Sodium Channel Blockers Identify Risk for Sudden Death in Patients With ST-Segment Elevation and Right Bundle Branch Block but Structurally Normal Hearts

Ramon Brugada, MD; Josep Brugada, MD; Charles Antzelevitch, PhD; Glenn E. Kirsch, PhD; Domenico Potenza, MD; Jeffrey A. Towbin, MD; Pedro Brugada, MD

Background—A mutation in the cardiac sodium channel gene (SCN5A) has been described in patients with the syndrome of right bundle branch block, ST-segment elevation in leads V1 to V3, and sudden death (Brugada syndrome). These electrocardiographic manifestations are transient in many patients with the syndrome. The present study examined arrhythmic risk in patients with overt and concealed forms of the disease and the effectiveness of sodium channel blockers to unmask the syndrome and, thus, identify patients at risk.

Methods and Results—The effect of intravenous ajmaline (1 mg/kg), procainamide (10 mg/kg), or flecainide (2 mg/kg) on the ECG was studied in 34 patients with the syndrome and transient normalization of the ECG (group A), 11 members of 3 families in whom a SCN5A mutation was associated with the syndrome and 8 members in whom it was not (group B), and 53 control subjects (group C). Ajmaline, procainamide, or flecainide administration resulted in ST-segment elevation and right bundle branch block in all patients in group A and in all 11 patients with the mutation in group B. A similar pattern could not be elicited in the 8 patients in group B who lacked the mutation or in any person in group C. The follow-up period (37±33 months) revealed no differences in the incidence of arrhythmia between the 34 patients in whom the phenotypic manifestation of the syndrome was transient and the 24 patients in whom it was persistent (log-rank, 0.639).

Conclusions—The data demonstrated a similar incidence of potentially lethal arrhythmias in patients displaying transient versus persistent ST-segment elevation and right bundle branch block, as well as the effectiveness of sodium channel blockers to unmask the syndrome and, thus, identify patients at risk. (Circulation. 2000;101:510-515.)

Key Words: electrocardiography ■ death, sudden ■ fibrillation ■ antiarrhythmia agents

Approximately 5% of patients who experience sudden death have no demonstrable structural heart disease or other external cause responsible for the episode.1,2 These patients are generally classified as presenting with idiopathic ventricular fibrillation. Patients without demonstrable structural heart disease who have an ECG showing right bundle branch block (RBBB) and ST-segment elevation in leads V1 to V3 are at high risk for sudden death.3-5 The recent demonstration of an association with mutations in SCN5A, the cardiac sodium channel gene, provides further support for the hypothesis that this syndrome is primarily an electrical disease, separate and distinct from previously described arrhythmogenic disorders accompanied by structural changes in the heart.6

The ECG pattern in these patients has been extensively studied; it shows variations over time, including transient normalization. In addition, these ECG patterns are modulated by autonomic and antiarrhythmic interventions.7,8 Normalization of the ECG signature of this syndrome by whatever mechanism may lead to an underestimation of the prevalence of the disease, thus placing some patients at risk. It is, therefore, of some importance to identify whether patients with the concealed versus overt syndrome are at similar risks for arrhythmic events and, if so, to identify an approach to unmask those cases that are concealed. Because genetic anomalies in the cardiac sodium channel are involved in the pathophysiology of this disease,6 we examined the effect of 3 sodium channel blockers representing antiarrhythmia classes IA and IC.

Methods

Patients

Since 1992, we have collected data on 58 symptomatic patients who experienced episodes of sudden cardiac death due to ventricular
fibrillation who did not have demonstrable structural heart disease but did have an ECG pattern of RBBB and ST-segment elevation in leads V1 to V3. Repeated ECG analysis revealed persistent anomalies in 24 of these patients (21 men; mean age, 49±15 years) and transient normalization of the ECG pattern in 34 (31 men; mean age, 42±19 years) (group A).

In 1995, we identified a familial form of the syndrome in which the disease was associated with a mutation in the cardiac sodium channel gene. The case index in the family experienced sudden death at age 23 and displayed the typical ECG pattern. The 13 living individuals of the family were screened. All members had a genotypic test, but 3 refused the intravenous administration of antiarrhythmic drugs. Two family members presented with a RBBB/ST-segment elevation ECG pattern. No other family members displayed an abnormal ECG at baseline. Since then, 2 other families with the syndrome and a mutation in the sodium channel gene have been identified and screened. One consisted of 5 members; 2 of them transiently presented with the typical ECG pattern. The other consisted of 4 members; one had the persistent ECG pattern (group B: 19 total tested, 8 men; mean age, 35±16 years).

We also evaluated the effects of sodium channel blockers in 53 patients without the syndrome (group C). Of them, 8 patients had arrhythmogenic right ventricular dysplasia, (6 men; mean age, 35±12 years), 10 patients had isolated RBBB (8 men; mean age, 43±14 years), and 35 patients had no previous history of syncope, ventricular arrhythmias, or sudden death and did have a normal ECG (30 men; mean age, 37±12 years).

