Determinants of Sudden Cardiac Death in Individuals With the Electrocardiographic Pattern of Brugada Syndrome and No Previous Cardiac Arrest

Josep Brugada, MD, PhD; Ramon Brugada, MD; Pedro Brugada, MD, PhD

Background—Patients with Brugada syndrome who were resuscitated from an episode of ventricular fibrillation are at high risk for recurrent sudden death. There is general agreement about the therapeutic strategy for these patients. Conversely, the prognosis and approach in patients with a diagnostic ECG but without a previous history of sudden cardiac death is controversial. We analyzed a large cohort of patients with Brugada syndrome without previous cardiac arrest to understand the determinants of prognosis.

Methods and Results—A total of 547 patients with an ECG diagnostic of Brugada syndrome and no previous cardiac arrest were studied. The mean age was 41 ± 15 years, and 408 were male. The diagnostic ECG was present spontaneously in 391 patients. In the remaining 156 individuals, the abnormal ECG was noted only after the administration of an antiarrhythmic drug. One hundred twenty-four patients had suffered from at least 1 episode of syncope. During programmed ventricular stimulation, a sustained ventricular arrhythmia was induced in 163 of 408 patients. During a mean follow-up of 24 ± 32 months, 45 patients (8%) suffered sudden death or documented ventricular fibrillation. Multivariate analysis identified the inducibility of a sustained ventricular arrhythmia (P < 0.0001) and a history of syncope (P < 0.01) as predictors of events. Logistic regression analysis showed that a patient with a spontaneously abnormal ECG, a previous history of syncope, and inducible sustained ventricular arrhythmias had a probability of 27.2% of suffering an event during follow-up.

Conclusions—Individuals with Brugada syndrome and no previous cardiac arrest have a high risk of sudden death. Inducibility of ventricular arrhythmias and a previous history of syncope are markers of a poor prognosis. (Circulation. 2003;108:3092-3096.)

Key Words: fibrillation ■ sudden death ■ electrocardiography ■ arrhythmia ■ genetics

Patients with an ECG compatible with the diagnosis of Brugada syndrome1 who have been resuscitated from near sudden arrhythmic death have a high risk of recurrent ventricular fibrillation.1-3 In these patients, there is general agreement that implantation of an automated cardioverter-defibrillator (ICD) is mandatory.4-6 Controversy exists, however, on the best therapeutic approach in individuals with a diagnostic ECG but without a previous history of sudden cardiac death.6-9 We prospectively analyzed the prognostic value of clinical and ECG variables in individuals with an ECG compatible with Brugada syndrome and no previous history of cardiac arrest.

Methods

Data on 547 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). None of the patients had suffered a sudden cardiac death before the diagnosis of Brugada syndrome was made on the basis of the ECG. Following recently proposed criteria,10 the ECG was defined as diagnostic if a terminal r’ wave, with a J-point elevation of ≥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 ECG abnormalities became evident after the intravenous administration of an antiarrhythmic drug with potent sodium-channel blocking properties, such as ajmaline, flecainide, or procainamide.11

Structural heart disease was excluded by clinical history, noninvasive methods (echocardiogram, stress test, nuclear magnetic resonance), and invasive methods (coronary angiography, left and right ventriculography, and myocardial biopsies) used at the discretion of the treating physician.

The abnormal ECG was identified during the investigation of syncope of unknown origin in 124 patients, during routine ECG screening in 170 individuals and during study of family members of patients with the syndrome in 253 individuals.

Electrophysiological study included basal measurements of conduction intervals and programmed ventricular stimulation. The protocol recommended used a single site of stimulation (right ventricular apex), 3 basic pacing cycles (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 a sustained ventricular arrhythmia (ventricular fibrillation, polymorphic ventricular tachycardia, or monomorphic ventricular tachycardia lasting ≥30 seconds or requiring emergency intervention) was induced.

Statistical Analysis
Data were analyzed by use of the STATA Statistical Software (StataCorp., 1999, 7.0). The Fisher exact test or the χ² test was used for categorical variables. One-way ANOVA was used for comparisons of continuous variables among the different groups. Survival curves were plotted by the Kaplan-Meier method and analyzed by the log-rank test. Cox regression models were used to analyze factors associated with occurrence of events. The variables that were significant were used in a logistic regression model to predict the probability of having an event. A probability value of P<0.05 was considered statistically significant. Where applicable, data are presented as mean±SD.

