ventricular tachycardia

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The signal-averaged electrocardiogram (SAECG) identifies patients at risk of sustained ventricular tachycardia (VT), but the influence of anti-arrhythmic agents on the SAECG is not yet established. We have evaluated the effects of flecainide on the SAECG (XYZ leads, high-pass filters 25 Hz and 40 Hz, noise level 0-2 µV–0-4 µV, Model 1200 EPX, ART) in 25 patients: 15 (VT group) had documented sustained VT (nine post-MI, two dilated cardiomyopathy, four normal hearts) and 10 (control group) had supraventricular arrhythmias and structurally normal hearts. The SAECG was recorded in all patients prior to, and 5 min following a flecainide infusion (2 mg. · kg⁻¹ over 10 min).

Before flecainide administration an abnormal SAECG was recorded in six patients from the VT group and in no control patient. Following flecainide, 13 patients from the VT group and eight control subjects demonstrated abnormal SAECG. Flecainide produced similar significant percentage changes in all SAECG indices in both the VT and control groups: total QRS duration was prolonged by 26.0 ± 10.4% vs 26.7 ± 15.7%, late potential duration under 40µV was prolonged by 55.5 ± 62.0% vs 106.1 ± 61.4%, and the root mean square voltage of the last 40 ms of the QRS was reduced by 42.1 ± 34.9% vs 55.3 ± 24.4%, respectively.

We conclude that flecainide significantly changes the SAECG parameters in patients with and without a history of VT, irrespective of the underlying disease.

Introduction

An abnormal signal-averaged electrocardiogram (SAECG) identifies patients prone to sustained ventricular tachycardia (VT)². The majority of these patients are treated with anti-arrhythmic drugs. However, the influence of anti-arrhythmic therapy on the SAECG and the clinical value of possible changes in SAECG indices caused by anti-arrhythmic agents are still not established. The aim of the present study is to evaluate the effect of intravenous flecainide acetate on the SAECG in patients with and without a history of sustained VT.

Patients

The study group consisted of 25 patients without significant congestive heart failure, with an ejection fraction > 30%. All subjects were studied in the absence of anti-arrhythmic medication and none of them was receiving amiodarone before inclusion into the study. Fifteen patients (VT group) (two female, 13 male, mean age 58 years) had a history of sustained VT, which occurred spontaneously while the patients were taking no anti-arrhythmic drugs, and was inducible by programmed ventricular stimulation. Underlying heart disease was previous myocardial infarction (MI) in nine and dilated cardiomyopathy (DCM) in two patients. Four patients had structurally normal hearts. Three post-MI patients had a right bundle branch block (RBBB) on the standard electrocardiogram and in the remaining 12 subjects no conduction disturbances were found.

The second group (controls) consisted of 10 patients (four female, six male, mean age 42 years) referred to St George’s Hospital for evaluation of paroxysmal supraventricular tachyarrhythmias. In six of these patients, the diagnosis was atrioventricular reentrant tachycardia secondary to a concealed accessory pathway demonstrated at electrophysiological study (there was no evidence of antegrade accessory pathway conduction at any time). In the remaining patients atrioventricular nodal reentrant tachycardia in one and paroxysmal atrial fibrillation in three patients were diagnosed. There was no history of ventricular arrhythmias, and at the electrophysiological study no arrhythmia of ventricular origin could be induced. The results of both cardiac catheterization and Doppler echocardiography were normal and the standard electrocardiogram showed no abnormalities in this group of patients.

The study protocol was approved by the local Ethics Committee and all patients gave informed consent.

