Malignant ventricular arrhythmias in patients with implantable cardioverter-defibrillators: electrical signals which are predictors of recurrence

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ABSTRACT

Introduction: There is a growing number of patients with implantable cardioverter-defibrillators. Recurrences are frequent and electrical shocks are the main factor affecting the quality of life.

Objective: To identify the electrocardiographic predictors of the recurrence of malignant ventricular arrhythmias in these patients.

Method: From a universe of 76 patients, who had undergone cardioverter-defibrillator implantation, 46 patients were selected and two groups were formed. Group A consisted of 27 patients with at least one episode of malignant ventricular arrhythmias after device implantation; and group B consisted of 19 subjects without recurrences. Measurements (prolonged QTc, abnormal QT dispersion, Tpeak-Tend interval and its abnormal dispersion) were averaged over three consecutive heartbeats in each lead, manually, by two independent observers.

Results: In group A, there was a predominance of structural heart disease and an ejection fraction less than 35%. The fragmentation of the QRS complex, bimodal T wave and early repolarization pattern were also present. There were significant differences in the mean values of the QT interval (428 vs. 390 ms), p=0.004; the corrected QT (476 vs. 436 ms), p=0.011; and Tpeak-Tend interval (108 vs. 87 ms), p=0.006. There were no significant differences in QT dispersion (51 vs. 48 ms), the Tpeak-Tend dispersion (35 vs. 27 ms), or QRS duration (121 vs. 105 ms).

Conclusions: QT, QTc and Tpeak-Tend intervals are electrocardiographic predictors of the recurrence of ventricular arrhythmias in patients with implantable cardioverter-defibrillators.

Key words: Implantable cardioverter-defibrillator, Electrical predictors, Recurrence, Malignant ventricular arrhythmias

Arritmias ventriculares malignas en pacientes con cardiodesfibrilador implantable: signos eléctricos predictores de recidivas
INTRODUCTION
Repeated electric shocks are among the main problems faced by patients with implantable cardioverter-defibrillators (ICD). There are numerous markers associated with this phenomenon; many are complex in their production and reproducibility. Surface electrocardiogram may show signals that reflect alterations in the processes of ventricular depolarization and repolarization. Identifying them would help to establish a more accurate individual risk stratification, define a therapeutic strategy and prevent complications in patients at high arrhythmic risk. The aim of this study was to identify electrocardiographic signals which are predictors of recurrence of malignant ventricular arrhythmias (MVA) in the clinical monitoring of patients with ICD.

METHOD
The universe consisted of 76 patients, who were treated at the Arrhythmia and Pacing Department of the Institute of Cardiology and Cardiovascular Surgery, aged between 15 and 80 years, of both sexes, with demonstrable structural heart disease or not, who had undergone ICD implantation as a secondary or primary (one case) prevention of MVA. The sample was defined by the study period (from February 2007 to February 2009) and the inclusion criteria (to have a baseline electrocardiogram near the moment of the arrhythmic event or device implantation, without the use of antiarrhythmic drugs), and consisted of 46 patients, 34 men (73.9%), aged between 40 and 70 years.

Two groups were formed. Group A consisted of 27 patients with at least one episode of MVA after implantation of the device, and group B, consisting of 19 subjects without recurrence.

The first episode of MVA after implantation of the device was defined as relapse. To be included in the group B, it was necessary two or more years of follow-up without MVA.

Measurements were averaged over three consecutive heartbeats in each lead, manually, by two independent observers. The results were compared, and the greatest value was considered valid. If the differences were greater than 20 ms, one was chosen by mutual agreement, or a third expert was consulted.

The following concepts were used:
- Prolonged QTc: greater than 460 ms
- Abnormal QT interval dispersion (QTd): greater
than 65 ms
- Prolonged Tpeak-Tend interval (Tp-Te): equal to or greater than 100 ms
- Abnormal Tp-Te interval dispersion (Tp-Ted): greater than 20 ms.

The mean, standard deviation and percentage were calculated for comparison of the descriptive summary measures. Pearson’s chi-square test for qualitative variables was used for determining the association of variables, and t-test was used to compare the means between groups. Survival of patients was assessed according to the values of Tp-Te, by analyzing the Kaplan-Meier curve$^3$.

RESULTS
Age and sex were distributed similarly in both groups (Table 1). Structural heart disease (66.7 %) predominated in patients with recurrences, including dilated cardiomyopathy (37%). Primary electrical disease predominated in group B (57.8 %).

Qualitative electrocardiographic parameters (QRS fragmentation, bimodal T wave and early repolarization pattern) were distributed similarly in both groups, although fragmentation of QRS (f-QRS) was slightly predominant in group A (Table 2).

Quantitative electrocardiographic variables are shown in Table 3. There were statistically significant differences in the mean values of QT, QTc and Tp-Te between the groups. It was not so with the other values; which showed a similar behavior (QTd, Tp-Ted and QRS duration).