Results
A total of 547 patients with the abnormal ECG were studied. Age at diagnosis (first abnormal ECG documented) was 41±15 years (2 to 85 years). A predominance of male patients was observed (408 male versus 139 female). In 302 individuals, a family history of sudden cardiac death was present. The ECG was spontaneously abnormal in 391 cases and abnormal only after the administration of a class I antiarrhythmic drug in 156. During electrophysiological testing, a sustained ventricular arrhythmia was induced in 163 of 408 individuals who underwent the study (162 ventricular fibrillation, 1 ventricular flutter). A total of 177 patients received an ICD: 138 inducible patients and 39 noninducible but with a family history of sudden death (15 patients), a previous history of syncope (10 patients), or both (14 patients). Demographic characteristics and results of the electrophysiological testing are shown in Table 1.

Follow-Up
The individuals were followed up prospectively for a mean of 24±33 months (range, 1 to 160 months) after the diagnostic ECG was recognized.

In 45 of the 547 individuals (8.2%), sudden cardiac death (16 patients) or ventricular fibrillation (29 patients) occurred during the follow-up period (Figure 2). By univariate analysis, inducibility of a sustained ventricular arrhythmia, a previous episode of syncope, a spontaneously abnormal ECG,
and male sex were predictors of events (Table 2). Multivariable analysis identified inducibility of a sustained ventricular arrhythmia and a history of syncope as predictors of sudden death or ventricular fibrillation (Table 2). Figure 3 shows the Kaplan-Meier curves of arrhythmic events during follow-up depending on the presence of a previous history of syncope and inducibility of arrhythmias during electrophysiological study.

By logistic regression analysis of these 2 variables and the presence or absence of a spontaneously abnormal ECG, 8 groups were identified with a risk of sudden death or documented ventricular fibrillation during follow-up varying from 0.5% to 27.2% (Table 3). The lowest-risk group is an individual with an ECG diagnostic of Brugada syndrome seen only after drug administration who is not inducible during programmed ventricular stimulation and who has no previous syncope. The highest-risk group included individuals with a spontaneously abnormal ECG who are inducible during programmed ventricular stimulation and have suffered at least 1 syncopal episode. The other risk categories are shown in Table 3.

### Discussion

This study includes a sufficiently large number of individuals with an ECG pattern diagnostic of Brugada syndrome and no previous sudden cardiac death to allow analysis of the prognostic value of clinical, ECG, and electrophysiological variables.

How the diagnosis was made in this population varied. In some individuals, a spontaneously abnormal ECG was recorded as part of a routine screening, for instance, before surgery or to obtain a license for competitive sports. In others, it was observed after an episode of syncope of unknown origin. In still others, the abnormal ECG was observed because of a family history of sudden death or Brugada

### Table 2. Probability of Sudden Death or Ventricular Fibrillation During Follow-Up Depending on Clinical and Electrophysiological Variables

<table>
<thead>
<tr>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>Inducible</td>
<td>8.33</td>
</tr>
<tr>
<td>Noninducible</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>2.79</td>
</tr>
<tr>
<td>No syncope</td>
<td>1</td>
</tr>
<tr>
<td>Basal ECG</td>
<td>7.69</td>
</tr>
<tr>
<td>AAD ECG</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>5.26</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Family history</td>
<td>1.29</td>
</tr>
<tr>
<td>No family history</td>
<td>1</td>
</tr>
</tbody>
</table>

Basal ECG indicates spontaneously abnormal ECG; AAD ECG, abnormal ECG only after antiarrhythmic drug administration.

### Table 3. Logistic Regression Analysis: Probability of Events (Sudden Death or Documented Ventricular Fibrillation) During Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Noninducible, % (CI)</th>
<th>Inducible, % (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously abnormal ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>4.1 (1.4–11.7)</td>
<td>27.2 (17.3–40.0)</td>
</tr>
<tr>
<td>No syncope</td>
<td>1.8 (0.6–5.1)</td>
<td>14.0 (8.1–23.0)</td>
</tr>
<tr>
<td>ECG abnormal only after antiarrhythmic drug challenge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>1.2 (0.2–6.6)</td>
<td>9.7 (2.3–33.1)</td>
</tr>
<tr>
<td>No syncope</td>
<td>0.5 (0.1–2.7)</td>
<td>4.5 (1.0–17.1)</td>
</tr>
</tbody>
</table>

