Signal-averaged electrocardiogram in patients with arrhythmogenic right ventricular cardiomyopathy and ventricular arrhythmias


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Objective The aim of the study was to assess the prevalence, sensitivity, specificity and predictive value of the signal-averaged ECG in patients with arrhythmogenic right ventricular cardiomyopathy and different forms of ventricular arrhythmias.

Methods The signal averaged ECG in 138 patients and 146 healthy subjects (control group), using a three bandpass filter system (25–250, 40–250, 80–250 Hz), was considered abnormal when at least two parameters were abnormal at each filter setting. Patients were divided into three groups according to the extent of the right ventricular enlargement (mild, moderate, extensive), and into five groups according to the type of ventricular arrhythmia.

Results The signal averaged ECG was abnormal in 57% of the patients and in 4% of the healthy subjects. The sensitivity was 57%, specificity 95% and positive predictive value 92%. The signal averaged ECG was abnormal in 94·4% of patients with the extensive form of the disease, in 77·7% of patients with the moderate form and in 31·8% of patients with the minor form, demonstrating good correlation with the extent of the disease. According to the type of ventricular arrhythmia, a higher correlation was found between signal averaged ECG abnormality and sustained ventricular tachycardia with superior axis (94·4%, P<0·02); the correlation for the other arrhythmias varied from 16·6% to 55·8%.

Conclusion There is a closer correlation between the signal averaged ECG and extent of disease than with the presence of ventricular arrhythmias. The signal averaged ECG is not helpful in diagnosing minor forms of the disease, but since it is a non-invasive method, it may be useful in evaluating progression of the disease.

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Key Words: Signal-averaged electrocardiogram, arrhythmogenic right ventricular cardiomyopathy, ventricular arrhythmias.

Introduction

Arrhythmogenic right ventricular cardiomyopathy is a disease of unknown origin[1–8], that primarily involves the right ventricular myocardium. The characteristic histological finding is the substitution of myocytes with fibrous and fatty tissue proceeding from the epicardium to the endocardium[9,10]. This process can be either localized or widespread. Ventricular arrhythmias with left bundle branch block morphology and/or sudden death are the main clinical manifestations of the disease.

Heart failure is unusual, appearing only when the fibro-fatty substitution is massive[1,11]. The histopathological abnormalities provide the substrate for the genesis of ventricular arrhythmias. The fibro-fatty tissue interrupts the electrical continuity of myocardial fibres creating fragmentation of ventricular depolarization and re-entrant circuits. These electrophysiological abnormalities produce ‘delayed ventricular potentials’ responsible for the appearance of either post-excitation waves on the surface electrocardiogram[12] or late potentials recorded by signal-averaged electrocardiography[13–16]. The use of the signal averaged ECG to predict susceptibility to ventricular tachycardia is well known[17–19]. Studies of the signal averaged ECG in right ventricular cardiomyopathy have mainly focused on the widespread forms of the disease that are often associated with late potentials[13–15]. The aim of this study was to assess the diagnostic value of the signal averaged ECG, its
relation to the extent of the disease and to the different types of arrhythmias in patients with right ventricular cardiomyopathy.

**Patients and methods**

**Patients**

The study group included 138 subjects (85 males, 53 females, mean age 33·7–14·5 years), with right ventricular cardiomyopathy and ventricular arrhythmias with left bundle branch block morphology or ventricular fibrillation. The diagnosis of right ventricular cardiomyopathy was made in the presence of structural and/or dynamic abnormalities, involving exclusively or mainly the right ventricle. These abnormalities were not due to valvular heart disease, intracardiac shunt, active myocarditis, clinical coronary artery disease or pulmonary hypertension. The criteria used for the diagnosis of arrhythmogenic right ventricular cardiomyopathy were those recently established by the Task Force on Arrhythmogenic Right Ventricular Cardiomyopathy.[20]

Patients were divided into three groups according to the extent of the disease: (a) mild forms were defined when the dynamic abnormalities were localized and the right ventricular end-diastolic volume was normal; (b) moderate forms were defined as having a right ventricular end-diastolic volume between 80 and 120 ml . m⁻² at 2D echo-scan (normal in our laboratory 70 ml . m⁻²), or between 110 and 179 ml . m⁻² at angiography (normal in our laboratory 90 ml . m⁻²); (c) extensive forms with a right ventricular end-diastolic volume greater than 120 ml . m⁻² at 2D echo-scan, or greater than 180 ml . m⁻² at angiography. Patients were also sub-divided according to the type of ventricular arrhythmia observed: (1) ventricular fibrillation; (2) sustained ventricular tachycardia (defined as a tachycardia that lasted >30 s); (3) non-sustained ventricular tachycardia (defined as three or more consecutive ventricular beats, lasting <30 s, at a rate >120 beats . min⁻¹); (4) premature ventricular beats, isolated or couplets; (5) low frequency ventricular tachycardia. Patients with sustained ventricular tachycardia were further subdivided into three subgroups according to the QRS axis in the frontal plane during tachycardia: (a) inferior axis (between +50° and +110°); (b) horizontal axis (between +50° and −10°); (c) superior axis (between −10° and −120°).