QRS duration in patients with recurrences, who had electrical storms, showed significantly prolonged mean values ($128.3 \pm 38.6$ ms), compared with the group without recurrence ($105.7 \pm 17.7$ ms), $p = 0.045$.

<table>
<thead>
<tr>
<th>Group</th>
<th>Diagnosis</th>
<th>Nº</th>
<th>Sex</th>
<th>Age (Years)</th>
<th>Follow-up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP A</td>
<td>With recurrences</td>
<td>Dilated cardiomyopathy</td>
<td>10</td>
<td>2 8</td>
<td>50,3</td>
</tr>
<tr>
<td></td>
<td>Primary electrical disease</td>
<td>9</td>
<td>2 7</td>
<td>41,6</td>
<td>11,9</td>
</tr>
<tr>
<td></td>
<td>Ischemic heart disease</td>
<td>7</td>
<td>1 6</td>
<td>66,2</td>
<td>7,1</td>
</tr>
<tr>
<td></td>
<td>Ebstein’s disease</td>
<td>1</td>
<td>1 0</td>
<td>19,0</td>
<td>5,0</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>27</td>
<td>6 21</td>
<td>52,2</td>
<td>6,9</td>
</tr>
<tr>
<td>GROUP B</td>
<td>Without recurrences</td>
<td>Dilated cardiomyopathy</td>
<td>1</td>
<td>0 1</td>
<td>53,0</td>
</tr>
<tr>
<td></td>
<td>Primary electrical disease</td>
<td>11</td>
<td>4 7</td>
<td>40,0</td>
<td>50,7</td>
</tr>
<tr>
<td></td>
<td>Ischemic heart disease</td>
<td>4</td>
<td>0 4</td>
<td>66,0</td>
<td>45,0</td>
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<tr>
<td></td>
<td>Hypertrophic cardiomyopathy</td>
<td>1</td>
<td>0 1</td>
<td>60,5</td>
<td>65,0</td>
</tr>
<tr>
<td></td>
<td>Mitral valve replacement</td>
<td>2</td>
<td>2 0</td>
<td>50,0</td>
<td>29,0</td>
</tr>
<tr>
<td></td>
<td>Subtotal</td>
<td>19</td>
<td>6 13</td>
<td>50,0</td>
<td>49,1</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>46</td>
<td>12 34</td>
<td>51,3</td>
<td>50,7</td>
</tr>
</tbody>
</table>

Table 2. Fragmentation of QRS and bimodal morphology of the T wave.

<table>
<thead>
<tr>
<th>Signal</th>
<th>With recurrences (A)</th>
<th>Without recurrences (B)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nº</td>
<td>%</td>
<td>Nº</td>
</tr>
<tr>
<td>f-QRS</td>
<td>10</td>
<td>37.0</td>
<td>17</td>
</tr>
<tr>
<td>Bimodal T wave</td>
<td>8</td>
<td>29.6</td>
<td>19</td>
</tr>
</tbody>
</table>
| f-QRS: fragmentation of QRS
Table 3. Distribution of quantitative variables.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (ms)</th>
<th>SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>Recurrences</td>
<td>428.14</td>
<td>42.70</td>
</tr>
<tr>
<td></td>
<td>No recurrences</td>
<td>390.52</td>
<td>40.75</td>
</tr>
<tr>
<td>QTc</td>
<td>Recurrences</td>
<td>476.29</td>
<td>54.15</td>
</tr>
<tr>
<td></td>
<td>No recurrences</td>
<td>436.42</td>
<td>43.24</td>
</tr>
<tr>
<td>QTd</td>
<td>Recurrences</td>
<td>51.11</td>
<td>22.41</td>
</tr>
<tr>
<td></td>
<td>No recurrences</td>
<td>48.42</td>
<td>27.74</td>
</tr>
<tr>
<td>Tp-e</td>
<td>Recurrences</td>
<td>108.88</td>
<td>27.36</td>
</tr>
<tr>
<td></td>
<td>No recurrences</td>
<td>87.36</td>
<td>20.23</td>
</tr>
<tr>
<td>Tp-Ted</td>
<td>Recurrences</td>
<td>35.55</td>
<td>16.94</td>
</tr>
<tr>
<td></td>
<td>No recurrences</td>
<td>27.36</td>
<td>17.99</td>
</tr>
<tr>
<td>QRS</td>
<td>Recurrences</td>
<td>121.11</td>
<td>35.76</td>
</tr>
<tr>
<td></td>
<td>No recurrences</td>
<td>125.26</td>
<td>68.18</td>
</tr>
</tbody>
</table>

SD: Standard deviation  
QTc: corrected QT interval  
QTd: QT interval dispersion  
Tp-e: Tpeak-Tend interval  
Tp-Ted: Tpeak-Tend interval dispersion  
ms: milliseconds

In this study, 58.7% of patients had recurrences, a high figure compared to another study at the same hospital (115 ICD recipients with 31.3% MVA recurrence). Another study showed a 74.6% recurrence in 67 patients who were resuscitated from sudden cardiac death (SCD), without demonstrable structural abnormality. Some international studies on ICD recipients report recurrences between 50 and 70% in the first two years. Its frequency is a reality and a problem to be resolved.