Methodology

The SAECG was performed before and after flecainide infusion, using commercially available equipment.
Cycles (range from 56 to 637 beats) were averaged. The endpoint of recording was to obtain the noise level considered as abnormal; (ii) duration of the terminal ST segment over a 40 ms window after a four-pole bidirectional Butterworth filter was applied to the averaged signal. The location of the 40 ms window used by the algorithm was determined automatically by the system. The endpoint of the averaged and filtered QRS complex was located at the centre of a 5 ms window which was an average of 3 to 3.5 standard deviation above the root mean square noise. Three computer-calculated SAECG indices were used: (i) duration of the filtered QRS complex (total QRS) — a duration longer than 120 ms was considered as abnormal; (ii) duration of the terminal QRS < 40 μV (late potentials duration, LP) — a duration longer than 40 ms was considered as abnormal; (iii) root mean square voltage of the last 40 ms of the QRS complex (RMS40) — values lower than 25 μV were defined as abnormal. Additionally, in three patients with right bundle branch block, modified abnormal criteria as proposed by Buckingham et al. were applied (total QRS > 145 ms, LP > 45 ms, and RMS40 < 17 μV). A tracing was defined as positive when two or more of the SAECG indices were abnormal at the 25 Hz filter setting. The endpoint of recording was to obtain the noise level ≤ 0.3 μV, and special care was taken to achieve the same range of noise level in each case at the time of the pre- and post-flecainide recordings.

After the first SAECG recording, flecainide acetate was given intravenously at a rate of 2 mg kg⁻¹ infused over 10 min. No patient received a dose in excess of 150 mg. The heart rhythm was continuously monitored before, during, and 1 h after flecainide administration. Five minutes after termination of the flecainide infusion, a second SAECG recording was obtained. A mean of 257 cardiac cycles (range from 56 to 637 beats) were averaged. The noise level measured at 25 Hz varied from 0.2 μV in 20 recordings to 0.3 μV in 22 recordings, and 0.4 μV in eight SAECGs. The noise levels of pre- and post-flecainide recordings were equal in nine patients, differed by 0.1 μV in 13, and by 0.2 μV in three.

### Table 1: Influence of flecainide on the standard QRS duration and on the signal-averaged electrocardiogram indices

<table>
<thead>
<tr>
<th></th>
<th>VT group</th>
<th>Control group</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Before flecainide</td>
<td>On flecainide</td>
<td></td>
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<tr>
<td>Standard QRS duration (ms)</td>
<td>112.7 ± 25.5</td>
<td>143.7 ± 32.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total QRS duration (ms)</td>
<td>127.5 ± 30.8</td>
<td>161.1 ± 48.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>LPD (ms)</td>
<td>38.2 ± 15.3</td>
<td>55.4 ± 24.2</td>
<td>0.003</td>
</tr>
<tr>
<td>RMS40 (μV)</td>
<td>33.7 ± 41.2</td>
<td>13.7 ± 7.6</td>
<td>0.07</td>
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</table>

VT = sustained ventricular tachycardia; LPD = late potential duration; RMS40 = root mean square voltage of the last 40 ms of the filtered QRS complex.

### Data analysis

Values are expressed as the mean ± one standard deviation, and P values are considered significant if less than 0.05. Student's paired and unpaired t-tests were used as appropriate to compare the mean values of the SAECG indices before and after flecainide infusion, and to compare the results between the VT and the control groups.

### Results

**Baseline SAECG Recording**

At the first SAECG recording, six patients out of 15 from the VT group had an abnormal SAECG (five post-MI patients and one patient with DCM). All three patients with RBBB had a normal SAECG. No abnormal SAECG was recorded in the control group.

The mean QRS duration on the standard electrocardiogram tended to be longer in the VT group than in the control group (112.7 ± 25.5 ms vs 97.1 ± 12.2 ms, P = 0.053). On the SAECG, both total QRS and LP durations were longer, and the RMS40 voltage tended to be lower in the VT group compared with the control group (127.5 ± 30.8 ms vs 104.7 ± 16.9 ms, P = 0.026; 38.2 ± 15.3 ms vs 21.0 ± 7.2 ms, P = 0.001; 33.7 ± 41.2 μV vs 67.4 ± 47.9 μV, NS, respectively).

**Flecainide Infusion**

The flecainide infusion was well tolerated by all subjects except one post-MI patient, who developed short runs (up to five complexes) of non-sustained VT after the administration of 65 mg of flecainide (dose received, 1.2 mg kg⁻¹). The infusion was stopped and the arrhythmia terminated spontaneously after 5 min. The results of SAECG recorded in this patient before and after flecainide infusion are presented in the next section.