To establish the reference value of the signal averaged ECG for our laboratory, the control group included 146 healthy subjects (93 males, 53 females, mean age 37 ± 12 years) who had a normal ECG and a QRS duration ≤90 ms.

**Method**

All patients underwent a 12-lead ECG, chest X-ray, 24 h Holter monitoring, and 2D colour Doppler echocardiography. Cardiac catheterization with right and left angiography was performed in 70 patients; 50 patients had right ventricular endomyocardial biopsy. Magnetic resonance imaging was performed in 15 patients. Details of the methods of these tests have been described previously[11]. The right ventricular end-diastolic volume was calculated using an area–length method derived from orthogonal planes (apical four-chamber and short-axis subostal views) with 2D echo scan, and with the surface–length method at angiography[21–23].

The signal averaged ECG was performed using a MAC 15 system (Marquette Inc., Milwaukee, Illinois, U.S.A.). Time-domain analysis was obtained in each patient using three different bandpass filters at 25–250, 40–250, 80–250 Hz. The following parameters for each filter were evaluated: filtered QRS duration, low amplitude signal duration, root mean square of the voltage in the last 40 ms of the filtered QRS (RMS). The graphic representation of late potentials as well as the numerical values of signal averaged ECG parameters were manually checked. The signal averaged ECG was considered abnormal when at least two parameters were abnormal at one filter setting. For each patient the number of abnormal parameters was also considered. Patients with a QRS duration of more than 95 ms were excluded from the study. Treatment with antiarrhythmic drugs was interrupted for an adequate period before the signal averaged ECG. The patients underwent an echocardiogram and a signal averaged ECG on the same day; different physicians performed the echocardiogram and signal averaged ECG evaluation. A third physician performed the statistical analysis and results correlation blindly.

**Statistical analysis**

Continuous variables were compared using Student’s t-test, with separate estimates for equal or unequal variances. Categorical variables were analysed using contingency tables and Pearson’s chi-square method. Data are expressed as mean ± SD. A $P$ value <0·05 was considered statistically significant.

**Results**

**Clinical data**

Sixty-six patients (47·8%) had a mild form of the disease; 54 (39·1%) had a moderate form and 18 (13·1%) an extensive form. A familial occurrence of the disease was revealed in 51 patients (37%). The arrhythmias considered in this study were those observed before the signal averaged ECG (mean time before evaluation 11·7 years), and after the examination for a mean follow-up of 2·3 years: seven patients (5·1%) had ventricular fibrillation and 50 (36·2%) sustained ventricular tachycardia. In the patients with sustained ventricular tachycardia, the QRS axis was superior in 18 (36%), horizontal in six (12%) and inferior in 26 (52%). Six patients (4·3%) had low frequency ventricular tachycardia. Non-sustained
ventricular tachycardia was documented in 32 patients (23.1%). Premature ventricular beats, isolated or couplets, were present in 43 patients (31.1%).

Ventricular arrhythmias and extent of the disease

All the patients with mild forms showed sustained ventricular tachycardia with inferior axis, while in the extensive forms the superior QRS axis during tachycardia was prevalent. In the patients with moderate forms sustained ventricular tachycardia with different QRS axis was observed (Table 1).

Signal averaged ECG data

The averaged number of analysed beats varied from 250 to 400, to obtain a noise level <0.7 μV.

The reference values (95% confidence interval) of the results obtained in the control group were: for the 25–250 Hz filter filtered QRS duration <120 ms, low amplitude signal <40 ms, RMS >25 μV; for the 40–250 Hz filter filtered QRS duration <118 ms, low amplitude signal <40 ms, RMS >20 μV; for the 80–250 Hz filter filtered QRS duration <106 ms, low amplitude signal <34 ms, RMS >12 μV. Our data are similar to those of others using the same recording system.[24,25]

Only six subjects (4.1%) in the control group had an abnormal recording. The signal averaged ECG was abnormal in 79 patients (57%). Comparing the results obtained in the two groups, the signal averaged ECG had an overall sensitivity of 57%, a specificity of 95% and a positive predictive value of 92%.

