Long-Term Follow-Up of Individuals With the Electrocardiographic Pattern of Right Bundle-Branch Block and ST-Segment Elevation in Precordial Leads V1 to V3

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Background—The electrocardiographic pattern of right bundle-branch block with ST-segment elevation in leads V1 to V3 is increasingly recognized among patients who have aborted sudden cardiac death, but also in asymptomatic individuals, raising questions about its prognostic significance.

Methods and Results—The clinical, electrophysiological, and follow-up data of 334 patients with the Brugada phenotype were analyzed. A total of 79 women and 255 men with a mean age at diagnosis of 42±16 years were studied. The abnormal ECG was recognized after a resuscitated cardiac arrest in 71 patients (group A), after a syncopal episode in 73 patients (group B), and in 190 asymptomatic individuals (group C). Sustained ventricular arrhythmias were inducible in 83%, 63%, and 33% of patients in group A, group B, and group C, respectively. During 54±54 and 26±36 months of follow-up, respectively, 62% of patients in group A and 19% of group B patients had a new arrhythmic event. Inducibility of ventricular arrhythmias was the only predictor of arrhythmia occurrence in both groups. During a mean follow-up of 27±29 months, 8% of group C individuals had a first arrhythmic event. In these individuals, inducibility of ventricular arrhythmias and a basal abnormal ECG were predictors of arrhythmia occurrence.

Conclusions—An ECG showing right bundle-branch block and ST-segment elevation in the right precordial leads is a marker of malignant ventricular arrhythmias and sudden death. Recurrence of malignant arrhythmias is high after the occurrence of symptoms. Among asymptomatic individuals, those with a spontaneously abnormal ECG and inducible to ventricular arrhythmias have the poorer prognosis. (Circulation. 2002;105:73-78.)

Key Words: death, sudden ■ syncope ■ electrocardiography

The existence of a subgroup of patients with aborted sudden death without demonstrable structural heart disease has long been recognized.1 Because the causes of the ventricular fibrillation are unclear in this group, a diagnosis of “idiopathic” ventricular fibrillation is usually made. Further investigations have shown that diagnostic subgroups could be identified having specific diseases. These disorders include the long-QT syndrome,2 arrhythmogenic right ventricular dysplasia,3 and patients with an abnormal electrocardiographic pattern of right bundle-branch block and ST-segment elevation in the right precordial leads, compatible with the diagnosis of Brugada syndrome4–7 (Figure 1). Brugada syndrome may be difficult to identify because the electrocardiographic manifestations can be intermittent and related to many influences including body temperature, adrenergic and vagal tone, and almost any known drug affecting ion channel function either directly or indirectly.8–11

Increased recognition of the Brugada electrocardiographic pattern, particularly in asymptomatic individuals and relatives of patients with the disease, has led to major questions and concerns about the prognostic value and significance of this electrocardiographic phenotype. We present long-term follow-up data on the prognostic value of clinical and electrocardiographic variables in individuals with an ECG compatible with Brugada syndrome.

Methods

Data on 334 individuals with an ECG compatible with Brugada syndrome and no demonstrable structural heart disease were analyzed. The data are available thanks to the collaboration of many centers and physicians around the world (Appendix). The ECG was defined as abnormal if a terminal r wave, with a J-point elevation of at least 0.2 mV, with a slowly descending ST segment in continuation with a flat or negative T wave (coved-type ECG) appeared spontaneously in leads V1 to V3 (Figure 1). The ECG was...
also defined as abnormal when the described electrocardiographic abnormalities became evident after the intravenous administration of an antiarrhythmic drug with potent sodium channel–blocking properties (ajmaline, flecainide, or procainamide). Structural heart disease was excluded by clinical history, noninvasive (echocardiogram, stress test, nuclear magnetic resonance), and invasive methods (coronary angiography, left and right ventriculography, and biopsy) used at the discretion of the treating physician. Individuals with diseases known to mimic the abnormal ECG of Brugada syndrome such as hypothermia, pericarditis, myocarditis, or acute ischemic events were excluded.