**SAECG After Flecainide Infusion**

The influence of flecainide on SAECG indices and standard QRS duration is presented in Table 1. After flecainide, the mean duration of the QRS complex on the standard electrocardiogram remained longer in the VT group compared with controls (143.7 ± 32.2 ms vs 117.4 ± 15.0 ms, P = 0.012). The SAECG also showed...
that mean total QRS and LP durations remained longer, and that RMS40 voltage was lower in the VT group compared with controls, although these differences were smaller than at the baseline recordings. Only the difference in total QRS duration was statistically significant (161.1 ± 48.6 ms vs 130.8 ± 14.3 ms, P = 0.036; 55.4 ± 24.2 ms vs 40.5 ± 11.9 ms, NS; 13.7 ± 7.6 μV vs 20.4 ± 9.8 μV, NS, respectively).

Flecainide produced significant prolongation in the mean QRS duration on the standard electrocardiogram, and in the mean total QRS and LP durations on the SAECG in the whole study group. The voltage of the RMS40 was also reduced to a great extent in both VT and control groups, but these values reached statistical significance only in control patients, in whom the effect of flecainide on the SAECG variables was more consistent. The difference in the voltage of the RMS40 before and after flecainide in the whole study group was statistically significant (47.2 ± 46.2 μV vs 16.4 ± 9.1 μV, P = 0.002). Examples of the SAECG recorded before and after flecainide infusion from patients with and without VT, are shown in Figs 1 and 2.

The percentage change in SAECG variables after flecainide administration is given in Table 2. Prolongation of the duration of the standard QRS, total QRS and LP durations, as well as lowering of the voltage of the RMS40, were similar in both groups (differences statistically not significant). The most pronounced changes occurred in LP duration, especially in the control group (as much as 106% of prolongation in the control group vs 56% of prolongation in the VT group, P = 0.06).

Analysis of the individual results in the VT group revealed that all patients developed prolongation of the QRS duration on the standard electrocardiogram and the total QRS duration on the SAECG. The shortest prolongation of the standard QRS complex (by 1%) and total QRS (by 13%) occurred in the patient in whom flecainide was stopped due to pro-arrhythmic effect after administration of 65 mg of the drug. The influence of flecainide on LP duration and RMS40 was not so uniform as on the standard and total QRS durations. Twelve patients developed LP prolongation, whereas in three cases the LP...
duration was shorter after flecainide (from 4% to 18%). The RMS40 voltage was lower after flecainide infusion in all but one patient, in whom the drug produced a 50% increase in RMS40 voltage. A summary of the results in the VT group is presented in Fig. 3. Out of nine patients with normal SAECG at the baseline recording, eight had an abnormal SAECG after flecainide infusion. Out of six patients with an abnormal SAECG at the baseline recording, flecainide further prolonged total QRS and LP durations: it lowered RMS40 voltage in five, but in one, the post-MI patient with a large antero-apical aneurysm whose basal rhythm was atrial fibrillation, the SAECG became normal after flecainide infusion. Anti-arrhythmic surgery was performed on this patient 20 days later, but he died due to progressive respiratory insufficiency and sepsis. In this case, the SAECG became normal after flecainide due to shortening of the LP duration (from 43 ms to 36 ms) and an increase in the RMS40 voltage (from 13-4 µV to 26-7 µV). Standard and total QRS durations were prolonged after flecainide compared to the baseline recording.

In the control group, the influence of flecainide on the standard electrocardiogram and the SAECG indices was uniform. All patients developed significant prolongation of standard QRS duration, total QRS and LP durations, as well as a reduction in the RMS40 voltage. Eight patients from this group showed an abnormal SAECG after flecainide infusion (see Fig. 3).