Signal averaged ECG and extent of the disease

Seventeen out of 18 (94.4%) patients with the extensive form had an abnormal signal averaged ECG. The percentage of abnormal signal averaged ECGs progressively decreased in patients with moderate and minor forms of the disease, being 77.7% and 31.8%, respectively, in the two groups (P<0.001) (Fig. 1). Table 2 shows the mean values ± SD for each parameter in the different groups, according to the extent of the disease. Considering the average number of positive parameters there was a significant difference among all the groups with different extent of the disease (Table 3).

Signal averaged ECG and type of arrhythmias

The highest percentages of abnormal signal averaged ECGs were found in patients with ventricular fibrillation (5 patients, 71%) and sustained ventricular tachycardia (36 patients 72%). Only one out of six patients (16%) with low frequency ventricular tachycardia had an abnormal signal averaged ECG. The signal averaged ECG was abnormal in 13 patients (40.6%) with non-sustained ventricular tachycardia and in 24 patients (55.8%) with less severe ventricular arrhythmias.

The average values of the parameters recorded by the signal averaged ECG in patients with sustained ventricular arrhythmias or non-sustained ventricular arrhythmias are shown in Table 4. The RMS demonstrated a significant difference at all filter settings, while the QRS duration did not show a significant difference between the two groups.

In patients with sustained ventricular tachycardia, the signal averaged ECG was abnormal in 14 patients (53.8%) with an inferior QRS axis, in five patients (83.3%) in whom ventricular tachycardia had a horizontal QRS axis and in 17 patients (94.4%) with a superior QRS axis (P<0.02). The average values of the parameters in the signal averaged ECG in the sustained tachycardias showed a significant difference in the tachycardias with left and right axis deviation (Table 5).

The root-mean-square at 25–250 Hz was the only signal averaged ECG parameter that distinguished

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**Table 1** Relationship between the extent of the disease and the QRS axis in patients with sustained ventricular tachycardia

<table>
<thead>
<tr>
<th>QRS axis</th>
<th>Mild forms</th>
<th>Moderate forms</th>
<th>Extensive forms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>13</td>
<td>12</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>→</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>↑</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>27</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

↓=inferior QRS axis; →=horizontal QRS axis; ↑=superior QRS axis.

**Figure 1** Bar graph showing the percentage of positive parameters in the signal-averaged ECG in patients with arrhythmogenic right ventricular cardiomyopathy and different extent of the disease.

**Signal averaged ECG and type of arrhythmias**

The highest percentages of abnormal signal averaged ECGs were found in patients with ventricular fibrillation (5 patients, 71%) and sustained ventricular tachycardia (36 patients 72%). Only one out of six patients (16%) with low frequency ventricular tachycardia had an abnormal signal averaged ECG. The signal averaged ECG was abnormal in 13 patients (40.6%) with non-sustained ventricular tachycardia and in 24 patients (55.8%) with less severe ventricular arrhythmias.

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The root-mean-square at 25–250 Hz was the only signal averaged ECG parameter that distinguished...
Table 2  Relationship between the average signal averaged ECG values for each filter and the extent of the disease

<table>
<thead>
<tr>
<th>Extent of the disease</th>
<th>Number of subjects</th>
<th>Unfiltered QRS</th>
<th>QRS25</th>
<th>LAS25</th>
<th>RMS25</th>
<th>QRS40</th>
<th>LAS40</th>
<th>RMS40</th>
<th>QRS80</th>
<th>LAS80</th>
<th>RMS80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>146</td>
<td>84.9 ± 7.9</td>
<td>116.4 ± 7.7</td>
<td>18.2 ± 5.3</td>
<td>111 ± 58.1</td>
<td>107.5 ± 7</td>
<td>26.6 ± 6.8</td>
<td>60.2 ± 32.4</td>
<td>94.6 ± 7.5</td>
<td>25.2 ± 7.1</td>
<td>38 ± 22.8</td>
</tr>
<tr>
<td>Mild forms</td>
<td>66</td>
<td>90.5 ± 15.2</td>
<td>121.1 ± 9.3</td>
<td>19.7 ± 8.1</td>
<td>79.6 ± 41.6</td>
<td>110.3 ± 9.6</td>
<td>28.6 ± 8.5</td>
<td>46.5 ± 28.6</td>
<td>99.1 ± 9.4</td>
<td>29.9 ± 9.2</td>
<td>22.8 ± 16.2</td>
</tr>
<tr>
<td>Moderate forms</td>
<td>54</td>
<td>97.4 ± 12.3</td>
<td>128.5 ± 11.7</td>
<td>29.7 ± 13.2</td>
<td>46.1 ± 43.4</td>
<td>120.8 ± 13.4</td>
<td>41.4 ± 15</td>
<td>24 ± 17.4</td>
<td>108.3 ± 12</td>
<td>41.4 ± 14.3</td>
<td>13.7 ± 11.7</td>
</tr>
<tr>
<td>Extensive forms</td>
<td>18</td>
<td>118.5 ± 24.8</td>
<td>145.8 ± 4.2</td>
<td>47.4 ± 17.2</td>
<td>29.4 ± 34.6</td>
<td>137.8 ± 23.7</td>
<td>55.4 ± 22.1</td>
<td>14.4 ± 13.9</td>
<td>127.1 ± 22.8</td>
<td>51.8 ± 22.5</td>
<td>8.8 ± 9.9</td>
</tr>
</tbody>
</table>