It is striking the early appearance of recurrences, as all of them occurred in the first year of follow-up, and 37% during the first three months. This could be explained because, in general, after implantation, antiarrhythmics are suspended, and only later, if necessary, they are administered again. Issues that are inherent in the devise have also been described.

The f-QRS did not show a statistically significant difference between the two groups, (it was found in both, in 1 of the 8 patients with Brugada syndrome). Morita et al., in 115 subjects with that channelopathy, found f-QRS in 43%, with the highest incidence in those with a history of ventricular fibrillation. This marker prevailed in patients diagnosed with ischemic dilated and non-dilated cardiomyopathy, as it has been described in the literature.

There was no difference between the two groups with regard to the presence of bimodal T wave, this parameter has been described in patients with long QT syndrome (LQTS). It was found in 2 out of 5 patients with this disease, and in 6 patients with structural heart disease.

The early repolarization pattern in inferolateral leads has been described as a predictor of MVA by other authors; however, it was not detected in this series.

The mean values of QT were within normal limits in both groups, with significant differences between those who had recurrences and those who did not have them (Table 3). The mean values of QTc (Bazett) were slightly prolonged in group A and showed significant differences with group B.

Prolongation of the QT interval is associated with an increased risk of MVA and SCD in various clinical conditions including congenital and acquired LQTS, myocardial infarction, hypertrophic cardiomyopathy, hypertension, patients who underwent surgery for tetralogy of Fallot, ventricular dysfunctions, and even in apparently healthy subjects. The MADIT II study found an association between QT prolongation and the occurrence of spontaneous ventricular tachycardia and fibrillation. Other studies have argued that the abnormal QT prolongation is an independent predictor of arrhythmic death in postinfarction patients.

The QT dispersion values above 60 ms are considered a prolonged dispersion and risk markers for SCD due to MVA. The average values of this series were normal in both groups, without significant differences. This may be justified by the variability of the parameters reflecting the dispersion of repolarization in a single patient at different times. If several baseline electrocardiograms had been measured in each one, maybe higher numbers would have been found.

The mean values of Tp-Te interval showed significant differences between groups A and B (Table 3). The Tp-Te interval reflects the transmural dispersion of repolarization and the consequent risk of MVA. This parameter has been studied as a predictor of malignant ventricular tachyarrhythmias in patients with Brugada syndrome, congenital and acquired LQTS, hypertrophic cardiomyopathy and ischemic heart disease.
In this study, 100 ms was used as the cutoff value of the Tp-Te interval\(^2\). Survival analysis (Kaplan-Meier) showed a statistically significant difference between the curves of patients with Tp-Te interval ≥ 100 ms and those with lower values. Most patients with equal or greater values had a “lower survival”, that is, they received shocks because of MVA. Most subjects with Tp-Te interval less than 100 ms did not require this type of therapy (Figure 1).

There were no statistically significant differences between the dispersion of the Tp-Te interval in the recurrence group and the no recurrence group; however, the mean values of both groups were above 27 ms. The dispersion of Tp-Te interval reflects changes in transmural repolarization and is a parameter that has been little studied. Castro et al\(^2\) demonstrated, in patients with Brugada syndrome, that a cutoff point higher than 20 ms was predictive of recurrence. Our sample included high-risk patients (secondary prevention of SCD), which justifies the presence of high values in both groups.

The mean QRS duration was 121 ms in group A and 105 ms in group B, with no statistical difference. However, it differentiated significantly the electrical storm subgroup (mean values above 120 ms) from those who did not have recurrences, reflecting an abnormal transmural activation. Several studies in subjects with and without structural heart disease have noted the role of QRS prolongation as a marker for risk of SCD\(^29,31\).

MVA recurrences in patients with ICD are very common. Risk stratification is extremely difficult: the signals that have been described lack absolute accuracy in terms of sensitivity and specificity; its variability is common; the actual boundary between “innocent” and arrhythmogenic findings is not known; the analysis of electrical sequences would be necessary. In addition, there is the fundamental fact of the great complexity of arrhythmic events.

In this research, quantitative electrocardiographic signals, such as QT, QTc and Tp-Te intervals, identified a subgroup of patients with ICD who were at very high risk of recurrence of MVA, allowing an appropriate course of action: a more aggressive treatment of the underlying disease, selection of the antiarrhythmic drug, device reprogramming and closer monitoring.

CONCLUSIONS
The QT, QTc and Tp-Te intervals are electrocardiographic predictors of the recurrence of MVA in patients with implantable cardioverter-defibrillators.

REFERENCES