Figure 3. Kaplan-Meier analysis of arrhythmic events (sudden cardiac death [SD] or documented ventricular fibrillation [VF]) during follow-up depending on presence or absence or a history of syncope (A) and on inducibility of sustained ventricular arrhythmias during electrophysiological study (B).
syndrome. In this last case, the abnormal ECG appeared in some individuals only during the administration of a sodium channel blocker to identify carriers of the disease within the family. Finally, in some individuals, the diagnostic ECG was seen during treatment with antiarrhythmic drugs given against atrial fibrillation or other cardiac arrhythmias.

The strongest predictor of outcome in patients with an ECG diagnostic of Brugada syndrome and no previous cardiac arrest is inducibility during programmed ventricular stimulation. Inducible individuals have a 6 times higher risk of suffering sudden death or ventricular fibrillation during the subsequent 2 years compared with noninducible individuals. The next best predictor was a previous history of syncope. Patients with a previous history of syncope have a 2.5 times higher risk than asymptomatic patients. Factors identified by univariate analysis, which were no longer predictive by multivariate analysis, included a spontaneously abnormal ECG and male sex. However, it has to be stressed that the prognostic value of programmed ventricular stimulation was highest in the group with no symptoms at all, i.e., without a previous history of syncope. Noninducible patients with a previous history of syncope still had an unacceptably high risk of (aborted) sudden arrhythmic death during the follow-up.

The implications of these observations can be very relevant for the daily management of individuals with Brugada syndrome and no previous cardiac arrest, as follows.

Individuals with a Brugada ECG and a previous history of syncope have a high risk for sudden death (27.2% in inducible patients but still 4.1% in noninducible patients at 2 years of follow-up with an upper 95% CI of 11.7%). Patients with a previous history of syncpe probably do not require programmed ventricular stimulation for risk stratification. Implantation of a defibrillator in these patients seems to be as mandatory as it is in patients with resuscitated sudden arrhythmic death until other effective therapeutic alternatives become available.

Programmed ventricular stimulation should be performed in asymptomatic individuals to stratify the risk. Those inducible during programmed ventricular stimulation should undergo implantation of a defibrillator. Noninducible individuals should be followed up carefully and made aware of the risks of fever, antiarrhythmic drugs, and other possible triggers of ventricular arrhythmias in Brugada syndrome.

Limitations of the Study
The principal limitation in this study is the way in which patients were selected for drug challenge or electrophysiological study determined in part by physician expertise and biases. This may have affected the outcome of the study.

A second important limitation is the mean follow-up of only 24 months, which is too short a period to allow for definitive conclusions about the management of patients with Brugada syndrome. It is quite conceivable that in some groups of patients, prognosis might worsen as follow-up prolongs. Only with large numbers of patients and long-term follow-up can one meaningfully ascertain the magnitude of the risk and, in turn, determine whether the level of risk in noninducible patients is sufficiently low as to justify not implanting an ICD.

Finally, the use of the information collected from the electrograms stored in the ICD might cause some overestimation of the risk of sudden death. This is because of (1) the difficult differentiation between some supraventricular tachycardias and ventricular arrhythmias and (2) the presence of some ventricular arrhythmias that might not cause sudden death because they are either well-tolerated or self-limited. In our study, patients had either sudden death or documented ventricular fibrillation. This significantly diminished the bias: first, because ventricular fibrillation episodes almost never are misdiagnosed as supraventricular, and second, because it can be reasonably assumed that most, if not all, cases of ventricular fibrillation produce subsequent sudden death if not treated.

Conclusions
Individuals with an ECG diagnostic of Brugada syndrome and no previous cardiac arrest have a significant risk (8%) of sudden death during a short-term follow-up period of 2 years. The lowest-risk group can be defined by the absence of syncopal episodes, a diagnostic ECG only after antiarrhythmic drug challenge, and noninducibility during programmed ventricular stimulation (0.5% incidence of events). The highest-risk group is defined by a combination of a previous history of syncpe, a spontaneously abnormal ECG, and inducible sustained arrhythmias during programmed ventricular stimulation (27.2% incidence of events).

Appendix

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