QRS25 = mean value of the filtered QRS duration at 25–250 Hz filter; LAS25 = mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 25–250 Hz filter; RMS25 = mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 25–250 Hz filter; QRS40 = mean value of the filtered QRS duration at 40–250 Hz filter; LAS40 = mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 40–250 Hz filter; RMS40 = mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 40–250 Hz filter; QRS80 = mean value of the filtered QRS duration at 80–250 Hz filter; LAS80 = mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 80–250 Hz filter; RMS80 = mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 80–250 Hz filter; \( P \) = \( P \) values between adjacent groups.
patients with ventricular fibrillation or sustained ventricular tachycardia from patients with non-sustained ventricular tachycardia, low frequency ventricular tachycardia or less severe forms of ventricular arrhythmias.

**Discussion**

The presence of late potentials in arrhythmogenic right ventricular cardiomyopathy varies from 50–80% [12-16] and was found to be 57% in the present study which included patients with mild, moderate and extensive involvement of the right ventricle and different forms of arrhythmias. In our study group, the signal averaged ECG had a high positive predictive value (92%), and a high specificity. On the other hand, this examination had a low sensitivity.

The signal averaged ECG does not seem to correlate well with ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy. Only RMS was higher, at all filter settings, in patients with non-sustained ventricular arrhythmias in comparison with patients with sustained ventricular arrhythmias.

Table 3 **Average number of positive signal averaged ECG parameters in the different groups of patients**

<table>
<thead>
<tr>
<th>Extent of the disease</th>
<th>Number of positive parameters (average ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>1·48 ± 1·94</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Mild forms</td>
<td>3·14 ± 2·92</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Moderate forms</td>
<td>6·52 ± 3·04</td>
<td>=0·003</td>
</tr>
<tr>
<td>Extensive forms</td>
<td>7·88 ± 2·51</td>
<td></td>
</tr>
</tbody>
</table>

P=P values between adjacent groups.

Table 4 **Relationship between the average signal averaged ECG values for each filter and different types of arrhythmia**

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>UQRS</th>
<th>QRS25</th>
<th>HFLA25</th>
<th>RMS25</th>
<th>QRS40</th>
<th>HFLA40</th>
<th>RMS40</th>
<th>QRS80</th>
<th>HFLA80</th>
<th>RMS80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sustained ventricular arrhythmias</td>
<td>75</td>
<td>93·9 ± 22</td>
<td>124·7 ± 16</td>
<td>24 ± 13</td>
<td>72·4 ± 35</td>
<td>115 ± 23</td>
<td>33·9 ± 16</td>
<td>39·5 ± 23</td>
<td>103·5 ± 16</td>
<td>35 ± 19</td>
</tr>
<tr>
<td>Non-sustained ventricular arrhythmias</td>
<td>63</td>
<td>97·8 ± 12</td>
<td>128·4 ± 11</td>
<td>30 ± 14</td>
<td>42·9 ± 24</td>
<td>119·8 ± 19</td>
<td>40·2 ± 16</td>
<td>25·6 ± 19</td>
<td>107·7 ± 11</td>
<td>39·1 ± 12</td>
</tr>
<tr>
<td>P</td>
<td>ns</td>
<td>ns</td>
<td>&lt;0·05</td>
<td>&lt;0·001</td>
<td>ns</td>
<td>&lt;0·05</td>
<td>&lt;0·001</td>
<td>ns</td>
<td>&lt;0·001</td>
<td></td>
</tr>
</tbody>
</table>