**Drug Administration**

After written informed consent was obtained, a single intravenous dose of one sodium channel blocker was administered to all patients in the 3 groups. Each patient received a single drug. The use of each drug was determined based on the availability of the drug at each center, although the use of ajmaline was encouraged. The patients were studied in the Electrophysiology Laboratory, where continuous ECG recordings were obtained. In 77 patients, 1 mg/kg ajmaline was administered over a 5-minute period. In 14 patients, 2 mg/kg flecainide was administered over a 5-minute period, and in the remaining 15 patients, 10 mg/kg procainamide was infused at a rate of 100 mg/min. The ECG changes during the infusion were considered positive when a terminal R wave and ST-segment elevation (>1 mm) occurred in leads V1 to V3. Each ECG was reviewed blindly by 2 of the authors who did not perform the test.

**Results**

Concordance between the 2 observers was 100% in patients in groups A and B. In 2 patients in group C, a discordance occurred between the 2 observers. These 2 cases were finally considered negative after consulting a third blinded observer (Figure 1). Ajmaline, flecainide, or procainamide tests were positive in all 34 patients in group A. Administration of a sodium channel blocker during transient ECG normalization resulted in an ST-segment elevation/RBBB ECG pattern in all group A patients (Figure 2). In group B, the ajmaline test was positive in 11 patients and negative in 8 patients. Genotype analysis of the family demonstrated that the ajmaline test was positive only in those 11 patients who had the mutation in the cardiac sodium channel gene (Figures 3 through 5). In contrast, sodium blockade was negative in all group C patients, including the 8 with arrhythmogenic right ventricular dysplasia, the 10 with isolated RBBB, and the 35 without a previous history of syncope or sudden death (Figure 3). In patients with a positive test, mean ST-segment elevation in lead V2 was 0.27±0.09 mV (Table). When comparing the effects of different drugs, ajmaline and flecainide tended to produce greater ST-segment elevation than procainamide, but this difference was not statistically significant.

One patient in group A developed spontaneous ventricular fibrillation during the infusion of the drug. Frequent ventricular premature beats were observed during infusion in 5 other patients with a positive test (4 in group A and 1 in group B).

**Follow-Up**

During a mean follow-up of 43±32 months in the 34 patients in group A diagnosed with a transiently concealed syndrome, 12 (35%) experienced recurring arrhythmic events consisting of ventricular fibrillation or sudden death. Among the 24 patients who displayed a persistent RBBB/ST-segment elevation, 5 (21%) experienced recurrent ventricular fibrillation or sudden death during a mean follow-up of 28±34 months (P=0.23). Kaplan-Meier analysis showed no differences in outcome between both groups (log-rank, 0.639) (Figure 6).

**Discussion**

Since the initial description of the syndrome of RBBB, ST-segment elevation in leads V1 to V3, and sudden cardiac death, many patients with it have been identified worldwide. Discovery of a genetic basis associated with an ion channel defect confirms the primarily electrical nature of the disease. Transient normalization and modulation of the ECG pattern by antiarrhythmic drugs has been described. Our results demonstrate that patients with the concealed form of the disease are at a similar risk for ventricular fibrillation and sudden death as those who manifest ST-segment elevation and RBBB persistently. These findings suggest that the
**Figure 2.** Surface ECG from patient with no demonstrable structural heart disease but who experienced ventricular fibrillation. One week after arrhythmic event, ECG showed RBBB and ST-segment elevation in leads V1 through V3 (Basal). One month after arrhythmic event, ECG was normalized (PRE); however, administration of 1 mg/kg IV ajmaline unmasked electrocardiographic abnormalities (POST).

**Figure 3.** Genealogical tree of familial form of syndrome of RBBB and ST-segment elevation in V1 through V3. Filled symbols indicate affected members; open symbols, unaffected members; slashed symbols, uncertain data; NEG, negative; POS, positive; N/A, not available; WT, wild type; and T/M, T_1640M mutation in cardiac sodium channel in chromosome 3. The star and the dot refer to Figure 4.
Figure 4. Electrocardiographic leads V1, V2, and V3 from 2 members of family shown in Figure 3, before (PRE) and after (POST) administration of single intravenous dose of 1 mg/kg ajmaline. Left panels are from an affected patient (marked with star in Figure 3), and right panels are from an unaffected patient (marked with dot in Figure 3).

Figure 5. Twelve-lead surface ECG from an asymptomatic family member of a patient with syndrome who has a proven mutation. Administration of single intravenous dose of 1 mg/kg ajmaline resulted in abrupt occurrence of electrocardiographic abnormalities. Ten minutes after end of ajmaline administration, ECG became normal again. Numbers indicate minutes (') and seconds (") after initiation of drug administration (START). END denotes end of drug administration.
syndrome may be underdiagnosed and that failure to unmask the disease may place patients at considerable risk. The high degree of concordance among different observers shows that the anomalies are easily recognized and could be identified by nonspecialists.