Three groups were classified according to the circumstances under which the abnormal ECG was documented. The diagnosis was made either after an episode of aborted cardiac arrest (group A), during study of syncopal episodes of unknown origin (group B), or during routine examination or as a consequence of family screening after the diagnosis of Brugada syndrome was made in a family member (group C).

Antiarrhythmic drug provocation was used to unmask the electrocardiographic abnormalities in patients with a normal or a "saddle-type" ECG and no demonstrable structural heart disease with one of the following presentations: 1, resuscitated from cardiac arrest; 2, after syncopal episodes of unknown origin; 3, family member of individual diagnosed with Brugada syndrome as part of diagnostic screening; and 4, asymptomatic individual with a "saddle-type" ECG during routine screening. Intravenous antiarrhythmic agents used included ajmaline (1 mg/kg body wt over 5 minutes), flecainide (2 mg/kg body wt over 10 minutes), or procainamide (10 mg/kg body wt over 10 minutes). The test was considered positive if the abnormal electrocardiographic pattern appeared during drug administration. An example of a positive test is shown in Figure 2.

Electrophysiological testing was performed in the fasting state, after written informed consent was obtained and under no or mild sedation. Electrophysiological study included basal measurements of conduction intervals and programmed ventricular stimulation. The protocol recommended used a single site of stimulation (right ventricular apex), three basic pacing cycle lengths (600, 500, and 430 ms), and induction of 1, 2, and 3 ventricular premature beats down to a minimum of 200 ms. A patient was considered inducible if sustained ventricular arrhythmias (ventricular fibrillation, polymorphic ventricular tachycardia, or monomorphic ventricular tachycardia lasting more than 30 seconds or requiring emergency intervention) were induced.

Patients were treated according to their clinical presentation. At the time this study started, no clear recommendations existed. However, common strategies were applied in all centers. Patients with a positive ECG and episodes of syncope or with aborted sudden cardiac death were recommended to receive an implantable cardioverter-defibrillator. Asymptomatic individuals with a positive ECG and a family history of sudden death related to the syndrome and/or inducible during electrophysiological testing were also recommended for an implantable defibrillator.

During follow-up, patients were considered to have an arrhythmic event if sudden death occurred or ventricular fibrillation was documented.

Statistical Analysis

Data were analyzed with the SPSS package for paired and unpaired data and for survival curves. Fisher’s exact test or the χ² test was used for categorical variables. An ANOVA test was used for comparisons of continuous variables among the different groups. Survival curves were plotted by use of the Kaplan-Meier method and analyzed by the log-rank test. A value of P<0.05 was considered statistically significant. Where applicable, data are presented as mean±1 SD.

Results

A total of 334 patients with the abnormal ECG were identified, 71 in group A (aborted sudden death), 73 in group B.
Arrhythmic Events During Follow-Up

Follow-Up

The mean follow-up time for the entire population was 33±39 months. Follow-up time was significantly longer in patients with aborted sudden cardiac death (54±54 months) as compared with patients with syncope (26±36 months) and asymptomatic individuals (27±29 months) (P=0.0001). This difference is explained by the fact that patients identified early in our experience were all survivors of a cardiac arrest.

Arrhythmic Events During Follow-Up

During follow-up, 44 of the 71 patients (62%) identified after an episode of aborted sudden cardiac death had a new arrhythmic event (sudden cardiac death in 4 patients and documented ventricular fibrillation in 40 patients). In patients identified after a syncopal episode, 14 of 73 patients (19%) had a new arrhythmic event (sudden cardiac death in 5 patients and documented ventricular fibrillation in 9 patients). In asymptomatic patients, 16 of 190 patients (8%) had a first arrhythmic event (sudden death in 7 patients and documented ventricular fibrillation in 9 patients). The difference in outcome in the three groups was statistically significant (P=0.00001) (Figure 3).