UQRS=mean value of the unfiltered QRS; QRS25=mean value of the filtered QRS duration at 25–250 Hz filter; HFLA25=mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 25–250 Hz filter; RMS25=mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 25–250 Hz filter; QRS40=mean value of the filtered QRS duration at 40–250 Hz filter; HFLA40=mean value of filtered QRS duration at 80–250 Hz filter; RMS40=mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 40–250 Hz filter; QRS80=mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 80–250 Hz filter; RMS80=mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 80–250 Hz filter; P=P values between adjacent groups.
Table 5  Relationship between the signal averaged ECG values for each filter and the QRS axis in patients with sustained ventricular tachycardia

<table>
<thead>
<tr>
<th>QRS axis</th>
<th>Number of subjects</th>
<th>QRS Unfiltered</th>
<th>QRS25</th>
<th>HFLA25</th>
<th>RMS25</th>
<th>QRS40</th>
<th>HFLA40</th>
<th>RMS40</th>
<th>QRS80</th>
<th>HFLA80</th>
<th>RMS80</th>
<th>Mean number of positive parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>26</td>
<td>95.6 ± 11.6</td>
<td>122.5 ± 9.6</td>
<td>25.3 ± 9.6</td>
<td>54.9 ± 19.2</td>
<td>112.5 ± 12.5</td>
<td>33.3 ± 12.8</td>
<td>34.0 ± 19.5</td>
<td>101.6 ± 9.8</td>
<td>34.7 ± 8.6</td>
<td>17.0 ± 7.6</td>
<td>4.35 ± 3.45</td>
</tr>
<tr>
<td>P</td>
<td>ns</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>=0.002</td>
<td>=0.001</td>
<td>=0.005</td>
<td>=0.005</td>
<td></td>
</tr>
<tr>
<td>↑</td>
<td>18</td>
<td>103 ± 13.8</td>
<td>141 ± 5.1</td>
<td>40.5 ± 13.6</td>
<td>21.3 ± 20.5</td>
<td>134.7 ± 44.4</td>
<td>57.8 ± 11.7</td>
<td>8.7 ± 6.4</td>
<td>119 ± 6.1</td>
<td>49.5 ± 13.3</td>
<td>6.1 ± 3.6</td>
<td>8.5 ± 0.76</td>
</tr>
</tbody>
</table>

UQRS = mean value of unfiltered QRS; QRS25 = mean value of filtered QRS duration at 25–250 Hz filter; LASH25 = mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 25–250 Hz filter; RMS25 = mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 25–250 Hz filter; QRS40 = mean value of filtered QRS duration at 40–250 Hz filter; LASH40 = mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 40–250 Hz filter; RMS40 = mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 40–250 Hz filter; QRS80 = mean value of filtered QRS duration at 80–250 Hz filter; LASH80 = mean value of low amplitude signal duration in the last 40 ms of the filtered QRS at 80–250 Hz filter; RMS80 = mean value of the root mean square of the voltage in the last 40 ms of the filtered QRS at 80–250 Hz filter; P = P values between adjacent groups; ↓ = inferior QRS axis   ↑ = superior QRS axis.
With regard to the different types of arrhythmias, there was a greater percentage of patients with ventricular fibrillation or sustained ventricular tachycardia who had abnormal signal averaged ECGs. In this group, abnormal signal averaged ECGs were found in 71% and 72%, respectively. However, the highest percentage of abnormal signal averaged ECGs was found in the subgroup of patients with sustained ventricular tachycardia and horizontal or superior QRS axis. In all these patients a moderate or widespread form of the disease was present. The absence of late potentials is particularly evident in patients with arrhythmic right ventricular cardiomyopathy who have right ventricular outflow tract ventricular tachycardias. This type of arrhythmia is often present in minor forms of the disease and is difficult to differentiate from idiopathic arrhythmias arising from this area. This is understandable because the minor forms of the disease almost always have this form of arrhythmia. The outflow region could be the first to become arrhythmogenic in this disease.

In conclusion, the signal-averaged ECG appears to be a useful method in the study of arrhythmic right ventricular cardiomyopathy, because it is able to differentiate idiopathic arrhythmias arising from this area. This is understandable because the minor forms of the disease almost always have this form of arrhythmia. The outflow region could be the first to become arrhythmogenic in this disease. We thank Dr. Frank I. Marcus (University of Arizona, College of Medicine, Tucson, Arizona) for critically reviewing the manuscript and offering suggestions and comments.

References