The effects of different filter settings on the results of the SAECG

All data presented so far were obtained using a 25 Hz high-pass filter. At the filter setting of 40 Hz the results were similar. In the VT group flecainide significantly prolonged tQRS and LP durations (128.0 ± 33.9 ms vs 157.0 ± 49.6 ms, P = 0.001; 49.9 ± 25.1 ms vs 61.2 ± 30.0 ms, P = 0.019, respectively), and non-significantly reduced the RMS40 voltage (21.6 ± 26.9 µV vs 10.1 ± 9.9 µV). In the control group, flecainide induced significant changes in all SAECG parameters: total QRS duration was prolonged from 101.9 ± 16.9 ms to 127.1 ± 16.3 ms (P = 0.0001), LP duration was prolonged from 27.3 ± 7.3 ms to 47.0 ± 13.3 ms (P = 0.001), and RMS40 voltage was reduced from 39.6 ± 19.5 µV to 13.9 ± 7.7 µV (P = 0.004).

Discussion

The effects of anti-arrhythmic drugs on the SAECG are not well established. Denniss *et al.* examined the influence of class la, Ib and class II anti-arrhythmic agents (quinidine, disopyramide, procainamide, mexiletine and metoprolol) on the SAECG and showed that the tested drugs had no consistent effect on the SAECG, even when VT inducibility was suppressed or occurrence of spontaneous VT was prevented*. Intravenous lignocaine was also shown to have no significant effect on the SAECG*.

Jauernig *et al.* studied the effects of various anti-arrhythmic drugs on the SAECG during sinus rhythm and also found no significant change in the SAECG variables. However, late potential duration during atrial pacing was consistently prolonged, but again these changes were not related to anti-arrhythmic drug efficacy, as assessed by programmed ventricular stimulation*. In another study, intravenously administered procainamide caused prolongation of late potentials and later, in higher dosage, change of slow conduction to intermittent conduction failure*. Borbola *et al.* showed that a high-dose of oral amiodarone significantly changed all SAECG indices: total QRS and LP durations were prolonged by 18% and 60%, respectively, and RMS40 voltage was reduced by 37%. Lombardi *et al.* reported (in abstract) that propafenone and flecainide significantly changed the SAECG: at baseline recording, 37% of patients with frequent and repetitive ventricular arrhythmias had abnormal SAECG, but after propafenone and flecainide administration, the incidence of abnormal SAECG increased to 42% and 67%, respectively. Finally, Freedman *et al.* recently reported that sodium channel blocking anti-arrhythmic agents prolong LPs which contributes to prolongation of VT cycle length*.
The aim of the present study was to investigate the influence of intravenous flecainide on the SAECG in patients with and without a history of VT. The QRS duration on the standard electrocardiogram was prolonged by 25% after flecainide in the whole study group, which is a well-known effect of this drug. This effect was almost identical in patients with a history of sustained VT compared to the control group. Also the SAECG changes (prolongation of total QRS and LP durations, and reduction in RMS40 voltage) after flecainide were similar in both groups. Moreover, the underlying heart disease did not influence the results: the drug caused similar changes in SAECG parameters in patients with VT, with and without organic heart disease, as well as in control subjects.

Of the SAECG indices, LP duration was the most affected by flecainide infusion. This phenomenon was more pronounced in control subjects compared with patients with a history of sustained VT (106% vs 56% of prolongation of LP duration, respectively). This can be explained in part by the fact that LP duration at the baseline recording was significantly shorter in the control than in the VT group. Thus, lengthening of LP by flecainide in the control group usually resulted in a greater percentage change than similar prolongation of already long LP in the VT group. The mean prolongation of LP duration in milliseconds was very similar in both groups: 20.5 ± 19 ms in VT patients vs 19.5 ± 11 ms in the control group (ns). Reduction in RMS40 voltage was also greater in the control group (55% vs 42%), whereas standard and total QRS durations were prolonged to a similar extent.