Analysis of clinical variables showed that the sex, a family history of sudden death, an abnormal ECG only after class I antiarrhythmic drug challenge, and the type of treatment were not predictors of the outcome in symptomatic patients. However, inducibility of ventricular arrhythmias during the electrophysiological study was a predictor of arrhythmia recurrence both in patients with aborted sudden cardiac death and in syncope patients (P=0.001 and P=0.03, respectively).

In asymptomatic individuals, the presence of an abnormal ECG without provocation (without class I antiarrhythmic drug challenge) (P=0.001) and inducibility of sustained arrhythmias during electrophysiological testing (P=0.007) were predictors of occurrence of arrhythmic events during follow-up (Table 4). Female sex showed a trend toward a better outcome but without reaching statistical significance (P=0.06). A family history of unexplained sudden cardiac death was not predictive of arrhythmia occurrence (P=0.57).

Discussion

This is the first study that includes a sufficiently large number of symptomatic and asymptomatic individuals with an electrocardiographic pattern diagnostic of Brugada syndrome to allow conclusions as to the prognostic value of such an ECG.

Symptomatic Patients

Our data confirm the generally accepted view that symptomatic patients with this syndrome have an unacceptably high rate of arrhythmic events (Figure 3). Because no effective antiarrhythmic drug or other therapies are available, implantation of a cardioverter-defibrillator appears to be mandatory in these patients. Better understanding of the genetic basis and electrophysiological mechanisms of the disease may

### TABLE 1. Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Aborted Sudden Death</th>
<th>Syncope</th>
<th>Asymptomatic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>71</td>
<td>73</td>
<td>190</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>61/10</td>
<td>59/14</td>
<td>135/55</td>
<td>0.007</td>
</tr>
<tr>
<td>Age, y</td>
<td>41±16</td>
<td>47±14</td>
<td>40±16</td>
<td>0.03</td>
</tr>
<tr>
<td>Basal abnormal ECG</td>
<td>61 (84%)</td>
<td>62 (85%)</td>
<td>111 (58%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>23 (38%)</td>
<td>26 (39%)</td>
<td>131 (72%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SCD indicates sudden cardiac death.

### TABLE 2. Results of Electrophysiological Testing

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Aborted Sudden Death</th>
<th>Syncope</th>
<th>Asymptomatic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducible, yes/no (%)</td>
<td>44/10 (83%)</td>
<td>41/21 (68%)</td>
<td>45/91 (33%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>No. of extrastimuli, 1/2/3</td>
<td>1/31/12</td>
<td>7/22/12</td>
<td>2/26/17</td>
<td>NS</td>
</tr>
</tbody>
</table>
TABLE 3. Treatment

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Aborted Sudden Death</th>
<th>Syncope</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>44</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quinidine</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ICD + β-blocker</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ICD + amiodarone</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ICD + quinidine</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No treatment</td>
<td>8</td>
<td>25</td>
<td>141</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator.

make other therapies possible in the future. Recurrent arrhythmic events were more frequent in patients with aborted sudden death as the presenting symptom as compared with patients with repetitive syncope episodes. This could suggest a more severe disease in the former group with more frequent and longer-lasting arrhythmias. However, a word of caution is in order because the mean follow-up period of patients with aborted sudden death was significantly longer than the mean follow-up of patients with syncope episodes. For both categories of symptomatic patients, the recurrence rates approximate a mean of 11% per mean follow-up year (8.8% per year in syncope patients and 13.7% per year in patients with aborted sudden cardiac death) and are unacceptably high. The gravity of the problem is amplified when one considers the mean age of the patients.

Asymptomatic Individuals

The major concern at present is with the group of individuals displaying an ECG compatible with the diagnosis of Brugada syndrome but who are asymptomatic. The initial diagnosis in these individuals was made by different means: In some individuals, a spontaneously abnormal ECG was recorded as part of a routine screening, for instance, before surgery. In other individuals, the abnormal ECG was obtained because of a family history of sudden death. In some, the abnormal ECG appeared only during treatment with antiarrhythmic drugs given for the treatment of atrial fibrillation or other arrhythmias. Finally, in still others, the abnormal ECG was obtained only after pharmacological challenge performed because of the suspicion or documentation of Brugada syndrome in the family. The data presented here allow important conclusions in terms of the treatment of these asymptomatic individuals.