Our data demonstrated the ability of ajmaline, flecainide, and procainamide to identify patients in whom the syndrome is concealed. Administration of the drug during transient normalization of the ECG in patients previously recognized as having the syndrome unmasked the ECG pattern characteristic of the syndrome. However, administration of the drug did not result in a similar pattern in any of the controls, even if they presented with isolated RBBB or arrhythmogenic right ventricular dysplasia. Moreover, in a given family, only individuals with a proven mutation of the cardiac sodium channel tested positive. Thus, the data demonstrated both a high sensitivity and specificity for the ability of these sodium channel blockers to unmask the syndrome.

Our findings also serve to further distinguish this syndrome from that of arrhythmogenic right ventricular dysplasia. Although structural heart disease could not be demonstrated in any of our patients, some authors have suggested that the ECG pattern could be the expression of right ventricular cardiomyopathy. However, the changing nature of the ECG pattern, the lack of ECG modification during class I drug testing in patients with proven right ventricular dysplasia, and the genetic data associating the syndrome with mutations in the cardiac sodium channel gene that are completely different from the loci thus far identified in familial forms of right ventricular dysplasia argue against this.

The occurrence of frequent ventricular premature beats in 5 patients and the spontaneous development of ventricular fibrillation in 1 patient during ajmaline administration indicate the need to perform such tests in an appropriate environment, where cardiopulmonary resuscitation facilities are available.

The mechanisms responsible for the electrocardiographic actions of class I antiarrhythmic agents in patients with Brugada syndrome have been the subject of extensive study by Antzelevitch and others. On the basis of these studies, our working hypothesis is that a strong sodium channel block facilitates the loss of the right ventricular epicardial action dome (plateau phase) by altering the balance of current at the end of phase 1 of the action potential from inward to outward. The result is an all or none repolarization of the right ventricular epicardial action potential and marked abbreviation of the epicardial action potential duration. The loss of the dome in right ventricular epicardium but not endocardium creates a transmural voltage gradient that manifests as an ST-segment elevation in the right precordial leads of the ECG and a transmural dispersion of refractoriness that can serve as the substrate for the development of functional reentry.

Loss of the action potential dome at some right ventricular epicardial sites but not others leads to the development of closely coupled extrasystoles via phase 2 reentry. When these extrasystoles capture the vulnerable window created by the transmural dispersion of refractoriness, they precipitate ventricular arrhythmias.

Because a prominent Ito (transient outward current) is pivotal to this mechanism, inhibition of Ito (with 4-aminopyridine) can restore the dome and normalize ST-segment elevation. Isoproterenol and dobutamine are also capable of restoring the dome via augmentation of Ica (calcium current). The much greater density of Ito in right versus left ventricular epicardium may also explain why Brugada syndrome is a right ventricular disease.

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**Table: Effects of Class I Antiarrhythmic Drugs on ECG Parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>Genotype +</th>
<th>Genotype -</th>
<th>ARVD</th>
<th>RBBB</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR pre, ms</td>
<td>181±12</td>
<td>174±14</td>
<td>164±21</td>
<td>187±12</td>
<td>162±8</td>
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<tr>
<td>PR post, ms</td>
<td>216±13</td>
<td>210±18</td>
<td>194±12</td>
<td>201±10</td>
<td>189±9</td>
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<tr>
<td>QRS pre, ms</td>
<td>105±7</td>
<td>108±6</td>
<td>98±10</td>
<td>109±5</td>
<td>127±6</td>
</tr>
<tr>
<td>QRS post, ms</td>
<td>114±6</td>
<td>112±7</td>
<td>104±9</td>
<td>115±6</td>
<td>136±5</td>
</tr>
<tr>
<td>STV2 pre, mV</td>
<td>0.09±0.01</td>
<td>0.08±0.03</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>STV2 post, mV</td>
<td>0.26±0.08</td>
<td>0.30±0.11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are means±SD. ARVD indicates arrhythmogenic right ventricular dysplasia; RBBB, isolated right bundle branch block; Controls, group C patients with no previous history of syncope or sudden death; STV2, ST-segment elevation in V2; pre, before treatment with study drugs; and post, after treatment with study drugs.
Limitations of the Study
The major limitation of this study is the limited number of patients with a known genotype. This group of patients is the only one in which we have a certain diagnosis; this allows the study of the sensitivity and specificity of the test. Also, results on genotyped patients are limited to individuals with a mutation in the coding region of the sodium channel. It is not known if the test performed in patients with Brugada syndrome and a different genetic defect will have the same power to unmask concealed forms of the disease.

References
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