There are at least two different possible explanations of the above findings. One is that flecainide indeed creates a new substrate for reentrant arrhythmias. On the other hand, flecainide-induced SAECG changes can simply depict QRS prolongation due to slower conduction through the myocardium after drug administration. In patients with a history of sustained VT, a greater increase in LP duration than in total QRS duration can indirectly suggest that slowing of conduction in the electrophysiological substrate of the reentry circuit exceeded the delay in the remaining ventricular myocardium, as is likely to be the case with amiodarone treatment. It is possible that the slow conduction substrate for arrhythmia, hidden or small reentry circuits, undetectable by SAECG, may become visible after flecainide infusion in patients with VT, who had normal SAECG before drug infusion. This is supported by the data from Kershenovich et al. who demonstrated improved sensitivity of SAECG in predicting the inducibility of sustained VT, when recordings were performed on anti-arrhythmic treatment. Of 12 patients with inducible sustained VT, all five with the false-negative SAECG became positive while receiving class I anti-arrhythmic agents. Moreover, Freedman et al. showed that the efficacy of sotalol in preventing VT induction was related to the degree of filtered QRS prolongation on the SAECG: the drug did not prevent VT induction in any patient in whom the duration of the filtered QRS was prolonged more than 3 ms. The relationship between the duration of LPs and ventricular vulnerability assessed by programmed ventricular stimulation has been also analysed. Breithardt et al. showed that the incidence of inducible non-sustained and sustained VT increased from 42% in patients with LPs of less than 20 ms to 56% in those with LPs of between 20 to 39 ms and to 92% in cases with LPs of 40 ms or more. Finally, Gessman et al. described one patient in whom procainamide created a new LP, and another in whom quinidine prolonged the duration of a pre-existing LP. In both cases, LP changes were coincident with inducibility of sustained VT, although in the second case the VT rate on quinidine was slower compared with the baseline results.

However, prolongation of LP duration after flecainide does not necessarily mean that spontaneous ventricular arrhythmia is made more likely. By prolonging the conduction and refractoriness within the reentry circuit, flecainide can further impair the already slow activation wave front (even to the point of complete block), making the initiation of a reentrant arrhythmia more difficult, or even preventing it. This idea is supported by the findings of Kidwell et al., that a flecainide-induced increase in the VT cycle length correlates well with the extent of drug-induced prolongation of the filtered QRS and LP durations on the SAECG (correlation coefficients 0.96 and 0.84, respectively). Other class I anti-arrhythmic agents were also shown to produce similar effects. One can speculate that prolonging the duration of the final portion of the filtered QRS complex under 40 μV after flecainide infusion may not represent the creation of new LPs, or prolongation of the duration of 'hidden' LPs, but may be simply prolonging conduction through normal, healthy myocardium. Thus, exaggeration of the normal temporal inhomogeneity of ventricular depolarization could result in low-amplitude electrical activity from the posterobasal region (normally the latest area of myocardial activation) being sufficiently delayed to meet the criteria for LP. In our study we observed significant reduction (mean 28%) of the RMS voltage of the whole filtered QRS complex, which may also contribute to this phenomenon.

In the present study, in all but one patient, who developed prolongation of the QRS and LP durations and RMS40 voltage reduction, flecainide showed no pro-arrhythmic effect during the hour after drug administration. The only patient in whom flecainide demonstrated a pro-arrhythmic action (short runs of non-sustained VT of the same morphology as the clinical sustained VT) developed less QRS and LP prolongation, but greater RMS voltage reduction compared with the whole VT group (13% vs 26%, 41% vs 56%, 60% vs 42%, respectively). However, this comparison is of limited value, since this patient received a significantly lower dose of flecainide (1.2 mg kg^-1) compared to the remaining patients (2 mg kg^-1).

On the basis of these initial findings, we conclude that flecainide, when administered intravenously, significantly changes SAECG parameters. Prolongation of total QRS and LP durations, as well as a reduction in the voltage of the last 40 ms of the QRS complex were similar in
patients with and without a history of VT, irrespective of the underlying disease. These results may suggest that flecainide-related SAECG alterations represent non-specific response due to drug-induced conduction prolongation rather than the development of true cardiac late potentials after flecainide infusion. The clinical relevance of the post-flecainide SAECG changes, both in patients with, and without a history of VT, needs further evaluation.

References