First, we confirm that a spontaneously abnormal ECG is a marker of possible sudden arrhythmic death: 16 of 111 (14%) asymptomatic individuals with a spontaneously abnormal ECG had an arrhythmic event during a mean follow-up period of only 27±29 months. The arrhythmic event occurred within 1 year of diagnosis in 7 individuals, within 2 years in another 3 patients, but after more than 4 years in the remaining 6 individuals. The longest time interval between diagnosis and first arrhythmic event was 10 years. These data demonstrate that a mean follow-up time of slightly more than 2 years underestimates the total number of events that can occur in this population. Asymptomatic individuals with a spontaneously abnormal ECG should undergo electrophysiological investigation. If a sustained arrhythmia is induced, an implantable cardioverter-defibrillator should be recommended. Only 1 (0.9%) event occurred in a noninducible patient with a spontaneously abnormal ECG. Because of the possible side effects and complications of the implantable cardioverter-defibrillator, it does not seem justified to give such a device to asymptomatic noninducible individuals with a spontaneously abnormal ECG. However, this recommendation may change in the future if a longer follow-up shows more events in this group.

Second, our data allow recognition of groups of asymptomatic individuals with a good prognosis. Previous publications failed to show a prognostic value of programmed electrical stimulation either because of a small number of patients or a short follow-up and lack of events. From our data it is clear that lack of inducibility in asymptomatic individuals is so far reassuring (negative predictive value of 99%). Not only programmed electrical stimulation can be used for risk stratification. The group of asymptomatic individuals in whom the abnormal ECG was recognized only after pharmacological challenge had no events during follow-up. This observation has important implications for the treatment of individuals who are members of a family with Brugada syndrome. When the individual is asymptomatic and the ECG is normal, the unmasking of the abnormal ECG with a drug identifies a carrier of the disease. However, because no events occurred in this group, it is not justified at present to recommend further investigations in terms of treatment.

Pharmacological Challenge

With the foregoing observations, one can ask: What is the value of pharmacological challenge? The major value of this test is its ability to confirm the disease in individuals or patients with a suspicious but not diagnostic ECG. Recent studies in the general healthy population suggest that an ECG compatible with Brugada syndrome can be seen in up to 6 per 1000 normal individuals. However, two different electrocardiographic patterns have been included in these studies: the “coved-type” ECG (Figure 1) and the “saddle-like” ECG (first panel of Figure 2). We would not diagnose Brugada syndrome in an individual with a “saddle-like” ECG without inducing a “coved-type” electrocardiographic pattern with...
pharmacological challenge. All symptomatic and asymptomatic individuals included in the present study had a spontaneous or drug-induced “coved-type.” These data support the thesis that this is a disease with a wide spectrum, ranging from a relatively good prognosis for asymptomatic individuals with an abnormal ECG only after the administration of class I antiarrhythmic drugs to a poor prognosis for patients with aborted sudden cardiac death. Between the two extremes are the asymptomatic individual with a spontaneously abnormal ECG and the group of patients with syncopal episodes. It remains to be defined whether this prognosis is the result of genetic background or causative mutations. This information will only become available when genetic analysis is routinely applicable to the majority of patients with the disease.

In conclusion, symptomatic individuals with Brugada syndrome have an extremely high recurrence rate of arrhythmic events. Asymptomatic individuals with a spontaneously abnormal ECG frequently become symptomatic, particularly when inducible during electrophysiological testing. In the absence of other therapeutic alternatives, these patients require protection against sudden death through implantation of a cardioverter-defibrillator.

Appendix 1

Physicians and Centers

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References
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